Feasibility of prostate robotic radiation therapy on conventional C-arm linacs

Peng Dong PhD, Dan Nguyen BS, Dan Ruan PhD, Christopher King PhD, MD, Troy Long BS, Edwin Romeijn PhD, Daniel A. Low PhD, Patrick Kupelian MD, Michael Steinberg MD, Yingli Yang PhD, Ke Sheng PhD,*

*Department of Radiation Oncology, University of California Los Angeles, Los Angeles, California

© 2014 American Society for Radiation Oncology. Published by Elsevier Inc. All rights reserved.

Introduction

Prostate cancer is the most commonly diagnosed malignancy in men (other than skin cancer) and external beam radiation therapy is frequently used to manage prostate cancer. A dose response has been well established demonstrating superior biochemical control from escalated radiation doses.1-6 The 78 Gy or greater conventionally fractionated treatment to the prostate gland has been shown to significantly reduce treatment failure. However, greater radiation doses have been associated with increased toxicity to organs such as the rectum,6,7 the sparing of which is challenging due to its proximity to the prostate. Methods, including 3-dimensional (3D) conformal radiation therapy, intensity modulated radiation therapy (IMRT), helical tomotherapy, and volumetric modulated arc therapy (VMAT), have been utilized to...
improve dose conformality by creating a steep dose falloff between the prostate and the nearby normal organs. The newer rotational IMRT methods have resulted in small incremental improvements. For example, in one study with VMAT, the maximum dose to the rectum has been slightly reduced compared against IMRT but VMAT typically exposed larger rectal volumes to greater radiation doses.10 The near plateaued dose conformality of modern IMRT coplanar techniques indicates that marked improvement using coplanar techniques is unlikely.

To overcome this, investigators have recently developed a noncoplanar radiation therapy planning and delivery platform, termed 4π radiation therapy, that utilizes the robotic couch and gantry on modern C-arm linacs.9,10 An efficient column generation method was utilized to optimize both the beam orientation and the fluence pattern. This approach has shown that a noncoplanar prostate treatment plan can be generated for nearly 100% of the prostate, indicating that marked improvement using noncoplanar techniques is unlikely.

To further show that in order to achieve such dosimetric gains that could potentially allow substantial dose escalation and improved local tumor control without exceeding critical organ dose limits set for the clinical plans,10 Although CyberKnife (Accuray, Sunnyvale, CA) has been used to deliver noncoplanar SBRT, there has been little evidence to support the utilization of noncoplanar beams for prostate treatments on C-arm gantry systems. A recent paper comparing CyberKnife with VMAT on conventional linac treatments on C-arm gantry systems. A recent paper comparing CyberKnife with VMAT on conventional linac showed that a noncoplanar prostate treatment plan can be significantly superior to a coplanar plan. The authors further showed that in order to achieve such dosimetric gains, a large number (>10) of noncoplanar beams would be needed, consistent with our observation from previous 4π planning studies of other sites.9,10 However, the theoretic method described by Rossi et al12 did not take into consideration of machine geometric limitations that would have excluded many noncoplanar angles. In practice, noncoplanar angles are rarely used in the prostate treatment on the widely available C-arm gantry platforms due to unclear dosimetric gains and the challenge to avoid collision. Therefore, it is of great interest to investigate if it is feasible to use 4π radiation therapy based on currently available C-arm machines to markedly improve prostate planning dosimetry.

Methods and materials

Clinical plans

Twelve low-risk prostate cancer patients previously treated by SBRT were selected for the dosimetry study under an approved internal review board protocol. A SBRT clinical trial dose of 40 Gy in 5 fractions was prescribed to the planning target volume (PTV) that consisted of a 5-mm volumetric expansion of the prostate, reduced to 3 mm in the posterior direction based on recommendations by King et al.13 VMAT plans utilizing 4 half arcs with collimator rotations were created on Eclipse (Version 10; Varian, Palo Alto, CA) to cover 95% of the PTV. Dose calculations and optimization were based on a NovalisTx machine equipped with a 2.5-mm micro-multileaf collimator and 6-MV x-rays. The dose calculation resolution was 2.5 mm isotropically. Organs-at-risk included rectum, bladder, penile bulb, and femoral heads. Rectal contents were included in the rectum contour, which includes the entire rectum between the anus at the level of the ischial tuberosities and the rectosigmoid flexure. The body contour was automatically created to include the entire patient CT volume. A skin contour was created as a 5-mm layer within the body surface. The rectal dose-volume histogram goals were <50% rectal volume receiving 50% of the prescribed dose, <20% receiving 80% of the dose, <10% receiving 90% of the dose, and <5% receiving 100% of the dose. The prescription dose was equivalent to tumor EQD2 (biologically equivalent doses in 2-Gy fractions) of 108 Gy (assuming α/β = 1.5), late responding normal tissue EQD2 of 88 Gy (α/β = 3), and acute responding tissue EQD2 of 60 Gy.

4π plans

The planning process began by distributing 1162 noncoplanar candidate beams throughout the entire 4π solid angle space with 6 degrees of separation between 2 nearest neighbor beam pairs. From the candidate pool, we eliminated those beams that would cause collisions between the gantry and the couch or patient. Collisions were determined using a precise computer-assisted design (CAD) model of the linear accelerator (TrueBeam, model provided by the vendor, Varian) and a human subject. The human CAD model was constructed by digitizing a volunteer using a high precision 3D camera (Artec MH, Palo Alto, CA). The machine and human model to deliver a noncoplanar beam to the prostate is shown in Figure 1. For future clinical applications, the model would be personalized by collecting a 3D digitized surface of the patient.

The remaining candidate beams were subdivided into 5 × 5 mm2 beamlets and the dose distribution matrices of each beamlet were calculated using collapsed-cone convolution or superposition codes and 6-MV x-ray polyenergetic kernels with heterogeneity corrections. The dose calculation model was tuned to match 6-MV machine commissioning data. The dose calculation resolution was 3 × 3 × 3 mm3.

The optimization algorithm details and validation results of the optimization modeling were previously described.14 As a brief review, we let $D_{b,k}$ denote the dose
where \( K_b \) represents the set of selected beam orientation, \( \mathcal{Z} \) is the 3D dose distribution, and \( q^0 \) is the 3D dose constraint. The optimization problem was subsequently solved. Beams were added iteratively until the desired number of beams was reached or the objective function plateaued. We used an objective function \( F(z) \) that is based on a linear approximation of equivalent uniform dose.\(^{15}\)

\[
\begin{align*}
F(\mathcal{Z}) &= \sum_{m} \alpha_m G_m(\mathcal{Z}) \text{ for } m = r, s, r_{50}, V_{20}, V_{10}, V_{5}, \alpha_m \geq 0 \\
G_r(\mathcal{Z}) &= \text{mean} \left( \max \left( \text{prescription dose} - \mathcal{Z}, 0 \right) \right), \text{ for PTV} \\
G_r(\mathcal{Z}) &= \gamma_r \text{mean}(\mathcal{Z}) + (1 - \gamma_r) \text{max}(\mathcal{Z}) \text{for OAR} \gamma_r \leq 1 \\
G_{r,50}(\mathcal{Z}) &= \gamma_{r,50} \text{mean} \left( \max \left( \mathcal{Z} - 5 \times \text{prescription dose}, 0 \right) \right) \text{ for pseudo structures}
\end{align*}
\]

where \( G_r, G_s, \) and \( G_{r,50} \) are objective functions for organs-at-risk, PTVs, and pseudo structures outside of the PTV to minimize \( V_{50\%} \), respectively. For the 4\( \pi \) plans, the maximum and mean doses of the rectum and bladder were penalized as well as the \( V_{50\%} \). The weights among multi objectives \( \alpha_m \) can be tuned to reach individual planning objectives. In this study, \( \alpha_m = 1 \) was used for all critical organ dose constraints. A paired Wilcoxon rank test was used to calculate statistical significance. After plan optimization and full dose calculation, the plans are renormalized to deliver the prescription dose to 95% of the PTV.

### Results

Figure 2 shows the collective Euler beam angle distribution of all 12 patients. Most beams were distributed within ±30 degrees of the coplanar plane and were straightforward to deliver. Figure 3A-C shows the dose distribution on a typical patient. The dose distribution patterns were visually different in that the 4\( \pi \) plan had sharper posterior, inferior, and superior penumbra than the clinical plans. 4\( \pi \) plans were able to achieve slightly superior target coverage and significantly better normal organ sparing, particularly at the anterior rectal wall. The reduction of rectum dose is best visualized in the sagittal dose difference image (Fig 3B), where the dose to entire anterior rectum wall abutting the prostate was reduced because of the steeper dose gradient between the posterior prostate and the anterior rectum wall as shown by the dose profile (Fig 4). In order to reduce the critical organ doses, 4\( \pi \) redistributed greater doses to some normal tissue volumes. However, as shown in the dose difference images, the higher 4\( \pi \) dose volumes are substantially smaller and outside of the rectum, bladder, and femoral head. The dose–volume histogram of the same patient is compared in Fig 5 showing clear reduction in the dose received by the critical organs. The 4\( \pi \) PTV doses are noisier with more fragmented distribution of hot spots. This is typical when comparing IMRT plans using discrete beam angles against rotational IMRT plans. However, the magnitude of the hot spots is within the same range of the VMAT plan, resulting in essentially the same dose–volume histogram. Table 1 shows the dose statistics of all 12 patients. On average, the rectum V50%, V80%, V90%, and \( D_{1cc} \) were reduced by 50%, 28%, 19%, and 11% (\( P < .005 \)). The mean body dose was reduced from 2.07 Gy to 1.75 Gy (\( P = .0001 \)). The mean bladder dose was reduced by 7.9% (\( P = .03 \)). The penile bulb dose was also reduced (\( P = .002 \)). The maximum 10-cc skin doses were significantly increased in the 4\( \pi \) plans but still significantly lower than the skin dose constraint of 30 Gy given in the lung SBRT protocol (Radiation Therapy Oncology Group 0813).

Approximately 4 hours were used to create a 4\( \pi \) prostate plan on a PC with an i7 6-core central processing unit and 24 GB of memory. The total planning time is a
The beamlet calculation took 3 hours but the time will be substantially reduced by using parallel computing and graphics processing unit dose calculation. The process to select 30 beams and optimize fluence maps for 1 patient consumed approximately an hour, which is comparable with VMAT planning time.

**Discussion**

Rectum sparing has been essential in reducing treatment-related toxicity and improving the overall success of prostate radiation therapy. In the study performed by Hardcastle et al., a reduction of 10%-30% in the rectum V30%-V95% was reported comparing IMRT to 3D conformal radiation therapy (3DCRT). Dosimetric improvements using IMRT have instrumented dose escalation and subsequently improved treatment success rates by many clinical practices. VMAT has moderately improved the plan quality over static beam IMRT. No clinically significant difference between Helical TomoTherapy and static beam IMRT has been observed for prostate planning. Placed in perspective, the dosimetric gains from using the $4\pi$ planning technique would be greater than or comparable with those gained when transitioning from 3DCRT to IMRT.

Compared with the rectum, the bladder dose improvement using $4\pi$ is modest. For critical organs abutting the PTV, the maximum dose would be close to the prescription dose and relatively independent of the optimization method. The bladder volume doses were lower and subsequently less penalized in the objective function. This can be compensated by increasing $\alpha_m$ for the bladder if deemed necessary.

A potential concern with the dosimetric comparison is the different dose calculation algorithms used in Eclipse and $4\pi$. The collapse cone convolution and superposition codes used in $4\pi$ was modified from the program originally developed by Mackie et al., which was used in a commercial planning system (Pinnacle, Philips). Compared with Monte Carlo dose calculation, the convolution and superposition algorithm is slightly more accurate than the anisotropic analytic algorithm used in Eclipse but both are accurate in a homogeneous tissue environment. Therefore, the difference between dose calculation algorithms is relatively small compared with the observed plan quality difference.

The dosimetric improvement when using a greater number of optimized noncoplanar beams in the $4\pi$ plan is consistent with the previous report, confirming that significant dosimetric gains are feasible. However, there are several important differences between the $4\pi$ and iCycle approaches. First, our planning model is based on a realistic commercially available linac with a built-in collision model and iCycle prostate plans were based on a hypothetical machine without considering collisions. Consequently, each of the noncoplanar angles in our approach is associated with achievable gantry-couch-patient clearance. The CAD model also facilitates potential nonisocentric delivery where a greater clearance or greater noncoplanar angles are needed. Second, treatment planning on the $4\pi$ platform took an average of 4 hours as opposed to the 40-50 hours using the iCycle algorithm on roughly the same computational hardware, benefitting from the more efficient implicit pricing approach. Third, the $4\pi$ dose calculation was based on convolution and superposition and Monte Carlo calculated dose kernels, while a pencil beam calculation was employed in the iCycle platform. Had the same dose calculation method been used, the computational performance difference...
would further increase. Therefore, in addition to validating the potential dosimetric gains from using noncoplanar beams, our study illustrated the practicality of the proposed optimization scheme and the use of existing C-arm gantry platforms.

One of the concerns regarding the automated and sequenced delivery of a large number of noncoplanar plans involves the potential for patient motion during the multiple couch translations and rotations. Linthout et al.\textsuperscript{26} examined secondary motion induced by robotic couch translation and rotation and found it to be within 3 mm and 2 degrees and primarily induced by couch roll and pitch; both were not used in this study. While this motion was not specific to $4\pi$ therapy, we anticipate that the motion could...
be limited by optimizing the total couch rotation and acceleration or deceleration. The SBRT body immobilization devices, such as BodyFix (Elekta, Stockholm) and Body Pro-Lok (Civco, Kalona, IA) indexed to the treatment couch should further minimize couch movement-induced patient body motion.

In a previous study of $4\pi$ therapy for lung tumors, the time to deliver $4\pi$ plans using the TrueBeam Developer Mode for automated maneuvering was measured. It was determined that approximately an additional 140 seconds would be spent for couch and gantry travel for up to 30 beams. It is also estimated to take an additional 200 seconds to deliver radiation doses for 30 beams. The total $4\pi$ treatment time compares well with VMAT plans using 2 arcs delivering SBRT plans with an 8-Gy prescription dose or greater, but will likely be longer for regularly fractionated plans. In our clinic, the 2 full-arc VMAT plans are divided into 4 half arcs to allow stereotactic x-ray imaging (ExacTrac; BrainLab Inc, Westchester, IL) images in between. We can adopt a similar approach for the $4\pi$ treatment to detect undesired patient motion that the sequence could be modified to allow intrafractional position verification using ExacTrac or a 3D surface monitoring system; eg, AlignRT. Therefore, in addition to demonstrating and validating the dosimetric improvement, a primary point of the study is to show that robotic noncoplanar radiation therapy can be efficiently performed on an existing hardware platform.

It is of great interest to compare CyberKnife with $4\pi$ due to their similar noncoplanar beam patterns. As mentioned, a recent publication showed that the dosimetric difference between CyberKnife and VMAT was not discernible. Without a direct comparison, a firm conclusion cannot be drawn but it is reasonable to assume dosimetric advantages for $4\pi$ due to the inclusion of posterior beams. We estimate the $4\pi$ beam-on time of 10-15 minutes including the automated gantry and couch movement between beams; longer than VMAT but substantially shorter than CyberKnife.

It is clear that critical organ doses from state-of-the-art prostate plans can still be substantially improved with the use of a large number of noncoplanar beams. Although improved critical organ sparing is appealing, a prospective clinical trial will be needed to determine if it can lead to improvements in clinical outcome. Individual $4\pi$ beams can be manually delivered to patients on existing linacs but the process will be very inefficient without automated gantry and couch movement, which is not Food and Drug

---

**Figure 4** The dose profile through the posterior prostate and anterior rectum shows steeper dose gradient with the $4\pi$ plan. (VMAT, volumetric modulated arc therapy.)

**Figure 5** Dose–volume histogram of the same patient as shown in Figs 3 and 4, showing a slight reduction in the prostate cold spots and improved bladder and rectum sparing. (PTV, planning target volume; VMAT, volumetric modulated arc therapy.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical</th>
<th>$4\pi$</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV dose (95%)</td>
<td>39.99</td>
<td>4.18</td>
<td>0.46%</td>
<td>.003 a</td>
</tr>
<tr>
<td>PTV dose (98%)</td>
<td>39.51</td>
<td>39.66</td>
<td>0.39%</td>
<td>.27</td>
</tr>
<tr>
<td>Rectum mean</td>
<td>13.23</td>
<td>9.49</td>
<td>-28.30%</td>
<td>.001 a</td>
</tr>
<tr>
<td>Bladder mean</td>
<td>9.02</td>
<td>8.31</td>
<td>-7.90%</td>
<td>.003 a</td>
</tr>
<tr>
<td>L femur head mean</td>
<td>5.91</td>
<td>5.53</td>
<td>-6.41%</td>
<td>.42</td>
</tr>
<tr>
<td>R femur head mean</td>
<td>6.49</td>
<td>5.57</td>
<td>-14.16%</td>
<td>.001 a</td>
</tr>
<tr>
<td>Body mean</td>
<td>2.07</td>
<td>1.75</td>
<td>-15.41%</td>
<td>.0005 a</td>
</tr>
<tr>
<td>Penile bulb mean</td>
<td>9.49</td>
<td>8.93</td>
<td>-5.90%</td>
<td>.57</td>
</tr>
<tr>
<td>Rectum (1cc) max</td>
<td>3.19</td>
<td>2.69</td>
<td>-1.91%</td>
<td>.001 a</td>
</tr>
<tr>
<td>Bladder max</td>
<td>42.99</td>
<td>42.64</td>
<td>-0.81%</td>
<td>.08</td>
</tr>
<tr>
<td>Bladder (1cc) max</td>
<td>34.04</td>
<td>34.67</td>
<td>1.87%</td>
<td>.11</td>
</tr>
<tr>
<td>Penile bulb max</td>
<td>27.13</td>
<td>24.60</td>
<td>-9.32%</td>
<td>.002 a</td>
</tr>
<tr>
<td>Rectum V50%</td>
<td>23.32</td>
<td>21.66</td>
<td>-6.80%</td>
<td>.005 a</td>
</tr>
<tr>
<td>Rectum V80%</td>
<td>7.41</td>
<td>5.34</td>
<td>-27.91%</td>
<td>.005 a</td>
</tr>
<tr>
<td>Rectum V90%</td>
<td>4.67</td>
<td>3.77</td>
<td>-19.29%</td>
<td>.003 a</td>
</tr>
<tr>
<td>Bladder V50%</td>
<td>17.02</td>
<td>14.25</td>
<td>-16.28%</td>
<td>.0024 a</td>
</tr>
<tr>
<td>Skin (10 cc) max</td>
<td>3.65</td>
<td>7.12</td>
<td>95%</td>
<td>.0001 a</td>
</tr>
</tbody>
</table>

L, left; PTV, planning target volume; R, right. a Statistically significant.
Administration (FDA) approved. In order to efficiently deliver $4\pi$ plans, both the planning software and automated delivery method need to be integrated in the workflow of a commercial system and approved by the FDA. Alternatively, for early phase clinical trials, an investigational device exemption is required.

Conclusions

By optimizing beam angles and fluences in the non-coplanar solution space, superior prostate treatment plan quality was achieved compared against state of the art VMAT plans. The dosimetric improvement could lead to either clinically meaningful prostate dose escalation, toxicity reduction, or both. Three-dimensional modeling of the treatment machine and patients can be used to determine the deliverability of a noncoplanar beam angle.

References


