



# Proton therapy vs. VMAT for prostate cancer: a treatment planning study

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## Abstract

**Purpose:** The main objective of this study was to compare the dosimetric quality of volumetric modulated arc therapy (VMAT) with that of proton therapy for high-risk prostate cancer.

**Patients and Materials:** Twelve patients with high-risk prostate cancer previously treated with uniform scanning proton therapy (USPT) were included in this study. Proton planning was done using the XiO treatment planning system (TPS) with two 180<sup>0</sup> parallel-opposed lateral fields. The VMAT planning was done using the RapidArc technique with two arcs in the Eclipse TPS. The VMAT and proton plans were calculated using the anisotropic analytical algorithm and pencil-beam algorithm, respectively. The calculated VMAT and proton plans were then normalized so that at least 95% of the planning target volume (PTV) received the prescription dose. The dosimetric evaluation was performed by comparing the physical dose-volume parameters, which were obtained from the VMAT and proton plans.

**Results:** The average difference in the PTV doses between the VMAT and proton plans was within  $\pm 1\%$ . On average, the proton plans produced a lower mean dose to the rectum (18.2 Gy (relative biological effectiveness [RBE]) vs. 40.0 Gy) and bladder (15.8 Gy (RBE) vs. 30.1 Gy), whereas the mean dose to the femoral heads was lower in the VMAT plans (28.3 Gy (RBE) vs. 19.3 Gy). For the rectum and bladder, the proton plans always produced lower (better) results in the low- and medium-dose regions, whereas the results were case-specific in the high-dose region.

**Conclusion:** For the same target coverage, in comparison to the VMAT technique, the USPT is significantly better at sparing the rectum and bladder, especially in the low- and medium-dose regions, but results in a higher femoral head dose.

**Keywords:** proton therapy; prostate cancer; volumetric modulated arc therapy; RapidArc; treatment planning

## Introduction

The most recent statistics released by the American Cancer Society states that prostate cancer will be the most commonly diagnosed cancer in American men in 2013 with an estimated 238,590 new cases and 29,790 deaths [1]. Among treatment options available for prostate cancer, volumetric modulated arc therapy (VMAT) and proton therapy are two of the most common. The VMAT technique delivers modulated photon beams

Submitted 08 Oct 2013  
Accepted 10 Dec 2013  
Published 13 May 2014

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DOI  
10.14338/IJPT.13-00003.1

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(megavoltage [MV] x-rays) with simultaneous adjustment of the multileaf collimator (MLC) field aperture, dose rate, and gantry rotation speed [2]. In uniform-scanning proton therapy (USPT), the proton beam is scanned laterally with a constant frequency to deliver a uniform proton dose for a near-rectangular scanning area, and the majority of the proton dose can be deposited in a region called the spread-out Bragg peak (SOBP).

Several groups [3–14] have investigated the dosimetric quality of proton therapy for prostate cancer. Previous treatment planning studies on prostate cancer showed that proton beams could have dosimetric advantages over photons [3–14]; however, most of those studies [3–14] compared the dosimetric results of proton plans with those of intensity-modulated radiation therapy (IMRT) plans. To our knowledge, a dosimetric study comparing VMAT and proton planning for high-risk prostate cancer had yet to be performed. Recently, the VMAT has become a popular delivery option over IMRT for prostate cancer since VMAT requires a smaller number of monitor units (MUs) and shorter delivery time while providing conformal dose distributions [2, 15, 16]. Since both the proton therapy and VMAT techniques are currently available as treatment options in external-beam radiation therapy, it is essential to address the dosimetric advantages and disadvantages of one technique over the other. The main purpose of the current study was to compare the dosimetric quality of the VMAT with that of proton therapy with a focus on USPT in a group of high-risk prostate cancer patients. The dosimetric evaluation was performed by comparing the physical dose-volume parameters, which were obtained from the VMAT and proton plans.

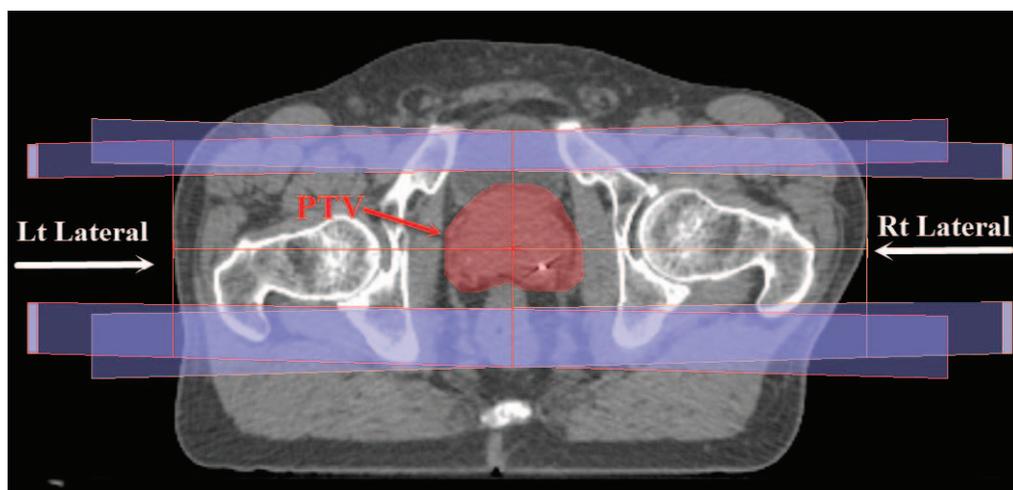
## Patients and Materials

### Patient Selection and Simulation

This study included a cohort of 12 high-risk prostate cancer patients previously treated with USPT at ProCure Proton Therapy Center, Oklahoma City (hereafter referred to as ProCure). The computed tomography (CT) simulation of all 12 cases was done at ProCure using the institutional protocol for prostate cancer patients. Prior to the CT simulation, all patients had VisiCoil linear fiducial markers (IBA, Schwarzenbruck, Sweden) placed within the prostate. During the CT simulation on a General Electric CT Scanner (General Electric Healthcare, Little Chalfont, United Kingdom), each patient was immobilized in the feet-in supine position using a Vac-Lok system (CIVCO Medical Solutions, Kalona, Iowa). The CT scans of all 12 cases were obtained with a thickness of 1.25 mm per slice.

### Proton Planning

The CT dataset of all 12 cases was transferred to Velocity<sup>AI</sup>, version 2.8.0 (Velocity Medical Solutions, Atlanta, GA) for delineation of the structures. The clinical target volume (CTV) was defined as the prostate and seminal vesicles, whereas the planning target volume (PTV) was generated by expanding the CTV (3 mm to the posterior and 4 mm elsewhere to the CTV). Additionally, the contouring was done for the organs at risk (OARs) (rectum, bladder, and femoral heads) and other relevant structures per our institutional protocol. The XiO TPS (CMS Inc., St. Louis, MO) was used to generate the proton plans. For each prostate case, two 180° parallel-opposed lateral fields were used to target the PTV as shown in Figure 1. The isocenter of both lateral fields was placed at the center of the PTV. The aperture margin was selected based on the penumbra, which is dependent on parameters such as proton range and air gap [17]. The range compensator of each field



**Figure 1.** An example of the proton beam arrangement for the high-risk prostate cancer treatment plans in the XiO treatment planning system. The figure shows two 180° parallel-opposed lateral fields (left lateral and right lateral) targeting the planning target volume.

was generated with a smearing radius of 1.2 cm to account for organ motion and patient setup uncertainties. Dose calculations were performed in the XiO TPS, using a pencil-beam algorithm [18] with a dose calculation grid size of  $3 \times 3 \times 3 \text{ mm}^3$ . The XiO TPS used the uniform-scanning proton beam commissioning data that were measured at ProCure on an IBA Cyclotron (IBA, Louvain-la-Neuve, Belgium). The description of our proton therapy has been previously described [19].

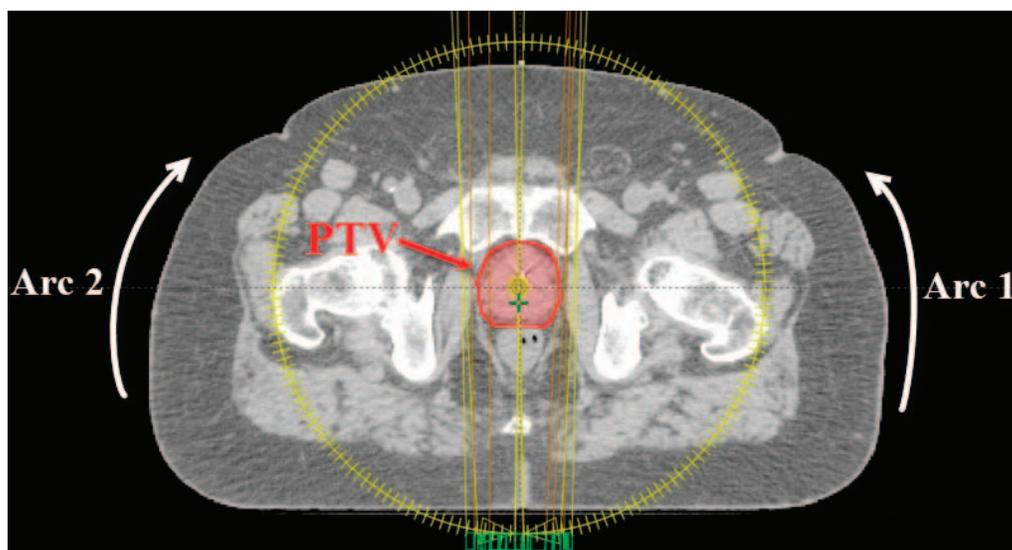
For all the 12 cases, a total dose of 79.2 Gy (relative biological effectiveness [RBE]) was prescribed to the PTV with a daily fraction of 1.8 Gy (RBE). The doses in the proton plans were calculated using a RBE of 1.1. The proton range, modulation, aperture margin, and weighting of each beam was manually adjusted with the goal of minimizing the dose to the OARs and meeting the prostate planning criteria implemented at ProCure:

- 95% of the PTV volume received 79.2 Gy (RBE) (i.e., PTV coverage = 95%),
- minimum dose to the PTV was  $\geq 75.2 \text{ Gy (RBE)}$  (i.e., 95% of the prescription dose),
- the 98% isodose line covered no greater than 50% of the pelvic wall in the anterior-posterior direction, and
- the 60% isodose line was away from the femoral head.

### VMAT Planning

For the VMAT planning in this study, we used the RapidArc technique in the Eclipse TPS, version 11.01 (Varian Medical Systems, Palo Alto, CA) combined with Varian Clinac iX 6 MV x-ray beams. Since proton therapy and VMAT planning were not available at the same institution, the Digital Imaging and Communications in Medicine (DICOM) CT images and structure set of all 12 cases were transferred to West Hills Radiation Therapy Center, Vantage Oncology, California (WHRTC) for the VMAT planning after de-identification of the patient information in the DICOM dataset.

For each prostate case, the VMAT plan was generated for the total dose of 79.2 Gy prescribed to the PTV with a daily dose of 1.8 Gy. The VMAT plan was set up using the standard delivery technique for prostate cancer at WHRTC. Specifically, the first arc was



**Figure 2.** An example of the VMAT plan setup for the high-risk prostate cancer treatment plan using the Varian Standard Scale in the Eclipse treatment planning system. The figure shows the 'arc 1' in a counter-clockwise direction and the 'arc 2' in a clockwise direction targeting the planning target volume.

set up in a counter-clockwise direction (arc angle:  $1^{\circ} \rightarrow 359^{\circ}$ ; collimator angle:  $170^{\circ}$ ) and the second arc was set up in a clockwise direction (arc angle:  $359^{\circ} \rightarrow 1^{\circ}$ ; collimator angle:  $190^{\circ}$ ). These beam parameters were based on the Varian Standard Scale in the Eclipse TPS. The isocenter of both arcs was placed at the center of the PTV. Additionally, the beam's-eye-view graphics in the Eclipse TPS was used to select the field sizes of each arc. Figure 2 shows an example of the VMAT plan set up in the Eclipse TPS.

The VMAT plans were optimized using the progressive resolution optimizer in the Eclipse TPS. During the optimization process, dose-volume constraints and weightings of the PTV and OARs were adjusted to (1) achieve the planning criteria of the proton plans, (2) minimize the dose to the OARs, and (3) maximize the PTV coverage. Dose calculations on the optimized VMAT plans were done with the anisotropic analytical algorithm (AAA) in the Eclipse TPS using a 2.5-mm dose calculation grid size. The calculated VMAT plans were then normalized so that at least 95% of the PTV volume received the prescription dose.

### Plan Evaluation

Dosimetric evaluation was performed using the DVHs of the VMAT and proton plans. In the current study, we used the same PTV coverage in both the VMAT and proton plans in order to compare their dosimetric results. The PTV was evaluated for the minimum dose, maximum dose, and mean dose. For the rectum and bladder, the mean dose and the relative volumes that received 70, 50, and 30 Gy (RBE) or Gy ( $V_{70}$ ,  $V_{50}$ , and  $V_{30}$ , respectively) were compared. For the right and left femoral heads, the mean dose and relative volume that received 40 Gy (RBE) or Gy ( $V_{40}$ ) were obtained. To test the observed differences between the VMAT and proton plans, a statistical analysis was done using paired two-sided Student's t-test in a spreadsheet. A  $P$  value of less than 0.05 (i.e.,  $P < 0.05$ ) was considered to be statistically significant.

**Table 1.** Comparison of the dosimetric parameters of the PTV, rectum, bladder, and femoral heads in the VMAT and proton plans. The values (average  $\pm$  standard deviation) are averaged over 12 analyzed cases.

Structure	Parameter	VMAT	Proton	P value
PTV	Minimum dose	74.2 $\pm$ 1.3 Gy	74.8 $\pm$ 1.4 Gy (RBE)	0.080
	Maximum dose	82.7 $\pm$ 0.8 Gy	82.4 $\pm$ 0.4 Gy (RBE)	0.104
	Mean dose	80.3 $\pm$ 0.4 Gy	80.2 $\pm$ 0.1 Gy (RBE)	0.199
Rectum	Mean dose	40.0 $\pm$ 7.7 Gy	18.2 $\pm$ 5.3 Gy (RBE)	<0.0001
	V <sub>30</sub> (%)	66.0 $\pm$ 13.2	25.5 $\pm$ 7.6	<0.0001
	V <sub>50</sub> (%)	41.2 $\pm$ 12.8	17.6 $\pm$ 6.0	<0.0001
	V <sub>70</sub> (%)	11.5 $\pm$ 4.4	9.2 $\pm$ 4.0	0.003
Bladder	Mean dose	30.1 $\pm$ 9.0 Gy	15.8 $\pm$ 4.9 Gy (RBE)	<0.0001
	V <sub>30</sub> (%)	46.3 $\pm$ 17.8	23.1 $\pm$ 9.2	<0.0001
	V <sub>50</sub> (%)	22.4 $\pm$ 10.8	17.7 $\pm$ 7.7	0.001
	V <sub>70</sub> (%)	9.3 $\pm$ 4.8	11.2 $\pm$ 5.0	0.004
Right Femoral Head	Mean dose	19.3 $\pm$ 4.8 Gy	28.3 $\pm$ 4.1 Gy (RBE)	<0.0001
	V <sub>40</sub> (%)	0 $\pm$ 0	0 $\pm$ 0	-
Left Femoral Head	Mean dose	18.0 $\pm$ 4.4 Gy	28.2 $\pm$ 4.8 Gy (RBE)	<0.0001
	V <sub>40</sub> (%)	0 $\pm$ 0	0 $\pm$ 0	-

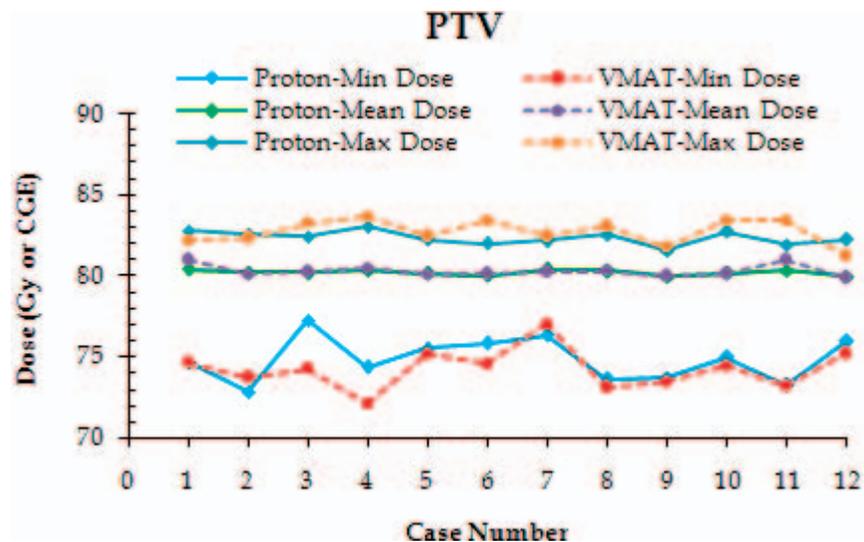
**Abbreviations:** PTV, planning target volume; V<sub>x</sub>, relative volume of the structure receiving x Gy or Gy (RBE); VMAT, volumetric modulated arc therapy

## Results

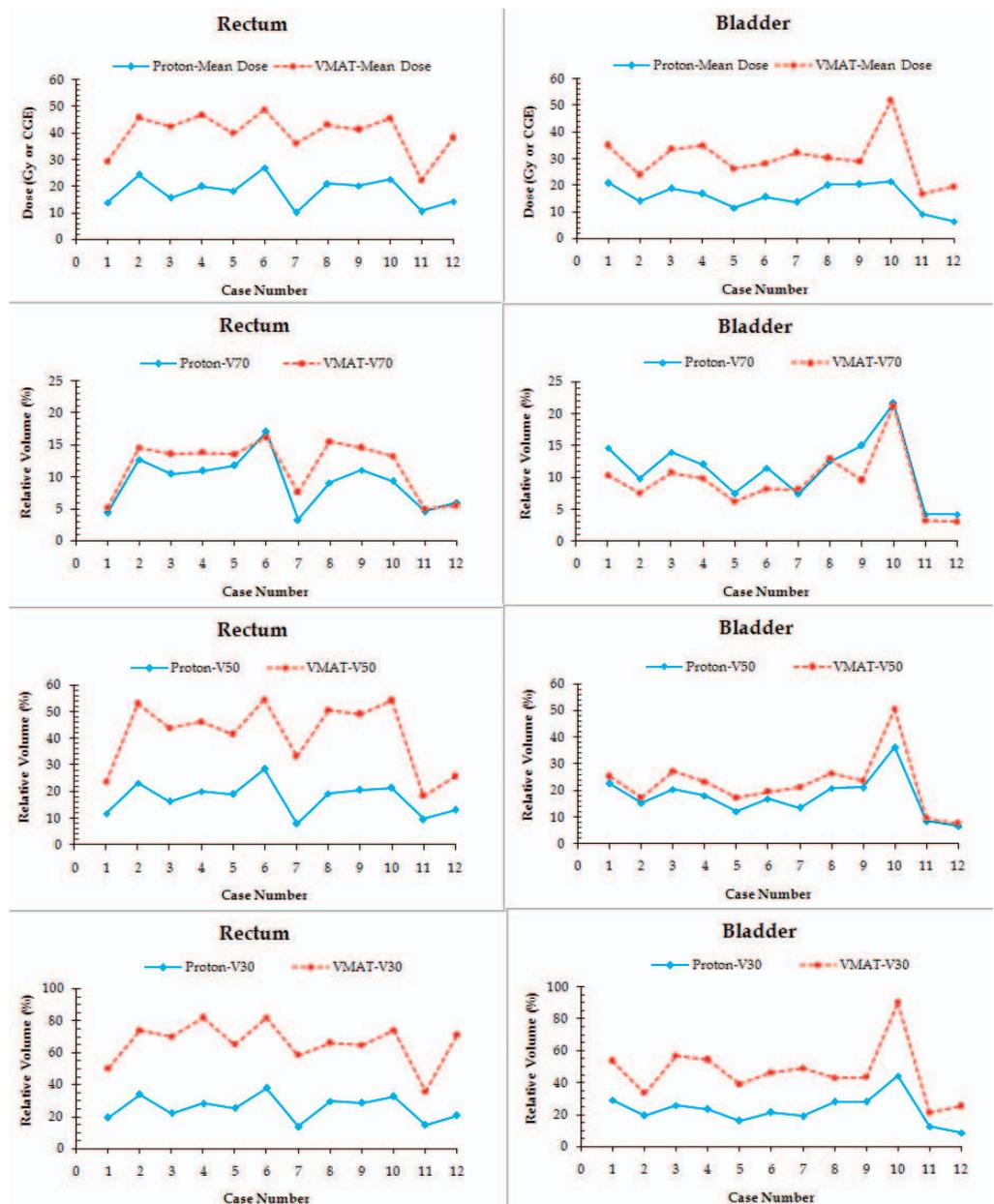
The dosimetric results for the PTV, rectum, bladder, and femoral heads are presented in Table 1 and Figures 3, 4, and 5.

### Planning Target Volume

In comparison to the VMAT plans, on average, the proton plans produced a slightly lower maximum PTV dose (82.4 Gy (RBE) vs. 82.7 Gy;  $P = 0.104$ ), a comparable mean PTV

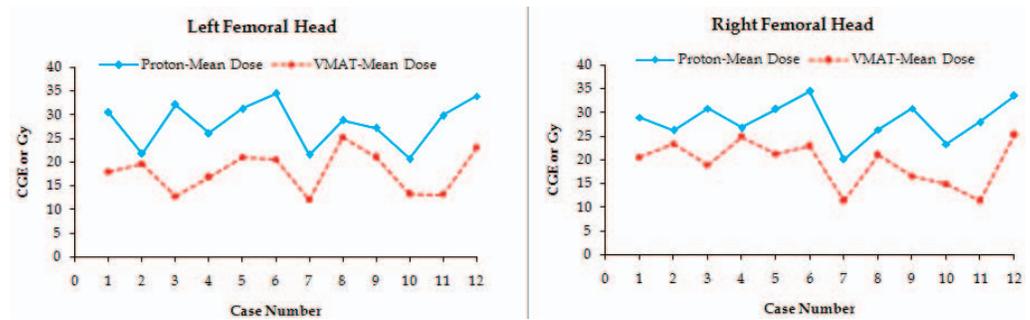


**Figure 3.** Comparison of the planning target volume doses (minimum, mean, and maximum) in the VMAT and proton plans for 12 high-risk prostate cancer cases (solid line = proton plan; dashed line = VMAT plan).



**Figure 4.** Comparison of the dosimetric results of the rectum (left column) and bladder (right column) in the VMAT and proton plans for 12 high-risk prostate cancer cases (solid line = proton plan; dashed line = VMAT plan). **Abbreviation:**  $V_x$  = relative volume of the structure receiving  $x$  Gy or Gy (RBE)

dose (80.2 Gy (RBE) vs. 80.3 Gy;  $P = 0.199$ ), and a higher minimum PTV dose (74.8 Gy (RBE) vs. 74.2 Gy;  $P = 0.080$ ). The PTV dose evaluation showed that the proton plans produced values closer to the prescription dose with smaller hot spots; however, the average difference in the PTV doses between the VMAT and proton plans was within  $\pm 1\%$  without any statistical significance.



**Figure 5.** Comparison of the mean dose to left femoral head (left column) and right femoral head (right column) in the VMAT and proton plans for 12 high-risk prostate cancer cases (solid line = proton; dashed line = VMAT).

### Rectum

The average mean dose to the rectum was lower in the proton plans (18.2 Gy [RBE]) compared to the VMAT plans (40.0 Gy), and the difference was statistically significant ( $P < 0.0001$ ). Similarly, on average, proton planning produced lower values of  $V_{70}$  (9.3% vs. 11.5%;  $P = 0.003$ ),  $V_{50}$  (17.6% vs. 41.2%;  $P < 0.0001$ ), and  $V_{30}$  (25.5% vs. 66.0%;  $P < 0.0001$ ) compared to the VMAT planning.

### Bladder

The average mean dose to the bladder was lower in the proton plans (15.8 Gy [RBE]) compared to the VMAT plans (30.1 Gy), and the difference was statistically significant ( $P < 0.0001$ ). On average, the proton plans produced lower values of  $V_{50}$  (17.7% vs. 22.4%;  $P = 0.001$ ) and  $V_{30}$  (23.1% vs. 46.3%;  $P < 0.0001$ ), but higher  $V_{70}$  (11.2% vs. 9.3%;  $P = 0.004$ ) when compared to the VMAT plans.

### Femoral Heads

In comparison to the VMAT plans, the average mean dose to femoral heads was higher in the proton plans for both the right femoral head (28.3 Gy [RBE] vs. 19.3 Gy;  $P < 0.0001$ ) and left femoral head (28.2 vs. 18.0 Gy;  $P < 0.0001$ ). The  $V_{40}$  of the right and left femoral heads was 0 for both the VMAT and proton plans.

### Discussion

Plan normalization techniques can affect the dosimetric results of treatment plans [20], and it is critical to maintain the same plan normalization technique when the dosimetric results of VMAT plans are compared with those of proton plans. In this study, both the VMAT and proton plans were normalized with the same PTV coverage so that 95% of the PTV volume received the prescription dose.

On average, the proton plans produced favorable results for the PTV and rectum, whereas the VMAT plans were superior in sparing the femoral heads. In the case of the bladder, proton beams significantly reduced the dose in the low- and medium-dose regions, whereas the VMAT technique was better at reducing the dose in the high-dose region (Table 1). Similar observations were reported by other groups. For instance, Trofimov *et al* [12] compared IMRT and proton therapy for 10 prostate cancer cases and

showed that, in the high dose regions, IMRT was better at sparing the bladder and rectum. However, in the low-dose regions, proton therapy was better at sparing both the rectum and bladder [12]. In another study, Chera *et al* [3] compared IMRT and proton therapy for 5 high-risk prostate cancer cases, and showed that, compared with IMRT, proton therapy reduced the dose to the bladder and rectum while providing adequate target coverage.

Although the average PTV doses from the proton plans in our study showed less deviation from the prescription dose, Figure 3 demonstrates that the PTV doses may vary depending on the nature of the prostate case. For instance, the VMAT plans produced values closer to the prescription dose in cases #2 and 7 for the minimum PTV dose, in cases #1 and 11 for the mean PTV dose, and in cases #1 and 12 for the maximum PTV dose. Similarly, in comparison to the proton plans, the average  $V_{70}$  in the VMAT plans was higher for the rectum, but lower for the bladder. However, Figure 4 shows that the VMAT plans produced lower  $V_{70}$  for the rectum in cases #6 and 12, but higher  $V_{70}$  for the bladder in cases #7 and 8. For the  $V_{50}$  and  $V_{30}$  of the rectum and bladder, the results of the proton plans were always lower compared to those of the VMAT plans. For the femoral head dose, although the discrepancy between the proton and VMAT plans was dependent on the case, the VMAT plans always produced a lower mean dose to the femoral heads. These results demonstrate that the average dosimetric results of a group of prostate patients from different treatment planning studies must be interpreted with caution, especially in the high-dose region for the rectum and bladder as well as in the target volume.

The current study employed two parallel-opposed lateral fields for proton planning, which is a standard treatment technique at ProCure for high-risk prostate cases that do not involve the metallic hip prosthesis. Recently, Tang *et al* [13] investigated using anterior-oblique proton beams for the prostate cancer, and showed that the anterior-oblique field arrangement can significantly reduce the dose to the anterior rectal wall at the high dose region when compared to two parallel-opposed lateral field arrangement. It would be interesting to compare the dosimetric quality of proton therapy using anterior-oblique beams with that of VMAT for high-risk prostate cancer patients. Additionally, the treatment planning method and dose calculation algorithms employed in the TPS can significantly affect the dose distribution. For instance, the VMAT planning using the double-arc technique may provide dosimetric results different from that of the partial-arc technique and single-arc technique [21–23]. Furthermore, the CT calibration curve for the proton plans differed from the VMAT plans, which may have contributed to the differences in the dosimetric results between the two modalities. In this study, we have used AAA to calculate the VMAT treatment plans, and a different photon dose calculation algorithm such as Acuros XB may provide slightly different dosimetric results for prostate cancer patients [24]. While the physical dose-volume statistics in this study provided information on certain aspects of the dose distribution, it is essential to further evaluate the VMAT and proton plans using radiobiological parameters such as tumor control probability, which can provide a quantitative biophysical measure of tumor dose.

Recently, Michalski *et al* [25] published a study on toxicity outcomes of Radiation Therapy Oncology Group (RTOG) 0126, reporting that small rectal volumes receiving a high dose (e.g.  $V_{70}$ ) were the most critical predictors of late toxicity. Few other studies have reported late rectal bleeding associated with lower doses [26, 27]. For instance, Cozzarini *et al*. [26] found  $V_{50}$  as a stronger indicator of RTOG grade 2 or higher late rectal bleeding than  $V_{60}$  and  $V_{65}$ . Similar findings were reported by Fiorino *et al*. [27] showing  $V_{50}$  as an important dosimetric metric to predict RTOG grade 2 or higher late rectal bleeding. Tucker and colleagues [28] reported a 50% or higher incidence of rectal bleeding when the

mean dose to the rectal wall exceeded 53.2 Gy. In one of the earlier treatment outcome studies, Storey *et al* [29] found a significant increase in late rectal complications if the rectal volume receiving  $\geq 70$  Gy was  $> 25\%$ . Based on the dosimetric results for the rectum presented in this study, prostate patients treated with USPT are likely to suffer less rectal complications; however, a correlation between toxicity and rectal dose-volume with USPT remains to be investigated with long-term follow up.

The current literature shows that a correlation between bladder dose-volume and toxicity is less straight-forward. Jain *et al*. [30] showed that acute bladder toxicity is highly dependent on bladder filling. The patient may not be able to maintain the same bladder volume throughout the treatment course. Lebesque *et al*. [31] reported that it is difficult to establish a correlation between late complications and the dosimetric parameters of the bladder, which can change from patient to patient. There is also no common consensus on the definition of the bladder structure, which can be contoured as a bladder wall alone [31] or bladder wall and its contents [32]. Despite the difficulties in establishing a proper correlation between bladder dose-volume and toxicity, QUANTEC [33] recommends that no more than 35% of the bladder volume (i.e., bladder wall + contents) receive a dose greater than 70 Gy, and this recommendation was based on the treatment outcome of patients treated with 3-dimensional conformal radiotherapy. Both techniques presented in this study (VMAT and USPT) met the QUANTEC recommendation, with  $V_{70}$  of the bladder ranging from 4.2% to 21.6% for USPT and from 3.0% to 21.2% for VMAT. The dosimetric constraint of the femoral head ( $V_{50} < 5\%$ ) [34] was also easily satisfied by both USPT and VMAT ( $V_{40} = 0\%$  for both techniques). Based on the femoral head results in this study, a choice of treatment technique is less likely to be a significant predictor for femoral head necrosis.

## Conclusion

USPT is feasible for treating high-risk prostate cancer involving the seminal vesicles. For the same target coverage, the proton plans always produce lower values for the rectum and bladder in the low- and medium-dose regions, whereas the results of the rectum, bladder, and PTV are patient-specific in the high-dose region. The VMAT technique was superior in sparing the femoral heads. The average dosimetric results when comparing VMAT and proton therapy for a group of prostate cancer patients must be interpreted with caution, especially in the high-dose region.

## ADDITIONAL INFORMATION AND DECLARATIONS

**Conflict of Interest Statement:** The authors declare that they have no conflict of interest.

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