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Research Article

Evaluation of the utility of rescans in the treatment of prostate and pelvic nodes with pencil beam scanning protons

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ABSTRACT

To determine the necessity of the first week CT simulation rescan of pencil beam scanning (PBS) prostate patients requiring treatment to the pelvic lymph nodes. Patients were treated on a prospective registry trial sponsored by the Proton Collaborative Group (PCG—NCT01255748). A total of 42 patients with high-risk prostate cancer requiring treatment to the pelvic lymph nodes were evaluated in a single calendar year. The cohort consisted of a mix of intact prostate and postprostatectomy patients. Most of the patients were treated with a simultaneous integrated boost (SIB) approach for the majority of the plan. The radiation prescriptions varied depending on whether the patient had an intact prostate or prostate bed. The plan geometry consisted of two lateral beams and a single field optimization (SFO) dosimetric matching technique using pencil beam scanning proton therapy. An in-house protocol was established wherein all high-risk prostate patients had at least 1 rescan evaluation performed during the first 5 ± 2 fractions, which was used to determine whether the nominal approved plan was robust to daily setup uncertainties and anatomical variations. If the evaluation failed clinical analysis, an adaptive replan was created. If 5% or more of the evaluated rescans resulted in a qualified adaptive plan, the planning technique would be considered insufficient. Of the 42 patients investigated, five (11.9%) required an adaptive plan. As it turned out, all five of these patients would have been rescanned within the first 5 fractions of treatment, independent of the established rescan protocol, due to a physician, dosimetrist, or therapist requesting a rescan to investigate specific areas of concern regarding setup or anatomic changes. Of the 5 adaptive plans, only one (2.4%) meets the criteria of a qualified adaptive plan. Our findings substantiated that this policy of a planned rescan with the 5th fraction was no longer necessary, the dosimetric technique had proven to be robust, and moving forward we will only perform these rescans if there is a significant issue with daily setups or observed changes in anatomy.

Introduction

For patients with higher risk localized prostate cancer, treatment with a combination of androgen deprivation therapy and external beam radiation therapy is frequently utilized. The treatment fields for radiation therapy will include the prostate, periprostatic tissues, and seminal vesicles. Treatment of the pelvic nodes has been evaluated in multiple studies, with improvement seen in biochemical disease-free survival and progression-free survival, but no clear evidence of improvement in overall survival.[1,2,3] Newer techniques of imaging such as PSMA PET scans, and newer prognostic testing such as genomic scoring of the primary tumor, may help to predict which patients would most benefit from treatment of the nodal volumes.[4]

The primary reason to avoid treatment of the pelvic nodes is because of the higher risk of side effects with larger treatment volumes.[5] One way to reduce the volume of normal tissue treated is through the use of proton beam therapy, especially with pencil beam scanning techniques.[6] However, proton beam therapy requires greater precision of daily treatment positioning and setup. Small differences in setup will cause greater uncertainties with proton beam therapy compared to IMRT. Treatment of the pelvic nodal volumes in addition to the prostate/seminal vesicles and/or prostate adds even more uncertainty, since two different methods for localization and reproducibility may be used: fiducial markers and rectal immobilization (rectal balloon or hydrogel spacer) for the prostate, but boney anatomy for the pelvic nodes.[7,8]

To evaluate the consistency and reproducibility of our setup, we initiated a procedure of a planned repeat CT simulation on the day

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Table 1
Summary of target structures and expansions.

High risk with pelvic nodes	
CTV_Nodal	Regional lymph nodes
PTV_Nodal	CTV_Nodal + 7mm
CTV boost	Prostate and SV -or- Prostate fossa + postbladder wall
PTV boost	Prostate: CTV boost + 3 mm post, 4 mm elsewhere -or- Prostate fossa: CTV boost + 3mm L/R, 5mm elsewhere
PTV_Eval	PTV boost + 5 mm L/R
PBS_Eval	PTV_Eval + 3 mm L/R
CTV	CTV(boost) + CTV_Nodal
PTV	PTV_Eval + PTV_Nodal

of the 5th treatment for patients with prostate/prostate bed plus pelvic nodal treatment. The original isodose planned was then re-calculated on the new scan to determine if coverage was sufficient. If coverage was insufficient, an adaptive plan was performed on the second scan. This is an analysis of the initial cohort of patients to determine if the initial treatment plans were clinically robust.

Methods and Materials

The study group consists of patients with high-risk prostate cancer requiring treatment to the pelvic lymph nodes, who received proton beam therapy (PBT) to the prostate (or prostate bed) plus pelvic nodes. These were consecutive patients treated at a single institution who underwent their initial simulation during a single calendar year. Patients were treated on a prospective registry trial sponsored by the Proton Collaborative Group (PCG—NCT01255748). A total of 42 patients were included in the study: 29 patients had intact prostates, and the remaining 13 were treated to the prostate bed in addition to the lymph nodes. Of these 42 patients, all but 7 were treated with a simultaneous integrated boost (SIB) approach for the majority of the plan. The radiation prescriptions varied depending on whether the patient had an intact prostate or prostate bed. Patients treated to the intact prostate had placement of 3 interstitial gold fiducials and a hydrogel rectal spacer prior to any planning or treatment. Patients treated following prostatectomy had two interstitial gold fiducials markers placed into the soft tissues lateral to the urethral anastomosis, one on the right side and one on the left, prior to planning, and a rectal balloon filled with 90 to 100 cc of saline during planning and treatment. The intact prostate patients received 70 Gy_{RBE} to the prostate at 2.5 Gy_{RBE} per fraction with the lymph node target simultaneously being treated at 1.8 Gy_{RBE} per fraction for a total of 28 fractions. The prostate bed patients received 56 Gy_{RBE} to the prostate bed at 2 Gy_{RBE} per fraction while treating the lymph node target simultaneously at 1.8 Gy_{RBE} per fraction for a total of 28 fractions. In addition, these patients received a boost to the prostate bed alone for an additional 10 Gy_{RBE}, at 2 Gy_{RBE} per fraction, bringing the total prescription dose to the prostate bed to 66 Gy_{RBE} in 33 fractions. The patients treated with a pure sequential approach received either 45 Gy_{RBE} or 50.4 Gy_{RBE} to the lymph node targets and prostate, followed by a boost to 54 Gy_{RBE} to the prostate and seminal vesicles (SVs), followed additionally by a boost to the prostate alone to a total dose of 79.2 Gy_{RBE} in 44 fractions of 1.8 Gy_{RBE} per fraction.

The physician drawn clinical target volume (CTV) included the prostate or prostate bed, seminal vesicles, and pelvic lymph nodes. Planning target volume (PTV) expansions for intact prostate CTVs were 4 mm in the left, right, superior, inferior, and anterior directions. The posterior expansion was 3 mm. The postoperative prostate bed patients' CTVs included the prostate fossa and posterior bladder wall and the PTV expansions on the CTV were 3 mm left/right and 5 mm in all other directions. PTV expansions around the pelvic lymph nodes were 7 mm in all directions. Reference Table 1 for all target structures and their respective expansions.

The plan geometry consisted of two lateral beams and a single field optimization (SFO) dosimetric matching technique. The prostate and common iliac pelvic nodes, were treated by both fields, whereas the left and right-sided internal and external iliac pelvic nodes were treated by their corresponding lateral beam only. In order to achieve the dosimetric matching this technique required, the targets were broken down into a series of optimization structures pictured in Fig. 1. A structure called Opti_Thru consisted of the regions treated with both fields. It was created by expanding the PTV, 1 cm in the left and right directions, as described in Table 1.

Additional optimization structures were derived from Opti_Thru. Opti_Match_Rt and Opti_Match_Lt encompass the right and left portions of the nodal target, respectively, that were treated by one field only. These structures were created using the expression PTV_50.4 minus (Opti_Thru+1.5cm), which separated the nodal chain parts between the patient's right and left sides only. Treating each side of the nodal volume with one field allowed for sparing of the bladder, rectum, sigmoid, and bowel by not treating through to the opposing side of the nodal chain.

Optimization structures were also created for the bladder, rectum, and sigmoid. These were created by subtracting the organ at risk (OAR) from the PTV_50.4 (*e.g.*, Opti_Bladder = Bladder-PTV_50.4).

In cases where the prescription dictated a simultaneous integrated boost (SIB), additional structures were required as seen in Fig. 2. The Opti_Falloff ring structure, centered around the prostate or prostate bed PTV was used to confine the high-dose volume. Opti_MaxCtrl limited the overall dose maximum. To create this structure, the dosimetrist would add a variable margin to the highest-dose PTV. The margin would expand 1.5cm in the anterior, posterior, superior, and inferior directions, and 2.5cm in the left and right directions. This expanded target would then be subtracted from the patient structure to create Opti_MaxCtrl.

Optimization parameters were created such that each beam delivered uniform dose (*i.e.*, SFO optimization) to the Opti_Thru structure, while simultaneously the entire prescription was delivered to the respective nodal volumes. In addition to the uniform dose objectives, multifield objectives were used to optimize target coverage and uniformity to the composite target structure as seen in Fig. 3. Finally, the OAR optimization structures were included to limit the maximum OAR dose to 95% of the prescription. Patient-specific considerations and physician directives were incorporated into each individual plan.

All plans utilized pencil beam scanning (PBS) and were optimized and calculated with a Monte Carlo algorithm. See Fig. 4 for the nominal dose objectives for OARs.

All plans were prospectively evaluated for robustness against positional and range uncertainty. The evaluation was done by moving the isocenter 3 mm in all cardinal directions and all combinations thereof to create robustness scenarios. The robustness scenarios simulated potential daily positioning uncertainty. Additionally, each individual scenario was calculated with the clinical CT calibration curve, as well as with the calibration curve shifted by ±3.5%. Shifting the CT calibration curve simulated potential range error. In total, 24 robustness scenarios were evaluated for target coverage for each plan. A plan was considered robust if CTV V95% > 95% for the prostate/prostate bed and lymph node CTVs, individually. OAR doses were evaluated for scenarios that contained simulated range error only, because positional uncertainty was considered random.

Prostate location with respect to bony anatomy was one variable that impacted this study. The prostate location was reliant on factors such as bladder fill, rectal fill, and patient hydration. It was likely that when aligning to the prostate via orthogonal kV x-rays during treatment, the anatomy in the beam path would be slightly different than what was seen on the planning CT. An evaluation was done to ensure that target coverage was maintained in the presence of these anatomical variations, given that daily IGRT tolerances are respected. To this end, copies of the prostate-specific CTV were created and shifted 3 mm in the patient right and left directions, 5 mm in the anterior and posterior directions, and 5 mm in the superior and inferior directions. The magnitude of the shifts in the anterior/posterior, and superior/inferior directions was based on daily IGRT tolerances. The 3 mm shift in the right/left (R/L) direction was based on clinical experience and an effort to keep femoral head dose as low as reasonably achievable. Modified plans were then created in which the isocenter was shifted to match the shifted CTV copies. This simulated the treatment being delivered in the presence of a prostate offset. It should be noted that the nodal CTV was not shifted, as this volume correlated with bony anatomy, rather than prostate position. Coverage of the shifted prostate CTV and the nominal nodal CTV was then evaluated. A plan was considered robust if each CTV V95% > 99.9%.

When the clinic began treating HR prostates with PBS, it was unclear whether the planning technique described above would be clinically robust, day to day. A protocol was put in place in which all HR prostate patients would receive an early-treatment rescan to verify the plan's efficacy and determine if there are any unforeseen factors that may affect treatment delivery. The protocol specified that this rescan would take place on the day of the fifth fraction ±2 days. Once patients received this rescan, the new scan was registered to the treatment planning CT (TPCT) according to daily imaging guidelines: implanted fiducials must be within their designated contours and bony anatomy must align to within 5 mm, as per daily IGRT tolerances. A QA plan was then created by recalculating the clinical plan on the new scan using a Monte Carlo calculation algorithm. CTV coverage was evaluated to determine whether the planning objectives continued to be fulfilled or if the plan needed to be adapted. To be considered clinically efficacious, 95% of the prescription dose must cover 99.9% or more of the prostate and lymph node CTVs individually. Dose to OARs may be considered; however, due to the random nature of daily OAR dose, this is rarely a disqualifying metric. If the target coverage criterion was not met, the plan was adapted, with physician approval.

All adapted plans were investigated for root cause. The aim of this study is to investigate the reliability of the planning technique under normal clinical conditions and, as such, plans that were adapted due to gross anatomic changes (*e.g.*, weight gain, swelling due to surgery, prosthetic implants, etc.) or other external factors were not considered to be indicative of planning efficacy. Rescans that showed degraded target coverage in the presence of a clinically acceptable fusion and no major anatomical deviations may indicate a need to revise our planning strategy. These cases are labeled "qualified adaptive plans." It was determined that the planning technique would not be considered robust if 5% or more of the patient population had qualified adaptive plans.

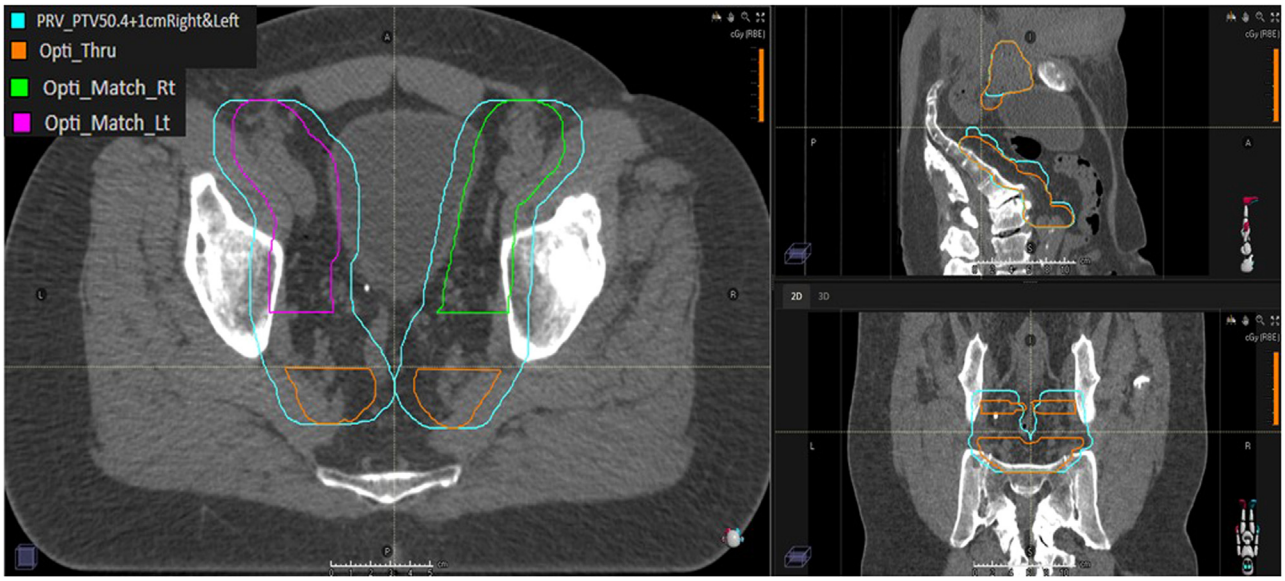

Fig. 1. Optimization target structures.

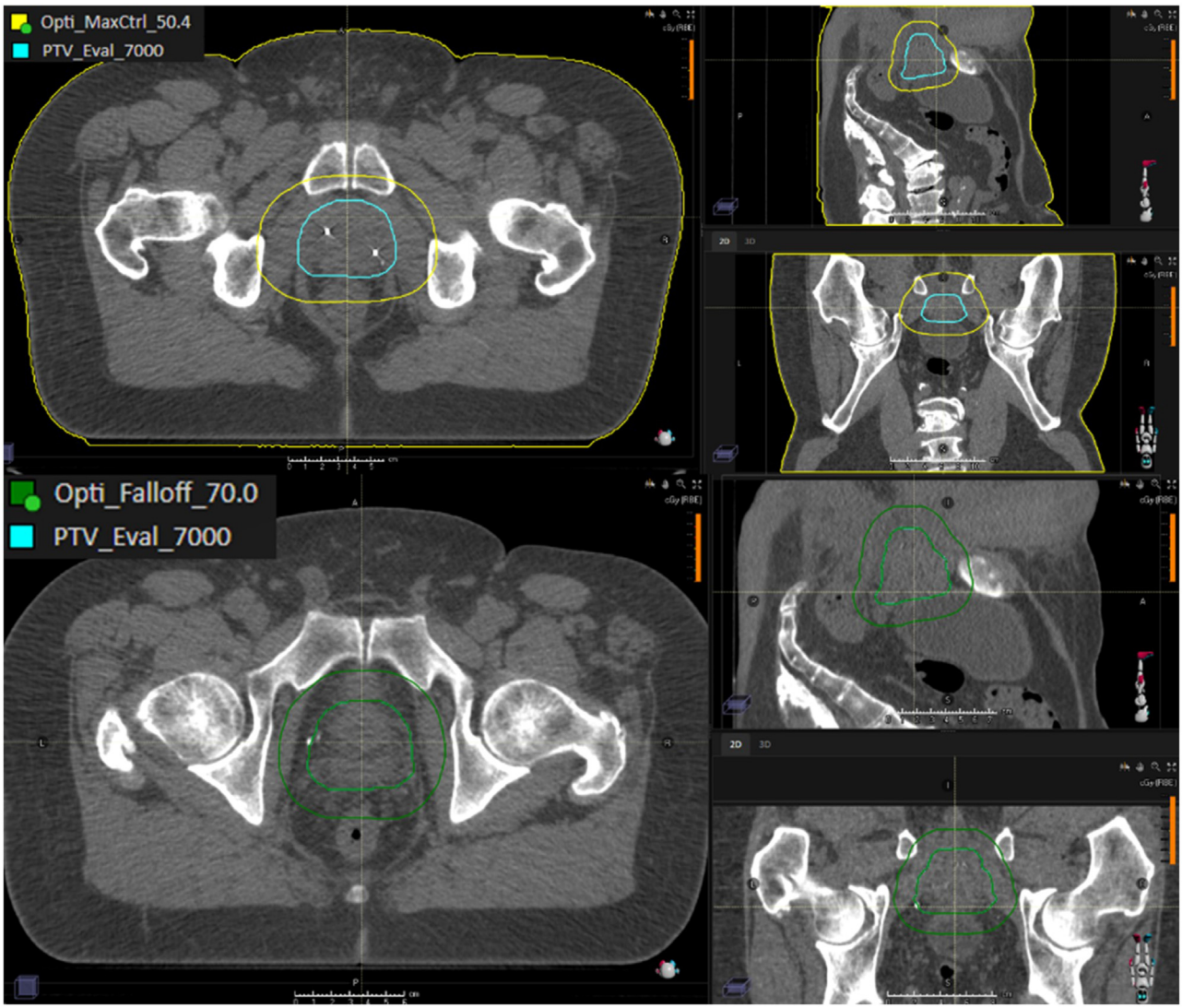

Fig. 2. Optimization structures for simultaneous integrated boost.

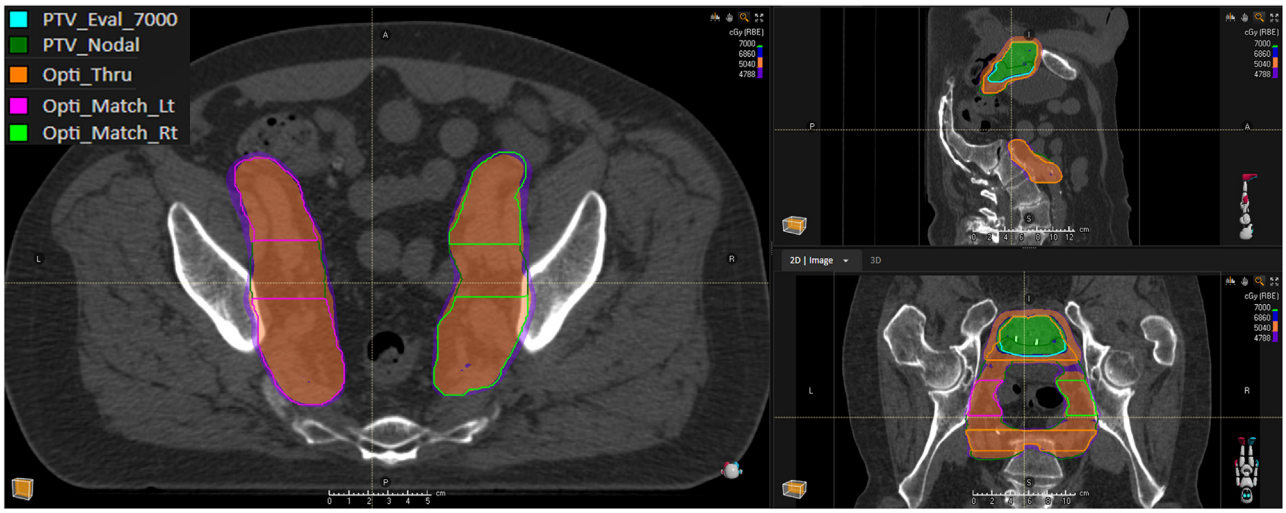

Fig. 3. Prescription dose coverage to composite target structure.

Checklist: PrHNH28 - Prostate HR- with Pelvic Nodes SIB Hypofx (28 fx)

Structure	Parameter	Equality	Objective	Minor Deviation	Major Deviation	Comments
PTV_Eval	V98					
PTV_Eval	D95					
PTV	V95					Nodes
PTV	D95					Nodes
Bladder	V72	<	1 cc			
Bladder	V71	<	8 cc	< 12 cc	> 12 cc	
Bladder	V62	<	10%			
Bladder	V44	<	30%			
Bladder	V35	<	35%			
Bladder	V31	<	50%			
Femur_Head_L	V39	<	5%	< 10%	> 10%	
Femur_Head_L	V35	<	35%			
Femur_Head_R	V39	<	5%	< 10%	> 10%	
Femur_Head_R	V35	<	35%			
IliacCrest	V50	<	5%			
IliacCrest	V40	<	35%			
IliacCrest	V30	<	50%			
PenileBulb	Mean	<	46.4 GyRBE			
Rectum	V72	<	1 cc			
Rectum	V62					
Rectum	V44					
Rectum_Eval	V62	<	10%	< 20%	> 20%	
Rectum_Eval	V44	<	35%	< 40%	> 40%	
Sigmoid	D0.03cc	<	57 GyRBE			
Spc_Bowel	V60	<	1 cc		> 1 cc	
Spc_Bowel	V45	<	195 cc	> 195 cc		

Fig. 4. Summary of organs at risk (OAR) dose objectives.

Results

Of the 42 patients investigated, five (11.9%) required an adaptive plan. They are identified in Table 2 as Patients 1 to 5. Patients 1, 2, 4, and 5 had daily set up issues due to unreproducible rectum and bladder fill. A clinically acceptable fusion and dose distribution was achieved for Patient 1; however, the plan was adapted because daily setup time was prohibitively long. Patient 2 had a discrepancy in rectal fill that prevented a clinically acceptable fusion. In this case, the discrepancy in rectal fill deformed the prostate to the point that it was not possible to align the implanted fiducial markers with their designated contours. The best fusion possible was used to create a QA plan, which failed. The rectal fill seen on Patient 4 in the simulation was not reproducible for daily setup. The relatively empty rectum at the time of treatment allowed the prostate fossa target to shift out of the field, which resulted in a failing QA plan, though the fusion was acceptable. Patient 5 had daily

Table 2
Fusion and QA plan summary of replanned patients.

Patient	Fusion status	QA plan status	CTV V95%	
1	Pass	Pass	Nodal	100.0%
			Prostate	99.8%
2	Fail	Fail	Nodal	98.2%
			Prostate	79.2%
3	Pass	Fail	Nodal	94.0%
			Prostate	96.7%
4	Pass	Fail	Nodal	99.4%
			Prostate	82.5%
5	Fail	Pass	Nodal	99.9%
			Prostate	100.0%

setup issues due to an overly full bladder at the time the treatment planning CT was acquired, which was not reproducible. A clinically acceptable fusion was not possible due to a large pitch being required to align the fiducial markers, though the QA plan did pass. Patient 3 was replanned due to weight gain (7.3%). This weight gain resulted in a path-length change within the fields, which caused both the prostate CTV and the nodal CTV to be undercovered. An acceptable fusion was achieved, but the QA plan analysis failed.

All five of these patients would have been rescanned within the first five fractions of treatment, as noted above; however, a physician or dosimetrist requested a rescan to investigate specific areas of concern for patients 2, 3, and 4. A physician requested a rescan for Patient 2 to check anatomy for reproducibility, which wound up being the reason for the adaptive plan. A dosimetrist requested an early-treatment rescan for Patient 3 at the time of CT sim to check bladder fill. Had the dosimetrist not requested a rescan at the time of CT sim, this patient would have been rescanned on or before the fifth fraction, per the rescan protocol. A first-fraction rescan for Patient 4 was requested by a physician in order to have a scan with contrast in the urethra. This scan passed clinical evaluation. Therapy had daily setup problems with the rectal balloon within the first few fractions, so the patient had a second rescan, in keeping with the five fraction rescan protocol. This second scan was determined to be representative of the internal anatomy at the time of treatment and failed clinical analysis, which initiated the replan. Therapy requested rescans for Patients 1 and 5 due to daily setup issues within the first few fractions.

Analysis of the rescans shows that only Patient 4 had a qualified adaptive plan. Patient 1 had a clinically acceptable rescan and QA plan, but was replanned due to scheduling issues. Patients 2 and 5 had anatomy in their TPCTs that was not reproducible to the point that a clinically acceptable fusion was not possible. Similarly, Patient 3 was replanned due to an anatomic change that cannot be accounted for in planning. Patient 4's replan is considered a qualified adaptive because there were no gross anatomic deviations and the rescan fusion was clinically acceptable.

Discussion

For radiation therapy treatment of the prostate ± seminal vesicles, the adjacent organs at risk include the bladder, rectum, sigmoid colon, and small bowel. The variability of bowel and bladder is the most significant factor in inter- and intrafraction changes in anatomy.[9] There are multiple ways to reduce this variability and improve reproducibility. One method is the use of implanted fiducial markers, which improves the accuracy of daily setup.[10,11] Treatment using a full bladder may improve the doses to organs at risk—both by moving more of the bladder away from the treatment volumes, and by simultaneously moving other organs (such as small bowel and sigmoid colon) away from the treatment volume. It is difficult to achieve an identical bladder fill at the time of treatment—and when more than one field is treated, there can be differential fill between the initial field and subsequent fields.[12] In addition, it may be difficult for patients with prostate issues to maintain a full bladder throughout setup and treatment—many of these patients have significant urinary symptoms at baseline. For rectal fill, the use of a rectal balloon may provide stability and a more consistent rectal volume.[13] In patients with an intact prostate, this may also compress the anterior wall of the rectum into the posterior aspect of the prostate, potentially increasing the rectal dose. Instead, the use of a hydrogel rectal spacer has been shown to provide significant spacing between the rectum and prostate, reducing the high dose volume in the rectum.[14] This has been shown to be a clinical benefit in reducing the risk of rectal toxicity from radiation therapy.

The pelvic nodes at risk are primarily in the iliac chain, more commonly internal and common iliac, but potentially external iliac as well. These nodal chains are retroperitoneal, and follow the course of the iliac arteries and veins. These are relatively stable in position, and correlate fairly well with boney anatomy. Changes in bladder or bowel fill can have an impact on the doses to organs at risk when treating the pelvic nodes. With a full bladder, the small bowel may be pushed superiorly and laterally, potentially closer to the pelvic nodes. Differences in bowel fill or bowel gas can also impact the position of the bowel, and thus the dose, as well.

The complexity in these patients is that the two volumes (prostate / prostate bed and pelvic nodes) will have separate factors which impact daily alignment. It may be possible to precisely align the prostate using fiducial markers, but to have significant misalignment of the pelvic lymph nodes.

Conclusions

The goal of this study was to determine if initial planning scans are sufficient to use for planning in these complex situations, and to identify patients in which additional scans would be necessary. All of the patients received a second CT scan at or near the 5th fraction of treatment. Out of the 42 patients, in only 5 was there a significant enough change to warrant an adaptive plan. However, all 5 of those patients also had issues with daily setup during the first five fractions. These patients would have been identified as requiring a rescan anyway. Thus, a policy of mandating a rescan after the first week of treatment did not identify any additional patients for whom an adaptive plan would be useful. For that reason, we stopped this policy of a planned rescan with the 5th fraction, and will only perform these rescans if there is a significant issue with daily setups.

These findings validate the center's technique for high-risk prostate and prostate bed patients using fiducials, rectal balloon or spacer, bladder fill, differential expansions, and tolerances.

Conflicts of Interest

The authors declare no conflicts of interest.

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