A planning study of focal dose escalations to multiparametric MRI-defined dominant intraprostatic lesions in prostate proton radiation therapy

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INTRODUCTION
Radiation therapy for localized prostate cancer, as delivered using external beam radiotherapy (EBRT), brachytherapy, or a combination thereof, treats the entire prostate gland to a single prescribed dose level since prostate cancer is presumed to be multifocal.\(^1\) However, histopathological studies have commonly identified dominant intraprostatic lesions (DILs) in prostate cancer.\(^6\) DIL is the area within the prostate containing the largest and/or highest grade of cancer lesion.\(^7\) One or a few DILs are responsible for the majority of the tumor burden despite typically representing less than 10% of the total gland volume,\(^6\) and are the most common sites of recurrence after radiation therapy.\(^8,9\) Studies have shown that escalating the dose to DILs when irradiating the whole prostate has the potential to increase tumor control probability (TCP) with acceptable toxicity.\(^10\)\(^-\)\(^13\) Thus, dose escalation to DILs during radiation treatment is an approach of particular clinical and research interest.\(^14\)

Although radiotherapy boost to DIL may improve disease control, it may come at the cost of increased toxicity of surrounding normal tissue such as bladder, urethra, and rectum. The dosimetric effect and potential clinical impact of different treatment schemes for prostate DIL dose escalation has been reported for both photon EBRT and high-dose rate (HDR) brachytherapy.\(^12,14,15\) For photon EBRT, intensity-modulated radiation therapy (IMRT)/volumetric-modulated arc therapy (VMAT) techniques for conventional fractionation, moderate hypofractionation, and stereotactic ablative radiation therapy (ultra-hypofractionation) have been proposed.\(^12,15\)\(^-\)\(^20\) The boost dose can be escalated to approximately 125% of the whole prostate prescription dose, covering 95% of DIL volume, before organs-at-risk

Objective:
The purpose of this study is to investigate the dosimetric effect and clinical impact of delivering a focal radiotherapy boost dose to multiparametric MRI (mp-MRI)-defined dominant intraprostatic lesions (DILs) in prostate cancer using proton therapy.

Methods:
We retrospectively investigated 36 patients with pre-treatment mp-MRI and CT images who were treated using pencil beam scanning (PBS) proton radiation therapy to the whole prostate. DILs were contoured on co-registered mp-MRIs. Simultaneous integrated boost (SIB) plans using intensity-modulated proton therapy (IMPT) were created based on conventional whole-prostate-irradiation for each patient and optimized with additional DIL coverage goals and urethral constraints. DIL dose coverage and organ-at-risk (OAR) sparing were compared between conventional and SIB plans. Tumor control probability (TCP) and normal tissue complication probability (NTCP) were estimated to evaluate the clinical impact of the SIB plans.

Results:
Optimized SIB plans significantly escalated the dose to DILs while meeting OAR constraints. SIB plans were able to achieve 125, 150 and 175% of prescription dose coverage in 74, 54 and 17% of 36 patients, respectively. This was modeled to result in an increase in DIL TCP by 7.3–13.3% depending on \(\alpha/\beta\) and DIL risk level.

Conclusion:
The proposed mp-MRI-guided DIL boost using proton radiation therapy is feasible without violating OAR constraints and demonstrates a potential clinical benefit by improving DIL TCP. This retrospective study suggested the use of IMPT-based DIL SIB may represent a strategy to improve tumor control.

Advances in knowledge:
This study investigated the planning of mp-MRI-guided DIL boost in prostate proton radiation therapy and estimated its clinical impact with respect to TCP and NTCP.
(OARs) constraints are violated. DIL dose escalation can also be implemented in HDR brachytherapy. Recent studies have demonstrated the potential of multiparametric MRI (mp-MRI)-guided DIL focal boost HDR brachytherapy based on CT or transrectal ultrasound (TRUS) images. Coverage to 150% of the prescription dose can be achieved for the DIL without violating dose constraints by standard peripheral loading with additional needle(s) within the DIL. The relatively higher boost dose can be attributed to the interstitial property of brachytherapy that avoids entrance dose and provides more conformal dose distribution when compared with photon EBRT. Using HDR for focal boost may be technically challenging when implanting individual needles. The mp-MRI images need to be deformably registered with real-time TRUS images in the operating room in order to propagate the mp-MRI-defined DIL contour to TRUS images for needle guidance. Such deformable registration is challenging in that it involves two imaging modalities with different contrast information and it is required to have high-speed performance to enable real-time guidance.

Proton radiation therapy has been an emerging treatment modality for prostate cancer. Due to favorable dosimetric properties related to the Bragg Peak, and virtually no exit dose, it may have better clinical outcomes when compared with photon EBRT. DIL dose escalation using proton radiation therapy is promising by utilizing its sharp dose gradient at the distal end of beam. Intensity modulated proton therapy (IMPT) using pencil beam scanning (PBS) has the ability to selectively boost DIL dose by applying more weight to the spots contributing to it. Recent studies comparing photon and proton radiation therapy in DIL simultaneous integrated boost (SIB) plan have demonstrated that passive scatter proton therapy and IMPT have comparable or superior DIL boost dose distributions over IMRT/VMAT/helical tomotherapy, respectively, with both having better OAR sparing. However, the dosimetric differences between proton DIL SIB plans and conventional non-boost whole prostate proton plans, which is important for clinicians in predicting disease control and toxicity, have not been studied.

In this study, we investigated the planning of IMPT-based boost to the DIL, and compared it to conventional whole-prostate proton irradiation. The purpose of this study was to determine the achievable level of DIL dose escalation, its estimated impact on tumor coverage and dose to OARs, and its modeled clinical impact. In a cohort of 36 patients, we retrospectively evaluated the dose coverage of mp-MRI-defined DILs in IMPT-based SIB treatment plans, and compared its OAR sparing and prostate coverage against conventional plans. TCP and normal tissue complication probability (NTCP) were estimated to further evaluate the clinical impact of the SIB plans.

**METHODS AND MATERIALS**

**Patients**

We retrospectively identified 36 patients who were treated using PBS proton therapy at a single institution. Median age was 69.5 years (range 49–83), clinical T classification were T1c to T3b, median PSA was 8.4 (range 3.1–40). Median MR-based prostate volume was 53.0 cc (range 24.1cc–214.0cc), and median Gleason score was 7 (range 6–9). The numbers of patients in ISUP grade group from 1 to 5 are 5, 13, 10, 5, and 3. Among the 36 patients, 24 patients had androgen deprivation (ADT). All patients received 70 Gy RBE dose (assuming a proton RBE of 1.1) in 28 fractions to the prostate and proximal seminal vesicles using pencil beam scanning proton beams. Institutional review board approval was obtained; informed consent was not required for this Health Insurance Portability and Accountability Act (HIPAA) compliant retrospective analysis.

**Image acquisition and contouring**

Recent advances in mp-MRI techniques have shown its efficacy in identifying DILs, and its reliability, accuracy, and reproducibility as validated against reference pathology. Multiple studies have supported its use for image guidance in treatment planning of EBRT and HDR brachytherapy for DIL boosts.

In our study, mp-MRI scans, which included T1W, T2W and diffusion-weighted MRI (DWI), were acquired on the same day as the planning CT on an Aera (Siemens, Germany) 1.5T scanner. T1W MRI used gradient recalled (GR) sequence with 10° flip angle, repetition time (TR) 6.9 ms, echo time (TE) 2.39 ms, echo train length 2, and 1.4 mm pixel size and slice thickness. T2W MRI used spin echo (SE) sequence with 170° flip angle, TR/TE = 1600 ms/166 ms, echo train length 76, 1.0 mm pixel size, and slice thickness. DWI MRI used a single-shot SE-echo planar imaging (EPI) with TR/TE = 5000 ms/61 ms, 1.8 mm pixel size, and 3.5 mm slice thickness. Apparent diffusion coefficient (ADC) maps were then generated with b-value = 800 s/mm² for analysis. Planning CT images were acquired with a SOMATOM Definition Edge (Siemens, Germany) with 120 kVp, 0.5 s rotation time, 500 to 650 mA tube current, 1.0 mm pixel size, and 1.5 mm slice thickness.

Each patient’s original approved clinical plan included a deformable registration between mp-MRIs and CT images. The whole prostate contour was delineated on MRIs and propagated to CT images. The bladder, rectum, left and right femoral heads were contoured on CT images. Eleven of the 36 patients had large bowel contours. For our dose escalation study, DILs contours were based on the above MRI images to reach a consensus between two radiation oncologists using VelocityAI 3.2.1 (Varian Medical Systems, Palo Alto, CA). An example of DIL delineation on T2W MRI and ADC map is shown in **Figure 1**. Each patient has one DIL defined within the prostate. The average DIL volume among the 36 patients was 0.63 ± 0.53 cc (range 0.09–2.27cc). The urethra was also contoured on MRIs for each patient. Both DIL and urethra contours were propagated from MRIs to planning CTs for SIB planning.

**Treatment planning study**

Two opposing lateral beams were used for both the conventional whole-prostate-irradiation plans and the proposed DIL SIB plans. While conventional plans were optimized with single field optimization (SFO) technique, DIL SIB plans were optimized with multifield optimization (MFO) technique to facilitate DIL coverage and OAR sparing. Both the conventional whole-prostate-irradiation plans and the proposed DIL SIB plans were...
robustly optimized with 6 mm setup uncertainty in all directions except for 0 mm laterally, which was covered by the 3.5% range uncertainty. Both plans were normalized to achieve whole prostate coverage at 100% of the prescribed dose to 98% of the CTV (V100 = 98%), with hard OAR dose constraints based on RTOG 0415 Arm 2. Additional optimization goals for OAR doses were used as constraints for both plans if further normal tissue sparing was feasible (Table 1). DILs and urethra were not considered as part of conventional plan optimization. DIL SIB plans were reoptimized as simultaneous boosts to the conventional plan based on additional DIL coverage. The goal for DIL dose coverage was D95 ≥ 140% and D90 ≥ 200% of the prescribed dose while meeting the above CTV/OAR constraints, as well as an additional urethra constraint (maximum dose ≤ 82 Gy (117%)).

In the following context, we refer to the above two scenarios as "conventional" and "SIB," respectively. Treatment planning was performed using Raystation 8B (RaySearch, Stockholm, Sweden). Clinically relevant dose-volume histogram (DVH) metrics were selected for comparison between the two scenarios for prostate with DIL cropped, DIL, bladder, rectum, femoral heads, large bowel, and urethra. A student t-test was performed between "Conventional" vs "Boost" to evaluate the significance of corresponding DVH metric changes. A p-value less than 0.05 was considered statistically significant.

TCP and NTCP modeling
The clinical impact of SIB plans was evaluated in terms of TCP and NTCP. TCP was calculated using the LQ-Poisson Marsden model, and NTCP was calculated for bladder, rectum, and urethra by Lyman-Kutcher-Burman (LKB) model with Niemierko’s equivalent uniform dose model. Equations and details of TCP and NTCP calculation were done as previously reported. All doses used for DVHs were converted to equivalent dose in 2 Gy/fraction (EQD2) based on the linear quadratic model in our calculation. TCP calculations assume the population of clonogenic cells (with initial cell density $\rho_{clon}$ and constant $\alpha/\beta$ ratio) with radiosensitivity ($\alpha$) varies according to a Gaussian distribution with mean $\bar{\alpha}$ and standard deviation $\sigma_{\alpha}$. To evaluate the possibility of varying tumor radiation resistance, we investigated two different $\alpha/\beta$ ratios (1.5 Gy and 3 Gy).

<table>
<thead>
<tr>
<th>CTV/OAR constraints</th>
<th>CTV</th>
<th>V100 = 98%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bladder</td>
<td>Dose to 15% (D15) ≤ 79 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D25 ≤ 74 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D35 ≤ 69 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D50 ≤ 64 Gy</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>D15 ≤ 74 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D25 ≤ 69 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D35 ≤ 64 Gy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D50 ≤ 59 Gy</td>
</tr>
<tr>
<td></td>
<td>Penile Bulb</td>
<td>Mean ≤ 51 Gy</td>
</tr>
</tbody>
</table>

**Table 1. Organ-at-risk dose constrains and additional optimizing goals for both the conventional whole-prostate-irradiation plans and the proposed DIL SIB plans**

<table>
<thead>
<tr>
<th>Additional optimizing goals</th>
<th>DIL*</th>
<th>D95 ≥ 140%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bladder</td>
<td>Max ≤ 71.5 Gy</td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>Max ≤ 71 Gy</td>
</tr>
<tr>
<td></td>
<td>Femoral head</td>
<td>Max ≤ 40 Gy</td>
</tr>
<tr>
<td></td>
<td>Urethra*</td>
<td>Max ≤ 82 Gy</td>
</tr>
</tbody>
</table>

*Used in SIB plan only
for prostate and DIL, each of which corresponds to a different set of parameters ($\bar{\alpha}$ and $\sigma_\alpha$) as previously reported. Note that EQD2 was also calculated separately for each $\alpha/\beta$ ratio. For all $\alpha/\beta$ ratios, $\rho_{\text{clon}}$ in non-DIL was assumed to be $6.2 \times 10^4$/$\text{cc}$, and in DIL was assumed to be $1 \times 10^7$/$\text{cc}$ and $2.8 \times 10^8$/$\text{cc}$ to represent lesions of high and very high risk, respectively, as previously reported.

NTCP calculations involve OAR-dependent parameters $TD_{0.03\text{cc}}$, $m$ and $n$ chosen according to existing studies. The $\alpha/\beta$ ratios were only used in EQD2 conversion, and were assumed to be three if not explicitly listed. Parameters for TCP and NTCP calculation are listed in Tables 2 and 3. The calculation was implemented by Biosuite software. NTCPs of left and right femoral heads were averaged.

**RESULTS**

The dose distributions of conventional and SIB plans were compared side-by-side for a representative patient (Figure 2). In conventional plan, the DIL received essentially the standard prescription dose (Figure 2(a)). The SIB plan successfully achieved the DIL V175 coverage (V175 = 98.5%) with increased dose on femoral heads (Figure 2(b) and (c)). The DVH comparison of this patient is shown in Figure 3. The DVH of DIL in the conventional plan overlapped with that of prostate in the conventional plan. The dose deposited to the DIL in the SIB plan was significantly higher than that of the conventional plan, with an increased hotspot in the non-DIL prostate region. Qualitatively, DVH curves of the SIB plan were similar to that of the conventional plan for OARs, with exception of the femoral heads.

Comparative DVH metrics for prostate and DIL between the two plans among 36 patients are summarized in Table 4. For the non-DIL prostate, although minimal differences were found in prescription dose coverage, the volume of high dose (>110% of prescription dose) spill was about 20% in the SIB plans. Figure 4 shows the percentage of patients receiving various levels of coverage to the DIL in the SIB plan. 74, 54, and 17% of patients had escalated doses to V125 > 95%, V150 > 95%, V175 >95% of DIL, respectively. These results are consistent with the above qualitative findings and quantitatively demonstrate the dose coverage improvement to the DIL in SIB plans.

Similarly, comparison of OARs is summarized in Table 5. All the SIB plans met OAR constraints and urethra V90Gy = 0. The largest discrepancy was found in maximum dose to the femoral heads. Increases in DVH metrics of bladder and rectum received were within 3% of prescription dose. There was no statistically significant difference between the two plans for large bowel $D_{0.03\text{cc}}$ and penile bulb $D_{\text{mean}}$.

The TCP and NTCP results are summarized in Table 6. Overall, the SIB plans significantly increased the TCP of DILs compared to the conventional plans, while maintaining the TCP of non-DIL prostate region. The greatest TCP improvement was seen for very high risk DILs with $\alpha/\beta=3$ (13.3%), and the least was for high risk DILs with $\alpha/\beta=1.5$ (7.3%). NTCP results for bladder and rectum had no significant differences between the two plans. For urethra and femoral heads, the SIB plans showed 2.3% ($p < 0.05$) and 0.6% ($p < 0.05$) higher NTCP, respectively.

**Table 2. Tumor control probability parameters**

<table>
<thead>
<tr>
<th>$\frac{\alpha}{\beta}$ (Gy)</th>
<th>$\bar{\alpha}$ (Gy$^{-1}$)</th>
<th>$\sigma_\alpha$ (Gy$^{-1}$)</th>
<th>$\rho_{\text{clon}}$ (cc$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>0.155</td>
<td>0.058</td>
<td>$6.2 \times 10^4$</td>
</tr>
<tr>
<td>Prostate-DIL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIL (high risk)</td>
<td>0.155</td>
<td>0.058</td>
<td>$1 \times 10^7$</td>
</tr>
<tr>
<td>DIL (very high risk)</td>
<td>0.155</td>
<td>0.058</td>
<td>$2.8 \times 10^8$</td>
</tr>
<tr>
<td>3</td>
<td>0.217</td>
<td>0.082</td>
<td>$6.2 \times 10^4$</td>
</tr>
<tr>
<td>Prostate-DIL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIL (high risk)</td>
<td>0.217</td>
<td>0.082</td>
<td>$1 \times 10^7$</td>
</tr>
<tr>
<td>DIL (very high risk)</td>
<td>0.217</td>
<td>0.082</td>
<td>$2.8 \times 10^8$</td>
</tr>
</tbody>
</table>

**Table 3. Normal tissue complication probability parameters**

<table>
<thead>
<tr>
<th>Source</th>
<th>$\frac{\alpha}{\beta}$ (Gy)</th>
<th>$TD_{0.03\text{cc}}$ (Gy)</th>
<th>$m$</th>
<th>$n$</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder Contracture/volume loss</td>
<td>3</td>
<td>80</td>
<td>0.11</td>
<td>0.5</td>
<td>Burman, et al.</td>
</tr>
<tr>
<td>Rectum Grade 2 + late toxicity or rectal bleeding</td>
<td>3</td>
<td>76.9</td>
<td>0.13</td>
<td>0.09</td>
<td>Michalski, et al.</td>
</tr>
<tr>
<td>Urethra Stricture requiring urethrotomy within 4 years after RT completion</td>
<td>5</td>
<td>70.7</td>
<td>0.37</td>
<td>0.3</td>
<td>Panettieri et al.</td>
</tr>
<tr>
<td>Femoral Heads Necrosis</td>
<td>3</td>
<td>65</td>
<td>0.12</td>
<td>0.25</td>
<td>Burman, et al.</td>
</tr>
</tbody>
</table>
DISCUSSION

In this study, we investigated the planning of mp-MRI-defined DIL dose escalation using IMPT-based proton radiation therapy, and estimated its clinical impact in terms of TCP and NTCP. SIB plans significantly escalated the dose to DILs while respecting prostate coverage and OAR constraints. DIL dose boost to 125, 150, and 175% of prescription dose could be achieved in 74, 54, and 17% of 36 patients, respectively. This resulted in an increase from conventional plan in DIL TCP by 7.3–13.3% depending on $\alpha/\beta$ and risk level.

DIL dose escalation using proton beam was first proposed by Schulte et al.54 A number of follow-up studies have since been published.26–28,55 These studies focused on comparing proton to photon-based plans (EBRT or HDR brachytherapy) in terms of achievable escalated dose and OAR sparing. DIL boost dose coverage varied from study to study, but generally was able to be pushed up to about 130% of prescription dose. However, these studies differ from our study in several ways, such that a direct comparison in feasible boost dose is not possible. Only bladder and rectum were considered in plan design/optimization in several studies.26,27,55 Others28 did include other common OARs (penile bulb, femoral head, etc.) in planning, but used a less common five-oblique-field setup. Neither of these dosimetric studies was closely based on the clinical workflow for prostate cancer proton treatment planning. Additionally, the urethra was not contoured, and thus unable to be used as a dose limiting structure in these prostate DIL boost studies (except for reference28 which assumed it to be the center of prostate on each slice). In conventional planning, it was widely assumed that the prostatic urethra received the uniform prescription dose;36 however, the urethra in SIB plans is likely to have substantial changes in the volume receiving more than 100% of the prescription dose, depending on boost dose and distance from DIL. Urethral hotspots are directly related to late urinary toxicity, including urethral strictures.37 Moreover, the limited patient sample sizes (ranging from 7 to 12) of prior studies also weakens the validity of their conclusions.

In this study, our purpose was to determine the feasible DIL dose boost and the resulting dosimetric changes to OARs. SIB plans were largely based on the conventional plan with the DIL and urethra added as additional optimizing constraints. The comparison between boost and conventional plans demonstrated both the dosimetric benefits for DIL coverage and also the dose increase to OARs, which provides a benchmark to clinicians about the relative advantage and risks of treating using a proton-based boost. To overcome other limitations discussed above, we included all common OARs (including urethra) in planning and evaluation, and an intermediate size of patients was involved in this study.

A potential tradeoff of SIB plans is the high dose spill from the DIL, and the increased high dose ($\geq $110% of prescription dose) volume in the non-DIL prostate. However, the necessities of enforcement on dose homogeneity in target volume in conventional fractionated EBRT are debatable.58 Ablative doses have proven effective for prostate tumor control,59 and studies have shown that dose heterogeneity may be beneficial in localized prostate cancer for its improvement in OAR sparing.60 Thus, the hotspot in non-DIL prostate can be accepted or even preferred. Another consequence from the hotspot in non-DIL prostate region is the increased urethral dose. Reducing the urethra dose is an important optimization goal in our treatment planning. In HDR brachytherapy, a commonly used urethra tolerance dose is $<125\%$ of prescription dose ($13.5\text{ Gy} \times2$).61 For the fractionation scheme in our study, it is equivalent to 90 Gy, assuming $\alpha/\beta=5$ in biological effective dose conversion.60 Table 4 shows that all the patients in our SIB plan met this constraint ($V90\text{ Gy} = 0$). Notably, the absolute urethra NTCP values are overestimated using the current parameters. They are much higher than previously reported rates of urethral stricture after EBRT (2%–3%).62–64 As discussed previously, one potential reason is the lack supporting...
clinical evidence for urethral NTCP LKB modeling parameters. The parameters of urethra used in this study and reference were cited from Panettieri et al, where the clinical studies of these parameters are not provided. Another set of NTCP parameters of urethra was provided in another study without additional sources. To the best of our knowledge, these are the only two publications presenting urethra NTCP LKB modeling parameters. Thus, the reliability of the NTCP calculation may be affected and therefore should be viewed with caution.

The largest DVH change among OARs was seen in $D_{\text{max}}$ of femoral heads (about 12 Gy), which was directly caused by the increased entrance dose from the two opposing lateral beams as shown in Figure 2. Considering only an absolute NTCP increase of 0.6%, it may be clinically acceptable after careful judgment. Future studies would investigate the dependence of OAR toxicity, especially femoral heads $D_{\text{max}}$ on the size and location of DIL. The closest OAR to the DIL would be usually more affected by the dose spilled out from DIL. Considering that two opposing lateral beams were used for both the conventional whole-prostate-irradiation plans and the proposed DIL SIB plans as well as more dose uncertainty at the end of beam than the lateral, femoral head would be more sensitive to DIL location than other OARs. Such study may predict the upper limit of dose escalation and the toxicity of femoral heads before plan optimization. Moreover, the use of non-lateral proton beams in treating prostate has been shown feasible with dosimetric advantage especially for hip. Such benefit is expected for DIL SIB plan, while dose sparing in other OARs may be compromised by the larger range uncertainty caused by bladder/rectum filling.

TCP/NTCP models are used to estimate the clinical impact of the SIB plans. TCP/NTCP models serve as a surrogate to reflect the potential treatment outcome/toxicity from the change of DVHs. The limitations of using TCP/NTCP models have been presented in several studies. In this study, specifically, the choice of the model parameters may change the TCP/NTCP scores. Thus the absolute values of TCP/NTCP are not proper to be applied for planning and decision-making due to the uncertainty of model parameters.

Among the 36 patients in this study, 24 patients had ADT. ADT has been shown to reduce the conspicuity of lesion in mp-MRI, which may affect the accuracy of DIL target delineation. In order to have an accurate DIL contour before plan optimization. Moreover, the use of non-lateral proton beams in treating prostate has been shown feasible with dosimetric advantage especially for hip. Such benefit is expected for DIL SIB plan, while dose sparing in other OARs may be compromised by the larger range uncertainty caused by bladder/rectum filling.

TCP/NTCP models are used to estimate the clinical impact of the SIB plans. TCP/NTCP models serve as a surrogate to reflect the potential treatment outcome/toxicity from the change of DVHs. The limitations of using TCP/NTCP models have been presented in several studies. In this study, specifically, the choice of the model parameters may change the TCP/NTCP scores. Thus the absolute values of TCP/NTCP are not proper to be applied for planning and decision-making due to the uncertainty of model parameters.

In this study, we evaluated the planning of a DIL boost only for patients with a single DIL. Boosting two anatomically distinct

<table>
<thead>
<tr>
<th>Prostate-DIL</th>
<th>D90(%)</th>
<th>V100(%)</th>
<th>V110(%)</th>
<th>D90(%)</th>
<th>D95(%)</th>
<th>V100(%)</th>
<th>V125(%)</th>
<th>V150(%)</th>
<th>V175(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>100.7±0.1</td>
<td>98.2±0.4</td>
<td>0</td>
<td>101.3±0.7</td>
<td>101.1±0.7</td>
<td>98.6±6.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SIB</td>
<td>100.4±0.1</td>
<td>98.0±0.1</td>
<td>20.4±8.5</td>
<td>155.2±24.6</td>
<td>147.3±25.2</td>
<td>99.9±0.3</td>
<td>93.0±17.2</td>
<td>81.8±28.5</td>
<td>64.0±33.9</td>
</tr>
<tr>
<td>P-values</td>
<td>&lt;0.001</td>
<td>0.023</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.203</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Prostate-DIL, Prostate with DIL cropped.

Figure 4. Percentage of patients receiving different dominant intraprostatic lesion dose coverage (125%, 150% and 175% prescription dose covering >95%, 90–95%, 80–90%, or 0–80% of DIL volume) in simultaneous integrated boost plan.
Multiparametric MRI-guided Dose Boost in Prostate Proton Therapy

DIL sites can be technically challenging for photon EBRT. Proton-based therapy could outperform photon-based plans by reducing the degree of overlap between the two lesions. The planning of delivering focal boosts to more than a single DIL is worth further examination. A comprehensive evaluation with a larger population of patients representing diverse pathological abnormalities would aid in revealing any potential limitations of the current SIB planning method and also proposing novel treatment techniques for future study.

**CONCLUSIONS**

We investigated the planning of mp-MRI-defined DIL dose escalation in proton radiation therapy, and reported the potential clinical impact of this technique using TCP and NTCP estimation. Overall, while respecting all OAR constraints, SIB plans were able to achieve 125, 150, and 175% of prescription dose coverage in 74, 54, and 17% of 36 patients, respectively. This was modeled to result in an increase in DIL TCP by 7.3–13.3% depending on α/β and DIL risk level. This retrospective study suggested the use of IMPT-based DIL SIB may represent a strategy to improve tumor control.

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