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ORIGINAL ARTICLE

Dosimetric and radiobiological impact of intensity modulated proton therapy and RapidArc planning for high-risk prostate cancer with seminal vesicles

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Abstract

Introduction: The purpose of this study was to evaluate the dosimetric and radiobiological impact of intensity modulated proton therapy (IMPT) and RapidArc planning for high-risk prostate cancer with seminal vesicles. **Methods:** Ten high-risk prostate cancer cases were included in this retrospective study. For each case, IMPT plans were generated using multiple field optimisation (MFO) technique (two fields) with XiO treatment planning system (TPS), whereas RapidArc plans were generated using double-arc technique (two full arcs) with Eclipse TPS. IMPT and RapidArc plans were optimised for a total prescription dose of 79.2 Gy (relative biological effectiveness (RBE)) and 79.2 Gy, respectively, using identical dose–volume constraints. IMPT and RapidArc plans were then normalised such that at least 95% of the planning target volume (PTV) received the prescription dose. **Results:** The mean and maximum PTV doses were comparable in IMPT plans (80.1 ± 0.3 Gy (RBE) and 82.6 ± 1.0 Gy (RBE) respectively) and RapidArc plans (80.3 ± 0.3 Gy and 82.8 ± 0.6 Gy respectively) with $P = 0.088$ and $P = 0.499$ respectively. The mean doses of the rectum and bladder were found to be significantly lower in IMPT plans (16.9 ± 5.8 Gy (RBE) and 17.5 ± 5.4 Gy (RBE) respectively) when compared to RapidArc plans (41.9 ± 5.7 Gy and 32.5 ± 7.8 Gy respectively) with $P < 0.000$ and $P < 0.000$ respectively. For the rectum, IMPT produced lower V_{30} (21.0 ± 9.6% vs. 68.5 ± 10.0%; $P < 0.000$), V_{50} (14.3 ± 5.8% vs. 45.0 ± 10.0%; $P < 0.000$) and V_{70} (6.9 ± 3.4% vs. 12.8 ± 3.6%; $P < 0.000$) compared to RapidArc. For the bladder, IMPT produced lower V_{30} (23.2 ± 7.0% vs. 50.9 ± 15.6%; $P < 0.000$) and V_{50} (16.6 ± 5.4% vs. 25.1 ± 9.6%; $P = 0.001$), but similar V_{70} (9.7 ± 3.5% vs. 10.5 ± 4.2%; $P = 0.111$) compared to RapidArc. RapidArc produced lower mean dose for both the right femoral head (19.5 ± 4.2 Gy vs. 27.4 ± 4.5 Gy (RBE); $P < 0.000$) and left femoral head (18.0 ± 4.3 Gy vs. 28.0 ± 5.6 Gy (RBE); $P < 0.000$). Both IMPT and RapidArc produced comparable bladder normal tissue complication probability (NTCP) (0.6 ± 0.2% vs. 0.5 ± 0.2%; $P = 0.152$). The rectal NTCP was found to be lower using IMPT (0.8 ± 0.7%) than using RapidArc (1.7 ± 0.7%) with $P < 0.000$. **Conclusion:** Both IMPT and RapidArc techniques provided comparable mean and maximum PTV doses. For the rectum, IMPT produced

better dosimetric results in the low-, medium- and high-dose regions and lower NTCP compared to RapidArc. For the bladder, the NTCP and dosimetric results in the high-dose region were comparable in both sets of plans, whereas IMPT produced better dosimetric results in the low- and medium-dose regions.

Introduction

External beam radiation therapy (EBRT) continues to be one of the most commonly used treatment techniques for cancer treatment. RapidArc (a form of volumetric modulated arc therapy (VMAT) implemented by Varian Medical Systems, Palo Alto, CA) and intensity modulated proton therapy (IMPT) are two most recent EBRT modalities that are used to treat prostate cancer.[1,2] One of the fundamental differences between these two techniques is that mega-voltage X-rays (photons) are used for RapidArc delivery, whereas protons are used for IMPT. Several researchers[2–10] have investigated the dosimetric impact of photon and proton therapy for the prostate cancer. Earlier studies[4–10] using proton therapy were mostly focused on double scattering and uniform scanning. One of the limitations of double scattering and uniform scanning is the lack of a plan optimisation feature. Specifically, in double scattering and uniform scanning proton therapy (USPT), treatment planning is based on the 3D conformal approach and utilises apertures and range compensators. A more recent study[5] on USPT planning for a high-risk prostate cancer showed that USPT consistently produced better organ at risk (OAR) results in the low- and medium-dose regions when compared to RapidArc; however, in the high-dose region, the dosimetric advantage of USPT over RapidArc was not distinct when evaluated for all the cases presented in the study.[5]

The literature comparing IMPT and VMAT for the prostate cancer is very scarce. Vees et al.[2] assessed various treatment techniques including VMAT and IMPT for six prostate cancer patients with sentinel nodes in the pararectal region. The authors[2] reported greater reduction in OARs volume exposed to radiation using IMPT than using VMAT. Georg et al.[3] assessed the dosimetric differences among VMAT, IMPT, carbon-ion therapy and brachytherapy treatment of localised prostate cancer. The comparison between IMPT and VMAT plans showed that the IMPT produced better rectal and bladder results in the low- and medium-dose regions, whereas the VMAT produced better OAR (rectum and bladder) results in the high-dose region.[3] The OAR volume exposed to medium and high doses could be potentially critical to reduce late toxicities, especially for the rectum.[11–13] Since the literature comparing VMAT (or RapidArc) and IMPT for a high-risk prostate cancer is very limited, further investigation of these two evolving EBRT techniques is needed. The main purpose of our study was to evaluate the dosimetric and radiobiological impact of IMPT and RapidArc for a high-risk prostate cancer with seminal vesicles.

Materials and Methods

A total of 10 high-risk prostate cancer cases previously treated with USPT at ProCure Proton Therapy Center, Oklahoma City were selected for this retrospective study. All 10 patients have consented to participation in the Proton Collaborative Group (PCG) protocol REG001-09 (NCT01255748). Each case had undergone VisiCoil fiducial markers (IBA, Schwarzenbruck, Sweden) placement within the prostate. The computed tomography (CT) simulation of each case was done on a General Electric CT Scanner (General Electric Healthcare, Little Chalfont, United Kingdom) in the feet-first supine position using a Vac-Lok system (CIVCO Medical Solutions, Kalona, Iowa) with slice thickness of 1.25 mm. Per institutional protocol at ProCure Proton Therapy Center, Oklahoma City, all patients were instructed to drink a 16–32 oz of water in order to maintain a full bladder 30–60 min prior to the CT simulation as well as the beam delivery. For the rectum, either a rectal balloon or 100 cc of saline was used based on the recommendation from the attending physician.

The CT data set and contoured structures of each case were reviewed in Velocity, version 2.8.0 (Varian Medical Systems, Palo Alto, CA). The clinical target volume (CTV) was defined as the prostate and seminal vesicles. The planning target volume (PTV) was created by expanding the CTV (i.e. 3 mm to the posterior and 4 mm elsewhere to the CTV). The rectum, bladder, femoral heads and other relevant structures for the prostate cancer treatment were contoured per PCG protocol REG001-09 (NCT01 255748).

RapidArc plans were generated in the Eclipse treatment planning system (TPS), version 11.01 (Varian Medical Systems, Palo Alto, CA) using Varian Clinac iX 6 MV beams. A total dose of 79.2 Gy was prescribed to the PTV with 1.8 Gy per fraction. RapidArc plan of each case consisted of 2 full arcs with their isocentre placed at the centre of the PTV. Field sizes were selected based on the

Table 1. Dose–volume constraints for the planning target volume (PTV), rectum, bladder and femoral heads.

PTV	Maximum dose 81.2 Gy or Gy (RBE)	Minimum 80.0 Gy or Gy (RBE)	
	$D_{15\%}$ (Gy or Gy (RBE))	$D_{35\%}$ (Gy or Gy (RBE))	$D_{50\%}$ (Gy or Gy (RBE))
Rectum	<70	<65	<60
Bladder	<75	<70	<65
Femoral heads	Mean dose < 40 Gy or Gy (RBE)		

$D_{x\%}$, dose received by x% of total OAR volume, where x% = 15, 25, 35 and 50. OAR, organ at risk; RBE, relative biological effectiveness.

beam's-eye-view graphics in the Eclipse TPS. RapidArc plans were optimised using dose constraints provided in Table 1. Dose calculations in RapidArc plans were performed with the anisotropic analytical algorithm, and the dose calculation grid size was set to 2.5 mm.

IMPT plan of each case was generated in the XiO TPS, version 5.00 (CMS Inc., St. Louis, MO) using an IBA proton machine (IBA, Louvain-la-Neuve, Belgium). For each prostate case in this study, dose prescription to the PTV was 79.2 (relative biological effectiveness (RBE)) with a fractional dose of 1.8 Gy (RBE). For the IMPT planning, two parallel-opposed lateral fields were used to target the PTV, and the isocentre of each proton field was placed at the centre of the PTV (Fig. 1). For a given proton field, a range uncertainty of 2.5% + 2 mm (i.e. 2.5% of water equivalent path length (skin edge to the distal and proximal edges of the CTV) plus 2 mm) was applied. During IMPT plan optimisation, both lateral fields were combined together, and dose–volume constraints (Table 1) in IMPT optimisation were selected as the same ones as in the RapidArc plan optimisation. Proton dose calculations were done using a pencil beam algorithm,[14] and the dose calculation grid size was set to 3 mm × 3 mm × 3 mm.

For plan evaluation purpose, both sets of plans (RapidArc and IMPT) were normalised such that at least 95% of the PTV volume received the prescription dose. For dose–volume histogram (DVH) analysis, the PTV was evaluated for the mean and maximum dose. The rectum and bladder were evaluated for the relative volumes that received 70, 50 and 30 Gy (RBE) or Gy (V_{70}, V_{50} and V_{30} respectively). The mean dose was obtained for the rectum, bladder, left femoral head and right femoral head.

In addition to the DVH analysis, normal tissue complication probability (NTCP) was calculated for the rectum and bladder. First, the DVHs of the RapidArc and IMPT plans were exported from the Eclipse and XiO TPSs, respectively, using the dose bin size of 50 cGy. Second, the NTCP[15] was calculated using following equation:

$$\mathrm{NTCP} = \frac{1}{1 + \left(\frac{\mathrm{TD}_{50}}{\mathrm{EUD}}\right)^{\gamma_{50}}} \quad (1)$$

where TD_{50} is the tolerance dose for a 50% complication rate at a specific time interval.[15] The γ_{50} is a unit less model parameter that is specific to the normal structure of interest and describes the slope of the dose–response curve.[15]

The equivalent uniform dose (EUD)[15,16] in Equation 1 is defined as

$$\mathrm{EUD} = \left(\sum_{i=1}\left(v_i \mathrm{EQD}_i^a\right)\right)^{\frac{1}{a}} \quad (2)$$

where a is a unit-less model parameter that is specific to the normal structure or tumour of interest, and v_i is unit-less and represents the ith partial volume receiving dose D_i in Gy.[15,16] Since the relative volume of the whole

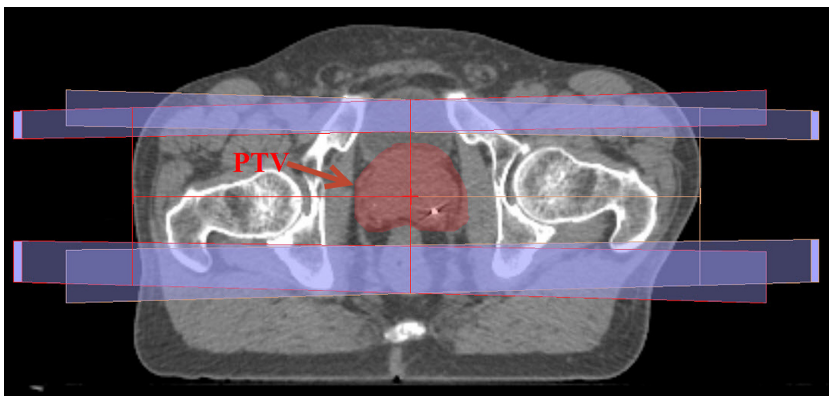

Figure 1. Two 180° parallel-opposed lateral proton fields targeting the planning target volume (PTV) in IMPT plan for prostate cancer.

Table 2. Parameters used to calculate normal tissue complication probability (NTCP) of rectum and bladder.

Tissue	Volume type	100% dpf	#f	a	γ_{50}	TD_{50} (Gy)	Dpf (Gy)	α/β (Gy)
Rectum	Normal	1.8	44	5	2.7	80	2	8
Bladder	Normal	1.8	44	7	3.6	80	2	3

100% dpf, 100% dose per fraction; #f, number of fractions; a, unit-less model parameter that is specific to the normal structure; γ_{50}, unit-less model parameter of normal tissue and describes the slope of the dose–response curve; TD_{50}, tolerance dose for a 50% complication rate at a specific time interval; dpf, parameters' source data's dose per fraction; α/β, alpha–beta ratio.

structure of interest corresponds to 1, the sum of all partial volumes v_i will equal 1.[15,16] The EQD is the biologically equivalent physical dose of 2 Gy. The EQD is defined as

$$\mathrm{EQD} = D \times \frac{\left(\frac{\alpha}{\beta} + \frac{D}{n_f}\right)}{\left(\frac{\alpha}{\beta} + 2\right)} \quad (3)$$

where n_f and $d_f = D/n_f$ are the number of fractions and dose per fraction size of the treatment course respectively. The α/β is the tissue-specific linear-quadratic parameter of the organ being exposed.[15,16] The EUD calculations in this study were based on the parameters listed in Table 2.

Two-sided Student's *t* test was performed to calculate the differences in the dosimetric and NTCP results between the IMPT and VMAT plans, with $P < 0.05$ being statistically significant.

Results

Table 3 provides averaged dosimetric and NTCP results, whereas Figure 2 shows the dosimetric results of the bladder and rectum of all 10 cases. The values inside the parenthesis in this section are averaged over 10 analysed cases.

The PTV maximum dose between IMPT and RapidArc plans among all cases was found to be comparable ($P = 0.499$). The PTV mean dose evaluation also showed no significant difference ($P = 0.088$) between IMPT and RapidArc plans. These PTV results suggest that the choice of technique (IMPT or RapidArc) is less likely to make a significant difference in the PTV doses.

However, the dosimetric impact of the treatment technique was more distinct in the case of OARs, especially in the low-dose (V_{30}) and medium-dose (V_{50}) regions as shown in the Figure 1. For the bladder, the V_{30} and V_{50} were consistently lower in IMPT plans (23.2% and 16.6% respectively) when compared to RapidArc plans (50.9% and 25.1% respectively) with $P < 0.000$ for V_{30} and $P = 0.001$ for V_{50}. Similarly, the V_{30} and V_{50} of the rectum were found to be lower in IMPT plans (21.0% and 14.3% respectively) than in RapidArc plans (68.5% and 45.0% respectively) with $P < 0.000$ for V_{30} and $P < 0.000$ for V_{50}. For the high-dose region (V_{70}), IMPT technique produced better rectal results compared to RapidArc technique (6.9% vs. 12.8%; $P < 0.000$). However, the V_{70} of the bladder was found to be comparable in IMPT and RapidArc plans (9.7% vs. 10.5%; $P = 0.111$).

Table 3. Comparison of the dosimetric and normal tissue complication probability (NTCP) results in intensity modulated proton therapy (IMPT) and RapidArc plans.

	PTV	IMPT	RapidArc	*P*-value
PTV (volume: 130 cc)	Mean dose	80.1 ± 0.3 Gy (RBE)	80.3 ± 0.3 Gy	0.088
	Maximum dose	82.6 ± 1.0 Gy (RBE)	82.8 ± 0.6 Gy	0.499
Rectum (volume: 123.9 cc)	Mean dose	16.9 ± 5.8 Gy (RBE)	41.9 ± 5.7 Gy	<0.000
	V_{30} (%)	21.0 ± 9.6	68.5 ± 10.0	<0.000
	V_{50} (%)	14.3 ± 5.8	45.0 ± 10.0	<0.000
	V_{70} (%)	6.9 ± 3.4	12.8 ± 3.6	<0.000
	NTCP (%)	0.8 ± 0.7	1.7 ± 0.7	<0.000
Bladder (volume: 239.4 cc)	Mean dose	17.5 ± 5.4 Gy (RBE)	32.5 ± 7.8 Gy	<0.000
	V_{30} (%)	23.2 ± 7.0	50.9 ± 15.6	<0.000
	V_{50} (%)	16.6 ± 5.4	25.1 ± 9.6	0.001
	V_{70} (%)	9.7 ± 3.5	10.5 ± 4.2	0.111
	NTCP (%)	0.6 ± 0.2	0.5 ± 0.2	0.152
Right femoral (volume: 68.8 cc)	Mean dose	27.4 ± 4.5 Gy (RBE)	19.5 ± 4.2 Gy	<0.000
Left femoral (volume: 72.0 cc)	Mean dose	28.0 ± 5.6 Gy (RBE)	18.0 ± 4.3 Gy	<0.000

The values are averaged over 10 analysed cases. (Note: Both IMPT and RapidArc plans were normalised for the same PTV coverage). V_x, relative volume of the rectum receiving x Gy or Gy (RBE); PTV, planning target volume; RBE, relative biological effectiveness.

The mean doses of the rectum and bladder were found to be significantly lower in IMPT plans (16.9 Gy (RBE) and 17.5 Gy (RBE) respectively) when compared to RapidArc plans (41.9 Gy and 32.5 Gy respectively) with $P < 0.000$ for rectal mean dose and $P < 0.000$ for bladder mean dose. However, RapidArc technique produced lower mean dose for both the left femoral head (28.0 Gy (RBE) vs. 18.0 Gy; $P < 0.000$) and right femoral head (27.4 Gy (RBE) vs. 19.5 Gy; $P < 0.000$).

The NTCP results of the bladder and rectum for each case are shown in Figure 3. For the bladder, there was no

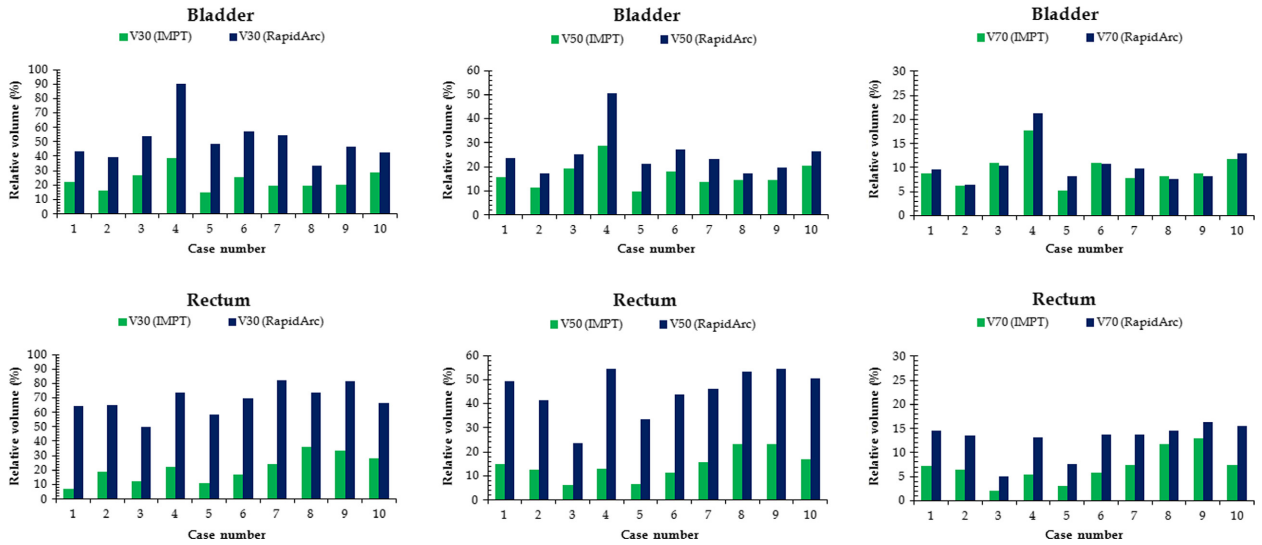

Figure 2. Comparison of the dosimetric results of the bladder (top row) and rectum (bottom row) in intensity modulated proton therapy and RapidArc plans of 10 high-risk prostate cancer cases. Vx = relative volume of the structure receiving x Gy or Gy(relative biological effectiveness (RBE)).

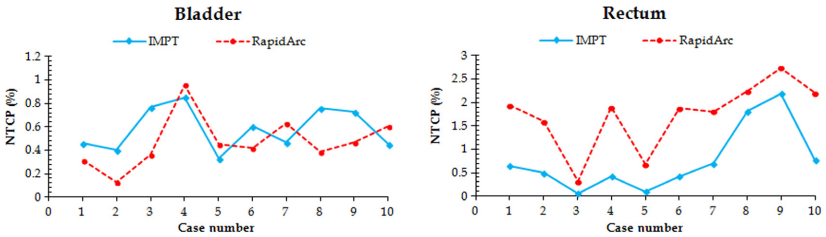

Figure 3. The normal tissue complication probability of rectum and bladder in intensity modulated proton therapy and RapidArc plans of 10 prostate cancer cases.

clear trend with IMPT technique producing smaller NTCP values over RapidArc, and the results in IMPT ($0.6 \pm 0.2\%$) and RapidArc ($0.5 \pm 0.2\%$) plans were found to be comparable ($P < 0.152$). However, for the rectum, IMPT consistently produced lower NTCP among all 10 cases with average values of $0.8 \pm 0.7\%$ and $1.7 \pm 0.7\%$ in IMPT and RapidArc plans respectively ($P < 0.000$).

Discussion

The data presented in the current study show that IMPT technique is capable of producing better dosimetric results of rectal and bladder for the same PTV coverage when compared to RapidArc technique. Similar findings were reported by Vees et al.[2] and Georg et al.[3] The reduction in bladder and rectal volumes exposed to irradiation is very essential in order to minimise the rectal and bladder toxicities. A paper by Michalski et al.[13] showed that small rectal volumes receiving a high dose were the most critical predictors of late toxicity. Interestingly, two different studies[11,12] correlated the late rectal bleeding to the medium-dose (V_{50}). The V_{70} and V_{50} values for the rectum in the current study revealed that IMPT could potentially reduce the late rectal toxicities compared to RapidArc technique if V_{70} and V_{50} are considered to be the late toxicity predictors for the rectum. Previous study[5] on the prostate cancer cases reported that RapidArc produced lower rectal V_{70} in two cases when compared to USPT. However, the current study shows that IMPT produced lower rectal V_{70} for all cases as IMPT planning allows plan optimisation, which is not available in USPT planning. Furthermore, lower NTCP of the rectum in IMPT plans shows the potential of reducing rectal toxicities compared to RapidArc plans.

A higher mean femoral head dose in IMPT plans is mainly due to two parallel-opposed lateral fields used in the planning, which passed through the left and right femoral heads. However, the V_{40} of the left and right femoral heads was found to be 0% for both IMPT and

RapidArc plans, and this satisfied the dosimetric constraint ($V_{50} < 5\%$) of the femoral head.[17] For the bladder, both IMPT and RapidArc techniques clearly met the QUANTEC[18] recommendation (i.e. no more than 35% of the bladder volume receive a dose greater than 70 Gy). The correlation between the toxicities of the bladder and its dosimetric parameter, however, is yet to be established.[19] On average, smaller volumes of the bladder were found to be exposed to irradiation using IMPT than using RapidArc; however, the NTCPs of bladder suggest that both the techniques are capable of producing NTCP below 1% for the high-risk prostate cases with seminal vesicles.

A number of assumptions were made in our study. Treatment delivery schema was assumed to be 2 fields/day and 2 arcs/day in IMPT and RapidArc planning respectively. Single field per day delivery schema can also be used for the prostate cancer treatment planning. Both the double- and single-field techniques were found to produce comparable dosimetric results in the proton[20] and RapidArc planning.[21] A nominal CT data set of each case was used for proton and photon dose calculations although it is possible to have a change in patient anatomy during the course of treatment.

The PTV margin (3 mm to the posterior and 4 mm elsewhere to the CTV) in the current study was based on the institutional protocol for the prostate cancer with seminal vesicles. More recent publication by Park et al.[22] has suggested using a beam-specific PTV margin for the proton plans which were generated based on single-field optimisation technique. The beam-specific PTV margin in proton therapy could account for setup and range uncertainties. However, for the multi-field optimisation (e.g. IMPT planning), the application of the beam-specific PTV margin is not straightforward in our current version of XiO TPS. Since our study was more focused on the comparison between two different modalities, it made more sense to use the geometry-based PTV for IMPT and RapidArc planning.

In the current study, proton planning was done using two parallel-opposed lateral beams. Some of the recent publications have shown the feasibility of using non-parallel-opposed proton beams in the treatment of prostate cancer. For example, Trofimov et al.[9] and Tang et al.[23] reported that the anterior-oblique proton beams could reduce the rectal dose when compared to two parallel-opposed lateral fields. Rana et al.[24] used anterior-oblique beams for treatment planning of the prostate cancer cases with a unilateral metallic hip prosthesis and reported more favourable rectum and bladder results in IMPT plans than in USPT plans. A clinical study by Cuaron et al.[25] reported acceptable low toxicities in the prostate cancer patients treated with anterior-oblique beams in USPT.

IMPT plans are typically evaluated in terms of their robustness, and dosimetric effect of translational and rotational alignment errors are analysed. Recently, Pugh et al.[26] performed a robust analysis for the prostate cancer plans generated by IMPT technique. It was reported that rotational errors of up to 5° and translational errors of up to 5 mm resulted in robust prescription dose coverage of the CTV.[26] Translational alignment errors could produce larger dose perturbations to the rectum and bladder.[26] Previous studies and the IMPT results from the current study demonstrate the use of proton beams for the prostate cancer treatment very promising; however, further study investigating the radiobiological consequences due to treatment setup variations (rotational and translational errors) is warranted.

Conclusion

Both IMPT and RapidArc techniques provided comparable mean and maximum PTV doses. For the rectum, IMPT produced better dosimetric results in the low-, medium- and high-dose regions and lower NTCP compared to RapidArc. For the bladder, the NTCP and dosimetric results in the high-dose region were comparable in both sets of plans, whereas IMPT produced better dosimetric results in the low- and medium-dose regions.

Conflict of Interest

The authors declare no conflict of interest.

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