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Intensity modulated proton therapy versus uniform scanning proton therapy: Treatment planning study of the prostate cancer in patients with a unilateral metallic hip prosthesis

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Abstract

The purpose of this study is to compare the dosimetric results between the uniform scanning proton therapy (USPT) and intensity modulated proton therapy (IMPT) plans for the prostate cancer in patients with a unilateral metallic hip prosthesis. Five prostate cancer cases with left (n = 3) and right (n = 2) metallic hip prostheses were included in this retrospective study. For each case, the USPT and IMPT plans were generated using two anterior-oblique beams and one lateral beam for a total dose of 79.2 Gy(RBE) to be delivered in 44 fractions. For a given case, the beam parameters, dose prescription, and delivery schema in the IMPT plan were kept identical to the ones in the USPT plan. The IMPT and USPT plans were compared for various dosimetric parameters. The mean dose to the target volume was comparable. Both the IMPT and USPT techniques achieved the target coverage goals. Dose homogeneity was found to be similar in the IMPT and USPT plans. For both the rectum and bladder, the IMPT plans produced favorable dosimetric results in the low-, medium-, and high-dose regions when compared to the USPT plans. For the high dose regions, the rectal V_{70} was lower in the IMPT plans by about 3.89 cc when compared to the one in the USPT plans. The rectal V_{80} in the IMPT plans (1.10 cc) was almost half than the one in the USPT plans (2.39 cc). In comparison to the USPT plans, the mean dose to the rectum, bladder, and femoral head were lower in the IMPT plans by about 8.91%, 4.15%, and 41.09%, respectively. Based on the preliminary results of five cases presented in this study, the IMPT plans provided slightly better dosimetric results compared to the USPT plans, especially in sparing the rectum and bladder in the low-, medium-, and high-dose regions, for the treatment of the prostate cancer in patients with a unilateral metallic hip prosthesis. Future studies need to address the impact of the setup uncertainties and intra-fraction prostate motion in the IMPT planning of the prostate cancer patients with prosthetic hip replacements.

Keywords: Proton Therapy; Prostate Cancer; IMPT; Prosthesis; Treatment Planning

Original Article

1. Introduction

Radiation therapy is one of the most commonly used techniques for the prostate cancer treatment. Among various radiation therapy techniques, proton therapy has become a popular option to treat the prostate cancer. A number of dosimetric studies on the prostate cancer have compared the results of proton therapy with that of mega-voltage (MV) X-ray (photon) therapy such as intensity modulated radiation therapy (IMRT) and volumetric

modulated arc therapy (VMAT).[1-10] Proton therapy planning for the prostate cancer typically includes two 180 degree parallel-opposed lateral fields, but such beam arrangement is not feasible for a complex prostate case, which involves a metallic hip prosthesis [Figure 1]. Prostate cancer cases involving a metallic prosthesis are very rare at our institution. The Task Group (TG) 63 of American Association of Physicists in Medicine (AAPM)[11] recommends avoiding beam passing through the metals such as hip prostheses that are composed of high-Z materials. Hence, proton therapy planning for a prostate cancer case with a unilateral metallic hip prosthesis may need to include at least one oblique field in addition to the lateral field.

Tang *et al.*[1] and Trofimov *et al.*[4] demonstrated the feasibility of using non-parallel-opposed lateral fields in proton therapy planning for the prostate cancer. Tang *et al.*[1] showed that the anterior-oblique proton fields are superior in reducing dose to the anterior rectal wall in the high-dose regions when compared to the bilateral fields. Similar result was reported by Trofimov *et al.*[4] showing anteriorly angled lateral proton fields can reduce the rectal dose when compared to two parallel-opposed lateral fields. Both the studies of Tang *et al.*[1] and Trofimov *et al.*[4] included the prostate cases which did not include a metallic hip prosthesis. To date, there are only two published studies[7, 12], which address the proton therapy for the prostate cancer patients with a metallic hip prosthesis. Rana *et al.*[7] demonstrated that the combination of one lateral and two oblique fields in the uniform scanning proton therapy (USPT) provides dosimetric advantage over the VMAT. Cuaron *et al.*[12] reported the clinical results with acceptable normal tissue toxicities for the prostate patients treated with the anterior-oblique proton beams.

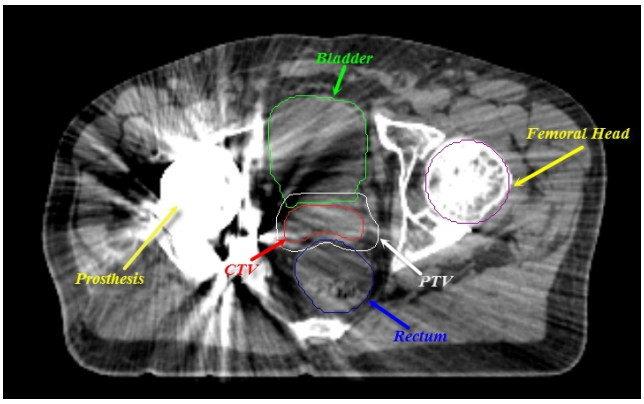

Figure 1: *Axial CT slice showing the clinical target volume (CTV), planning target volume (PTV), rectum, bladder, femoral head, and metallic hip prosthesis in a prostate cancer case.*

Proton therapy community is showing increasing interest in intensity modulated proton therapy (IMPT), which is a more advanced proton therapy technology, compared to the uniform scanning (US) and double scattering (DS) proton therapy. In US and DS proton therapy, the treatment planning is based on a 3D conformal approach, which utilizes beam specific apertures and compensators. By contrast, the IMPT plans can be generated using single field optimization (SFO) and multiple field optimization (MFO) techniques. For the SFO-IMPT, the treatment plan is optimized such that each field covers the target volume; whereas for the MFO-IMPT, the treatment plan optimization involves the sum of multiple fields producing uniform dose coverage to the target volume.

In a more recent study by Kirk *et al.*[13], the authors found that the IMPT plans are more conformal than the USPT plans, but differences in the organs at risk (OAR) doses among various proton plans were not significant. Existing proton therapy treatment planning studies on the prostate cancer reported either the US technique involving a metallic hip prosthesis[7, 12] or the IMPT techniques but with no involvement of a metallic hip prosthesis[3, 13, 14, 15]. The purpose of this study is to compare the dosimetric results between the USPT and MFO-IMPT plans (hereafter referred as IMPT plans) for the prostate cancer in patients with a unilateral metallic hip prosthesis.

2. Materials and Methods

A total of 5 prostate cancer cases with unilateral left (n = 3) or right (n = 2) metallic hip prostheses were selected for this retrospective study. All 5 cases are included in the Proton Collaborative Group (PCG) research study (REG01-09, WIRB Protocol #20091082). Patients were treated using the USPT technique at our institution (ProCure Proton Therapy Center, Oklahoma City) between January 2012 and December 2014. The IMPT planning on five cases was done for a comparative purpose.

2.1 Simulation

Computed tomography (CT) simulation was done on a General Electric CT Scanner (GE Healthcare, Waukesha, WI) by immobilizing patients in a supine position using the vac-lok system (CIVCO Medical Solutions, Kalona, IA, USA). Each patient had fiducial markers placement within the prostate. Per institutional protocol, all patients were instructed to drink 16 to 24 oz of water to maintain a full bladder prior to the CT simulation and during treatment. Additionally, 100 cc of saline was inserted into the rectum of each patient. The CT dataset with slice thickness of 1.25 mm were then transferred to the treatment planning station for the contouring and planning.

2.2 Contouring

The clinical target volume (CTV) was contoured by the radiation oncologist. The CTV included either the prostate and seminal vesicles (n = 3) or the prostate only (n = 2). The planning target volume (PTV) expansion among these 5 clinical cases, however, varied slightly with a setup

technique (i.e., 5 mm uniform expansion with a rectal balloon and no fiducial markers; 3 mm posterior and 5 mm elsewhere for high-risk cases with fiducial markers and saline injection into the rectum). For a comparative purpose in this study, we used a 5 mm uniform PTV expansion around the CTV, and each case was re-planned with the USPT, which was then compared to the corresponding IMPT plan using the same PTV (i.e., 5 mm uniform expansion around the CTV). The OARs such as the rectum, bladder, and femoral head as well as the streaking artifacts were contoured too. All the artifacts were overridden by relative stopping power values, which were obtained by sampling the tissues in the CT dataset.

2.3 Treatment planning

Proton plans were generated in the XiO treatment planning system (TPS), version 5.00 (CMS Inc., St. Louis, MO, USA). Our XiO TPS used the beam commissioning data that were measured on an IBA Cyclotron (IBA, Louvain-la-Neuve, Belgium). The uniform scanning proton beam is scanned laterally with a constant frequency in order to deliver a uniform dose for a near rectangular scanning area, whereas the IMPT modulates the dose in the beam direction and lateral to the beam direction. For each prostate case in this study, dose prescription to the PTV was 79.2 Gy (RBE) with a daily fractional dose of 1.8 Gy(RBE) (i.e., 44 fractions).

Proton dose calculations were done using a pencil beam algorithm[16] with a grid size of 3 mm × 3 mm × 3 mm. Treatment planning was done based on the same CT calibration curve, which has a maximum relative stopping power of 2.5 (obtained from the linear extrapolation). However, beam angles were chosen so that the beam did not pass through the metal device, thus the actual stopping power of hip implants did not have an effect on the dose calculations.

For both the USPT and IMPT, the treatment planning goal was to minimize the dose to the OARs as much as possible while maintaining dose to 99% of the CTV more than 98% of the prescription dose (CTV D99 > 98%) and dose to 98% of the PTV volume more than 95% of the prescription dose (PTV D98 > 95%).

2.3.1 USPT planning

USPT plans were generated using three fields: lateral (left or right), left-anterior-oblique (LAO), and right-anterior-oblique (RAO). The lateral field was weighted 50% , whereas each oblique field was weighted 25%. Beam angles in each case were selected such that the beam entrance through a metallic hip prosthesis and rectum was avoided. The isocenter of each proton field was placed at the center of the PTV. For each beam in the USPT plans, the distal and proximal ranges were calculated based on the uncertainties of 2.5% of proton range for the CT to stopping power ratio conversion inaccuracy plus an additional 2 mm to account for a systematic range uncertainty. The margins for the aperture were 0.8 – 1.0 cm and range compensators had a smearing distance of 1.2 cm. Tapering was not used for the compensators. The beam delivery schema in the USPT plans was such that the lateral field was delivered daily, whereas the LAO and RAO fields were delivered alternatively.

2.3.2 IMPT planning

IMPT plans were generated by optimizing all three fields together by applying dose-volume constraints to the PTV, rectum, and bladder. The rectal and bladder constraints used during plan optimization were as follows: $V_{50\ Gy(RBE)} < 30\%$, $V_{70\ Gy(RBE)} < 15\%$, $V_{79.2\ Gy(RBE)} < 5\%$. Since the XiO TPS does not have a feature to generate a beam-specific PTV margin based on the range uncertainty calculations, especially for the anterior-oblique beams, the PTV (a 5 mm uniform expansion from the CTV) was chosen as the optimization volume. The calculated range of each layer was adjusted by applying a shift (i.e., 2.5% of water equivalent path length [skin edge to the distal and proximal edges of the CTV] plus 2 mm) to account for the range uncertainties along the beam direction. For a given case, the IMPT plan had the same beam parameters (e.g., distal and proximal ranges), isocenter, outlined structures, and delivery schema as in the corresponding USPT plan. The layer spacing was set to 8 mm for all cases. The available spot positions for each beam in the XiO TPS are defined by a three-dimensional rectangular grid passing through the beam isocenter, within the target boundaries.

2.4 Plan evaluation

USPT and IMPT plans were compared based on the dose-volume histograms (DVH) results generated in the XiO TPS. The absolute dose normalization mode available in XiO was applied in all the IMPT and USPT plans. The CTV and PTV were evaluated for the mean dose and dose coverage. The PTV was also evaluated for the homogeneity index (HI). The rectum and bladder were evaluated for the mean dose, and the relative volume (in percentage) of the structure receiving 70, 50, and 30 Gy(RBE) (V_{70}, V_{50}, and V_{30}, respectively). Additionally, the rectum and bladder were evaluated for the absolute volume (in cc) of the structure receiving 75, 79.2, and 80 Gy(RBE) (V_{75}, $V_{79.2}$, and V_{80}, respectively). The femoral head was evaluated for the mean dose.

$$HI = \frac{(D_{5\%} - D_{95\%})}{Prescription\ Dose} \qquad (1)$$

where, $D_{5\%}$ and $D_{95\%}$ represent the doses to 5% and 95% of the PTV, respectively.

Table 1: *Comparison of the dosimetric parameters in the IMPT and USPT plans for a prostate cancer case with a metallic hip prosthesis. The results are averaged over five analyzed cases*

		IMPT	USPT
CTV	Mean Dose (Gy(RBE))	80.42 ± 0.27	80.24 ± 0.43
	D_{99} (%)	100.91 ± 0.59	100.36 ± 0.76
PTV	Mean Dose (Gy (RBE))	80.37 ± 0.11	80.24 ± 0.23
	D_{98} (%)	98.50 ± 1.43	97.99 ± 1.41
	V_{95} (%)	99.62 ± 0.44	99.47 ± 0.61
	HI	0.02 ± 0.01	0.03 ± 0.02
Rectum	Mean Dose (Gy(RBE))	15.76 ± 4.79	17.97 ± 7.21
	V_{30} (%)	21.71 ± 6.68	24.83 ± 10.24
	V_{50} (%)	14.53 ± 5.08	18.22 ± 8.08
	V_{70} (%)	7.12 ± 3.50	10.08 ± 5.70
	V_{75} (cc)	5.83 ± 4.21	9.42 ± 7.09
	$V_{79.2}$ (cc)	2.25 ± 2.50	4.54 ± 4.41
	V_{80} (cc)	1.10 ± 1.54	2.30 ± 2.90
Bladder	Mean Dose (Gy(RBE))	24.19 ± 10.91	25.23 ± 11.16
	V_{30} (%)	34.94 ± 18.43	37.76 ± 20.37
	V_{50} (%)	18.34 ± 7.87	19.91 ± 8.23
	V_{70} (%)	9.52 ± 4.21	11.90 ± 4.70
	V_{75} (cc)	20.49 ± 12.07	28.45 ± 16.71
	$V_{79.2}$ (cc)	10.20 ± 7.86	16.04 ± 10.31
	V_{80} (cc)	6.44 ± 6.68	8.76 ± 6.44
Femoral	Mean Dose (Gy(RBE))	18.59 ± 3.25	31.43 ± 1.52

Abbreviations: *CTV = clinical target volume; PTV = planning target volume; IMPT = intensity modulated proton therapy plan; USPT = uniform scanning proton therapy; V_{95} of PTV = relative volume of the PTV receiving x% of the prescription dose; V_x for the rectum and bladder = volume (in % or cc) of the structure receiving x Gy (RBE); D_X = dose at x% (relative volume) of the PTV; HI = homogeneity index*

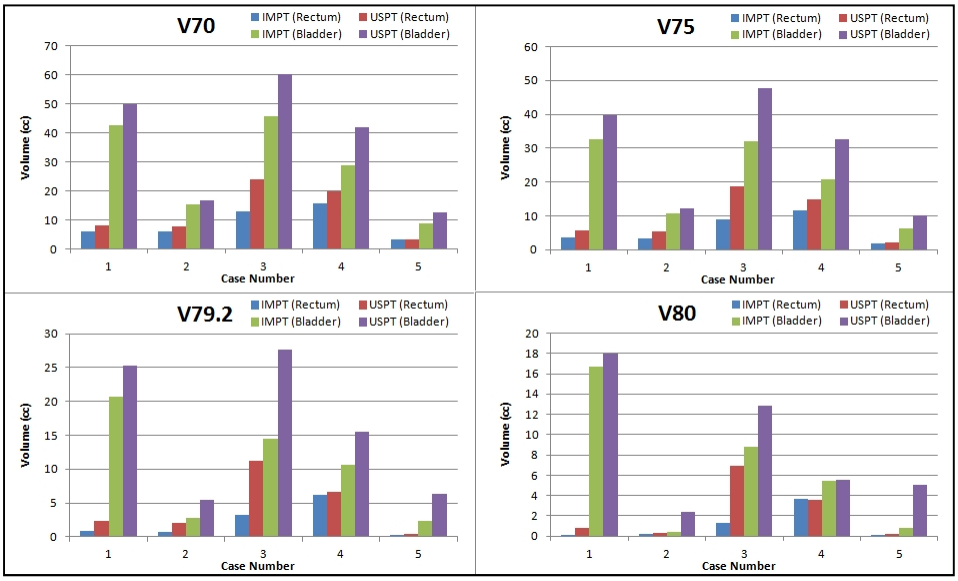

Figure 2: *Rectal and bladder volume (in cc) receiving at least 70, 75, 79.2, and 80 Gy (RBE) (V70, V75, V79.2, and V80, respectively) in five prostate cancer cases with a unilateral metallic hip prosthesis.*

3. Results

Table 1 provides the dosimetric results in the IMPT and USPT plans. The results are averaged over five analyzed cases. Figure 2 shows the rectal and bladder volume (cc) receiving 75, 79.2, and 80 Gy(RBE) in each case analyzed in this study.

3.1 Target volume

The mean CTV doses in the IMPT (79.5 Gy (RBE)) and USPT (79.5 Gy (RBE)) plans were comparable. The mean PTV doses in the IMPT and USPT were also almost identical (80.4 Gy (RBE) vs. 80.3 Gy (RBE)). Dose homogeneity was found to be similar in the IMPT (HI = 0.02) and USPT (HI = 0.03) plans. Both the IMPT and USPT plans met coverage goals for the CTV (D_{99} > 98%) and PTV (D_{98} > 95%).

3.2 OARs

3.2.1 Low-dose region

IMPT plans produced slightly smaller volumes of the bladder being irradiated to the low dose (V_{30}) when compared to the USPT plans (34.9% vs. 37.8%). Similarly, the rectal volume exposed to 30 Gy (RBE) was smaller in the IMPT plans (21.7%) when compared to the USPT plans (24.8%).

3.2.2 Medium-dose region

The V_{50} evaluation shows that the IMPT plans produced lower values when compared to the USPT plans for both the rectum (14.5% vs. 18.2%) and bladder (18.3% vs. 19.9%).

3.2.3 High-dose region

IMPT plans were better at reducing the bladder and rectal volume exposed to higher-dose (V_{70}, V_{75}, $V_{79.2}$, and V_{80}) when compared to the USPT plans. For example, the rectal V_{70} was lower in the IMPT plans (7.12%) when compared to the one in the USPT plans (10.1%). The rectal V_{80} in the USPT plans (2.39 cc) was almost twice than the one in the IMPT plans (1.10 cc).

3.2.4 Mean dose

The mean dose to the bladder and rectum were slightly lower in the IMPT plans (24.2 Gy (RBE) and 15.8 Gy (RBE), respectively) than in the USPT plans (25.2. Gy (RBE) and 18.0 Gy (RBE), respectively). The mean femoral head dose was also found to be lower in the IMPT plans (18.6 Gy (RBE) vs. 31.4 Gy (RBE))

4. Discussion

In this study, we assessed the dosimetric impact of proton therapy planning techniques for the prostate cancer patients with metallic hip replacements. Both the IMPT and USPT techniques met the target coverage goals. Dose homogeneity within the PTV as well as the mean dose to the CTV and PTV were comparable too. Dosimetric results of the OARs, however, demonstrated that the IMPT is slightly better than the USPT in sparing the rectum and bladder in the low-, medium-, and high-dose regions while maintaining excellent target coverage. For the IMPT planning, we applied dose-volume constraints to the OARs during plan optimization process, which helped in reducing dose to the rectum and bladder in the IMPT plans.

Cuaron *et al.*[12] reported the clinical results of the prostate cases, which were treated using USPT. The findings of Cuaron *et al.*[12] are encouraging in the sense that the patients treated with the anterior-oblique beams had no biochemical or distant failures with acceptable low toxicities. However, the reported median follow-up was 6.4 months[12], and further follow-up will be crucial in determining long term outcome and toxicities. Several studies have correlated the dosimetric results to the rectal toxicities. For example, Michalski *et al.*[17] reported that the small rectal volumes receiving a high dose (e.g. V_{70}) were the most critical predictors of late toxicity. Cozzarini *et al.*[18] and Fiorino *et al.*[19] have reported the late rectal bleeding associated with the lower doses. The rectal dose-volume results from our study demonstrated that the IMPT is capable of further decreasing the rectal dose when compared to the USPT, thus the IMPT has a potential of further reducing the rectal toxicities. For the bladder, the QUANTEC[20] recommends V_{70} < 35%, and both the techniques (IMPT and USPT) were able to meet the criteria.

In this study, the PTV in each case was expanded by 5 mm from the CTV. Although we used a range uncertainty in the beam direction, we were unable to generate a beam-specific PTV margin based on the range uncertainty calculations, especially for the anterior-oblique beams. Current literature[21] shows no common consensus on the use of range uncertainty, which may depend on the treatment delivery unit, treatment planning system, patient anatomy, and tumor location. A review article by Paganetti[21] reported that the Massachusetts General Hospital uses the range uncertainty 3.5% + 1 mm, whereas the MD Anderson Proton Therapy Center and Loma Linda University Medical Center use range uncertainty 3.5% + 3 mm. These range uncertainties are different from the recommended range uncertainty at our center (2.5% + 2 mm). The consensus on range uncertainties for different disease sites is yet to be reached among different proton centers.

Treatment plans in this study were generated in an ideal scenario assuming that (i) the patient anatomy will remain identical to the CT simulation during the entire course of

the treatment, (ii) bladder filling does not vary daily, and (iii) daily setup variations are minimal. However, in a more realistic situation, the prostate cancer treatments are susceptible to inter- and intra-fraction motions. The daily change in the bladder filling can also affect the penetration depth of anterior-oblique beams. Figure 3 shows the axial CT slice of an obese case with a substantial abdominal adipose mass, which can produce a considerable challenge to the reproducibility of setup in the path of anterior-oblique beams. The combination of day-to-day variations in the setup of the soft abdominal tissue and bladder filling can substantially affect the penetration in tissue for anterior-oblique beams, and result in a geometric miss of the target. In the case of IMPT, the misalignment of inhomogeneous doses from individual beams may result in target underdose. Since our study is limited by the retrospective design, the effect of an intra-fraction prostate motion on the USPT and IMPT prostate plans was not investigated.

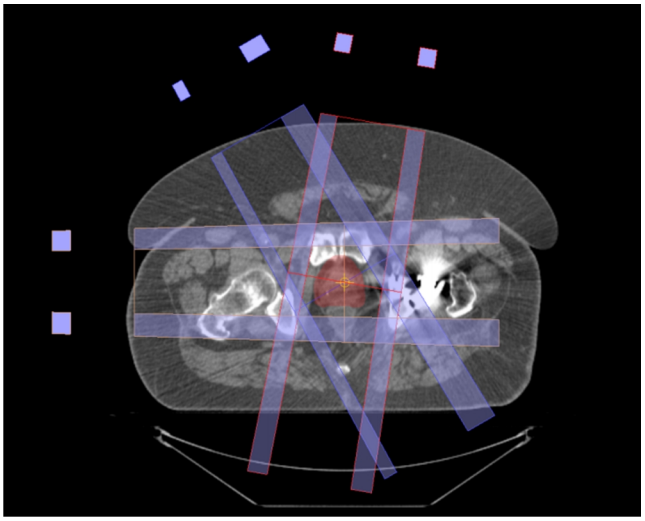

Figure 3: *Proton beams arrangement for the prostate cancer case with a metallic hip prosthesis.*

A number of studies[22, 23] have recommended to perform robust plan optimization for the IMPT planning in order to ensure sufficient target coverage and improved normal tissue sparing. Several studies have reported that the dosimetric quality of the IMPT plans is more sensitive to the treatment setup and delivery uncertainties.[13, 22, 23] The current version of our XiO TPS does not provide robust optimization feature. Hence, we were unable to evaluate the dosimetric impact of setup and treatment uncertainties on the daily IMPT planned dose distributions. The IMPT plans were generated by optimizing a lateral field (44 fractions) and two anterior-oblique fields (each field 22 fractions) together; however, the daily dose in the IMPT plans include dose contributions from 2 fields (one lateral and other anterior-oblique field) only. The main reason to use a schema of 2 fields per day in the IMPT plans was to maintain the same delivery schema as in the USPT plans. In the next study, we aim to investigate the dosimetric impact of IMPT optimization technique and delivery schema on a daily fractional dose for the prostate cancer plans. Also, the robustness of the IMPT planning based on the range uncertainties and treatment setup variations needs to be addressed in the future studies. Another limitation of our work is the limited number of cases presented in this study. Since the prostate cases with metallic hip replacements are rare at our institution, it is most likely that a multi-institutional study will be needed to include a large number of such cases. Further studies with a large number of prostate cancer cases with metallic hip replacements are warranted in order to determine the dosimetric advantages of the IMPT plans over the USPT plans.

5. Conclusion

Based on the preliminary results of five cases presented in this study, the IMPT plans provided slightly better dosimetric results compared to the USPT plans, especially in sparing the rectum and bladder in the low-, medium-, and high-dose regions, for the treatment of the prostate cancer in patients with a unilateral metallic hip prosthesis. Future studies need to address the impact of the setup uncertainties and intra-fraction prostate motion in the IMPT planning of the prostate cancer patients with prosthetic hip replacements.

Conflict of Interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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