Original paper

Pre-plan parameters predict post-implant D_{90} ≥ 140 Gy for ^{125}I permanent prostate implants

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Abstract

Purpose: To find permanent prostate implant (PPI) pre-plan dosimetric parameters that predict post-implant D_{90} ≥ 140 Gy.

Material and methods: Pre-plans were evaluated for 504 patients undergoing PPI with ^{125}I seeds for low or intermediate risk prostate cancer. Baseline patient and disease factors, numbers of seeds, ratios of number of seeds to available positions (occupancy proportion), and distances between the 100% isodose line and edge of the prostate (margin) planned for the whole prostate (WP), superior (S), inferior (I), anterior (A), and posterior (P) halves, SA, SP, IA, and IP quarters, and superior (S_T), inferior (I_T), and middle (M_T) thirds, and anterior (A_T) and posterior (P_T) middle one-sixth segments were analyzed by post-implant D_{90} subset (≥ 140 Gy vs. < 140 Gy).

Results: 20% had post-implant D_{90} < 140 Gy (mean: 128.0 Gy, range: 97.5-139.2) vs. ≥ 140 Gy (mean: 154.4 Gy, range: 140.0-193.5). The D_{90} ≥ 140 Gy subset had larger A_T and IA segment mean numbers of seeds (p = 0.01, 0.046), larger WP, S, A, SA, S_T, A_T, and M_T segment mean margins (p = 0.01, 0.01, 0.001, 0.0001, 0.03, 0.005, 0.02), and lower P_T segment occupancy proportion (p = 0.004). On multivariate analysis, independent predictors of post-implant D_{90} ≥ 140 Gy were increased SA mean margin, no pre-implant 5-α-reductase inhibitor, higher pre-plan D_{90}, decreased P occupancy proportion, no pre-implant hormone therapy, and decreased SP mean margin.

Conclusions: Higher occupancy proportion and larger margins anteriorly and reduced occupancy proportion, and smaller margins posteriorly on PPI pre-plans predict post-implant D_{90} ≥ 140 Gy.

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Key words: LDR brachytherapy, prostate cancer, pre-plan dosimetry.

Purpose

The goal of pre-planning for permanent prostate implants (PPI) is to develop treatment plans, consisting of the number of seeds and their locations (pre-plan), that when implemented during the implant procedure will result in acceptable dosimetry and clinical outcome [1]. After PPI for low and intermediate risk prostate cancer, approximately 4-30% of patients experience biochemical failure [2-12]. One possible cause of biochemical failure is poor post implant dosimetry, which might in turn be due to a less than optimal pre-plan. To improve outcomes, a better understanding of the optimal number and locations of seeds on pre-plans is required. Few, if any, studies have attempted to correlate pre-plan dosimetric parameters with dosimetric or clinical failure outcomes. Post-implant dosimetry for whole and sections of the prostate has been analyzed [3,12-24]. However, it is not straightforward to extrapolate backwards from post-implant dosimetry to the number and position of seeds planned on pre-plans, because post-implant dosimetric parameters measure combinations of multiple variables, some of which may not be "actionable" and may reflect poor execution of a pre-plan.

In this study, we sought to determine pre-plan dosimetric parameters that predict post-implant D_{90} ≥ 140 Gy in patients undergoing PPI for low and intermediate risk prostate cancer. We chose D_{90} ≥ 140 Gy as our definition of acceptable post-implant, because it has been reported to predict longer freedom from biochemical failure, making the results of this study potentially clinically useful [20,24]. We focused on pre-plan seed counts, ratio of number of seeds to available positions (occupancy proportions), and margins for segments of the prostate, because these parameters are most easily manipulated on pre-plans and will facilitate translation of the results into practice.

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Material and methods

Institutional review board approval was obtained before initiation of this retrospective study. Between January 1, 2000 and December 31, 2008, 567 patients underwent primary PPI monotherapy for low or intermediate risk prostate cancer (PSA ≤ 20, Gleason Score ≤ 7, and T-stage ≤ T2c) using ^{125}I seeds (Oncoseed 6711™, Oncura, Inc., Arlington Heights, IL, USA) to a prescription dose of 144 Gy. Of these patients, 504 were included in this study. Patients were excluded if pre-plan or post-implant dosimetry data were unavailable. TRUS planning studies were used for pre-plan development. Planning and implants were performed by four brachytherapists. Strata Suite (Rosses Medical Systems, Inc., Columbia, MD, USA) was used for planning. Our pre-plan dosimetric guidelines are, for the prostate, $V_{100} \geq 95\%$, $V_{200} < 30\%$, $V_{150} < 65\%$, $D_{90} \geq 100\%$, and minimize V_{200} without compromising other parameters and, for both the urethra and rectum, $V_{150} < 0.1$ cc and $V_{200} = 0\%$ using a modified peripheral loading approach [9]. No explicit PTV was used in planning, but a margin of approximately 3 mm was added all around the prostate, except where margin would overlap with the rectum. Implants were performed with non-stranded seeds with a mean strength of 0.389 mCi. Pre-plans were followed without purposeful deviations with the exception that an extra one or two seeds were available to be implanted at the discretion of the brachytherapist. These seeds were often implanted at the site of biopsy-proven tumor. The CT for post-implant dosimetry was performed 4-6 weeks after implant (median: 4.3 weeks). Patients with pubic arch interference as assessed by TRUS were treated with 5-α-reductase inhibitor (5-αRI) or hormone therapy (HT) consisting of luteinizing hormone releasing hormone (LHRH) agonist, anti-androgen, or both prior to implant to reduce prostate volume and pubic arch interference. Twenty-nine patients received HT and another 22 received 5-αRI.

Prostates were segmented on pre-plans into superior (S), inferior (I), anterior (A), and posterior (P) halves and superior-anterior (SA), superior-posterior (SP), inferior-anterior (IA), and inferior-posterior (IP) quarters (Figs. 1A-C). A second segmentation, the tripartite segmentation, consisted of dividing the prostate on pre-plans into superior (S_T), mid (M_T), and inferior (I_T) segments, each representing approximately one third of the prostate with the mid segment further divided into anterior (A_T) and posterior (P_T) halves (Figs. 1D-E).

For segmentation in the superior-inferior direction, TRUS slices were partitioned evenly between segments. For the half and quarter segmentations, if the number of TRUS slices was not evenly divisible by 2, the inferior segment contained the extra slice. For the tripartite segmentation, if the number of TRUS slices was not evenly divisible by 3, the I_T and S_T segments contained an equal number of slices and the remaining slices were included in the M_T segment making the M_T segment 1 or 2 slices larger than the other two. The division of the prostate into anterior and posterior segments for halves, quarters, and tripartite segmentations was defined as the coronal plane halfway between the anterior and posterior edges of the prostate. The position used for measuring the distance between the anterior and posterior edges of the prostate was the center of the prostate in the right-left dimension as designated by the original setup on the planning TRUS (Fig. 1F). If the dividing coronal plane coincided with a row of seed positions, the anterior segment included this extra row. The position of the dividing coronal plane could be different on each TRUS image of a prostate depending on the position of the anterior and posterior edges of the prostate on that image. Custom software was developed in JavaFX™ version 1.3.1 and Java™ version 6 (Oracle Corporation, Redwood Shores, CA, USA) for segmentation.

Seed count was defined as the number of seeds planned per segment within the prostate. Occupancy proportion was defined as the ratio of the number of seeds planned within the prostate in a segment to the total number of grid positions within the prostate in that segment.

Dosimetric margins were defined as the distance between the 100% isodose line and the edge of the prostate on pre-plans. Margins were measured radially at 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315° in transverse planes to the nearest half millimeter (Fig. 1G). 0° was defined as the direction directly anterior to the center point of the prostate. P half, IP and SP quarter, and P_T segment margins included measurements from 135° to 225°. A half, IA and SA quarter, and A_T segment margins included measurements from 315° to 45°. S and I half and S_T, M_T, and I_T segment margins included measurements from 0° to 315°. For measurement of margins, the center of the prostate was defined as the point half-way between the anterior and posterior edges of the prostate on the center line of the prostate in the right-left dimension as designated by the original setup on the planning TRUS. The center of the prostate could be different on each TRUS image of the prostate depending on the position of the anterior and posterior edges on that image.

For analysis, patients were dichotomized on post-implant D_{90} using a threshold of 140 Gy ($D_{90} < 140$ Gy vs. ≥ 140 Gy). The Student *t*-, the χ^2, the Mann-Whitney test, and analysis of variance (ANOVA) methods for repeated measures were used for the univariate analysis with linear contrasts included for planned comparisons. For the multivariate analysis, a logistic regression model was applied to identify independent pre-plan predictors of post-implant $D_{90} > 140$ Gy. A forward stepwise model was used with the likelihood ratio test determining statistical significance of predictors and the order of importance. The probability to enter a variable into the model was < 0.05 and the probability to remove a variable was > 0.10. Baseline patient, disease factors and pre-plan seed counts, occupancy proportions, and margins using the different segmentation schemes were considered as predictors of outcome. It was possible to combine measurements of halves and quarters segmentations as long as the same outcome was not included (e.g. margins for the superior half and seed count for the SP quarter could be combined, but margins for the superior half and margins for the SP quarter could not).

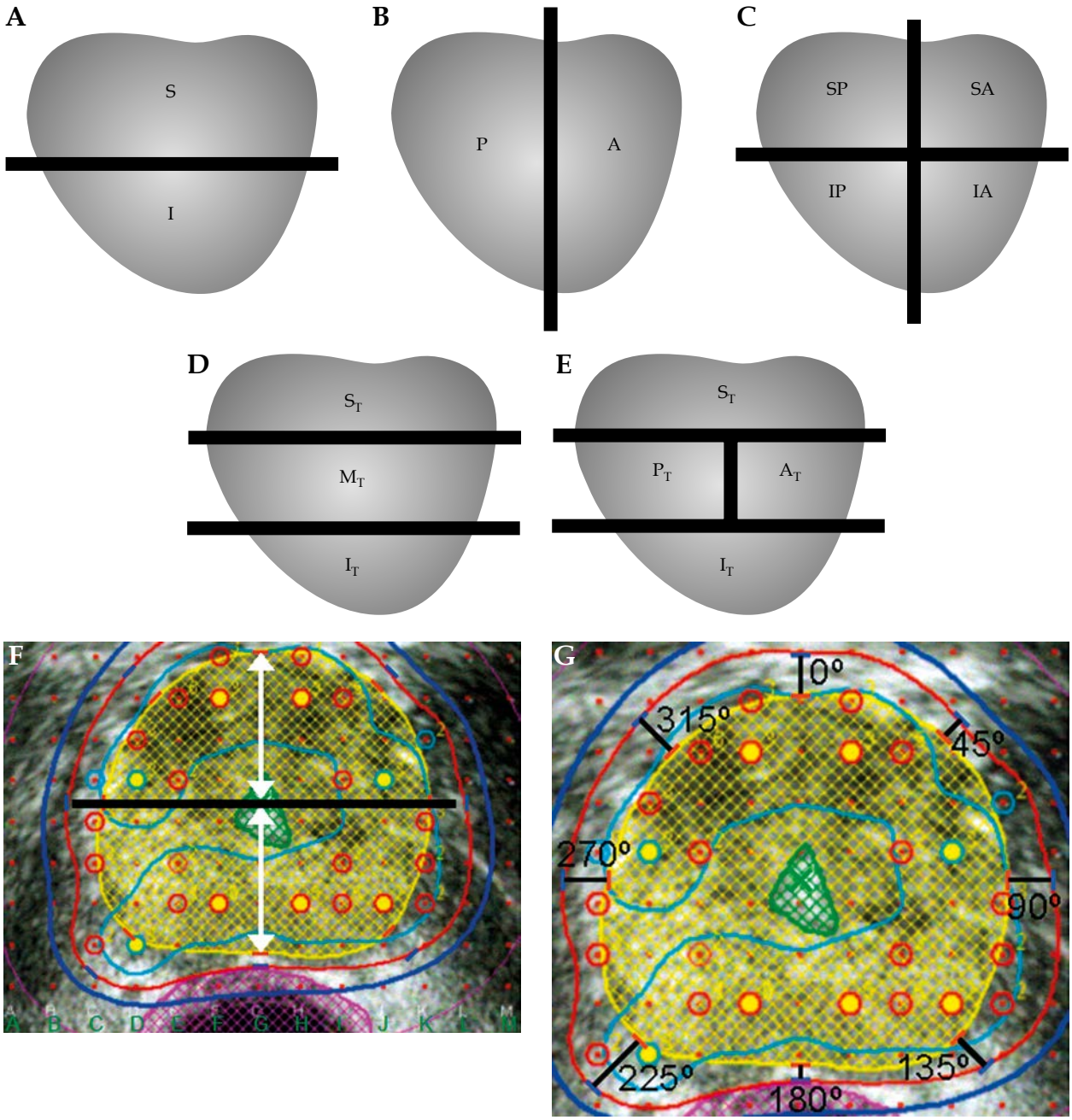

Fig. 1. Definitions of prostate segmentations and margins. Black lines demarcate segments on a prostate seen in right lateral view: A) superior (S) and inferior (I) halves; B) anterior (A) and posterior (P) halves; C) superior-anterior (SA), superior-posterior (SP), inferior-anterior (IA), and inferior-posterior (IP) quarters; D) superior (S_T), mid (M_T), and inferior (I_T); and E) superior (S_T), anterior (A_T), posterior (P_T), and inferior (I_T) segments of the tripartite segmentation. F) The black line equidistant from anterior and posterior edges of the prostate demarcates anterior and posterior segments shown on a pre-plan TRUS transverse image with prostate in hatched yellow and centered on the center seed position grid column. The centered white double arrows are of equal length. G) The black lines represent the measured margins shown on a pre-plan TRUS transverse image with the 100% isodose line shown in red, and prostate in hatched yellow and centered on the center seed position grid column

The tripartite segmentation was considered separately, because these segments partially overlapped with the halves and quarters segments. The fit of final models was summarized by the area under the receiver operating characteristic curve (AUC), which was evaluated using a bootstrapped distribution of 700 repetitions. All data were analyzed using STATISTICA™ v6.0 (StatSoft, Inc, Tulsa, OK) or STATA™ v8.0 (StataCorp, LP, College Station, Texas, USA).

Results

Table 1 describes patient and tumor characteristics and pre-plan and post-implant dosimetric parameters. Patients

Table 1. Patient and disease characteristics and pre-plan and post-implant dosimetric parameters for the full cohort and by D_{90} subset (*p*-values by *t*-test, χ^2 test, or Mann-Whitney test)

	Total (n = 504)	Post-implant D_{90}		*p*-value
		D_{90} < 140 Gy (n = 102)	D_{90} ≥ 140 Gy (n = 402)	
Mean age at implant (years) (range)	62.6 (40-84)	63.4 (40-79)	62.4 (45-84)	(0.21)
Median PSA (ng/mL) (range)	5.7 (0.55-14.3)	5.3 (0.8-14.3)	5.8 (0.6-14.1)	(0.69)
< 4.0 ng/mL	75 (15%)	17 (17%)	58 (14%)	
4.0 ≤ 10.0 ng/mL	404 (80%)	76 (74%)	328 (82%)	
≥ 10.0 ng/mL	25 (5%)	9 (9%)	16 (4%)	(0.10)
Gleason score				
4-6	438 (87%)	92 (90%)	346 (86%)	(0.33)
7	66 (13%)	10 (10%)	56 (14%)	
T stage				(0.89)
T1b-T1c	335 (66%)	69 (68%)	266 (66%)	
T2a	160 (32%)	31 (30%)	129 (32%)	
T2b-T2c	9 (2%)	2 (2%)	7 (2%)	
Mean TRUS volume (cc) (range)	39.6 (11.9-84.1)	39.0 (11.9-72.0)	39.7 (14.8-84.1)	(0.60)
Mean CT volume (cc) (range)	39.2 (14.0-77.1)	40.4 (14.0-77.1)	38.9 (15.1-76.0)	(0.30)
Pretreatment 5-αRI[1]	22 (4%)	10 (10%)	12 (3%)	0.01
Pretreatment HT[2]	29 (6%)	11 (11%)	18 (4%)	0.03
Pretreatment TURP[3]	17 (3%)	3 (3%)	14 (3%)	(1.00)
Mean seed strength (mCi) (range)	0.39 (0.30-0.46)	0.39 (0.30-0.46)	0.39 (0.31-0.46)	(0.74)
Pre-plan mean D_{90} (Gy) (range)	175.3 (147.5-213.1)	172.2 (152.5-202.2)	176.1 (147.5-213.1)	0.0002
Post-implant mean D_{90} (Gy) (range)	149.1 (97.5-193.5)	128.0 (97.5-139.2)	154.4 (140.0-193.5)	–
Post-implant mean V_{100} (%) (range)	91.7% (59.3-100.0)	81.8% (59.3-89.9)	94.3% (67.6-100.0)	–

[1]5-α-reductase inhibitor; [2]Hormone therapy (luteinizing hormone-releasing hormone agonist and/or anti-androgen); [3]Transurethral resection of prostate

were dichotomized into post-implant D_{90} < 140 Gy and D_{90} ≥ 140 Gy subsets. Of 504 patients, 102 (20%) and 402 (80%) were in the post-implant D_{90} < 140 Gy and ≥ 140 Gy subsets. The subsets did not differ by age at implant, year of implant, post-implant CT prostate volume, or pre-treatment features including Gleason score, T-stage, PSA, prior transurethral resection of prostate, and TRUS prostate volume. A higher proportion of patients in the post-implant D_{90} < 140 Gy subset received pre-implant HT or 5-αRI (10% vs. 3%, p = 0.01; 11% vs. 4%, p = 0.03). By definition, there was a difference in the mean post-implant D_{90} between subsets (128.0 Gy vs. 154.4 Gy). The post-implant V100, which is highly correlated with post- implant D_{90} (r = 0.88; p < 0.0001), was also lower for the D_{90} < 140 Gy subset (mean: 81.8% vs. 94.3%). There was a significant difference in mean pre-plan D_{90} for the post-implant D_{90} subsets (post-implant D_{90} < 140 Gy vs. ≥ 140 Gy: 172 Gy vs. 176 Gy; p = 0.0002). There was also a larger mean decrease in D_{90} from pre-plan to post-implant dosimetry in the post-implant D_{90} < 140 Gy subset (44.2 Gy vs. 21.7 Gy, p < 0.0001). The subsets did not differ in seed strength. None of the other pre-plan dosimetric parameters analyzed including prostate D_{100}, V_{90}, V_{100}, V_{150}, and V_{200}; rectal and urethral D_{90}, D_{100}, V_{90}, V_{100}, V_{150}, and V_{200}; and rectal and urethral TRUS volume, were different between post-implant D_{90} subsets (not shown in Table 1).

Seed counts for whole, half, quarter, and tripartite prostate segments were analyzed (Table 2). Overall, on average 68 seeds were planned inside, and 10.4 seeds were planned outside the prostate. The mean number of seeds in the whole or in halves of the prostate was not significantly different between subsets. Analysis by quarters revealed a larger mean number of seeds in the IA quarter for the D_{90} ≥ 140 Gy subset (11.0 vs. 10.2, p = 0.046). A slightly greater mean number of seeds were planned for the M_T segment for the D_{90} ≥ 140 Gy subset and this

Table 2. Planned mean seed counts for segments of the prostate for the full cohort and by post-implant D_{90} subset (*p*-values for planned comparisons of means in the ANOVA model for repeated measures)

	Total (n = 504)	Post-implant D_{90}		*p*-value
		D_{90} < 140 Gy (n = 102)	D_{90} ≥ 140 Gy (n = 402)	
Whole prostate: mean (range)				
Inside and outside	79.3 (43-119)	77.4 (43-118)	79.8 (49-119)	(0.13)
Inside	68.1 (33-118)	66.6 (38-103)	68.4 (33-118)	(0.25)
Outside	10.4 (0-29)	10.1 (1-24)	10.5 (0-29)	(0.48)
Halves segmentation: mean (range)				
Superior	43.7 (20-73)	43.2 (20-66)	43.8 (21-73)	(0.57)
Inferior	24.4 (6-48)	23.4 (7-42)	24.7 (6-48)	(0.15)
Anterior	29.1 (11-51)	28.1 (11-45)	29.3 (13-51)	(0.13)
Posterior	39.0 (18-67)	38.5 (20-60)	39.1 (18-67)	(0.53)
Quarters segmentation: mean (range)				
Superior-anterior	18.2 (5-34)	17.9 (7-30)	18.3 (5-34)	(0.47)
Superior-posterior	25.4 (12-43)	25.3 (13-39)	25.5 (12-43)	(0.75)
Inferior-anterior	10.8 (3-22)	10.2 (3-20)	11.0 (3-22)	0.046
Inferior-posterior	13.6 (2-30)	13.3 (3-26)	13.6 (2-30)	(0.47)
Tripartite segmentation: mean (range)				
S_T	22.9 (6-45)	22.6 (6-41)	23.0 (8-45)	(0.66)
I_T	10.9 (0-35)	10.9 (2-27)	11.0 (0-35)	(0.85)
M_T	34.2 (15-56)	33.2 (15-52)	34.5 (16-56)	(0.11)
A_T	14.6 (5-27)	13.7 (6-23)	14.8 (5-27)	0.01
P_T	19.6 (7-34)	19.4 (8-34)	19.7 (7-31)	(0.65)

increase was significant only in the A_T segment (14.8 vs. 13.7; p = 0.01).

Occupancy proportions were analyzed for whole, half, quarter, and tripartite prostate segments (Table 3). The mean occupancy proportion was 0.26 overall and means for segments ranged between 0.20 for the M_T and 0.25 for the S_T segment. The occupancy proportion was not significantly different for whole, half, or quarter prostate segments between subsets. For the D_{90} < 140 Gy subset, there was a trend towards greater occupancy proportion in the P half (0.23 vs. 0.22, p = 0.06) and a significantly greater occupancy proportion in the P_T segment (0.21 vs. 0.20, p = 0.004). This was not a result of a greater number of planned seeds in the P half or P_T segment.

Post-implant D_{90} ≥ 140 Gy subset planned margins were significantly larger for multiple segments when analyzed by whole prostate, halves, quarters, and tripartite segmentation (Table 4). Overall, the mean planned margin of the I half was larger than that of the S half (3.9 vs. 2.6 mm, p < 0.0001), the mean planned margin of the A half was larger than that of the P half (3.4 vs. 2.7 mm, p < 0.0001), and there was a significant difference in mean margins among the 4 prostate quarters (p < 0.0001). The mean margins of the whole prostate, S and A halves, SA quarter, and S_T, A_T, and M_T segments were significantly larger in the D_{90} ≥ 140 Gy subset than the D_{90} < 140 Gy subset (3.2 vs. 3.1 mm, p = 0.01; 2.7 vs. 2.5, p = 0.01; 3.5 vs. 3.2, p = 0.001; 3.0 vs. 2.5, p = 0.0001; 2.9 vs. 2.7, p = 0.03; 3.0 vs. 2.8, p = 0.005; 2.5 vs. 2.4, p = 0.02).

Using logistic regression, two models were developed to predict a post-implant D_{90} ≥ 140 Gy (Table 5). In model 1, the prostate was segmented by halves and quarters, and the significant independent predictors were: increased SA mean margins, no pre-implant 5-αRI, increased pre-plan D_{90}, decreased P half occupancy proportion, no pre-treatment HT, and smaller SP quarter mean margins. The AUC for model 1 was 0.70 (bias-corrected 95% confidence interval 0.64-0.75). For model 2, based on the tripartite segmentation, the significant independent predictors were: increased pre-plan D_{90}, decreased P_T segment occupancy proportion, increased A_T segment occupancy proportion, increased A_T mean margins, no pre-implant 5-αRI, and no pre-implant HT. The AUC for model 2 was 0.71 (bias-corrected 95% confidence interval 0.64-0.76).

Table 3. Mean planned occupancy proportions for segments for the full cohort and by post-implant D_{90} subset (*p*-values for planned comparisons of means in the ANOVA model for repeated measures)

	Total (n = 504)	Post-implant D_{90}		*p*-value
		D_{90} < 140 Gy (n = 102)	D_{90} ≥ 140 Gy (n = 402)	
Whole prostate: mean (range)	0.26 (0.18-0.45)	0.26 (0.19-0.45)	0.26 (0.18-0.38)	(0.61)
Halves segmentation: mean (range)				
Superior	0.22 (0.16-0.38)	0.23 (0.16-0.38)	0.22 (0.16-0.34)	(0.40)
Inferior	0.21 (0.12-0.39)	0.21 (0.13-0.33)	0.21 (0.12-0.39)	(0.54)
Anterior	0.22 (0.13-0.38)	0.22 (0.13-0.38)	0.22 (0.13-0.36)	(0.44)
Posterior	0.22 (0.15-0.36)	0.23 (0.16-0.36)	0.22 (0.15-0.33)	(0.06)
Quarters segmentation: mean (range)				
Superior-anterior	0.22 (0.12-0.38)	0.22 (0.14-0.38)	0.22 (0.12-0.38)	(0.37)
Superior-posterior	0.23 (0.15-0.38)	0.23 (0.16-0.38)	0.22 (0.15-0.36)	(0.10)
Inferior-anterior	0.21 (0.09-0.48)	0.21 (0.09-0.41)	0.21 (0.09-0.48)	(0.65)
Inferior-posterior	0.21 (0.09-0.40)	0.21 (0.11-0.40)	0.21 (0.09-0.37)	(0.20)
Tripartite segmentation: mean (range)				
S_T	0.25 (0.17-0.42)	0.25 (0.17-0.42)	0.25 (0.17-0.40)	(0.80)
I_T	0.21 (0-0.44)	0.21 (0.06-0.44)	0.21 (0.00-0.39)	(0.83)
M_T	0.20 (0.14-0.36)	0.21 (0.15-0.36)	0.20 (0.14-0.34)	(0.19)
A_T	0.20 (0.12-0.35)	0.20 (0.13-0.35)	0.20 (0.12-0.31)	(0.21)
P_T	0.20 (0.13-0.40)	0.21 (0.14-0.40)	0.20 (0.13-0.37)	0.004

Table 6 presents examples of model 1 predicted probabilities of post-implant D_{90} ≥ 140 Gy for patients matched based on similar values for all but one significant predictor. Each comparison demonstrates the impact on the predicted probability due to that predictor and gives a sense for the approximate range that will result in a high predicted probability of post-implant D_{90} ≥ 140 Gy. Figure 2 shows representative slices from pre-plans resulting in post-implant D_{90} ≥ 140 Gy and < 140 Gy to illustrate model 1 multivariate analysis parameters.

Discussion

In this series of 504 PPIs, 20% had a post-implant D_{90} < 140 Gy. In two previously published series 48.5% and 30% of implants resulted in post-implant D_{90} < 140 Gy [20,24]. Our series compares favorably with these series, but leaves room for improvement. One possible cause for poor post-implant dosimetry in our series is that residents and other new users learning implant techniques are involved in our implants. Another possible cause is suboptimal pre-planning, which was the focus of this study. In this analysis of PPI pre-plans, we found that a higher occupancy proportion and larger margins anteriorly and lower occupancy proportion, and smaller margins posteriorly independently predicted post-implant D_{90} ≥ 140 Gy.

Previous studies have examined post-implant dosimetry of sections of the prostate and reported the importance of the dosimetry of the SA and superior segment over other regions for overall post-implant dosimetry and that lower IA quarter V100 approached significance for predicting biochemical relapse as part of a multivariate model [13,22,23]. A multi-institutional study comparing 17 centers pre-plans for a single post-TURP patient, showed a propensity to lower doses anteriorly as compared to posteriorly [25]. Neither the previous studies nor our results showed statistical significance of IA quarter metrics as predictors in multivariate models. Overall, our results are consistent with previous studies, suggesting the importance of the superior anterior region in attaining better post-implant dosimetry. One group suggested that it may be appropriate to reduce dose to the superior anterior region to reduce urethral toxicity given their finding of a low rate of cancer anteriorly [26]. Supporting this idea, another group found no association between post-implant dosimetry of the superior anterior region and biochemical failure [23]. However, the idea of reducing dose to the superior anterior region is controversial. Other pathology studies have demonstrated high rates of cancer in this region, and the study analyzing post-implant dosimetry of segments and biochemical failure included only a small number of failures and lacked a full analysis of the locations of those failures [23,27-29]. In light of this lack of consensus and because of the im-

Table 4. Mean planned margins for segments for the full cohort and by post-implant D_{90} subset (*p*-values for planned comparisons of means in the ANOVA model)

	Total (*n* = 504)	Post-implant D_{90}		*p*-value
		D_{90} < 140 Gy (*n* = 102)	D_{90} ≥ 140 Gy (*n* = 402)	
Whole prostate (range)	3.2 (1.7-5.5)	3.1 (2.0-4.6)	3.2 (1.7-5.5)	0.01
Halves segmentation (range)				
Superior	2.6 (0.2-4.8)	2.5 (1.0-4.8)	2.7 (0.2-4.7)	0.01
Inferior	3.9 (1.6-6.5)	3.8 (1.8-5.5)	3.9 (1.6-6.5)	(0.18)
Anterior	3.4 (1.1-6.9)	3.2 (1.3-5.1)	3.5 (1.1-6.9)	0.001
Posterior	2.7 (0.1-5.3)	2.6 (0.1-4.9)	2.7 (0.5-5.3)	(0.52)
Quarters segmentation (range)				
Superior-anterior	2.9 (–0.6-7.3)	2.5 (–0.1-5.4)	3.0 (–0.6-7.3)	0.0001
Superior-posterior	2.0 (–0.6-5.4)	2.0 (–0.6-4.9)	2.0 (–0.3-5.4)	(0.82)
Inferior-anterior	3.9 (0.1-6.9)	3.9 (0.1-6.2)	4.0 (0.7-6.9)	(0.42)
Inferior-posterior	3.5 (–0.6-6.6)	3.4 (–0.6-6.2)	3.5 (0.9-6.6)	(0.30)
Tripartite segmentation (range)				
S_T	2.9 (0.2-5.9)	2.7 (0.5-5.9)	2.9 (0.2-5.9)	0.03
I_T	4.6 (1.3-8.3)	4.4 (1.9-7.8)	4.6 (1.3-8.3)	(0.16)
M_T	2.5 (0.8-4.3)	2.4 (0.9-3.8)	2.5 (0.8-4.3)	0.02
A_T	3.0 (–0.8-6.8)	2.8 (–0.8-5.9)	3.0 (0.4-6.8)	0.005
P_T	1.9 (–1.6-5.0)	1.9 (–1.6-4.0)	1.9 (–1.0-5.0)	(0.72)

portance of this region in attaining a high post-implant D_{90} ≥ 140 Gy, we do not recommend under-dosing the superior or anterior region. Studies analyzing locations of PPI failures might settle this question.

Previously, post-implant margins have been analyzed with respect to outcomes, but the results have been conflicting [30-32]. In some studies, larger post-implant whole prostate and anterior margins were associated with better biochemical outcomes [31,32]. In another study, there was no association between post-implant margins and biochemical outcomes [30]. This issue of the relationship between margins and biochemical outcomes remains to be resolved. Making the situation more complicated, a recent study analyzing post-implant dosimetry of community performed implants suggested that margins on these implants were less adequate than margins in high volume centers [33]. Our data show larger pre-plan mean margins for whole, superior, and anterior regions of the prostate in the post-implant D_{90} ≥ 140 Gy subset, supporting the importance of the superior anterior margin over the inferior anterior margin in obtaining better post-implant dosimetry. Given these results, data showing extracapsular extension tends to be larger superiorly than inferiorly, and a lack of consensus on the role of margins in biochemical outcomes, it may be useful, where possible and safe, to increase margins superiorly, particularly for the SA quarter [34].

Smaller SP quarter mean margins (model 1) and smaller posterior region occupancy proportion predicted post-implant D_{90} ≥ 140 Gy in this study. It is unclear why reduced margins or a smaller occupancy proportion would predict higher post-implant D_{90}, but possible explanations include prostate geometry and/or the necessity of balancing anterior and posterior occupancy proportion with urethral and other dose constraints.

For the multivariate analysis, two models to predict post-implant D_{90} ≥ 140 Gy were developed based on different segmentations: halves and quarters versus tripartite segmentation. The models had similar AUC values, suggesting they are similar in predictive ability and that the segmentations are equivalent for PPI planning purposes. Both models included increased pre-plan D_{90}, no pre-treatment HT, and no pre-treatment 5-αRI as significant predictors of post-implant D_{90} ≥ 140 Gy, with similar odds ratios in each model. Our data suggest that a higher D_{90} than the desired post-implant D_{90} must be planned, because the average change in D_{90} from pre-plan to post-implant was a decrease of 26.4 Gy. It is somewhat unexpected that no pre-treatment HT or 5-αRI predicts higher post-implant D_{90}, because these medications are prescribed for reducing prostate volume to eliminate pubic arch interference, which is expected to improve post-implant dosimetry. Previously, we (data not published) and others have seen that no pre-implant HT predicted better post-implant D_{90},

Table 5. Models based on different segmentations developed using logistic regression analysis to determine independent predictors of post-implant $D_{90} \geq 140$ Gy

Predictor (Listed in order of importance)	LLR test probability value	Odds ratio	95% Confidence interval (CI)	Wald *p*-value
Model 1: Halves and quarters segmentation (AUC = 0.70; Bootstrapped 95% CI: 0.639-0.754)				
SA quarter mean margin	0.0001	1.49	1.17-1.91	0.001
Pre-treatment 5-αRI[1]	0.006	0.29	0.12-0.72	0.008
Pre-plan D_{90}	0.01	1.05	1.02-1.08	0.001
P half occupancy proportion	0.01	0.0001	> 0-0.06	0.005
Pre-treatment HT[2]	0.02	0.38	0.17-0.86	0.021
SP quarter mean margin	0.04	0.77	0.60-0.99	0.045
Model 2: Tripartite segmentation (AUC = 0.71; Bootstrapped 95% CI: 0.64-0.76)				
Pre-plan D_{90}	0.0001	1.05	1.02-1.08	0.001
P_T occupancy proportion	0.0008	> 0	> 0-0.0004	< 0.001
A_T occupancy proportion	0.007	5930	3.47 - > 10,000	0.02
A_T mean margin	0.007	1.42	1.09-1.86	0.01
Pre-treatment 5-αRI[1]	0.02	0.29	0.12-0.74	0.01
Pre-treatment HT[2]	0.04	0.41	0.18-0.93	0.03

[1]5-α-reductase inhibitor, [2]Hormone therapy (luteinizing hormone-releasing hormone agonist and/or anti-androgen)

Table 6. Examples comparing logistic regression predicted probabilities for model 1 for paired patients matched on all but one independent significant predictor of post-implant $D_{90} \geq 140$ Gy with the values of the unmatched significant predictor for each pair of patients displayed on a gray background

Patient	Model 1 Logistic regression significant predictors of $D_{90} \geq 140$ Gy						Post-implant D_{90} (Gy)	Logistic regression predicted probability
	Pre-plan D_{90} (Gy)	Pre-treatment 5-αRI[1]	Pre-treatment HT[2]	SA quarter mean margin (mm)	SP quarter mean margin (mm)	P half occupancy proportion		
1	162.5	No	No	3	1	0.23	132.5	0.77
2	182.7	No	No	2.9	1	0.23	175	0.90
3	167.5	Yes	No	2.1	1.8	0.21	122.5	0.46
4	167.5	No	No	2	1.8	0.22	172.5	0.73
5	177.5	No	No	0.4	1.6	0.21	137.5	0.72
6	172.5	No	No	3.3	1.6	0.22	157.5	0.85
7	177.5	No	No	2.9	2.8	0.26	137.5	0.76
8	171.8	No	No	2.8	0.3	0.24	163.1	0.85
9	177.5	No	No	3.3	1.8	0.30	122.5	0.78
10	172.5	No	No	3.4	1.8	0.18	147.5	0.90

[1]5-α-reductase inhibitor, [2]Hormone therapy (luteinizing hormone-releasing hormone agonist and/or anti-androgen)

but other groups have found that hormones were either not predictors or were predictors of better biochemical outcomes for low and intermediate risk patients [35-37].

The remaining significant independent predictors of post-implant $D_{90} \geq 140$ Gy were increased SA quarter mean margin, decreased P half occupancy proportion, and reduced SP quarter mean margin in model 1 and decreased P_T and increased A_T segment occupancy proportion, and increased A_T segment mean margin in model 2. The predictors are similar between models and show how

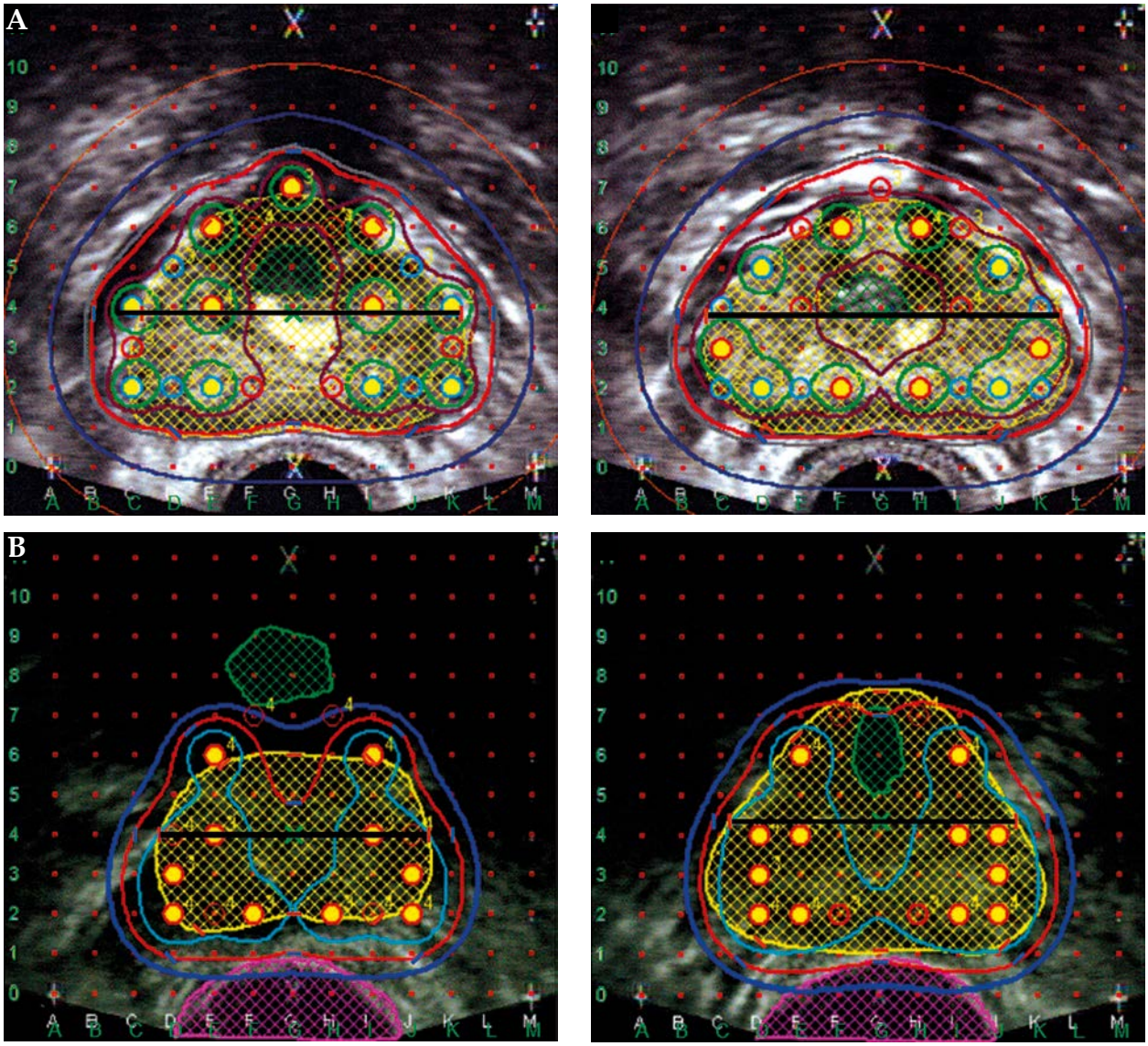

Fig. 2. Pre-plans illustrating model 1 multivariate analysis parameters associated with post-implant D_{90} (A) ≥ 140 Gy (155 Gy): larger SA mean margins (4.6 mm), smaller SP mean margins (0.5 mm), and smaller P occupancy proportion (0.19) and (B) < 140 Gy (132.5 Gy): smaller SA mean margins (1.0 mm), larger SP mean margins (2.7 mm), and larger P occupancy proportion (0.26). Representative superior slices shown. Isodose lines: 100%, red; 50%, dark blue. Contours: prostate, hatched yellow; urethra and bladder, hatched green; rectum, hatched purple. Black line demarcates anterior and posterior segments. Orange and blue bars mark positions where margins were measured

consistent the models are with each other. These models suggest that during planning more emphasis should be placed on coverage of the anterior prostate with a margin and less emphasis on the posterior prostate to attain a high post-implant D_{90} (Fig. 2, Table 6). For guidance in pre-plan development, these models can be used to calculate the probability of a given pre-plan achieving a post-implant D_{90} ≥ 140 Gy. However, we do not recommend under-dosing any part of the prostate as this may reduce post-implant D_{90}. In our experience, with careful assessment for pubic arch interference and appropriate prostatic volume reduction, we do not have problems accessing the anterior prostate or tissue just anterior to the prostate with needles for seed placement. Therefore, in our practice, we are planning larger margins for the SA quarter.

A limitation of this study is that there is no external validation set. Multi-institutional studies have shown substantial variability in pre-plans with respect to treatment margins and seed placement, among other parameters, between the different participating institutions [25,38]. This may mean that external validation of this study is necessary or that each institution must analyze its own data to determine institution-specific parameters that best predict higher post-implant D_{90}. For the latter case, this study outlines how such an analysis could be performed. However, our data are consistent with other published data, suggesting that they may have broad applicability. A second limitation is that this study specifically analyzed pre-plans, and it is unclear whether the results will also apply to intraoperative planning. A third

limitation is that there is uncertainty in the pre-plan and post-implant parameters used in this study, because of the inherently subjective nature of contouring. In other similar studies, each case was re-contoured by multiple physicians to estimate uncertainty in contouring. This was not feasible for this study due to the large number of cases included. However, the same brachytherapist contoured the pre-plan TRUS for all cases in this study, and only two brachytherapists contoured the post-implant CT for all cases in this study. Of these two brachytherapists, 87% of the post-implant CTs were contoured by one of them. This consistency in contouring would be expected to reduce the uncertainties in the dosimetric parameters. However, systematic error in contouring cannot be excluded and would be more likely to affect the division between anterior and posterior segments rather than the division between superior, mid, and inferior segments. A fourth limitation is that this study is retrospective and 63 patients were excluded due to lack of available data, possibly affecting the results. Finally, the main limitation is that dosimetric outcomes were used as intermediary measures to predict clinical outcomes. An analysis of pre-plan parameters with respect to clinical outcomes is currently underway.

Conclusions

In this analysis for PPI pre-plan parameters that predict post-implant dosimetry, we focused on pre-plan seed counts, occupancy proportions, and margins for segments of the prostate to facilitate translation of the results into changes on pre-plans that will improve implant quality. We found that higher occupancy proportion and larger margins anteriorly, and lower occupancy proportion and smaller margins posteriorly independently predicted post-implant $D_{90} \geq 140$ Gy, which has been reported to predict longer freedom from biochemical failure. Because these findings are based on pre-plan dosimetry, they are less sensitive to inadvertent seed misplacement than findings based on post-implant dosimetry, and thus, may provide "actionable" guidance for clinical care.

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Research conducted

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Disclosure

Authors report no conflict of interest.

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