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Volumetric modulated arc therapy planning for primary prostate cancer with selective intraprostatic boost determined by ^{18}F -choline PET/CT

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Abstract

Objective—Evaluate expected tumor control and normal tissue toxicity for prostate volumetric modulated arc therapy (VMAT) with and without radiation boost to an intraprostatic dominant lesion (IDL) defined by ^{18}F -fluorocholine PET/CT.

Methods—Thirty patients with localized prostate cancer underwent ^{18}F -fluorocholine PET/CT before treatment. Two VMAT plans, plan_{79Gy} and plan_{100-105Gy}, were compared for each patient. The whole-prostate planning target volume (PTV_{prostate}) was prescribed 79 Gy in both plans, however plan_{100-105Gy} added simultaneous boost doses of 100 Gy and 105 Gy prescribed to IDLs defined by 60% and 70% of maximum prostatic uptake on ^{18}F -fluorocholine PET (IDL_{suv60%} and IDL_{suv70%}, respectively, with IDL_{suv70%} nested inside IDL_{suv60%} to potentially enhance tumor specificity of the maximum point dose). Plan evaluations included histopathologic correspondence, isodose distributions, dose-volume histograms, tumor control probability (TCP), and normal tissue complication probability (NTCP).

Results—Planning objectives and dose constraints proved feasible in 30/30 cases. Prostate sextant histopathology was available from 28 cases, confirming that IDL_{suv60%} adequately covered all tumor-bearing prostate sextants in 27 cases and provided partial coverage in one case. Plan_{100-105Gy} had significantly higher TCP than Plan_{79Gy} across all prostate regions for α/β ratios

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ranging from 1.5 Gy to 10Gy ($p < 0.001$ each case). There were no significant differences in bladder and femoral head NTCP between plans, and slightly lower rectal NTCP (endpoint: grade 2+ late toxicity or rectal bleeding) for plan_{100-105Gy}.

Conclusion—VMAT can potentially increase the likelihood of tumor control in primary prostate cancer while observing normal tissue tolerances through simultaneous delivery of a steep radiation boost to an ^{18}F -fluorocholine PET-defined IDL.

Keywords

fluorocholine; PET/CT; prostate cancer; volumetric modulated arc therapy; boost

Introduction

Radiation dose escalation for prostate cancer external beam radiotherapy (EBRT) can lower the risk of biochemical relapse[1,2]. This radiation dose-response relationship for tumor control is evident across patients with low-, intermediate-, and high-risk prostate tumors[1,3]. Improvements in conformal radiation delivery have made it easier to intensify radiation doses to the planning target volume (PTV) without exceeding normal tissue tolerances. Unfortunately, while toxicity from intensity-modulated radiotherapy (IMRT) appears manageable at whole-prostate doses up to 86 Gy[4], recurrent disease at or near the original tumor volume can still occur at this dose magnitude [5,6]. Thus, more aggressive dose escalation may be necessary to advance local tumor control.

The selective delivery of “boost” radiation doses to tumor regions in the prostate is a promising strategy to limit tissue toxicity while pursuing radiation dose escalation [7,8]. Pathology studies have shown that prostate cancer is often a multifocal disease, and that large prostate tumors are frequently accompanied by small well-differentiated secondary tumors (< 0.5 cm diameter and Gleason score < 5). However, it is the largest tumor that almost always shows the most aggressive histologic characteristics and is thus driving prognosis [9,10]. Eradication of this so-called intraprostatic dominant lesion (IDL) could therefore have the greatest clinical impact in treating organ-confined prostate cancer.

Molecular imaging techniques such as positron emission tomography (PET) or magnetic resonance spectroscopy (MRS) are increasingly being used to detect prostate tumors [8]. Upregulated choline metabolism is common in prostate cancer and several molecular imaging modalities exploit this feature [11-13]. Such modalities include PET using carbon-11 or fluorine-18 labeled radiopharmaceuticals bearing the choline moiety [14,15], with recent studies supporting its use to define IDLs for radiotherapy planning [16,17]. In a prospective pilot trial, IMRT dose escalation to IDLs defined by fluorine-18 fluoromethylcholine (^{18}F -choline) PET was achieved without impacting quality of life after treatment [18]. This demonstration of clinical feasibility has opened the way to exploring further dose escalation guided by ^{18}F -choline PET.

RapidArc, a form of volumetric modulated arc therapy (VMAT), can produce steeper dose fall-off gradients than IMRT [19], and could therefore enable more intense and selective boost radiation treatment while observing normal tissue tolerances. For example, improved

rectal sparing has been associated with VMAT delivering 95 Gy to an IDL defined by MRS as compared to IMRT [20]. We hypothesize that a VMAT plan to deliver a minimum dose of 79 Gy to the whole prostate can accommodate selective boosts up to 105 Gy to an IDL defined by ^{18}F -choline PET/CT without further jeopardizing adjacent organs at risk. We preliminarily tested this hypothesis by estimating the effects of radiation boosts up to 105 Gy based on the calculated tumor control probability (TCP) and normal tissue complication probability (NTCP) of the VMAT plan.

Methods and Materials

Patients

Thirty patients with localized prostate cancer diagnosed by transrectal ultrasound guided biopsy gave written informed consent under an institutional review board approved research protocol. All patients were candidates for radical prostatectomy or radiation therapy based on National Comprehensive Cancer Network (NCCN) risk criteria [21]. Patients with non-skin malignancies diagnosed within the last 5 years, suspected extraprostatic lesions, and those who had previously received androgen deprivation therapy, prostate surgery, or radiotherapy to the pelvis were excluded.

Clinical risk status was based on age at diagnosis, pretreatment PSA, prostate biopsy results, Gleason score, and tumor staging (Table 1). The study excluded patients with very low risk or very high risk disease based on NCCN criteria. Patients with Gleason 5 and 6 tumors had expected longevities exceeding 10 years and no comorbidities precluding primary treatment of prostate cancer. Radiopharmaceutical synthesis and the PET/CT imaging protocol are detailed in the Supplemental Materials.

Delineation of Target Volumes and Organs-at-risk

PET/CT images were transferred to an image analysis workstation (MIM Maestro 6.2.7, MIM Software, Inc., Cleveland, OH). Prostate, seminal vesicles, rectum, bladder, penile bulb, and femoral heads were contoured based on guidelines from Radiation Therapy Oncology Group (RTOG) protocol 0126 [22]. IDL segmentation was performed using PET quantitation software (PMOD 3.5, PMOD Technologies, Ltd, Zurich, Switzerland) to define one or several volumes of interest (VOI) within the prostate and seminal vesicle containing those voxels with SUV exceeding 60% of prostate SUV_{max} ($\text{IDL}_{\text{SUV}60\%}$). This threshold was based on previously reported intraprostatic tumor-to-normal ratios for ^{18}F -choline [15,23] and carbon-11 choline [24]. A smaller $\text{IDL}_{\text{SUV}70\%}$ was drawn within $\text{IDL}_{\text{SUV}60\%}$ as the VOI containing voxels with SUV exceeding 70% of prostate SUV_{max} to confine the maximum point dose to a smaller contoured region with potentially higher tumor specificity [24].

Definitions of gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) were based on RTOG protocol 0126 [22]. Briefly, the $\text{GTV}_{\text{prostate}}$ is the prostate alone, while the $\text{CTV}_{\text{prostate+SV}}$ is the $\text{GTV}_{\text{prostate}}$ plus the proximal 1 cm of bilateral seminal vesicles (SVs). $\text{PTV}_{\text{prostate}}$ and the $\text{PTV}_{\text{prostate+SV}}$ were created by adding 6 mm lateral, superior and inferior margins and 3 mm anterior and posterior margins on the $\text{GTV}_{\text{prostate}}$ and $\text{CTV}_{\text{prostate+SV}}$, respectively. Similarly, 3 mm and 6 mm radial and 6 mm

craniocaudal expansions were used for generating PTV_{s60} and PTV_{s70} from $IDL_{suv60\%}$ and $IDL_{suv70\%}$, respectively. PTV_{s60} and PTV_{s70} structures were also excluded from rectum and bladder structures by 6mm. If necessary, minor adjustments were made to fit all IDL vertices within the PTV.

VMAT Planning

Planning details are in the Supplemental Materials. Both $Plan_{79Gy}$ and $Plan_{100-105Gy}$ were scheduled for 39 fractions (one fraction per day, five work days per week).

TCP and NTCP Modeling

TCP was calculated via the LQ-Poisson Marsden Model using DVH data for $IDL_{suv60\%}$, $IDL_{suv70\%}$, and non-IDL prostate (i.e., $GTV_{prostate} - IDL_{suv60\%}$) [25-27]. NCTPs for the rectum, bladder, and femoral heads were calculated using the Lyman-Kutcher-Burman formula with Nirmierko's equivalent uniform dose (EUD) [28-32]. Modeling parameters and procedure are in the Supplemental Materials.

Histopathologic Correlation

Histopathologic data from prostate biopsy or post-surgical step-section analysis was collected to determine dominant tumor site on a prostate sextant basis [15]. Since small (< 0.5 cc) and well-differentiated (Gleason < 5) tumors are not clinically significant [10], secondary tumors meeting these criteria were not considered part of the IDL.

Statistical methods

The Wilcoxon signed-rank test was used to compare the plan parameters, TCPs and NCTPs, respectively (SAS 10.0/JMP 11, SAS Institute, Cary, NC). Median values and ranges were reported. A P-value <0.05 was taken as statistically significant.

Results

From 30 patients, one was found to have two separate foci of increased prostatic ^{18}F -choline uptake from which two $IDL_{suv60\%}$ s and two $IDL_{suv70\%}$ s were drawn. Thus, a total of 31 $IDL_{suv60\%}$ and 31 $IDL_{suv70\%}$ volumes were analyzed. Clinical characteristics and treatment volumes are shown in Table 1. Planning results and volumes are shown in Table 2.

Whole-prostate step-section histopathology was available in 6 patients following radical prostatectomy. In each case, the dominant tumor localized to prostate sextants within the PET-defined IDL. In one case, a prostate sextant encompassed by the PET-defined IDL did not have tumor identified on step-section analysis. Biopsy results were available from the other 24 patients. In 2 patients, not all sextants were biopsied but the results were positive only on the PET-defined IDL side. This left 22 cases for sextant-level analysis. In 21/22 cases, the $IDL_{suv60\%}$ contour included all biopsy-positive prostate sextants. $IDL_{suv60\%}$ also encompassed biopsy-negative sextants in 11 cases, suggesting either overestimated tumor extent by PET or biopsy sampling error. In one case, a biopsy-positive sextant was not included in the $IDL_{suv60\%}$ contour. Lowering the contouring threshold to 50% of SUV_{max} allowed all biopsy-positive sextants to be included in this case.

All planning objectives and dose constraints were met (Table 2). Figure 1 compares isodose distributions for Plan_{79Gy} and Plan_{100-105Gy} along with PET. Figure 2 shows the corresponding cumulative DVH results. Both plans maintained less than 9% of rectal volumes receiving more than 75 Gy and less than 6.5% of bladder volumes receiving more than 80Gy. Femoral head and penile bulb were similarly spared in both plans.

Figure 3 illustrates the TCP and NTCP results. Plan_{100-105Gy} was associated with significantly higher TCP in IDL_{SUV60%}, IDL_{SUV70%} and non-IDL prostate regions compared to Plan_{79Gy} at all four α/β ratios examined ($p < 0.001$ in each case). The lower α/β ratio, the greater the benefit of radiation boost to the IDL, with gains in median TCP IDL_{SUV60%} of 9.4% (from 84.4% to 93.7%) for an α/β ratio of 10 Gy compared to 9.9% (from 84.2% to 94.1%) for an α/β ratio of 5 Gy, and 10.0% (from 84.8% to 94.7%) for an α/β ratio of 3 Gy, and 10.6% (from 85.2% to 95.8%) for an α/β ratio of 1.5 Gy. The absolute difference in rectal NTCP for grade 2+ late toxicity or rectal bleeding between Plan_{100-105Gy} and Plan_{79Gy} was small but statistically significant in paired testing (2.2% vs. 2.8%, $p < 0.001$) (Figure 3). There were no significant differences in bladder and femoral head NTCPs between two plans.

Discussion

This study examined the technical feasibility of simultaneous integrated boost for primary prostate cancer using VMAT to deliver up to 105 Gy to an IDL defined by ¹⁸F-choline PET/CT. A similar study by Ost et al. compared IMRT with VMAT for prostate cancer treatment incorporating radiation boosts to an IDL defined by MRS [20]. In that study, both IMRT and VMAT delivered a median of 93 Gy to the IDL, however VMAT was associated with better sparing of the rectum. VMAT has also been associated with improved rectal sparing in treatment plans not involving an IDL boost [19]. These gains may be due to greater control over dose distribution and fall-off with VMAT. Other clinical advantages of VMAT are improved patient comfort and delivery time.

Choline PET has been used previously to define IDLs for planning IMRT boost. Pinkawa et al. conducted several investigations using ¹⁸F-choline PET/CT leading to a prospective pilot trial of PET-guided IMRT boost treatment [17,18,33]. They combined a 76 Gy whole-prostate dose with a PET-directed boost to 80 Gy, finding comparable EUD to the rectum and bladder between boost and non-boost treatment [17]. Longitudinal follow-up revealed no significant differences in urinary and bowel quality of life after boost treatment [18]. Chang et al. similarly applied ¹¹C-choline PET to generate boost IMRT contours that were prescribed 90 Gy [16]. They reported slightly lower rectal NTCPs and higher TCPs for boost treatment relative to whole-prostate IMRT at doses of 72 Gy or 78 Gy. A high-dose salvage radiation therapy trial to deliver up to 80 Gy to ¹⁸F-choline PET-positive areas of the prostate also reported a low rate of toxicity with 1.7% of grade 2 gastrointestinal late toxicity and 0% of grade 2 genitourinary late toxicity [34]. The current study follows these previous technical and clinical accomplishments with results supporting even more aggressive dose escalation in the context of VMAT.

Dose escalation is tempered by increased risks of normal tissue toxicity and long-term morbidity. This study based dose constraints on relatively conservative values from QUANTEC [35] and RTOG protocol 0126 [22]. Adherence to these constraints should result in 15% late grade 2+ rectal complications [35]. Chang et al. reported that 11C-choline PET guided boost IMRT for localized prostate cancer could achieve a 4.6% of late grade 2+ rectal NTCP value for the non-boost plan (78Gy), and a 3.7% of rectal NTCP value for the boost plan (90 Gy prescribed to IDLs) [16]. In a ten-year outcomes study evaluating high-dose prostate IMRT prescribing 81 Gy to the PTV, the 10-year likelihood of grade 2 and 3 late genitourinary toxicity was 11% and 5%, respectively, and grade 2 and 3 late gastrointestinal toxicity was 2% and 1%, respectively [36]. The current study using a 79 Gy PTV dose with simultaneous 100-105 Gy boost in IDLs achieved similar NTCP results.

Our radiobiological results associate higher TCP with VMAT boost while keeping NTCP within ranges reported for high-dose IMRT for primary and salvage radiation therapy [34,36]. Similar to the study by Chang et al. [16], rectal NTCP was slightly lower for the boost plan. While probably not clinically significant, this statistical difference (Fig 3d) may seem curious at first glance. However, consistent with adequate confinement of boost dose fall off during the process of VMAT planning, EUDs to the rectum were higher in Plan_{79Gy} than in Plan_{100-105Gy} (5766.8 cGy median rectal EUD in Plan_{79Gy} (Range 3761.1 – 6435.2 cGy) vs. 5677.2 cGy median rectal EUD in Plan_{100-105Gy} (range 3829.5 – 6488.6 cGy), *paired test* $p < 0.001$). Since NTCP calculations are based on EUD measures, Plan_{100-105Gy} resulted in lower rectal NTCPs as compared to Plan_{79Gy}.

In this study, TCP in the IDL and non-IDL regions were evaluated based on expected tumoral variation in clonogen density and other radiobiologic parameters. Several studies show dose escalation up to 95 Gy with EBRT to be feasible for most patients with a resulting absolute increase in TCP of 2–15% based on the assumption of higher radioresistance in IDLs [16-18,24,33,37,38]. These results are consistent with the current study findings of higher TCPs associated with Plan_{100-105Gy}. It may be advantageous in terms of local tumor control to pursue both a high whole-prostate dose and a high boost differential, since a high boost dose at the expense of a lower whole prostate dose (< 70–75 Gy) has been associated with relatively high failure rates [39-42]. In contrast to the > 20 Gy differential boost dose of the current study, the average differential dose (PTV_{IDL}–PTV_{prostate}) reported in a systematic review was 8 Gy (biologically effective dose 2 Gy per fraction, $\alpha/\beta = 3$ Gy, range 3–35 Gy) and the most common rectal dose constraints used were V70Gy < 15–30% with D_{max} of 76–80 Gy [8]. While some studies used relatively low (60 Gy) whole prostate dose combined with IDL boost delivered by HDR or IMRT, their favorable control rates (78% and 98% 5-year biochemical disease free survival rate, respectively) may have stemmed from having large boost volumes that encompassed most of the gland [41,43]. Thus, both the IDL and non-boost regions of the PTV should be considered in boost treatment plan evaluations.

In addition to applying VMAT to pursue dose intensification without further compromising normal tissues, this study explored the use of a second focal boost region (IDL_{SUV70%}) within a larger boost region (IDL_{SUV60%}) to confine the maximum point dose centrally in the tumor with histopathology confirming the tumor-affected prostate sextants or lobes in all cases.

Chang et al. also verified the appropriateness of using a 60% SUV threshold to define IDLs on ^{11}C -choline PET, through correspondence with coregistered prostate specimens [16]. Although limited to a prostate sextant basis, our histologic correlation results bear resemblance to a study by Pinkawa et al. that reported 97% PET concordance with the biopsy positive lobe in 66 patients that underwent ^{18}F -choline PET/CT for IMRT planning [17]. Also similar is our finding that biopsy-negative sextants were included within the IDL contour in more than one-third of cases. While increased ^{18}F -choline uptake due to benign prostatic disease could cause this apparent radiopathologic discordance [44], this is not a forgone conclusion since false-negative biopsy could also lead to underestimated tumor extent and discordance with PET. Since NTCP estimates for boost-treatment compared favorably against non-boost treatment plans, no apparent penalty from potentially overestimating the IDL boundary was found in this study.

Multi-parametric MRI has also been used to define IDLs [8]. MRI provides superior soft tissue contrast and additionally can measure chemical composition, vasculature, perfusion, and water mobility within potential IDLs. In contrast, choline PET isolates intracellular delivery and uptake of choline [8,15,45]. IDLs defined by one modality may therefore not fully overlap with that of the other, and differences may exist in how diagnostic sensitivity and specificity is weighted by each modality. Sensitivity may be desirable for delineating IDLs for radiotherapy, and our NTCP results suggest that VMAT can be suitably paired with imaging that favors tumor sensitivity over specificity. With the advent of PET/MRI, it is possible that complementary information from both MRI and PET will lead to more optimized IDL definitions.

This study has limitations as a single institution study to determine the expected radiobiologic effects in patients eligible for radiation therapy based on NCCN guidelines. This study estimates the advantage of selective dose escalation through calculations of TCP and NTCP. As such, these results require validation in a prospective trial that will be susceptible to many of the common radiation therapy clinical uncertainties. Interventions to minimize variations in setup and organ position/motion, as well as image-guidance, were not considered in the approach of this study, and yet may help to truly realize the theoretical benefits of selective dose augmentation.

The current study included patients with low-, intermediate-, and high-risk tumors. It has been debated whether all patients with Gleason 5 or 6 tumors require radical treatment. The reason low-risk patients were included in the current study was not only because they qualified for radiotherapy based on current guidelines, but also to demonstrate feasibility for applying ^{18}F -choline PET/CT to define IDLs in low as well as high risk patients. As imaging and treatment planning tools used for selective dose escalation can also be applied for dose sparing, it may be worthwhile to explore more focused treatment options for lower risk patients [10,46].

Conclusion

This radiobiologic analysis shows potential for VMAT to achieve a high differential boost dose (21 to 26 Gy) to a ^{18}F -choline PET/CT defined IDL while not exceeding theoretical

normal tissue tolerances beyond that of conventional high-dose (79 Gy) whole-prostate radiotherapy. Based on histopathologic correspondence, contouring derived by static ^{18}F -choline PET thresholding can potentially lead to an overestimated IDL volume. However, no corresponding penalty with regards to NTCP was observed in this preliminary study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Corresponding PET/CT and dose distribution images. Axial (a), coronal (b), and sagittal (c) PET/CT images show increased activity corresponding to a biopsy-confirmed IDL (b, arrow) involving the left basal prostate. Left seminal vesicle invasion is also evident (c, short arrow). Note the IDL appears distinct despite ^{18}F -choline being present in the urinary bladder. Axial (d, g), coronal (e, h) and sagittal (f, i) projections for Plan_{100-105Gy} (middle row) and Plan_{79Gy} (bottom row) show contours for PTV_{s70} (red), PTV_{s60} (blue), PTV_{prostate} (magenta), PTV_{prostate+SV} (green), bladder (yellow), rectum (brown), penile bulb (cyan), and femoral head (purple). Plan_{100-105Gy} allocates highest dose in PTV_{s70}, with dose dropping slightly inside PTV_{s60}, and declining further in “non-boost” regions (i.e., PTV_{prostate} and PTV_{prostate+SV}). Color scale ranged from 1000 – 11017 cGy. The maximum point dose (0.03cc) in Plan_{100-105Gy} was 11017 cGy, confined within PTV_{s70}. In contrast, the maximum point dose (0.03cc) in Plan_{79Gy} was 8261.4 cGy, located outside the IDL. Anchoring the “hot spot” in Plan_{100-105Gy} close to the prostate SUVmax could have a radiobiological advantage by allocating the highest radiation dose to the tumor epicenter. A: anterior; P: posterior; L: left; R: right; H: head; F: feet.

Figure 2.

Dose volume histogram corresponding to Figure 1 demonstrates significant differences in PTV dose coverage and comparable doses to surrounding organs-at-risk between Plan_{100-105Gy} and Plan_{79Gy}.

Figure 3.

Box-whisker plots comparing Plan_{79Gy} and Plan_{100-105Gy} for (a) IDL_{suv60%} TCP, (b) IDL_{suv70%} TCP, (c) non-IDL TCP, and (d) rectal NTCP (endpoint: grade 2+ late toxicity or rectal bleeding). Boxes represent interquartile range between 25th and 75th percentiles. Diamond and horizontal lines represent mean and median, respectively. Vertical lines represent range from maximum and minimum values.

Table 1

Clinical characteristics (n = 30)

Age (years)	
Median (range)	69 (52 – 87)
Pre-Treatment PSA (ng/mL)	
Median (range)	5.9 (0.9 – 41.0)
Gleason Sum	
5	1 (3.3)
6	8 (26.7)
7	12 (40.0)
8	6 (20.0)
9	3 (10.0)
10	0 (0.0)
NCCN Risk Group	
Low (T1c, PSA <10 ng/mL, Gleason <=6, <50% core positive)	9 (30.0)
Intermediate (T2b-2c, or PSA 10-20 ng/mL, or Gleason 7)	12 (40.0)
High (T3a, or PSA > 20 ng/mL, or Gleason 8-10)	9 (30.0)
Anatomic Stage/Prognostic Group (AJCC)	
I	9 (30.0)
IIA	11 (36.7)
IIB	10 (33.3)
Prostate Volumes (cm³)	
Median (range)	35.6 (15.8 – 62.8)
Intraprostatic Dominant Lesions (IDL)	
Total Number Defined	31
IDL _{SUV60%} Volume (cm ³)	2.7 (0.3 – 10.8)
Median (range)	
IDL _{SUV70%} Volume (cm ³)	0.7 (0.04 – 7.10)
Median (range)	

Values are number (percentage) unless otherwise noted.

Table 2

Summary of the DVH analysis for the PTVs and Organs at Risk

Parameter	Volume (cm ³) Median (Range)	Plan _{79Gy} Median (Range)	Plan _{100-105Gy} Median (Range)	p value
PTV _{prostate+SV}	101.4 (55.4–156.2)			
D95% [cGy]		6154.5 (6069.3 – 7268.3)	6143.4 (6055.7 – 7288.5)	0.026
D _{min} [cGy]		5676.8 (5123.4 – 5912.2)	5672.6 (5163.9 – 5890.1)	0.600
PTV _{prostate}	75.2 (42.3–121.3)			
D95% [cGy]		7938.0 (7888.1 – 7961.3)	7967.0 (7907.0 – 8078.5)	<0.001
D _{min} [cGy]		7522.1 (7074.8 – 7665.6)	7477.6 (6799.8 – 7746.4)	0.178
PTV _{s60}	12.9 (1.9 – 44.8)			
D _{max} [cGy]		8250.6 (8148.8 – 9311.4)	10964.6 (10751.1 – 11461.3)	<0.001
D _{mean} [cGy]		8046.7 (7982.8 – 8115.3)	10584.4 (10246.3 – 10702.1)	<0.001
D95% [cGy]		7979.0 (7676.3 – 8029.2)	10236.6 (10034.4 – 10483.3)	<0.001
D _{min} [cGy]		7852.0 (7553.5 – 8244.7)	9758.3 (8646.0 – 9940.8)	<0.001
PTV _{s70}	6.1 (1.5 – 25.9)			
D _{max} [cGy]		8225.9 (8148.8 – 8436.8)	10938.6 (10751.1 – 11191.4)	<0.001
D _{max} [%]		104.2 (103.1 – 106.8)	104.2 (102.4 – 106.6)	0.955
D _{mean} [cGy]		8046.0 (7984.6 – 8112.2)	10681.9 (10585.4 – 10805.2)	<0.001
D95% [cGy]		7984.3 (7907.8 – 8041.2)	10531.3 (10497.0 – 10635.6)	<0.001
D _{max,0.03cc} [cGy]		8166.1 (8094.5 – 8306.7)	10858.9 (10685.1 – 11009.7)	<0.001
D _{min} [cGy]		7888.7 (7707.9 – 7986.9)	10288.5 (9738.6 – 10480.4)	<0.001
PTV _{prostate} – PTV _{s60} (i.e., non-IDL prostate volume)	60.3 (20.6 – 111.8)			
D _{max} [cGy]		8312.3 (8161.9 – 8606.8)	10833.6 (10663.4 – 11078.2)	<0.001
D _{mean} [cGy]		8036.5 (7971.8 – 8100.1)	8992.4 (8449.0 – 9242.5)	<0.001
D95% [cGy]		7930.1 (7883.3 – 7952.7)	7947.3 (7900.1 – 8016.9)	<0.001
Rectum	73.2 (37.4 – 164.6)			
D _{max} [cGy]		8129.1 (6203.6 – 8279.0)	8356.1 (6445.0 – 8896.4)	<0.001
D _{max,0.03cc} [cGy]		8043.2 (5953.7 – 8213.0)	8138.0 (6091.0 – 8493.8)	<0.001
D _{mean} [cGy]		3623.1 (2463.5 – 4707.2)	3562.0 (2455.8 – 4660.4)	0.003
D50% [cGy]		3852.5 (1045.1 – 3141.4)	3786.9 (1069.0 – 4775.4)	0.005
V75Gy [%]		2.2 (0.0 – 8.8)	1.6 (0.0 – 9.0)	<0.001
V70Gy [%]		4.2 (0.0 – 12.5)	3.4 (0.0 – 12.7)	<0.001
V65Gy [%]		6.9 (0.0 – 17.2)	6.3 (0.0 – 17.6)	<0.001
V60Gy [%]		11.2 (0.0 – 25.6)	10.9 (0.1 – 25.0)	<0.001
V50Gy [%]		24.5 (5.6 – 48.5)	24.2 (5.1 – 45.8)	<0.001
Bladder	72.2 (21.0 – 272.6)			
D _{max} [cGy]		8267.8 (8158.7 – 8465.8)	8317.1 (8123.6 – 8665.0)	<0.001
D _{max,0.03cc} [cGy]		8168.2 (8072.3 – 8363.8)	8181.8 (8050.0 – 8454.8)	0.180
D _{mean} [cGy]		3391.4 (805.4 – 5077.4)	3427.1 (835.3 – 5117.6)	0.016

Parameter	Volume (cm ³) Median (Range)	Plan _{79Gy} Median (Range)	Plan _{100-105Gy} Median (Range)	<i>p</i> value
D50% [cGy]		2898.6 (285.3 – 5286.6)	2882.2 (293.7 – 5298.9)	0.034
V80Gy [%]		2.3 (0.4 – 6.5)	1.6 (0.5 – 5.3)	0.002
V75Gy [%]		7.0 (1.2 – 19.7)	7.0 (1.1 – 20.3)	0.718
V70Gy [%]		9.9 (1.6 – 26.7)	9.2 (1.5 – 27.6)	0.592
V65Gy [%]		11.9 (2.0 – 33.0)	12.1 (1.8 – 34.1)	0.556
Left femoral head	56.7 (35.4 – 83.2)			
D _{max} [cGy]		2967.6 (486.9 – 3731.4)	3185.8 (546.0 – 3971.0)	<0.001
D _{mean} [cGy]		1602.3 (193.4 – 2357.2)	1737.4 (206.4 – 2350.1)	<0.001
D50% [cGy]		1585.1 (173.7 – 2398.8)	1739.1 (185.1 – 2316.1)	<0.001
Right femoral head	58.7 (25.9 – 103.6)			
D _{max} [cGy]		2697.0 (1523.5 – 3885.6)	3005.6 (1442.4 – 4000.6)	0.007
D _{mean} [cGy]		1518.0 (276.5 – 2185.4)	1656.8 (298.3 – 2537.9)	0.003
D50% [cGy]		1550.3 (207.4 – 2275.1)	1671.7 (220.3 – 2551.4)	0.003
Penile bulb	1.6 (0.9 – 2.7)			
D _{max} [cGy]		6156.5 (696.6 – 8593.1)	5919.3 (728.2 – 8794.5)	0.011
D _{mean} [cGy]		2008.4 (421.1 – 4636.5)	1887.7 (460.9 – 4914.9)	1.000
D50% [cGy]		1470.1 (398.8 – 4406.9)	1408.8 (437.3 – 4846.4)	0.034

Abbreviations: Dx%: dose received by at least x% of the volume; VxGy: volume receiving at least x Gy; D_{mean}: the mean dose received within the designated volume; D_{max,0.03cc}: the maximum point dose (size: 0.03 cc) received within the designated volume; D_{min}: the minimum dose received within the designated volume; D_{max}: the maximum dose received within the designated volume.