Proton therapy of prostate cancer by anterior-oblique beams: implications of setup and anatomy variations

To cite this article: M Moteabbed et al 2017 Phys. Med. Biol. 62 1644

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Proton therapy of prostate cancer by anterior-oblique beams: implications of setup and anatomy variations

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Received 29 July 2016, revised 8 November 2016
Accepted for publication 29 November 2016
Published 6 February 2017

Abstract
Proton therapy of prostate by anterior beams could offer an attractive option for treating patients with hip prosthesis and limiting the high-dose exposure to the rectum. We investigated the impact of setup and anatomy variations on the anterior-oblique (AO) proton plan dose, and strategies to manage these effects via range verification and adaptive delivery. Ten patients treated by bilateral (BL) passive-scattering proton therapy (79.2 Gy in 44 fractions) who underwent weekly verification CT scans were selected. Plans with AO beams were additionally created. To isolate the effect of daily variations, initial AO plans did not include range uncertainty margins. The use of fixed planning margins and adaptive range adjustments to manage these effects was investigated. For each case, the planned dose was recalculated on weekly CTs, and accumulated on the simulation CT using deformable registration to approximate the delivered dose. Planned and accumulated doses were compared for each scenario to quantify dose deviations induced by variations. The possibility of estimating the necessary range adjustments before each treatment was explored by simulating the procedure of a diode-based in vivo range verification technique, which would potentially be used clinically. The average planned rectum, penile bulb and femoral heads mean doses were smaller for initial AO compared to BL plans (by 8.3, 16.1 and 25.9 Gy, respectively). After considering interfractional variations in AO plans, the target coverage was substantially reduced. The maximum reduction of \( V_{79.2}/D_{95}/D_{mean}/EUD \) for AO (without distal margins) (25.3%/10.7%/1.6%/4.9 Gy, respectively) was considerably larger than BL plans. The loss of coverage was mainly related to changes in water equivalent path length of the prostate after fiducial-based setup, caused by discrepancies in patient anterior surface and...
bony-anatomy alignment. Target coverage was recovered partially when using fixed planning margins, and fully when applying adaptive range adjustments. The accumulated organs-at-risk dose for AO beams after range adjustment demonstrated full sparing of femoral heads and superior sparing of penile bulb and rectum compared to the conventional BL cases. Our study indicates that using AO beams makes prostate treatment more susceptible to target underdose induced by interfractional variations. Adaptive range verification/adjustment may facilitate the use of anterior beam approaches, and ensure adequate target coverage in every fraction of the treatment.

Keywords: proton therapy, prostate cancer, anterior beams

(Some figures may appear in colour only in the online journal)

1. Introduction

Proton therapy (PT) is a promising and expanding modality for treatment of cancer, owing to its unique capability to spare considerable volumes of healthy tissue surrounding the tumor by utilizing sharp dose gradients (Suit et al 1990). This modality has been realized to provide dosimetric benefits over photon-based radiation treatments in terms of reducing the low dose bath and potentially lowering the rate of toxicities (St Clair et al 2004, Durante and Loeffler 2010, Yoon et al 2010, Romesser et al 2016). For prostate cancer, however, the overall clinical advantage of PT over modern photon treatment options namely intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) is still unclear and is the subject of ongoing controversy and clinical investigation (Nguyen et al 2008, Efstathiou et al 2009, Efstathiou 2012, Efstathiou et al 2013, Zietman 2013, Hoppe et al 2014).

PT for prostate cancer conventionally involves the use of bilateral beams with generous margins to compensate for the uncertainties involved in the highly sensitive particle beam delivery (Carabe et al 2012, Paganetti 2012). The lateral penumbra (~10 mm width at 25 cm range, 50–95%) rather than the sharper distal falloff (~4 mm width at 25 cm, 50–95%) is aimed at the radiosensitive anterior rectal wall (ARW) due to concerns regarding range uncertainty, thus delivering 95% of the prescribed dose to at least 15% of the ARW, which in many cases could mean high risk of rectal injury (Michalski et al 2010, Tang et al 2012). The use of alternative beam directions such as anterior or anterior-oblique beams could potentially significantly reduce high dose to the rectum and penile bulb compared to the lateral beam arrangement, allowing for possible reduction of patient toxicities and/or further dose escalation. Also importantly, AO proton beam delivery could be an attractive option for treatment of patients with hip prosthesis since these beams fully avoid the femoral heads and hence the implanted hardware (Rana et al 2014).

Previous studies have clearly demonstrated improved rectal dosimetry especially at high dose levels when including anterior beams in prostate cancer proton plans (Trofimov et al 2007, Tang et al 2012, Polf et al 2016). Other studies have concluded that the combination of lateral and oblique fields in PT planning could provide dosimetric advantage over VMAT for prostate treatment of patients with hip implants (Rana et al 2014). Also anterior beams were suggested to reduce the risk of serious rectal bleeding compared to VMAT or lateral PT, without increasing the bladder complication rates (Polf et al 2016). However, despite the demonstrated dosimetric benefits, the impact of inevitable setup and anatomy variations on the planned dose using anterior proton beams has not yet been fully evaluated. Given the anticipated increase in the number of institutions that might consider applying this technique
for prostate treatments in the near future, it is of sufficient urgency to comprehensively assess the sensitivity of dose distribution to common sources of variation for such technique.

This study focuses on quantifying the dosimetric changes induced by interfractional anatomy and setup variations when using exclusively anterior-oblique (AO) beams for treating the prostate compared to standard bilateral (BL) beams. Understanding the magnitude and sources of dose deviations could be an important step toward devising mitigation techniques and routine clinical implementation. We hypothesize that adaptive delivery measures would be the most efficient and reliable method to ensure treatment robustness using AO beams. We test this hypothesis by quantifying and comparing the efficacy of using fixed planning margins and adaptive range adjustments in ensuring plan robustness, and assess the tradeoffs between robustness and potential toxicities.

2. Methods and materials

2.1. Patient cohort

This study included ten patients with low or intermediate risk prostate cancer who were treated with BL proton beams at our institution. These patients agreed to participate in an image guidance study as an optional component of a randomized clinical trial (Efstathiou 2012). Proton treatments were delivered by passive scattering technique on an IBA gantry (IBA Inc, Louvain La Neuve, Belgium). Three Visicoil gold markers were implanted in the prostate for setup verification, and water-filled endorectal balloons (60 ml) as well as knee/leg support were applied for immobilization. Patients had a simulation CT scan 2–3 weeks prior to treatment for planning purposes on a GE RT16 simulator (GE Healthcare, Waukesha, WI). During their course of treatment, they underwent one additional CT scan per week for a total of 9 weekly images. The weekly scans were acquired within an hour of the treatment session. The scan quality was similar to the simulation CT (1.25 mm slice thickness close to the prostate region and 2.5 mm elsewhere) but it covered a smaller superior–inferior region (from top of the S1 vertebra to ~5 cm inferior to the bottom of the ischium). Table 1 summarizes the specifications for patients included in this study.

2.2. Treatment planning and adaptation

The patient treatments were planned by clinical dosimetrists using the XiO planning system (Elekta, Stockholm, Sweden). BL beams were used as per the clinical standards (Efstathiou et al 2009, Efstathiou 2012). Target volumes were delineated on the simulation CT by the treating physicians. Target constraints for these plans required 50.4 Gy(RBE\(^1\)) dose to 100% of the prostate plus 5–15 mm of proximal seminal vesicles (CTV5040) and 79.2 Gy(RBE) dose to larger than 90% of the prostate gland only (CTV7920). The CTVs were expanded by 5 mm (4 mm posterior) to create the respective PTVs. For clinical BL plans, 95% of the PTVs were required to receive larger than 98% of their respective CTV’s prescribed doses. Organs at risk (OAR) dose constraints followed the recommendations of the protocol (see table 2). Aperture margins of 1.0–1.2 cm and range margins of 3.5% of the prescribed range were applied to the PTV volumes. Range compensator smearing of 1 cm was used. Treatments were delivered at 1.8 Gy/fraction in 44 fractions during 9 weeks.

In addition to the clinical plans, passive scattering anterior beam proton plans were created for all patients. These plans were comprised of AO fields with ±35° inclination from

\(^1\)RBE is the relative biological effectiveness and its value is assumed to be 1.1.
Table 1. Patient/plan specifications, and mean and standard deviation of patient anatomy variations (weekly—simulation CT) during the treatment course.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Stage/Gleason score</th>
<th>BMI</th>
<th>Prostate volume (cc)</th>
<th>Mean planned beam range (cm)</th>
<th>Mean and standard deviation of anatomy variations</th>
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<td>Alignment translations</td>
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<td>1.9 ± 0.7</td>
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<td>24.0</td>
<td>18.5</td>
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<td>24.3</td>
<td>38.2</td>
<td>13.9</td>
<td>6.2 ± 3.3</td>
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<td>12.9</td>
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<td>78</td>
<td>T2a/3 + 3 = 6</td>
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<td>6.2 ± 1.6</td>
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<tr>
<td>9</td>
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<td>T2a/3 + 3 = 6</td>
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<td>14.7</td>
<td>5.2 ± 1.7</td>
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<td>84.3</td>
<td>17.9</td>
<td>6.2 ± 2.5</td>
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</table>
the anterior–posterior (A–P) direction, delivering 100% of the prescribed dose to 100% of the respective CTV volumes. Isotropic aperture margins of 1.2 cm were applied on the CTV, equivalent to a standard 5 mm PTV expansion to accommodate lateral position uncertainties, and a 7 mm additional margin to account for the proton beam penumbra in the 14–19 cm range needed for anterior beam delivery.

Range compensators were optimized to allow very conformal distal falloff matched to the CTV volume. The smearing radius was reduced to 3 mm due to the smaller range, and the absence of dense and variable femoral heads in the beam path. No PTV expansion was applied distally because the ARW is immediately adjacent to the CTV and the added margin would ensure full dose delivery to ARW that is in conflict with a primary purpose of using AO beams.

First, plans with no added range uncertainty margins (AO-0) were created in attempt to isolate and quantify the dosimetric effects due to setup and anatomy variations alone, assuming (for now) no range uncertainties related to CT Hounsfield Unit (HU) to stopping power conversion. Such plans (with smaller margins) were designed in the assumption that in vivo range verification procedures would be in place, providing the ability to monitor and adjust the range as needed. Reducing the margins without appropriate verification and adaptive techniques is not advisable.

Next, in order to explore ways to manage the dose effects induced by daily interfractional variations, plans with fixed margins equal to 2.5% of the planned range (AO-1) were considered. The reason for using 2.5% to manage the daily variations was based on findings of previous studies (Trofimov et al 2011, Schuemann et al 2014). Clinical application of 2.5% margin for prostate treatments has been recently reported (Rana et al 2014). Note again that the margins investigated here are meant to compensate for the daily variations only and the common range uncertainty due to CT conversion is not included (see section 4).

To examine the applicability of adaptive range adjustments, we recalculated the AO-0 planned dose on all weekly CTs and estimated the size of range adjustments needed to distally match the 100% prescription isodose to the CTV volume (AO-0A: includes adaptive range adjustments, based on AO-0 plans). This was accomplished by small incremental range variations until the desired coverage was achieved. The range compensator geometries were identical to ones used in AO-0 and AO-1 plans. The same range adjustment was applied to all beams within a plan for a certain week, since the assessment was based on the total dose and not individual beam doses. This process was performed for 5 patients who showed the largest range inconsistencies among others. This method aimed to empirically evaluate if adaptive range adjustments would be of added value compared to fixed planning margins. In clinical practice, the size of range adjustment would instead be determined by in vivo range verification methods. An example of such method is beam-specific measurements of the dose and difference in water equivalent path length (WEPL) between the planning and daily anatomy at several points of interest immediately distal to the beam, which is currently under development (Lu 2008, Bentefour et al 2015). The result of this method should in principle be equivalent to the

<table>
<thead>
<tr>
<th>OAR</th>
<th>Planning constraints</th>
</tr>
</thead>
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<tr>
<td>Bladder</td>
<td>$V_{10} &lt; 10%$, $V_{15} &lt; 15%$, $V_{20} &lt; 25%$, $V_{30} &lt; 30%$, $V_{45} &lt; 45%$, $V_{50} &lt; 50%$</td>
</tr>
<tr>
<td>Rectum</td>
<td>$V_{15} &lt; 10%$, $V_{20} &lt; 15%$, $V_{30} &lt; 30%$, $V_{40} &lt; 45%$, $V_{50} &lt; 50%$, Point (&gt;1 cc) $\leq 105%$</td>
</tr>
<tr>
<td>Femoral heads</td>
<td>$V_{45} &lt; 5%$</td>
</tr>
<tr>
<td>Penile bulb</td>
<td>Mean dose $&lt;$ 51 Gy</td>
</tr>
</tbody>
</table>

Table 2. Planning constraints for organs at risk (OAR).
values empirically estimated here by direct evaluation of the weekly prescription isodose. An example of examining such equivalence for one patient case is given in the discussion.

2.3. Dose accumulation and data analysis

The dose for all plans was recalculated on each weekly CT scan using XiO. For this purpose, the fiducial markers on weekly and planning CTs were rigidly aligned as per clinical setup guidelines: Rotations were determined through bony anatomy alignment and translations through reducing the average differences between fiducial positions. The plans were then recomputed on the weekly images using the original isocenters and beam shaping devices. The weekly dose distributions (weighted equally at 1/9th of the total dose) were transferred (using deformable image registration), and accumulated (summed) on the planning CT image (MiMVista v6.4, MiM Software, Inc.), creating the ‘accumulated dose’ that includes the effects of weekly setup and anatomy variations. Dose volume histograms (DVH) for the original and accumulated plans were compared to investigate the changes in target coverage and OAR exposure induced by interfractional variations captured by the weekly images. The process was repeated for BL, AO-0 and AO-1 plans. Additionally, AO-0A doses were created by deformable dose accumulation of weekly range-adjusted AO-0 plans. Dose differences were evaluated by comparing the DVH indices, namely mean dose ($D_{\text{mean}}$), dose received by at least x% of the organ volume, ($D_{x}$, $x = 95$ and 5), organ volume receiving at least y Gy dose ($V_{y}$, $y = 79.2, 77.6$ and 50.4 (targets), 70 and 40 (OARs)), and equivalent uniform dose ($EUD = (\sum v_{i}D_{i}^{a})^{1/a}$, where $v_{i}$ is the fractional organ volume receiving a dose $D_{i}$ and $a$ is a tissue-specific parameter) (Niemierko 1997). EUD represents the uniform dose that is biologically equivalent to a non-uniform dose distribution (causing the same radiobiological effects in tissue). The EUD parameters used in this analysis were $a = -10$ for target, 8.0 for bladder and rectum and 12.0 for femoral heads (Li et al 2012).

3. Results

3.1. Plan comparison

We briefly compare the nominal planned doses for BL, AO-0 and AO-1 cases. The AO-0 plans are assuming in vivo range monitoring/adjustment as mentioned previously, hence the absence of planning range margins will be adaptively compensated during treatment delivery (i.e. AO-0A). Figures 1(a) and (b) illustrates an example of BL and AO-0 dose distributions and DVHs for a representative patient. AO-0 plans typically achieved highly conformal CTV coverage, slightly larger bladder dose than BL as expected, and significantly lower dose to the rectum, femoral heads and the penile bulb. The dose to the seminal vesicles was slightly lower in AO-0 than BL plans due to the more conformal 100% isodose but well within the clinical tolerance ($V_{50.4} = 100\%$). The average differences between AO-0 and BL dose-volume indices for all OARs over all patients are quantified in figure 1(c). Although the average bladder mean dose was 7.4 Gy larger for the AO plans compared to BL, the average bladder $D_{5}$ was 0.7 Gy smaller, and the average $D_{\text{mean}}/D_{5}$ for the anterior rectal wall (ARW), rectum, penile bulb and average femoral heads were 10.6/2.9 Gy, 8.3/13.1 Gy, 16.1/18.3 Gy and 25.9/33.9 Gy smaller than BL, respectively. Regarding the AO-1 plans, although the addition of margins (2.5% of range) did not generally lead to violation of the rectal dose constraints, it on average cancelled the dose benefits and in some cases increased the ARW and rectum $D_{\text{mean}}/D_{5}$ compared to BL plans, while maintaining the femoral head and penile bulb sparing.
3.2. Effect of variations on the planned dose

Figure 2 shows the difference maps between planned and accumulated dose distributions for BL, AO-0 and AO-1 plans, for three representative patients. Red and blue indicate the regions of over and underdose with respect to the original plans. Figure 3 displays the corresponding DVH curves for the same patients. Unlike BL plans, the AO dose distributions were generally very sensitive to interfractional variations. For example, for patient 3 shown in figures 2 and 3(a), although the target coverage in the AO-0 plan was fairly stable, the dose to bladder and rectum increased after accumulation due to differences in bladder filling (larger during treatment than at simulation), balloon orientation and soft tissue surrounding the prostate and rectum. In this case, adding a margin did not affect the coverage, and only further increased the ARW/rectum planned and accumulated doses. For patient 4 (figures 2 and 3(b)), the AO-0 plans suffered severe target underdose mainly due to inconsistencies in the position of bony anatomy and patient anterior body surface between simulation and weekly CT when the two images were aligned with respect to the fiducials. The BL plan on the other hand experienced minor changes in target coverage, even though some variations in bladder and rectal dose occurred after accumulation. The variations were generally caused by prostate rotations, inconsistencies in positioning of the legs hence affecting the femur angles, or differences in the distribution of anterior soft tissue. Through the assessment of the registered images, it became clear that even small differences could make an impact. Prostate rotations (up to 15°) and bony anatomy variations could lead to an extra setup rotation around the R-L axis.
(pitch angle) between weekly and simulation CTs, causing inconsistencies in the position of the anterior patient surface in the beam direction (see figure 4(a)). All effects, individually or combined, could cause changes in beam-specific WEPL and hence variations in the steep distal dose falloff position relative to CTV, and introducing a dose discrepancy that largely impacted the AO case. With added distal margins (AO-1 plans), CTV underdose could be resolved (patient 5- figures 2 and 3(c)) or reduced (patient 4- figures 2 and 3(b)). In cases with small or no underdose (patient 3- figures 2 and 3(a)), the ARW and rectum doses were substantially increased due to margins.

Figure 4 illustrates the sources of variation described above for patient 6, whose AO-0 plan presented significant target underdose after accounting for interfractional variations. Figure 4(a) shows the simulation and weekly CT alignment by bony anatomy (left) versus fiducials (right). The arrows show the areas of inconsistency between two images. After final setup (combining bony landmark rotations and fiducial-based translations) the alignment of the pubic symphysis and patient anterior surface are visibly different in both transverse and sagittal views. Figure 4(b) shows the effect of these differences on the weekly 100% isodose (8.8 Gy) calculated on each CT image relative to CTV7920. Dose distributions and DVH indices suggest a systematic shift in the position of the distal edge of the prostate relative to the anterior patient surface, consistent with visual assessment of the registered images.

3.3. Adaptive range adjustment and robustness assessment

Figure 5 quantitatively compares the robustness of different scenarios (BL, AO-0, AO-1 and AO-0A) to interfractional variations for all patients. It illustrates the means and standard deviations of the differences between accumulated and planned dose-volume indices (for each scenario) over the entire patient cohort for all key organs. In case of AO-0A, the AO-0 planned dose was subtracted from the range adjusted accumulated dose. Regarding the target coverage, the largest impact on BL plans was the reduction of $V_{79.2}$ for CTV7920 by 5.5% for
patient 7, while the largest reduction in $D_{95}/D_{mean/EUD}$ was 1.1/0.7/0.7 Gy for patient 10. The average $V_{79.2}/D_{95}/D_{mean/EUD}$ reduction for CTV7920 was 0.7%/0.1/0.1 Gy for BL and 10.6%/3.2/0.5/1.3 Gy for AO-0 plans. The maximum target coverage reductions for AO-0 plans were 25.3%/10.7/1.6/4.9 Gy for $V_{79.2}/D_{95}/D_{mean/EUD}$, respectively, for patient 4. This patient had up to ~8.5 mm difference in skin surface (A–P position) when aligned by the fiducials. For CTV5040 in AO-0 plans, the largest reduction in $V_{50.4}$ was 1.9% and the protocol constraint on the seminal vesicle coverage was a minor violation for 2 cases. Adding the 2.5% distal margin improved the target coverage in AO-1 case, but $V_{79.2}/V_{50.4}$ still remained 6.0/0.1% below that of the planned case when accumulated. When the range was adjusted on weekly basis in AO-0A case, the maximum reduction in $V_{79.2}$ and $V_{50.4}$ were equivalent to the BL plans. Thus, target coverage degradation found in A-0 and A-1 was entirely recovered. The reason for superiority of the adaptive method to using fixed planning margins (i.e. AO-1) was that the variations were typically not consistent/predictable and were patient/treatment-specific. For many cases changes in WEPL required range adjustments (up to 16 mm) substantially larger than provided by the pre-defined margins (~4–5 mm). On the other hand, in some

![Figure 3. Dose volume histograms for planned (solid) and accumulated (dashed) dose for bilateral (BL), anterior-oblique with no distal margins (AO-0) and anterior-oblique with fixed distal margins (AO-1) for (a) patient 3, (b) patient 4 and (c) patient 5.](image-url)
instances when the beam undershoot was smaller than the fixed margin, the range adaptation method allowed for reducing the rectal dose.

Regarding the OARs, although the average bladder $D_{\text{mean}}$ and $V_{40}$ increased for both BL ($3.8 \text{ Gy and } 4.4\%$) and AO-0 ($5.5 \text{ Gy and } 6.8\%$) after accumulation, $D_{2}/V_{70}$ decreased for both scenarios by $3.3 \text{ Gy/0.7\% (BL), and } 2.4 \text{ Gy/1.3\% (AO-0), respectively.}$ The accumulated DVH indices for ARW and rectum were not much different than planned for BL beams, but were significantly smaller than planned for AO-0 and AO-1 cases. This is expected considering the presence of under-shoot even after adding fixed range margins. For AO-0A case, the decrease in rectal dose (seen for AO-0/1 cases) was generally reversed. The femoral heads and penile bulb also experienced changes in dose after accumulation, more so for AO than BL. Since the femoral head dose was originally negligible for AO, the slight increase was not expected to be of significance.

Figure 6 shows a comparison between the accumulated dose-volume indices for different scenarios (BL, AO-0, AO-1 and AO-0A) and all organs. The protocol constraints for the volume indices are indicated by asterisks. It clearly demonstrates the advantage of AO-0A
as shown, in some cases fixed planning margins are not sufficient in preventing violation of CTV7920 constraints, whereas in other cases it is larger than necessary, causing increased rectal $D_5$ compared to BL. Although, according to figure 5, the mean reduction in CTV7920 $V_{79.2}$ was larger for AO-0A delivery than BL, the accumulated $V_{79.2}$ was generally larger than BL due to the assignment of 100% prescription dose to CTVs in the anterior plans. The accumulated OAR dose-volume indices for all delivery methods remained below the constraints, except for bladder $V_{40}$ that included a few outliers due to large bladder variations. The AO-0A accumulated dose volume indices for rectum, femoral heads and penile bulb were considerably smaller than the conventional BL case.

Figure 7 illustrates the relationship between CTV7920 and rectum volume indices, and the anatomy variations (quantified in table 1). It primarily shows that AO-0 plans are most affected by patient variations and are hence not sufficiently robust. Although the correlations are not strong due to the involvement of several different factors causing a certain dose effect, nevertheless some trends could be identified. For example, the increased difference in fiducial versus bony alignment as well as prostate pitch angle played important roles in decreased CTV coverage. In case of outliers, e.g. patients 4, 6 and 8 labeled in the top right panel, factors other than prostate rotation were the main attributors to dose discrepancies, namely differences in bony versus fiducial alignment or changes in the thickness of the bones in the beam path. After adaptively adjusting the range, these trends were no longer observed, similarly to BL.

### 4. Discussion

The role of anterior-oriented proton beams for the treatment of prostate cancer patients who are not qualified to receive conventional BL beams due to hip prosthesis has been a recent area of interest. Using IMRT for these patients has been previously investigated, although optimizing the appropriate beam arrangement and segment weight remains challenging (Su et al 2005, Fattahi and Ostapiak 2012). Other studies demonstrated the benefits of AO proton beams in treatment planning of prostate over IMRT and VMAT, regarding reducing the rectal

<table>
<thead>
<tr>
<th>CTV7920</th>
<th>CT25040</th>
<th>Bladder</th>
<th>ARW</th>
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<tbody>
<tr>
<td>BL</td>
<td>AO-0</td>
<td>AO-1</td>
<td>AO-0A</td>
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</tbody>
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**Figure 5.** Robustness assessment: mean and standard deviation of differences between accumulated and planned DVH indices for all organs and all plan scenarios: bilateral (BL), anterior-oblique with no distal margins (AO-0), anterior-oblique with fixed distal margins (AO-1) and anterior-oblique with adaptive range adjustment (AO-0A).
high dose and sparing the femoral heads and penile bulb (Trofimov et al 2007, Tang et al 2012, Rana et al 2014, Polf et al 2016). A multi-institutional study has reported on treating patients with hip prosthesis by AO proton beams alone (2 cases) or at least one such beam in combination with BL beams (18 cases) (Cuaron et al 2015). They reported acceptable toxicity levels at a median follow-up of 6 months.

Our study was the first to quantify the impact of interfractional variations on the planned dose for AO proton beams. We demonstrated that although superior dosimetry can be provided due to the full avoidance of femoral heads and the use of smaller margins for rectal sparing, plans with exclusively anterior-oriented beams might suffer insufficient robustness to setup and interfractional variations if used without range adaptation strategies. In fact the CTV coverage was reduced to below the clinical constraints in 70% and 40% of cases studied, without and with the use of distal margins, respectively. This was due to the increase in the WEPL along the beam direction between skin surface and prostate, in weekly CT images relative to simulation CT when the two images were registered according to the clinical setup guidelines. Therefore, clinical consequences of such beam delivery, even with pre-defined range margins, might not only be increased rectal toxicity but also loss of target coverage and thus compromised disease control, which might not be as readily evident based on short-term outcomes. Adding a 2.5% distal expansion resulted in rectal planned doses equivalent or slightly larger than BL and persisting clinically unacceptable target underdose after dose accumulation. We

Figure 6. Box-whisker plot (illustrating the maximum, minimum, first and third quartiles and median) of the distribution of accumulated dose-volume indices for all patients, compared between bilateral (BL), anterior-oblique with no distal margins (AO-0), anterior-oblique with fixed distal margins (AO-1) and anterior-oblique with range adjustment (AO-0A). Asterisks represent the planning constraints.
found that using adaptive range adjustment is more effective and reliable than applying predefined distal expansions in mitigating the loss of target coverage, while maintaining superior rectum, femoral heads and penile bulb dosimetry compared to BL beam delivery.

To estimate the size of required adaptive range adjustment and assess its effect on the robustness of delivered dose, we adopted an empirical method to recover the CTV coverage. In cases where the range adjustment was large (>8 mm), small increase in modulation was also found necessary to fully recover the 100% prescription dose to the target. In clinical practice, the size of range adjustments can be determined by in vivo range verification techniques. The modulation could also be potentially adjusted adaptively, accordingly with the range adjustments. Otherwise, the possible loss of proximal target coverage due to insufficient modulation width could be addressed by the use of proximal planning margins.

As a part of ongoing efforts to develop an in vivo range verification workflow for PT of prostate and esophageal cancers, our group has developed a technique to calculate the difference between planning and daily WEPLs from the patient skin surface to a diode array placed in an anatomic cavity immediately distal to the beam. This would verify the beam range and delivered dose at 12 points immediately distal to the beam, prior to each treatment session. For prostate, the diodes would be affixed to the anterior surface of the rectal balloons (Lu 2008, Bentefour et al 2015, Hoesl et al 2016). To determine whether the empirical range margins found in this work could represent what we would be able to extract clinically using the diodes, we examined the correlation between these two quantities for one test patient case with relatively large variations (patient 9). Figure 8(a) shows the difference between planning and a weekly (week 9) WEPL (from the skin surface to the anterior surface of the rectum) for right and left AO beams, calculated using an in-house algorithm (Matlab-based). Each point represents a WEPL value (indicated by the colorwash) along a beamlet in the beam direction. Figure 8(b) shows the relation between the 90% maximum of the WEPL difference distributions (average of right and left beams) at the location where the rectal wall is in its closest proximity to the prostate (2 mm wide in R-L direction), and the empirically estimated range adjustments used in this study for 6 non-consecutive weeks. The result found using these two techniques were strongly correlated ($R^2 = 0.86$), suggesting the promising role of
WEPL-based range adjustment technique in mitigating the dose effects induced by interfractional variations in the future clinical setting. The WEPL difference was found to be beam-dependent in some cases given the possible asymmetries in daily variations, which justifies the need for beam-specific range adjustments. A potential source of uncertainty in WEPL/dose measurement by diodes could be balloon insertion (i.e. diode placement) inconsistency. We observed balloon inconsistencies of up to ~6 mm between planning and weekly CTs. Upon the clinical availability of anterior beam treatments, stricter balloon insertion protocols should be established. Additionally, the variations could be non-uniform across each beam (e.g. rotation of prostate around the A-P axis), which might warrant the inclusion of residual uniform distal planning margins.

It should be noted again that the applicability of AO beams was based on the assumption that the range can be verified with sub-millimeter accuracy, hence the distal falloff of the beams could be fully exploited. The validity of this assumption depends on the availability of accurate in vivo range verification systems, which are mostly in investigation and development phase through dedicated research efforts and out of scope of this work. Examples of such systems include WEPL measurements by diodes (described above) or other detectors.

Figure 8. (a) Differences in water equivalent path length (WEPL) along beamlets in beam-eye-view between week 9 and simulation CT for patient 9, for right and left anterior-oblique (AO) beams. The R-L region highlighted in red shows the smallest prostate-rectum proximity, where the central diodes are expected to be placed, and hence the data points used for analysis. (b) Correlation between the 90% max of WEPL differences shown in (a) (average of right and left beams) and empirically estimated adaptive range margins used to calculate AO-0A dose (figures 5 and 6), for 6 weeks for patient 9. The black solid and dashed lines illustrate a linear fit to the data and the 95% confidence interval, respectively.
combined with rectal balloons (Hardcastle et al 2010), prompt gamma detectors (Testa et al 2014, Richter et al 2016) and proton radiography (Han et al 2011, Doolan et al 2015).

A limitation of our study was the unavailability of 3D imaging in the treatment room and the fact that offline weekly CT images might not fully represent the patient anatomy at the time of treatment. However, differences are expected to be very small given the special care taken to replicate the patient treatment setup during imaging. The largest impact is expected to be on the bladder dose due to the susceptibility to volume changes. But since these variations are random, they partially cancel out due to fractionation.

Apart from interfractional changes, other factors could lead to further degradation of delivered dose when using AO proton beams. One such effect is intrafractional motion, which in case of BL beams was shown to cause additional loss of target coverage (Yoon et al 2008, Tang et al 2013). Further robust planning measures might be necessary to compensate for these effects. Range uncertainty due to conversion of CT HU to proton relative stopping power was not directly included in this analysis. The assumption was that in vivo measurements intrinsically eliminate this uncertainty, and the uncertainty will be defined by the verification method rather than CT conversion. Therefore standard range uncertainty margins will not be applicable to adaptive treatments. Another potential source of loss of plan integrity is the possible variations in relative biological effectiveness (RBE) relative to the assumed constant value of 1.1. Our recent study showed that AO beams are not sufficiently robust to the application of variable RBE modeling, and in vivo validated RBE models are needed for designing more robust AO treatment plans (Underwood et al 2016).

Some studies have indicated potential benefits of hydrogel spacers for prostate radiotherapy regarding the rectal dose (Christodoulou et al 2013, Rucinski et al 2015). Spacers are foreseen to facilitate the use of AO beams by increasing the separation between ARW and prostate, accommodating the addition of fixed margins to further improve the robustness. They would also allow avoiding the placement of the end of range i.e. the region of highest linear energy transfer directly at the ARW surface, alleviating the concerns regarding escalated RBE-weighted dose to rectum.

Future studies may explore the use of pencil beam scanning (PBS) proton therapy for AO beam delivery. Range monitoring/adaptation for PBS is also currently under investigation. While for single field optimized dose similar findings are expected, intensity modulated treatments might involve additional factors of uncertainty, which could be managed by robust optimization strategies. The application of these strategies in the context of anterior beams and adaptive delivery should be further assessed.

5. Conclusion

Although treatment of prostate with anterior beams is not currently a standard of practice, it is a topic of increasing interest. This study demonstrated that treatment of prostate with AO beams is not sufficiently robust to interfractional variations without the application of in vivo range monitoring and adaptation methods. The concern is not only related to the risk of significant increase in rectal toxicity, but importantly, substantial prostate underdose even when pre-defined planning distal margins are used, which could lead to insufficient disease control or relapse. Since anatomy/setup variations are patient and treatment-specific, the dose effects cannot be efficiently compensated by a general planning approach (e.g. adding margins), and adaptive strategies are superior. Therefore, great care should be taken when considering the use of anterior-oriented proton beams in the treatment of prostate cancer, and in vivo range verification is strongly advised. A potential direction for the clinical implementation
of anterior beams for prostate proton therapy could include the use of hydrogel spacers that would accommodate residual distal expansions, in the context of adaptive range verification.

Acknowledgments

This project was supported by the Federal Share of Program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and Treatment Center and the Prostate Cancer Foundation.

Conflict of interest

None

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