Original paper

Influence of zonal dosimetry on prostate brachytherapy outcomes

Cheng William Hong, MS[1], Chandana A. Reddy, MS[2], D. Allan Wilkinson, PhD[2], Eric A. Klein, MD[3], Jay P. Ciezki, MD[2]

[1]Lerner College of Medicine, Cleveland Clinic, Cleveland, OH, [2]Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, [3]Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA

Abstract

Purpose: To examine the influence of zone-specific dosimetry on outcomes during permanent prostate implantation (PI), where the peripheral zone (PZ) and transitional zone (TZ) may receive varying radiation doses.

Material and methods: Four hundred and sixteen patients treated with I-125 PI (target dose: 144 Gy) between 1996 and 2003 were included in this Institutional Review Board (IRB) approved, retrospective analysis. Whole prostate (WP), TZ, and PZ were contoured, and zone-specific D_{90} and V_{100} were computed. Their influence on biochemical failure (BF) was evaluated using Cox proportional hazards analysis.

Results: The median age and initial prostate-specific antigen (PSA) was 68 years and 6.1 ng/ml, respectively, and the median follow-up time was 8.8 years. There were 329 subjects with Gleason score (GS) 6 disease (79.1%), and 82 subjects had GS 7 disease (19.7%). Androgen deprivation therapy (ADT) was used in 20.4% of patients. Median D_{90} and $V_{100\%}$ in the WP, PZ, and TZ were 141.2 Gy, 156.1 Gy, and 134.5 Gy; and 88.8%, 93.3%, and 84.2%, respectively. Ten-year rates for biochemical recurrence-free survival, distant metastasis-free survival, and prostate cancer-specific mortality were 82.4%, 92.4%, and 0.97% respectively. Only initial PSA, GS7+ disease, ADT, and PSA frequency were significant on multivariate analysis. Ten-year rates of grade 3 or higher GU and GI toxicity was 10.9% and 1.8%, respectively. TZ V_{200} and TZ V_{300} were significantly associated with late genitourinary toxicity.

Conclusions: The TZ received significantly lower doses of radiation compared to the PZ. On multivariate analysis, no dosimetric parameter was associated with efficacy. Higher TZ doses may be associated with higher late GU toxicity without improving efficacy.

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Key words: prostate cancer, toxicity, zonal dosimetry.

Purpose

Prostate brachytherapy is commonly used for the definitive treatment of prostate cancer. Brachytherapy using permanent implantation of low-dose-rate (LDR) seeds alone for clinically localized prostate cancer can be achieved in a single outpatient visit. It allows for a higher dose of radiation to be given to the prostate while minimizing radiation exposure to the surrounding normal structures, and has similar efficacy to radical prostatectomy or external beam radiation therapy [1-3]. However, brachytherapy requires accurate placement of radioactive seeds and is more operator-dependent than external beam radiation therapy (EBRT), and implant quality can impact long-term outcome [4,5].

Quality assurance mandates a post-implant computed tomography (CT) scan to ensure proper implant positioning, and dosimetric parameters such as the D_{90} and V_{100} of the whole prostate (WP) are used to assess treatment adequacy [6]. The majority of prostate cancers, however, occur in the peripheral zone, and the WP dosimetric parameters do not account for the zonal anatomy of the prostate nor capture the heterogeneity in dose distribution within the prostate [7,8]. Herein, the influence of zone-specific dosimetry on rates of biochemical failure and toxicity is described.

Material and methods

Study design

This was an Institutional Review Board (IRB) approved retrospective review of 416 patients treated between 1996 and 2003 at our institution. All patients were treated according to the American Brachytherapy Society (ABS) guidelines for I-125 permanent prostate implantation (PI) (target dose of 144 Gy to the prostate), and no patient was excluded from therapy based on pre-operative urinary function or prostate volume. None of our patients were included in the RTOG 98-05 study.

Address for correspondence: Jay P. Ciezki, MD, Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic, Mail Code T28, 9500 Euclid Avenue, Cleveland, OH 44195, USA, phone: +1 216-445-9465, fax: +1 216-445-1068, ✉ e-mail: ciezkij@ccf.org

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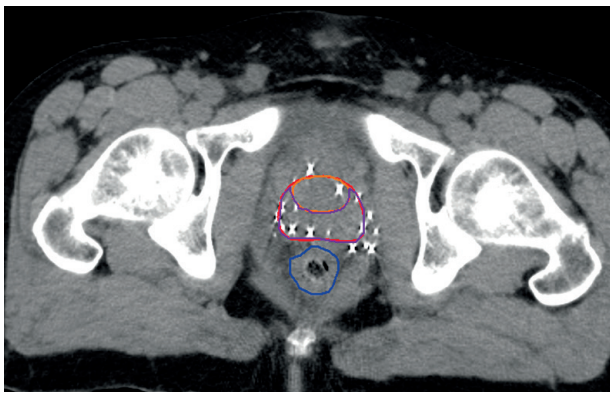

Fig. 1. Transition zone (TZ) (orange) and peripheral zone (PZ) (purple) are contoured on axial slices of the post-implant prostate computed tomography. Whole prostate (WP) (red) and rectum (blue) were already contoured as part of the standard QA process

Brachytherapy technique

Transrectal ultrasound (TRUS) images of the prostate were obtained at 0.5 cm intervals using the brachytherapy stepper (Amertek Medical Inc, Singer Island, FL, USA). Intra-operative physics planning was done with a 0.5 cm radial margin at the apex and base, ensuring that the urethra did not overlap with the 150% isodose line, and $V_{100\%}$ of the rectum was less than 1 cm^3 (VariSeed 8.0, Varian Medical Systems, Palo Alto, CA) [9]. Rapid strands were placed peripherally and loose seeds were placed centrally; needles were placed beginning with the position furthest from the ultrasound probe to minimize image distortion.

Evaluation of dosimetric quantifiers and clinical variables

The volumes of the whole prostate were already contoured on post-implant CT scans as part of the standard quality assurance process and calculation of D_{90} and V_{100} for clinical purposes. As the contours by treating physicians were used as a reference for contouring the transitional zone (TZ) and peripheral zone (PZ), the WP was not re-contoured for this study. The TZ was contoured as an area of similar shape to the WP but extending to approximately half of the anterio-posterior diameter of the prostate on axial CT slices (Fig. 1). The PZ was defined to be the remainder of the previously contoured prostate that was not included in the TZ. This method was chosen in order to yield zonal volumes that are consistent with known relative sizes of each zone of the prostate [10,11]. Urethral dose was not quantified as imaging was performed without catheter placement. Post-implant dosimetric analysis was performed according to ABS guidelines, and D_{90}, D_{100}, V_{100}, V_{150}, V_{200}, V_{300}, and V_{400} were calculated for the WP, TZ, and PZ. Pairwise *t*-tests comparing V_{100} (as a percentage of the zone volume) and D_{90} (in Gy) between zones of the prostate were done.

Clinical and treatment characteristics were examined as well, including the duration of androgen deprivation therapy (ADT), race, clinical stage, initial prostate-specific antigen (PSA), Gleason score, National Comprehensive Cancer Network risk stratification, and post PI PSA measurements (Table 1). Biochemical failure was defined using the Phoenix criteria (increase in 2.0 ng/ml over nadir PSA) [12]. Five-year and 10-year rates for biochemical recurrence-free survival, distant metastasis-free

Table 1. Characteristics of the study population

Characteristic	Median or *n*	Range or %
Age (years)	68	45-87
Initial PSA	6.1	0.4-33.9
Race		
Non-African American	366	88.0
African American	50	12.0
Clinical T stage		
T1-T2a	406	97.6
T2b or T2c	10	2.4
Initial PSA (ng/ml)		
< 4	41	9.9
4-10	317	76.2
10-20	54	13.0
> 20	4	1.0
Gleason score		
6	329	79.1
7	82	19.7
8-10	5	1.2
NCCN risk category		
Low	279	67.1
Intermediate	112	26.9
High	25	6.0
ADT		
None	331	79.6
1-6 months	74	17.8
> 6 months	11	2.6
Biochemical failure		
No	369	88.7
Yes	47	11.3
Distant metastases		
No	398	95.7
Yes	18	4.3
Follow-up time (years)	8.8	0.2-15.1
Number of post PI PSA measurements	9	0-41
PSA frequency (#PSAs/year)	1.5	0.3-12
Status		
Alive	326	78.4
Dead, of disease	5	1.2
Dead, other	85	20.4

Numbers and percentages are provided for categorical variables; medians and ranges are provided for continuous variables.
ADT – androgen deprivation therapy, PI – prostate implant, NED – no evidence of disease

survival, and prostate cancer-specific mortality were computed. Only patients with three or more PSA measurements were included in the analysis of biochemical recurrence-free survival, as two PSA measurements are required for the definition of biochemical recurrence, and a third is needed to rule out PSA bounce.

Toxicity data was collected during clinical follow-up visits, and analyzed retrospectively. Toxicity was scored according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 criteria, and descriptive statistics for late genitourinary (GU) and gastrointestinal (GI) toxicity was tabulated [13]. Five-year and 10-year rates for grade 3 or higher late GU and GI toxicity were computed using Kaplan-Meier analysis.

Statistical analysis

Statistical analysis was performed using SAS 9.2 and JMP 9.0 software (SAS Institute, Cary, NC, USA). Cox proportional hazards regression was used to assess clinical and dosimetric parameters as predictors for biochemical failure and late toxicity. Variables found to be significant on univariate analysis and were included in multivariable analysis. All *t*-tests were performed as two-tailed analyses, and a significance level of 0.05 was used for all statistical testing.

Results

Population characteristics

The median age and initial PSA was 68 years (range: 45-87 years) and 6.1 ng/ml (range: 0.4-33.9 ng/ml), respectively. The median follow-up time for the study population was 8.8 years (range: 0.2-15.1 years) with a median number of 9 post PI PSA measurements (range: 0-41). The characteristics of the study population are as described in Table 1, and dosimetric measurements and implant characteristics are described in Table 2. Dosimetric parameters are compared between the WP, TZ, and PZ (Table 3). As intended by peripheral loading of sources, the TZ received lower doses of radiation than the WP ($p < 0.0001$), which in turn received lower doses than the PZ ($p < 0.0001$).

Biochemical failure

The 5-year and 10-year rates for biochemical recurrence-free survival were 92.4% (95% CI: 89.6-95.3%) and 82.4% (95% CI: 77.2-87.7%) (Fig. 2). The 5-year and 10-year rates for distant metastasis-free survival were 97.8% (95% CI: 96.2-99.4%) and 92.4% (95% CI: 88.4-96.5%). The 5-year

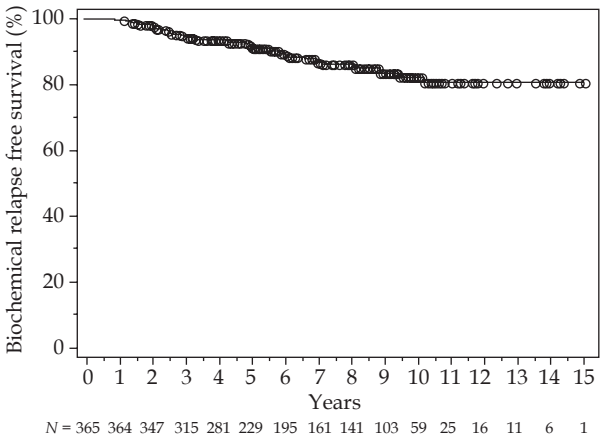

Fig. 2. Kaplan-Meier curve depicting biochemical relapse-free survival. Only patients with three or more PSAs were included for this analysis. N indicates the number of patients at risk at each time point

Table 2. Intra- and post-implantation variables

Variable	Median	Range
Number of sources	104	56-221
Activity (U)	0.430	0.337-0.546
Number of needles used	28	16-50
Pre-PI prostate volume (cm^3)	34.5	13.7-122.5
Length (cm)	4.5	2.6-7.0
Width (cm)	4.9	2.2-7.0
Height (cm)	3.1	2.0-6.4
Post-PI prostate volume (cm^3)	31.3	8.0-115.7

U – air KERMA units, PI – prostate implant

Table 3. Zone-specific dosimetric parameters assessed on post-implant computed tomography

Variable	WP	TZ	PZ	TZ vs. WP	PZ vs. WP	TZ vs. PZ
D_{90} [Gy (range)]	141.2 (66.0-222.6)	134.5 (55.3-219.5)	156.1 (73.4-239.9)	< 0.0001	< 0.0001	< 0.0001
D_{100} [Gy (range)]	80.7 (32.1-155.2)	91.5 (34.5-184.6)	85.5 (37.7-155.0)	< 0.0001	< 0.0001	< 0.0001
Volume [cm^3 (range)]	31.3 (8.0-115.7)	10.2 (1.5-41.8)	20.2 (5.9-75.8)	–	–	–
V_{100} [% (range)]	88.8 (39.0-100.0)	84.2 (12.6-100.0)	93.3 (52.0-100.0)	< 0.0001	< 0.0001	< 0.0001
V_{150} [% (range)]	52.6 (9.7-93.3)	29.0 (1.9-94.2)	63.7 (11.9-94.4)	< 0.0001	< 0.0001	< 0.0001
V_{200} [% (range)]	23.6 (4.1-64.2)	9.0 (0.8-46.5)	31.0 (4.5-76.9)	< 0.0001	< 0.0001	< 0.0001
V_{300} [% (range)]	7.0 (2.0-23.9)	3.3 (0.0-13.5)	8.5 (1.8-32.0)	< 0.0001	< 0.0001	< 0.0001
V_{400} [% (range)]	3.8 (0.6-11.3)	2.0 (0.0-6.9)	4.5 (1.0-13.9)	< 0.0001	< 0.0001	< 0.0001

Pairwise statistical testing was performed using two-tailed t-tests.
WP – whole prostate, TZ – transition zone, PZ – peripheral zone, D_{90} – minimum dose received by 90% of the anatomic volume, D_{100} – minimum dose received by 100% of the anatomic volume, V_{100} – volume of the anatomic volume receiving 100% of the prescribed dose, V_{150} – volume of the anatomic volume receiving 150% of the prescribed dose, V_{200} – volume of the anatomic volume receiving 200% of the prescribed dose, V_{300} – volume of the anatomic volume receiving 300% of the prescribed dose, V_{400} – volume of the anatomic volume receiving 400% of the prescribed dose

and 10-year rates for prostate cancer-specific mortality were 0.58% (95% CI: 0-1.37%) and 0.97% (95% CI: 0-2.08%).

On univariate Cox proportional hazards regression analysis, initial PSA, Gleason 7+ disease, duration of ADT, WP V_{100}, TZ V_{100}, TZ D_{90}, PZ V_{100}, length and width of the prostate, and PSA frequency were significant predictors for the presence/absence of biochemical failure (Table 4). As PSA frequency is associated with biochemical failure, it was included in the multivariable analysis so that its effect can be adjusted for. On multivariable analysis of these variables, only initial PSA, Gleason 7+ disease, and PSA frequency remained significant (Table 5).

Toxicity

Thirty-six patients (8.7%) developed late grade 3 or higher GU toxicity, whereas 7 patients (1.7%) developed late grade 3 or higher GI toxicity (Table 6). The 5-year and 10-year rates of grade 3 or higher GU toxicity was 6.1% (95% CI: 3.7-8.6%) and 10.9% (95% CI: 7.0-14.7%). The 5-year and 10-year rates of grade 3 or higher GI toxicity was 1.8% (0.5-3.2%) and 1.8% (0.5-3.2%). Genitourinary toxicity was classified as obstructive or irritative, and the grade 3 or greater GU toxicity was predominately because of the need to relieve urinary obstruction (94.4%). On univariate Cox proportional hazards regression, only V_{200} and V_{300} in the TZ was significantly associated with grade 3 or higher late GU toxicity (Table 7). Age, race, duration of ADT, activity, prostate volume, length, width, height, TZ D_{90}, TZ V_{100}, TZ V_{150}, TZ V_{400}, TZ_{Volume}, BMI, and history of diabetes were not. Due to the low event rate, Cox proportional hazards regression to identify factors predictive of late grade 3 or higher GI toxicity was not performed.

Table 4. Univariate analysis of clinical and dosimetric parameters as predictors for biochemical failure

Variable	Hazard ratio (95% CI)	*p*-value
Age	0.988 (0.948-1.031)	0.5815
Race (AA vs. non-AA)	1.560 (0.749-3.250)	0.2348
T2bc vs. T1T2a	2.618 (0.633-10.870)	0.1838
Initial PSA	1.106 (1.045-1.171)	0.0005
Gleason score 7+	4.950 (2.740-9.009)	< 0.0001
Duration of ADT	1.129 (1.029-1.238)	0.0105
WP V_{100} (%)	0.973 (0.949-0.998)	0.0321
WP D_{90} (Gy)	0.989 (0.978-1.001)	0.0746
TZ V_{100} (%)	0.985 (0.969-1.001)	0.0644
TZ D_{90} (Gy)	0.989 (0.978-1.000)	0.0472
PZ V_{100} (%)	0.966 (0.937-0.995)	0.0238
PZ D_{90} (Gy)	0.993 (0.983-1.003)	0.1566
Activity (U)	0.257 (0-1276)	0.7542
Length (cm)	0.559 (0.356-0.878)	0.0117
Width (cm)	0.485 (0.328-0.718)	0.0003
Height (cm)	0.745 (0.429-1.291)	0.2938
PSA frequency	13.766 (4.948-38.300)	< 0.0001
PSA frequency *BF time	0.986 (0.966-1.006)	0.1696

AA – African American, ADT – androgen deprivation therapy, WP – whole prostate, TZ – transition zone, PZ – peripheral zone, D_{90} – minimum dose received by 90% of the anatomic volume, V_{100} – volume of the anatomic volume receiving 100% of the prescribed dose, U – air KERMA units, BF – biochemical failure

Discussion

Although there are established guidelines for PI target dosage, this study demonstrates that radiation dose delivered to the prostate is not uniform. At our institution, the peripheral distribution of sources is intended to reduce radiation dose delivered to the urethra within the constraints of whole prostate dosimetry guidelines.

Based on target dosimetric parameters for the whole prostate, the TZ appears to be underdosed. Yet, on multivariable analysis, neither WP nor zone-specific dosimetry was significantly associated with biochemical failure, suggesting that overall, lower TZ dose is not necessarily associated with worse outcomes. In the absence of significant benign prostate hypertrophy, the PZ constitutes the majority of prostate [14]. The majority of prostate cancers arise from the PZ, which tends to receive a higher treatment dose, using the technique described here, than WP dosimetry would suggest. In this analysis, the 10-year rates of late grade 3 or higher GU and GI toxicity was 10.9% and 1.8%. In addition, the TZ volume, which receives particularly high doses, as characterized by V_{200} and V_{300}, may be associated with increased late GU toxicity, a finding which has been consistently observed in HDR brachytherapy studies having less follow-up than this series [15-17]. This is likely due to islands of high dose that are in close proximity to the urethra. High-dose-rate brachytherapy has the technical advantage of control over post-implant dosimetry, although it is much more invasive than LDR brachytherapy [18]. While there is some evidence to suggest that prostate length is associated with late GU toxicity likely due to greater medial lobe size and correspondingly higher doses to the bladder neck, presumably due to backscatter from the medial

Table 5. Multivariable analysis of clinical and dosimetric parameters, which were significant on univariate analysis as predictors for biochemical failure

Variable	Hazard ratio (95% CI)	*p*-value
Initial PSA	1.123 (1.057-1.193)	0.0002
Gleason score 7+	4.937 (2.507-9.721)	< 0.0001
Duration of ADT	0.884 (0.774-1.010)	0.0696
WP V_{100} (%)	1.050 (0.910-1.210)	0.5045
TZ D_{90} (Gy)	0.989 (0.963-1.017)	0.4357
PZ V_{100} (%)	0.936 (0.835-1.049)	0.2560
Length (cm)	0.760 (0.447-1.290)	0.3084
Width (cm)	0.662 (0.401-1.090)	0.1052
PSA frequency	17.838 (5.730-55.526)	< 0.0001
PSA frequency *BF time	0.983 (0.962-1.004)	0.1113

ADT – androgen deprivation therapy, WP – whole prostate, TZ – transition zone, PZ – peripheral zone, D_{90} – minimum dose received by 90% of the anatomic volume, V_{100} – volume of the anatomic volume receiving 100% of the prescribed dose

Table 6. Late genitourinary and gastrointestinal toxicity stratified by toxicity grade

Toxicity grade	Irritative genitourinary *n* (%)	Obstructive genitourinary *n* (%)	Total genitourinary *n* (%)	Total gastrointestinal *n* (%)
None	376 (90.4%)	375 (90.1%)	335 (80.5%)	398 (95.7%)
Grade 1	5 (1.2%)	0 (0%)	5 (1.2%)	3 (0.7%)
Grade 2	33 (7.9%)	7 (1.7%)	40 (9.6%)	8 (1.9%)
Grade 3	2 (0.5%)	33 (7.9%)	35 (8.4%)	7 (1.7%)
Grade 4	0 (0%)	1 (0.2%)	1 (0.2%)	0 (0%)
Grade 5	0 (0%)	0 (0%)	0 (0%)	0 (0%)

lobe to the bladder neck, our data did not demonstrate such a relationship [19-21].

The rates of long-term biochemical failure and late toxicities following the use of brachytherapy for prostate cancer with or without EBRT have been investigated in RTOG 00-19 and RTOG 98-05 [22,23]. In RTOG 00-19, which combined brachytherapy with EBRT, there was a 15% rate of grade 3 or higher GU/GI toxicities after four years, even though the target dose of PI was lowered to 108 Gy to account for the addition of EBRT [22]. In contrast, the rate of late (beyond 9 months) grade 3 toxicities was 3.2% in RTOG 98-05 using the same protocol management as RTOG 00-19 [23]. The high degree of variation in toxicity may be due to the oversimplification of treating the whole prostate as a single homogenous organ. It is also possible that the grading of toxicity can be highly subjective and that patient selection may play a role. In our series, a simple urethral dilation was graded as a grade 3 GU toxicity as was a TURP or similar procedure, in which prostate tissue was removed to relieve obstruction. We also had no pre-treatment selection bias relative to urinary function while RTOG 98-05 required all patients to have an AUA voiding score of < 18. Even if V_{100} and D_{90} are similar for two patients, there can be substantial differences in dose distributions, suggesting that standard dosimetric parameters may not be fully representative of the implant quality and dose distribution [24]. It is interesting to note that shorter width and length were significant predictors of biochemical failure on univariate analysis, as the TZ is closer to the PZ, and these glands would be more difficult to implant.

Given the learning curve of prostate brachytherapy, in RTOG 00-19 it would not be unusual that centers with less accrual would deliver higher treatment doses based on dosimetric quantifiers than centers with more experience, as a higher treatment dose is not necessarily a superior treatment [25,26]. An even distribution of seeds results in uneven dose distributions, with the central region receiving a higher dose, and an overtreatment of the urethra, as well as surrounding organs may also contribute to higher than expected genitourinary toxicity [27]. In contrast to EBRT, which delivers a relatively homogenous treatment dose to the tissues within the beam, the advantage of brachytherapy is the ability to deliver a higher dose to the prostate as a whole, while being able to manipulate the dose distribution within the prostate to account for zonal anatomy by judicious placement of sources. As such, attention to dose painting is critical for tumor control and limiting toxicities. This is especially important for patients at higher risk of significant toxicity, such as those with a history of TURP [28].

Table 7. Univariate analysis of clinical and dosimetric parameters as predictors for late grade 3 or higher genitourinary toxicity

Variable	Hazard ratio (95% CI)	*p*-value
Age	1.048 (0.997-1.101)	0.0635
Race (AA vs. non-AA)	0.981 (0.381-2.527)	0.9684
Duration of ADT	0.990 (0.870-1.125)	0.8735
Activity (U)	672.220 (0.048-9.361E+06)	0.1811
Prostate volume	0.991 (0.969-1.015)	0.4702
Length (cm)	0.973 (0.615-1.539)	0.9062
Width (cm)	0.937 (0.600-1.461)	0.7727
Height (cm)	0.599 (0.315-1.140)	0.1182
TZ D_{90} (Gy)	0.999 (0.988-1.011)	0.9131
TZ V_{100} (%)	1.001 (0.981-1.021)	0.9286
TZ V_{150} (%)	1.008 (0.992-1.025)	0.3260
TZ V_{200} (%)	1.043 (1.004-1.082)	0.0296*
TZ V_{300} (%)	1.163 (1.006-1.344)	0.0408*
TZ V_{400} (%)	1.232 (0.952-1.595)	0.1132
TZ Volume (cm^3)	1.001 (0.946-1.059)	0.9762
BMI (kg/m^2)	0.931 (0.858-1.012)	0.0920
Diabetes (N vs. Y)	1.406 (0.547-3.623)	0.4786

AA – African American, TZ – transition zone, BMI – body mass index, D_{90} – minimum dose received by 90% of the anatomic volume, V_{100} – volume of the anatomic volume receiving 100% of the prescribed dose, V_{150} – volume of the anatomic volume receiving 150% of the prescribed dose, V_{200} – volume of the anatomic volume receiving 200% of the prescribed dose, V_{300} – volume of the anatomic volume receiving 300% of the prescribed dose, V_{400} – volume of the anatomic volume receiving 400% of the prescribed dose

Limitations of this study include its retrospective nature, as well as the reflection of outcomes at a single tertiary-care referral center. As prostate zonal anatomy is not clearly visualized on CT, there may be significant variability in contouring, although a standardized method was used in order to minimize this effect [29].

Conclusions

In conclusion, dose distribution within the prostate can be heterogeneous and standard whole prostate dosimetric parameters based on a prescription dose may not

be fully representative of implant quality [30]. Acceptable clinical outcomes can be obtained even when the TZ systematically receives a lower radiation dose than the rest of the prostate to spare the urethra. Increased awareness of zonal anatomy of the prostate during treatment planning may reduce late toxicities without sacrificing efficacy.

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Disclosure

Authors report no conflict of interest.

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