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SHORT COMMUNICATION

Multiparametric prostate MRI-based intensity-modulated radiation therapy guided by prostatic calcifications

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Objectives: The optimal technique to administer image-guided radiation therapy for prostate cancer remains poorly defined. This study assessed outcomes after multiparametric prostate MRI-based planning was delivered with image-guided radiation therapy using prostatic calculi observed on cone beam CT (CBCT).

Methods: Between January 2015 and December 2017, 94 consecutive patients were treated with CBCT-based image-guided radiation therapy (IGRT) without fiducial markers. MRI was routinely incorporated for target delineation and intraprostatic tumor nodules were boosted to allow reduced doses to normal appearing prostate. The primary endpoint was the prevalence of prostatic calcifications while toxicity and biochemical control were secondary endpoints.

Results: Median follow-up was 39.7 months with 82% NCCN intermediate to very high risk. Intraprostatic calculi were noted in 68% of patients. The 3-year biochemical control, late grade ≥ 2 rectal toxicity and late grade ≥ 2 urinary toxicity rates were 96%, 3 and 7%, respectively. Biochemical control and toxicity were not significantly impacted by the presence of prostatic calculi.

Conclusion: Prostatic calcifications can serve as natural fiducial markers to allow for non-invasive IGRT for prostate cancer with promising early disease control and toxicity outcomes.

Advances in knowledge: Prostate calcification-guided IGRT is technically feasible.

INTRODUCTION

Prostate radiotherapy is a non-invasive treatment modality that has been shown to be comparable to radical prostatectomy for prostate cancer in terms of metastasis-free survival, prostate cancer-specific survival and overall survival.¹ While radical robotic prostatectomy is a standard option for patients with clinically localized prostate cancer, some men select radiotherapy as an evidence-based approach that holds promise to reduce the risk of treatment-related urinary and sexual disability.²

In the spirit of promoting high value care for prostate cancer patients, all components of care should be critically evaluated. Transrectal ultrasound-guided fiducial markers have been utilized to guide high precision prostate radiotherapy since the 1990s and resulted in more precise target localization compared to using bony landmarks alone.³ Fiducial marker-based image-guided radiation therapy (IGRT) reduced the risk of late gastrointestinal and genitourinary toxicity while facilitating radiation dose escalation for prostate cancer.^{4,5}

Cone beam CT (CBCT) is an accurate and precise tool for IGRT that is considered equivalent to fiducial marker placement for patient setup correction in prostate patients.⁶ An adaptive CBCT-based IGRT strategy without fiducial markers improved biochemical control in patients with rectal distension on CT simulation and was associated with decreased grade ≥ 2 rectal toxicity compared to IMRT without image guidance.^{7,8} Some authors now argue that implanted fiducial markers are no longer needed for prostate radiotherapy.⁹ Safely eliminating fiducial marker placement would obviate the risks of transient pain, bleeding, inflammation and a symptomatic infection rate of up to 7.7%.¹⁰

More recently, prostate calcifications have been proposed as natural fiducial markers to reduce interobserver variability in interpreting CBCT scans.¹¹ Prostatic calcifications are present in 89% of radical prostatectomy specimens and are associated with increasing age.¹² On CT, 35% of prostate cancer patients had clearly defined calcifications measuring

>2 mm in each direction while 79% of patients had visible intra-prostatic calcifications ranging in size from 0.5 to 15 mm.^{13,14} We hypothesized that prostatic calcifications are frequently present and can facilitate highly accurate and effective CBCT-based IGRT for prostate cancer without requiring implanted fiducial markers.

METHODS AND MATERIALS

Patients

This retrospective study was approved by the Institutional Review Board. Between January 2015 to December 2017, consecutive patients with clinical T1-3N0-1M0 that underwent curative intent radiotherapy were included in this study. Data elements captured are summarized in the [Supplementary Material 1](#).

Imaging prostatic calculi

Planning CT scans (GE Medical Systems) were acquired at 2.5 mm and were exported to Eclipse (Varian Medical Systems). Prostatic calculi with a minimum Hounsfield unit of 130 were identified on planning CT scans and the prevalence of calcifications was the primary endpoint. These calculi were confirmed to be visible on CBCT using Aria Off-line Review (Varian Medical Systems).

Calcifications were classified as peripheral lobe, anterior/central or periprostatic. Periprostatic calcifications were included if located within the prostate planning target volume. For each patient, the size of the largest calcification in greatest dimension and the maximum Hounsfield units were measured using Eclipse. Daily vector shifts from CT simulation to each cone beam CT in the anteroposterior (AP), superior-inferior (SI) and left-right (LR) axes. When available, vector rotations for yaw, pitch and roll were also recorded.

Treatment

Contemporary treatment techniques employed were previously described.⁸ Briefly, prostate radiotherapy was performed on a Varian True Beam linear accelerator equipped with kilovoltage CBCT with instructions to maintain an empty rectum and a comfortably full bladder. Automatic image registration was performed at the treatment console by setting the prostate as the region of interest with manual adjustment informed by prostatic calculi. The radiation oncologist reviewed the registration with feedback given to the treating therapists. Daily CBCT was performed during the first five treatments to personalize imaging frequency. If the average shifts were <5 mm, the frequency of CBCT was reduced to twice per week thereafter.⁷ A 6 degree of freedom robotic couch was installed in October 2016. Planning directives were previously described and were scaled accordingly when hypofractionation was prescribed.⁸ When available, multiparametric prostate MRI were fused to the CT simulations using Eclipse using a volume of interest limited to the prostate and anterior rectal interface to assist with accurate target delineation. The mean radiation dose was 78 Gy (range 60 to 81 Gy). Intensity-modulated radiation planning, typically with seven static fields, was performed on Eclipse (Varian) using a simultaneous-integrated boost plan. Additional treatment information is summarized in the [Supplementary Material 1](#).

Androgen ablation was recommended for patients with NCCN high-intermediate, high and very high risk prostate cancer. The high intermediate-risk group was prescribed 6 months of androgen ablation. Patients with high and very high risk prostate cancer were prescribed 18 to 36 months of androgen deprivation

Follow-up and toxicity assessment

Patients were evaluated weekly during radiotherapy and acute toxicity was recorded. Following completion of treatment, patients underwent clinical evaluations and prostate-specific testing every 3 to 6 months for the first 2 years and every 6 to 12 months thereafter. Acute and late side effects were graded using the Common Toxicity Criteria for Adverse Events v5.0. Further information on clinical endpoints is summarized in the [Supplementary Material 1](#). Data were analyzed in Stata 13.1 (StataCorp, College Station, TX, USA). The log-rank test was performed to assess differences in actuarial survival and late toxicity risk. Differences in acute toxicity with or without calcifications were analyzed using a chi-squared test. Differences in translations or rotations with or without calcifications were analyzed using a 2-sided t-test with unequal variances. Statistical significance was defined as $p < 0.05$.

RESULTS

Patient characteristics

Patient characteristics are summarized in [Table 1](#). A total of 94 patients were analyzed with a median follow-up of 39.7 months (interquartile range 30.2 to 46.2 months). The patient population included 49% non-white race, 13% NCCN very high risk, 15% Gleason 9, 9% T3, 6% node positive, 10% PSA >20 ng ml⁻¹ and 20% with ≥50% biopsy cores positive. The median pre-treatment IPSS score was 7 (interquartile range 3 to 13) and the median pre-treatment SHIM is 16 (interquartile range 5 to 23).

Intraprostatic and periprostatic calculi on CT

Characteristics of prostatic calcifications are summarized in [Table 2](#). The median prostate volume was 44.8 cc (range 13.7 to 233.7 cc) including 39% with a prostate volume ≥50 cc. The overall incidence of patients with intraprostatic or periprostatic calculi on CT simulation was 81%. The median number of calculi within a patient was 3 (range 1 to 8). The location of calculi was peripheral for 29%, central for 30% and periprostatic in 41%. Additionally, 41% of patients had calculi within the boost volume. Taken together, 68% of patients had one or more calcifications within the prostate. The median calcification size was 6 mm (range 2 to 26 mm) and the median Hounsfield unit was 454 (range 132 to 1451). Representative imaging of prostatic calculi on CT simulation and CBCT are shown in [Figure 1](#).

Mean vector translations in the AP, SI and LR were 2.7 mm (interquartile range 2.0 to 3.1 mm), 3.4 mm (interquartile range 2.6 to 4.0 mm) and 2.0 mm (interquartile range 1.4 to 2.5 mm), respectively. Mean vector rotations for yaw, pitch and roll were 0.3° (interquartile range 0.0 to 0.5°), 1.3° (interquartile range 0.6 to 2.4°) and 0.7° (interquartile range 0.5 to 0.9°), respectively. Intraprostatic calcifications were associated with smaller left-right translations (1.8 mm vs 2.4 mm, $p < 0.01$). There were no significant differences in the other 5 degrees of freedom ([Table 3](#)).

Table 1. Patient and Treatment Characteristics

Characteristic	Value (N = 94)	Percentage
Age		
Mean (SD), y	68 (8)	
Median (range), y	68 (50–88)	
Race		
White	48	51
Non-White	46	49
NCCN Prognostic Group		
Low	17	18
Favorable Intermediate	19	20
Unfavorable Intermediate	27	29
High	13	14
Very High	12	13
Node Positive	6	6
Gleason Score		
6	25	27
7 (3 + 4)	26	28
7 (4 + 3)	17	18
8	12	13
9	14	15
Clinical Stage		
T1b-T1c	47	50
T2a	18	19
T2b-c	21	22
T3a-b	8	9
Initial prostate-specific antigen level		
Mean (SD), ng/ml	13.8 (22.0)	
Median (range), ng/ml	7.8 (1.2–178.0)	
Percent positive cores		
Mean (SD), %	38 (27)	
Median (range), %	33 (7–100)	
Radiation dose		
Mean (SD), Gy	78 (6)	
Median (range), Gy	81 (60–81)	
Fractionation scheme		
Standard (1.8 to 2 Gy fractions)	85	90
Moderate hypofractionation (3 to 3.1 Gy fractions)	9	10
MRI-guided boost		
Yes	77	82
No tumor on MRI	9	10
MRI not available	7	7
Entire prostate involved	1	1

(Continued)

Table 1. (Continued)

Characteristic	Value (N = 94)	Percentage
Pelvic radiation		
Elective (45 Gy)	9	10
Positive node (50.4 to 59.4 Gy)	6	6
None	79	84
Androgen deprivation		
Short course (less than 12 months)	47	50
Long course (≥ 12 months)	27	31
None	18	19

Treatment and survival outcomes

Treatment characteristics are summarized in Table 1 and a representative radiation dose distribution is shown in Figure 1a. The most common radiation dose schedules were 81 Gy for 55%, 79.2 Gy for 15%, 80 Gy for 13% and 62 Gy for 6%. MRI-based planning was performed in 90% of patients and the median boost to the dominant prostatic nodule was 3.6 Gy (range 1.8 to 4 Gy). Hypofractionated radiation was used in 10% and pelvic radiotherapy was used in 16%. Overall, 50% received androgen deprivation therapy. Although 33% of patients had NCCN high risk, very high risk or node positive disease, only 19% received ≥ 12 months of androgen ablation due to non-compliance.

The 3-year biochemical control rate was 96% (95% CI, 88–99%) Figure 2. The 3-year biochemical control was similar with or

without calculi (98% vs 92%, $p = 0.18$) Figure 2. The 3-year overall survival was 97% (95% CI, 90–99%) Figure 2.

Adverse events

Acute grade 2 genitourinary toxicity occurred in 54% of patients primarily consisting of obstructive or irritative urinary symptoms primarily treated with α blockers and less commonly phenazopyridine, oxybutynin or ibuprofen. Acute grade 2 gastrointestinal toxicity occurred in 12% of patients that was most commonly diarrhea requiring loperamide and infrequently rectal irritation requiring topical steroids and gas pain requiring simethicone.

The median post-treatment IPSS score was 5 (interquartile range 3 to 13) and the median post-treatment SHIM was 10 (interquartile range 2 to 19). The rate of late grade 2 rectal toxicity was 3% (95% CI, 1–11%) Figure 2. The 3-year rate of late grade 2 bladder toxicity was 7% (95% CI, 3–15%) Figure 2. The seven cases of late grade 2 genitourinary toxicity consisted of one case of gross hematuria and six patients requiring medication for urinary symptoms. There were no cases of acute or late grades 3 to 5 toxicity. There was no correlation between prostatic calculi and acute or late grade 2 rectal or bladder toxicity ($p > 0.5$ for all).

DISCUSSION

IGRT remains a remarkably well-tolerated, effective and versatile non-invasive treatment for localized or locoregional prostate cancer.⁸ Despite decades of research, the optimal technique to deliver IGRT for prostate cancer remains poorly defined and current NCCN guidelines allow for a variety of dose schedules and methods of image guidance. While daily CBCT for prostate cancer has been assessed in multiple randomized trials, fiducial markers were adopted without randomization.¹⁵ Prostate IGRT would become an even more convenient, comfortable and cost-effective treatment option if fiducial marker placement can be safely eliminated and by reducing number of visits through hypofractionation.^{8,16}

In the current study, the dose distributions and late toxicity rates compare favorably to the control arm of the recently published SpaceOAR System Pivotal Study.^{8,17} Specific strategies to safely improve dose distributions include routine use of multiparametric MRI, strict dosimetric limits on organs at risk and boosting intraprostatic nodules to allow for selectively

Table 2. Characteristics of intraprostatic and periprostatic calcifications

Characteristic	Value (N = 94)	Percentage
Number		
0	18	19
1	15	16
2	16	17
3	17	18
4	14	15
5 to 8	14	15
Location (N = 234)		
Peripheral	65	29
Central/Anterior	67	30
Periprostatic	92	41
Greatest diameter		
Mean (SD), mm	7 (4)	
Median (range), mm	6 (2–26)	
Hounsfield units		
Mean (SD)	603 (382)	
Median (range)	454 (132–1451)	

Table 3. Mean Vector Shifts or Rotations by Presence of Intraprostatic Calcifications

Mean Vector Shift or Rotation by Degree of Freedom	Intraprostatic Calcifications (Interquartile Range)	No Intraprostatic Calcifications (Interquartile Range)	P value
Anterior Posterior (mm)	2.8 mm (2.0 to 3.2 mm)	2.5 mm (1.8 to 2.8 mm)	0.25
Superior Inferior (mm)	3.4 mm (2.5 to 4.1 mm)	3.5 mm (2.6 to 3.9 mm)	0.74
Left Right (mm)	1.8 mm (1.3 to 2.2 mm)	2.4 mm (1.7 to 2.9 mm)	<0.01
Yaw (°)	0.3° (0.0 to 0.5°)	0.3° (0.0 to 0.5°)	0.32
Pitch (°)	1.4° (0.6 to 2.0°)	1.2° (0.5 to 1.3°)	0.47
Roll (°)	0.7° (0.5 to 0.9°)	0.7° (0.4 to 0.9°)	0.84

reducing dose to the normal appearing prostate to 76 to 77.4 Gy using a simultaneously integrated boost technique. Additionally, CBCT was utilized in an adaptive rather than daily schedule with the goal of reducing potentially detrimental imaging dose without compromising biochemical control.¹⁵

The incidence and location of prostatic nodules has been comprehensively analyzed and reported by O'Neill and colleagues.¹⁴ In this report, we characterize the radiointensity of prostatic calcifications and propose a minimum intensity for suitability as a natural fiducial. The size and prevalence of intraprostatic and periprostatic calcifications was high enough to effectively and safely perform CBCT-based image-guided radiation therapy with shifts comparable to using fiducial markers.⁶

Important limitations of this study that limit generalizability include relatively small sample size, single institution retrospective design, short follow-up, heterogeneous study population, various dose fractionation schedules, adjuvant hormonal therapy and user-dependent CBCT correction strategy. The automatic image guidance protocol registered the prostate with manual adjustments informed by the prostate calculi. Therefore, the contribution of prostatic calculi to setup accuracy or clinical outcomes cannot be isolated from the available data.

This study describes the outcomes of patients treated with a novel and non-invasive approach to prostate IGRT that can feasibly be performed with resources available to a community hospital. The ongoing CASPIR trial will clarify the precision of IGRT using

Figure 1. Multiparametric prostate MRI-based intensity-modulated radiation therapy guided by prostatic calcifications (a) T2 MRI demonstrating an 8mm PI-RADS four nodule in the right apex with superimposed dose distribution delivering 81Gy to the prostate nodule, 77.4Gy to the prostate and 70Gy to the prostate and proximal seminal vesicles with additional margin. (b) CT simulation demonstrating two calcifications in the mid prostate with a maximum Hounsfield unit of 452. (c) Cone beam CT demonstrating prostatic calculi in the mid-prostate.

Figure 2. Study Outcomes. (A) Cumulative incidence of biochemical recurrence. (B) Cumulative incidence of biochemical recurrence with or without prostatic calculi. (C) Kaplan-Meier curve of overall survival. (D) Cumulative incidence of late grade 2 rectal bleeding. (E) Cumulative incidence of late grade 2 urinary toxicity.

prostate calculi compared to bony landmarks, prostate gland and fiducial markers.¹⁸ Our center currently is applying knowledge-based planning to further improve plan quality for prostate plans treated with a MRI-guided boost to the dominant intraprostatic nodule without fiducial markers.¹⁹

CONCLUSION

Prostatic calcifications can serve as natural fiducial markers to assist with CBCT-based image-guided radiation therapy for the majority of patients with prostate cancer.

CONFLICTS OF INTEREST

Johnny Kao led an educational webinar for Varian Medical Systems

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