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Is it necessary to perform week 3 dosimetric analysis in low dose rate brachytherapy for prostate cancer when day 0 dosimetry is done? A quality assurance assessment

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Abstract

Purpose—To determine if computerized tomography/magnetic resonance imaging based day 0 (d0) dosimetry is a meaningful predictor of day 21 (d21) dosimetry in low dose rate brachytherapy for localized prostate cancer.

Methods and Materials—The study population consisted of 277 men with localized (T1-2 N0 M0), low-/intermediate-risk prostate cancer treated with low dose rate brachytherapy. CT/MRI-fusion was used for post-implant dosimetry at d0 and d21. Logistic regression was used to construct receiver operating characteristic curves for achieving each constraint at d21, based on d0 D90 and V100, and Youden's index was used to evaluate cut-points. Freedom from biochemical failure (FBCF) was estimated using the Kaplan Meier method.

Results—The median d0 D90 increased from 133 to 150 Gray (Gy) at d21, and median d0 V100 increased from 87% to 91%. For achieving the D90 constraint at d21, the optimal cut-point for d0 D90 was 135 Gy with 84% of these patients maintaining a d21 D90 > 145 Gy. For achieving the D90 constraint at d21, the optimal cut-point for d0 V100 was 87%, with 83% of these patients maintaining a d21 V100 > 90%. There was no improvement in FBCF in patients with a d0 D90 > 135 Gy or D90 > 145 Gy. Similarly, there was no improvement in FBCF in patients with a d0 V100 > 87% or V100 > 90%.

Conclusions—Meeting dosimetric constraints on d0 does not obviate d21 dosimetric analysis. Constraints used for dose prescriptions on d0 are not the ideal predictors of d21 dosimetry.

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Keywords

LDR; brachytherapy; prostate cancer; dosimetry; quality assurance; D90; V100

Introduction

Prostate cancer is the most common noncutaneous malignancy and the second leading cause of cancer death among men in the United States (1). Prostate seed implants are a safe and effective treatment modality for localized prostate cancer. As an alternative to external beam radiation, low-dose rate (LDR) brachytherapy provides the advantage of being able to deliver high dose radiation while sparing normal surrounding tissue over a shorter treatment course. Multiple institutions have published data demonstrating comparable results to external beam radiation as well as surgery in patients with low to intermediate risk prostate cancer (2-4).

Studies have demonstrated dosimetric variables as strong predictors for outcomes in patients treated with LDR brachytherapy. Stock et al demonstrated a strong correlation between the minimum dose covering 90% of the prostate (D90) and risk of recurrence (5). Similarly, the volume of the prostate receiving 100% of the prescription dose (V100) has also been found to correlate with outcomes (6). The importance of implant quality has been adapted by multiple brachytherapy consortiums (7-9).

Traditionally dosimetric variables are obtained approximately 21-30 days after the LDR implant, allowing for the resolution of edema to provide more accurate dosimetric data. Although many institutions will undertake a day 0 (d0) computed tomography (CT) scan to ensure the quality of the implant, studies examining the utility of d0 dosimetry are limited (10). Although d0 and day 21 (d21) constraints are correlated, it is unclear if meeting d0 dosimetric constraints would obviate the need for d21 dosimetry. We hypothesized that d0 dosimetry would be a good predictor of d21 values and to help other providers by establishing d0 cutpoints that would predict for optimal d21 dosimetry and favorable patient outcomes.

Materials and Methods

Patients

The study population consisted of men with low-/intermediate-risk (T1-2, N0, M0) localized prostate cancer treated with I-125 LDR prostate brachytherapy alone at a National Cancer Institute-designated comprehensive cancer center. Patient demographics, tumor characteristics, and treatment-related information were entered prospectively into an IRB approved database that was maintained and updated by data managers. The collection, storage, and retrieval of data were all done in compliance with the hospital's Institutional Review Board and the Health Insurance Privacy and Portability Act. Risk groups were stratified per National Comprehensive Cancer Network (NCCN) criteria, with low risk comprised of patients with clinical stage T2a, PSA < 10 ng/ml and Gleason score ≤ 6. Intermediate risk patients consisted of clinical stage T2b-T2c, PSA 10-20 ng/ml and Gleason

score 7. At our institution, high-risk patients are not offered I-125 monotherapy per NCCN guidelines (11).

In addition to clinical criteria, patients offered I-125 prostate seed implants at our institution must meet criteria set forth by the American Brachytherapy Society (7). Relative contraindications include large prostate volumes ($> 60 \text{ cm}^3$), high international prostate symptom score (> 20), history of pelvic radiation, large median lobe, or transurethral resection defects. Patients are also evaluated by a board-certified anesthesiologist and urologic oncologists to evaluate for operative risk prior to the procedure.

Treatment technique

Planning and procedure technique have been previously described (12). Briefly, the number and activity of I-125 seeds for each patient is calculated using an MRI-generated, physician-contoured volume with experience in the procedure (i.e. > 50 cases performed) and reviewed with at least one other experienced attending physician. During the procedure, patients were placed under general anesthesia in extended dorsal lithotomy position. Intraoperative planning and seed placement is under real-time ultrasound guidance using physician-generated contours of the prostate. A 3 to 5-mm anterior and lateral expansion was applied to the prostate volume to generate a planning target volume which is ultimately used for treatment. A total of 145 Gray (Gy) is prescribed to cover 100% of the prostate volume. Per ABS guidelines, an acceptable plan must achieve a $D90 > 90\%$, $V100 > 90\%$, urethral maximum dose $< 150\%$, and $V100$ of the rectum to be less than 1 cm^3 . Midway through treatment and at the end of treatment, patients undergo fluoroscopic examination to document proper seed placement. Rigid cystoscopy was performed by the urologic oncologist to ensure the absence of needles or seeds in the urethra or bladder at the end of the procedure. Approximately four hours after the implant, patients have the foley catheter removed and undergo d0 post-implant CT and MRI to establish baseline dosimetry. Patients return in approximately 3-4 weeks after implant to repeat the CT and MRI and generate the d21 post-implant dosimetry for confirmation of dosimetric quality indicators and ensure seed stability and prostate dose coverage.

Dosimetric analysis

The primary dose constraint was $> 145 \text{ Gy}$ prescribed to 90% of the prostate volume ($D90 > 145 \text{ Gy}$); a secondary constraint was that the volume of the prostate receive $> 90\%$ of the prescription dose ($V100 > 90\%$). CT/MRI-fusion was used for post-implant dosimetry at d0 and d21. D0 and d21 contours were typically completed by the same resident physician and always verified by the same treating attending physician. We used logistic regression to construct receiver operating characteristic (ROC) curves for achieving each constraint at d21, based on d0 $D90$ and $V100$ as continuous variables. These predictors were evaluated by estimating AUC, the area under the ROC curve, where $\text{AUC}=1$ would indicate a d0 predictor that perfectly discriminates between below and above the constraint at d21, and $\text{AUC}=0.5$ is not predictive (same as random chance). We used Youden's index to determine optimal dose and volume cut-points, which gives equal weight to sensitivity and specificity. Biochemical failure was defined according to the Phoenix definition, 2 ng/ml rise above the PSA nadir. Freedom from biochemical failure (FBCF) was estimated using the Kaplan-

Meier product limit method where patients without biochemical failure were censored at the date of their most recent PSA determination. Log rank tests were used to evaluate differences in FBCF curves between groups. Statistical analyses were done using SAS 9.3 (SAS Institute, Cary, NC) and ROC curves were generated with Stata 12 (StataCorp 2011).

Results

There were a total of 277 men with a median follow-up of 33.7 months. The majority of patients had low risk features including T2a disease (n=274, 98.9%), Gleason 6 disease (n=273, 98.6%), and PSA <10 (n=271, 97.8%). At least one post-implant PSA value was available in 98.9% (n=274) patients. Patient and treatment characteristics are further demonstrated in table 1.

The median real-time trans-rectal ultrasound (TRUS) prostate volume was 45.7ccs which increased to 46.0ccs at d0 and decreased to 37.0 ccs at d21. The median V100 on d0 was 86.6%, which increased to 91.2% on d21 (Figure 1). Similarly, the median D90 increased from 133.5 Gy on d0 to 149.6 Gy on d21 (Figure 2).

For patients who had a D90 > 145 Gy constraint at d0, 90% maintained this constraint at d21; of those below the D90 constraint at d0, 46% had an increase to D90 > 145 Gy at d21. For d0 D90, the area under the curve (AUC) was 0.79 (95% CI=0.74 to 0.85). The optimal d0 cut-point was 135 Gy based on Youden's index, with 84% of the patients above this 135 Gy cutpoint at d0 achieving d21 D90 > 145 Gy. Of patients with a d0 D90 < 135 Gy, only 37% had d21 D90 > 145 Gy (Figure 3). For patients who had a V100 > 90% at d0, 90% maintained this level at d21; of those below the V100 constraint at d0, 47% had an increase to V100 > 90% at d21. For d0 V100, the AUC was 0.80 (95% CI=0.75 to 0.85). For d0 V100, the optimal cut-point based on Youden's index was 87%, with 84% of the patients above this cutpoint at d0 achieving d21 V100 > 90%. Of patients with a d0 V100 < 87%, only 37% achieved a d21 V100 > 90%.

Including both d0 V100 and d0 D90 as covariates did not improve the prediction of the d21 D90 constraint or V100 constraint (results not shown). This was not surprising given the high correlation between D90 and V100 at d0 (Pearson $r=0.85$, $p<0.0001$).

In this cohort, eight patients had recurrence as determined by biochemical failure (BCF). There was no difference in FBCF for any of the d0 cutpoints (D90 or V100, standard or ROC determined). FBCF at 36 mo was 98.3% for d21 D90 above 145 Gy, and 95.4% for those below, but this did not reach statistical significance (logrank test $p=0.15$). Results were similar for d21 V100 >90%. Further results are demonstrated in Table 2.

Discussion

The importance of implant quality is a well-established surrogate for outcomes in patients undergoing interstitial prostate implants. Dosimetric parameters obtained 3-4 weeks after implant are followed to ensure quality control and efficacy and promoted by national consortiums (7). Although many institutions undertake d0 post-implant dosimetry as well, guidelines and quality control parameters are not well established regarding the use of d0

dosimetry to predict for d21 dosimetry (13). The advantage of d0 dosimetry is assumed to be earlier intervention if under dosing or seed misplacement is evident. Unfortunately, prostatic edema post-procedure typically gives an inaccurate view of the final dosimetric values. Studies have demonstrated that early post-implant dosimetry may underestimate prostate coverage by approximately 10% versus late dosimetry (14). Currently, there are no guidelines established regarding d0 dosimetric constraints. We hypothesized that d0 dosimetry was a good predictor of d21 dosimetry, our goal was to generate d0 cut-points for predicting d21 constraints.

In our cohort of patients, ROC curves were generated using established d21 constraints as the target endpoints. A d0 D90 > 137 Gy and a d0 V100 > 87% were deduced as the most sensitive and specific markers for the goal D90 and V100, respectively. In terms of outcomes, the generated d0 D90 and V100 constraints did not correlate with FBCF. In addition, achieving a d0 D90 > 145 Gy or V100 > 90% did not improve FBCF. As there were only eight BCFs in this cohort, this result is difficult to interpret. However, in previous studies, d21 dosimetric values had a trend towards improved outcomes. This variability and shift in the dosimetry values from d0 to d21 (figures 1 and 2) illustrate the difficulty in obtaining early quality control measures due to the dynamic post-procedure prostate.

One of the first studies examining the importance of dosimetric quality control measures was by Stock et al in a cohort of 134 patients undergoing LDR implants alone (5). The authors reported an improved 4-year biochemical relapse free survival (BRFS) in patients with a higher D90. Patients with a D90 > 140 Gy had a BRFS of 92% versus 68% for those with a D90 < 140 Gy (p=0.02). In their updated series, this remained significant with an 8-year BRFS of 82% for patients with a D90 > 140 Gy versus 68% for those with a D90 < 140 Gy (p=0.007) (15). Potters et al later confirmed these findings in a more heterogeneous cohort of 719 men (6). In the latter study, patients were either treated with I-125 or Pd-103, and nearly a third also received ADT. Regardless, D90 remained a significant predictor of BRFS with 4-year BRFS of 80.4% in patients with a D90 < 90% versus 92.4% in patients with a D90 > 90% (p=0.001).

The usage of post-implant dosimetry is variable amongst radiation oncologists. A recent survey of practitioners demonstrated that 37% performed d0 dosimetry alone, 73% performed day 30 dosimetry alone, and only 10% perform both. Multiple large institutions have also adopted d0 post-implant dosimetry as part of their post-brachytherapy evaluation (16-18). A recent study from Memorial Sloan-Kettering Cancer Center showed that obtaining a d0 D90 > 140 Gy predicted for improved outcomes although suboptimal dose coverage did not necessarily result in inferior outcomes (19). Wallner et al examined d0 dosimetry as a surrogate for outcomes in a prospective trial comparing I-125 and Pd-103 prostate implants (20). In their series, patients with a D90 > 100% or a V100 > 90% at d0 had an improved FBCF versus patients not meeting these thresholds. Another study out of this institution examining external beam irradiation with a Pd-103 prostate implant boost also demonstrated a trend towards improved biochemical control with higher D90 and V100 values (21).

The dose-response relationship in prostate cancer has been demonstrated in multiple trials and dose escalation is the standard of care in these patients (22, 23). The D90 variable ensures adequate dosing to the post-implant variable and has been demonstrated to be a predictor of outcomes. In our cohort of patients, the d21 D90 had a correlation towards improved FBCF even with only nine treatment failures. This coincides with other reported studies in the literature (5, 6). The ideal d0 endpoints remain more elusive due to the variable immediate post-procedure factors.

Post-implant edema is commonly seen following interstitial implants. This inflammatory response has the potential to impact the measurement of dosimetric quality measures. The variability of post-implant dosimetry has been demonstrated in multiple cohorts. Waterman et al found that prostate edema increases exponentially following implants and decreases with a half-life of 9 days (24). Tausky et al demonstrated a longer half-life of 16 days (17). Chung et al found that patients with smaller prostate volumes had the greatest potential for post-implant edema although this did not significantly impact D90 parameters (25). In our cohort of patients, there was a significant decrease in the prostate volume from d0 to d21 from 48 ccs to 39 ccs. This speaks to the peri-prostatic changes that exist following interstitial implants.

Yue et al sought to determine the ideal interval for evaluating post-implant dosimetry (14). In their evaluation, they found the ideal time to be 7 +/- 2 weeks for I-125 versus 3 +/- 1 weeks for Pd-103. In addition, they found that pre-implant dosimetry might overestimate target coverage by 6% for I-125 and 14% for Pd-103. Concordantly, they advocated increasing target coverage during the pre-implant procedure. In our cohort of patients there was a significant reduction in dosimetric outcomes from pre-implant dosimetry to final d21 values similar to the above study. The mean real-time V100 was 98.1% which decreased to 85.3% during d0 dosimetry and increased to 90.7% at week 3. Similarly, the mean real-time D90 was 176.6 Gy which decreased to 133.5 Gy at d0 and finally increased to 149.9 Gy at d21.

An important consideration for determining dosimetric outcomes is the inter- and intra-observer variability when delineating the post-implant volume. Small changes in volume delineation can result in significantly different quality outcome measures. Al-Qaiseh et al evaluated the changes in these values caused by contouring variability (26). In their study, the D90 ranged from 46 Gy to 123 Gy in the same patient on post-implant CTs conducted 4-6 weeks after treatment. Dubois et al had evaluated these outcomes using CT and MRI post-implant dosimetry in a cohort of 41 patients (27). Two physicians delineated the post-implant prostate volume within 24 hours after implant and found a significant difference between CT and MRI based contouring. MRI post-implant imaging resulted in a decrease in inter-observer variability with a difference of 1.9 cc +/- 11.7 (p=0.492) with MRI versus 8.5 cc +/- 9.7 cc (p=0.001) with CT. Contouring on early post-implant imaging is likely particularly variable due to the expected post-implant edema, hemorrhage and artifact. In our cohort of patients, d0 and d21 contours were typically completed by the same resident and always verified by the same attending physician. Although this limits the inter-observer variability in contouring, intra-observer variability may ultimately impact dosimetric values and is a shortcoming of our findings.

In conclusion, d21 dosimetry remains an important factor in predicting outcomes in patients undergoing interstitial LDR prostate implants. Although d0 may be an important quality control measure, identifying specific d0 dosimetric constraints remains difficult to the dynamic post-implant prostate. Our study coincides with other literature demonstrating the importance of achieving quality control outcomes in interstitial prostate implants. Further research is needed to better define ideal d0 dosimetric target constraints.

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List of abbreviations

BCF Biochemical Failure

BRFS	Biochemical Relapse Free Survival
CT	Computed Tomography
d0	day 0
d21	day 21
D90	minimum dose covering 90% of the prostate
FBCF	Freedom from biochemical failure
LDR	low dose rate
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
PSA	Prostate specific antigen
ROC	Receiver operating characteristic curve
V100	Volume of the prostate receiving 100% of the prescription dose

Figure 1. Dosimetric outcomes real time, day 0, and week 3 for D90 (A) and V100 (B)

A D90: minimum dose covering 90% of the prostate

B V100: Volume of the prostate receiving 100% of the prescription dose

Figure 2. Receiver operating curves for meeting d21 D90 (A) and V100 (B) constraints

A d0: Day 0

d21: Day 21

B D90: minimum dose covering 90% of the prostate)

V100: Volume of the prostate receiving 100% of the prescription dose

Table 1
Patient and treatment characteristics

Characteristic	N	%
Number of Patients	277	
Age distribution		
40-49 yrs	7	2.5
50-59 yrs	78	28.2
60-69 yrs	133	48.0
70-79 yrs	59	21.3
Age, yrs	Median=64	Range=41-78
T Stage		
T1C	249	89.9
T2A-T2C	28	10.1
Gleason		
5-6	273	98.6
7	4	1.4
PSA		
10 ng/mL	271	97.8
10- 20 ng/mL	6	2.2
Pre-implant ADT		
Yes	3	1.1
No	274	98.9
NCCN Risk Groupings		
Low Risk	266	96.0
Intermediate Risk	11	4.0
Median (25th, 75th pctl)		
Volume, cc		
Real-Time	45.7	(37.5, 53.0)
d0	46.0	(37.0, 56.2)
d21	37.0	(29.1, 47.5)
Dosimetric Measures		
Real-Time V100, %	98.7	(97.6, 99.3)
d0 V100, %	86.6	(80.9, 90.7)
d21 V100, %	91.2	(87.1, 94.9)
Real-Time D90, Gy	178.2	(169.5, 183.3)
d0 D90, Gy	133.5	(121.4, 146.5)
d21 D90, Gy	149.6	(135.6, 164.7)

Table 2
Summary of freedom from biochemical failure using D90 and V100 cutpoints

Cutpoint	N	n	BCF	FBCF (%) at 24mo	FBCF (%) at 36mo	Logrank	p-value
Day 0							
D90 >135 Gy, d0	No	146	6	94.5	96.3	0.34	
	Yes	128	2	98.8	97.5		
D90 >145 Gy, d0	No	195	6	98.0	97.1	0.98	
	Yes	79	2	98.2	96.0		
V100>86.7%, d0	No	141	6	97.4	96.2	0.31	
	Yes	133	2	98.9	97.6		
V100 >90%, d0	No	192	6	98.0	97.1	0.95	
	Yes	82	2	98.2	96.1		
Day 21							
D90 >145 Gy, d21	No	114	6	97.9	95.4	0.15	
	Yes	160	2	98.3	98.3		
V100 >90%, d21	No	112	6	97.8	95.3	0.14	
	Yes	162	2	98.3	98.3		

D90: minimum dose covering 90% of the prostate

V100: Volume of the prostate receiving 100% of the prescription dose

BCF: Biochemical Failure

FBCF: Freedom from biochemical failure