Comparison of low and intermediate source strengths for ^{125}I prostate brachytherapy implants

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ABSTRACT   **PURPOSE:** To compare the implant quality and clinical outcomes for patients treated with low and intermediate strength ^{125}I seeds in prostate brachytherapy implants.
METHODS AND MATERIALS: This retrospective review included 390 consecutive patients treated with prostate brachytherapy from 1999 to 2006. The first 142 patients were implanted with source strengths lower than 0.415 U (0.327 mCi), with the subsequent 248 patients implanted with source strengths higher than 0.493 U (0.388 mCi). Clinical, dosimetric, toxicity, and outcome data were compared between these two cohorts of patients.
RESULTS: Despite having similar prostate volumes, fewer sources (median, 95 vs. 113; $p <$ 0.0001) and fewer needles (median, 23 vs. 29; $p < 0.0001$) were implanted in the intermediate strength cohort. The postimplant dosimetry demonstrated better quality implants in patients treated with intermediate strength sources (median D_{90}, 160.0 Gy vs. 139.6 Gy; $p < 0.0001$), with greater dose inhomogeneity identified in the intermediate strength cohort of patients. A higher incidence of late rectal toxicity was identified in patients treated with intermediate strength sources despite lower rectal doses in this cohort. The biochemical relapse-free survival, prostate cancer survival, and overall survival were not significantly different between the two cohorts.
CONCLUSIONS: The transition from low to intermediate strength sources has led to fewer resources being used and improved postoperative dosimetry. Although there were more rectal complications identified in the intermediate strength cohort of patients in this analysis, there were no other significantly worse clinical or biochemical outcomes for patients implanted with intermediate strength sources. Crown Copyright © 2013 Published by Elsevier Inc. on behalf of American Brachytherapy Society. All rights reserved.

Keywords: Brachytherapy; Source strength; Prostate cancer; Toxicity; Outcomes

Introduction

The last two decades have seen a dramatic rise in the utilization of prostate brachytherapy implants for men with localized prostate cancer (1, 2). A survey of clinical practices

identified a range of source strengths that are used by different institutions (3). Proponents of low strength sources point to the improved dose homogeneity and greater error tolerance, as source placement errors or loss of sources have a lower impact on the postoperative dosimetry (4). In contrast, advocates of higher strength sources emphasize the lessened surgical trauma and cost savings that can be achieved with this approach because of the lower cost of sources and shorter implanting time (5). As a result, there is no practitioner consensus on an optimal source strength for permanent prostate brachytherapy implants (6).

With these issues in mind, our group performed planning studies to determine if a preferred source strength exists for permanent prostate brachytherapy implants (7). This study

demonstrated that higher strength sources can provide better dose coverage and improved organ sparing compared with lower strength sources, with 0.5–0.6 U (U = unit of air kerma strength = $1\ cGy \cdot cm^2 \cdot h^{-1}$) sources emerging as optimal source strengths. A subsequent study by our group compared the postoperative dosimetry of two groups of patients with different source strengths and confirmed that the D_{90} was significantly better for patients implanted with higher strength sources (8). Other studies have also compared implants of different source strengths (9, 10), but there are few comparisons of clinical outcomes of patients treated with different source strengths (11), particularly long-term outcomes. This study reports the dosimetry, toxicity, and outcomes of two consecutive cohorts of patients implanted with either low or intermediate strength sources. The purpose of this study was to confirm that the clinical outcomes of patients treated with intermediate strength sources were not compromised in comparison with patients implanted with low strength sources.

Methods and materials

Study cohort

This study included 390 consecutive patients treated with permanent prostate brachytherapy implants at the Cross Cancer Institute, Edmonton, Alberta, Canada between May 4, 1999 and December 19, 2006. The cutoff date was chosen to allow a minimum potential followup of 5 years. The institutional research ethics committee approved this study.

Men eligible for brachytherapy included those with low-risk disease (defined as clinical stage of T2 or lower, Gleason score of 6 or less, and pretreatment prostate-specific antigen [PSA] level of 10 ng/mL or lower) and low-tier intermediate-risk disease (defined as organ-confined disease and either Gleason score of 7 and PSA of 10 ng/mL or lower or PSA of 10–15 ng/mL and Gleason score of 6 or lower).

Treatment characteristics

Patients were treated with ^{125}I sources (model 6711; Oncura, Arlington Heights, IL and model MED3631-AM; North American Scientific, Chatsworth, CA) using an implant technique that our group has previously described (7). Briefly, a transrectal planning ultrasound was performed by a radiation oncologist before implantation with aerated gel in the urethra. The planning target volume was defined as the prostate gland with a 3-mm margin anteriorly and laterally, 0-mm margin posteriorly and superiorly, and a 5-mm margin inferiorly. A modified peripheral loading pattern delivered a minimum peripheral dose of 145 Gy to the planning target volume. A transrectal ultrasound-guided transperineal technique under general or spinal anesthesia was used to deliver the sources.

Aerated gel was used to visualize the urethra during the procedure.

Each patient underwent a CT scan approximately 28 days after the initial implantation, using 3-mm thick slices to assess postoperative dosimetry. The CT scans were acquired using a Philips PQ-5000 (Philips Healthcare, Picker, Cleveland, OH) scanner and imported into the Vari-Seed treatment planning system (Varian Medical Systems, Palo Alto, CA) for postoperative dosimetry. The prostate, bladder neck, and complete rectum (all slices containing sources) were contoured by a radiation oncologist, whereas a medical physicist identified the source coordinates using a combination of manual selection and automated seed finding, including redundancy checks available in Variseed. The dosimetric values calculated included the postoperative D_{90} (defined as the minimum dose covering 90% of the postimplantation CT prostate volume) and the V_{100}, V_{150}, and V_{200} (percentage of the postimplantation CT prostate volume covered by 100%, 150%, and 200% of the prescription dose, respectively).

The first 142 patients (low strength cohort) were treated with a median source strength of 0.398 U (0.313 mCi; range, 0.387–0.414 U [0.305–0.326 mCi]). Following a planning exercise that demonstrated improved dose coverage and urethra protection with higher strength sources (7, 8), the source strength was increased (intermediate strength cohort) to a median strength of 0.494 U (0.389 mCi; range, 0.494–0.572 U [0.389–0.450 mCi]) for the following 248 patients. Variability in the source strength was owing to a lack of availability of desired source strength or by the postponing of a patient's treatment. In addition, it should be noted that our institution transitioned from loose sources to stranded sources in July 2001 (patient number 125), with subsequent implants using RapidStrands (Oncura, Arlington Heights, IL) for all sources except the periurethral sources.

Followup

The day of the brachytherapy implant was considered Day 0 for followup. The followup of these patients consisted of assessments at 4 weeks, then semiannually for 2 years, and then annually. The toxicity and PSA outcomes were retrospectively entered into a database. A large proportion of patients at our institution travel from out of town for their treatment and are discharged from followup at our institution, with guidelines provided to family physicians for followup including physical examinations, toxicity, and PSA assessments. To capture information on patients discharged from our followup, the Alberta electronic medical record was reviewed to capture toxicities and biochemical information for patients. In the province of Alberta, patients' electronic medical records contain all PSA measurements performed in the province, with procedure notes, operative notes, and hospitalizations also available for patients suffering complications. It should also

be noted that hormonal therapies are only dispensed through the cancer centers in Alberta, ensuring that all hormonal interventions were captured during our review of patients' charts. To supplement and improve the retrospective collection of information for this study, a questionnaire was mailed to all patients in this cohort in 2010, with specific questions about toxicity, outcomes, and quality of life (International Prostate Symptom Score [IPSS] and Expanded Prostate cancer Index Composite) collected in this questionnaire. Of the 390 patients in this study, 187 patients returned completed questionnaires to update their status.

Endpoints

The endpoint of freedom of biochemical relapse was defined as patients who did not have an increase in PSA level by 2 ng/mL or higher greater than the nadir value (Phoenix definition) [12]. Patients without biochemical relapse were censored at death or at the date of last PSA assessment. Patients who met the criteria for relapse, but subsequently had a decrease in the PSA level to a new nadir of 0.5 ng/mL or lower without intervention were classified as having a benign increase in the PSA level [13] and were not coded as having biochemical relapse.

Statistical analysis

Descriptive statistics were used to describe the data. Median and range values were used to describe the overall patient baseline characteristics and postoperative dosimetry for the low and intermediate seed strength cohorts. Dose to rectum was reported using mean and standard deviations for all patients and by the study cohort. Percentages were also used for categorical parameters. The comparison of

the study cohort (low vs. intermediate) for the continuous variables was conducted using the Student's t test. Independent test of proportions was used to compare the proportions for categorical variables. Logistic regression analysis was used to analyze the dichotomous variable catheter use (yes vs. no). Baseline IPSS, diabetes, number of seeds, number of needles, prostate volume, and strength of sources (<0.415 U vs. >0.493 U) were included in the univariate model, and variables significant at p-value lower than 0.10 level were chosen for the multivariate model. Odds ratios and their respective 95% confidence intervals were reported. Kaplan–Meier survival tables were used to calculate the biochemical recurrence. Log-rank tests were used to compare the survival curves for low and intermediate strength cohorts. Biochemical recurrence was calculated as the difference between date of implant and date of biochemical recurrence. All of the patients who did not experience biochemical recurrence were considered censored, and time was calculated as the difference between the date of implant and last date of followup. A p-value of 0.05 was used for all statistical significance, unless otherwise specified. All statistical analysis was conducted using SAS version 9.1.3 software (Cary, NC, USA).

Results

Baseline patient characteristics

The patient and implant characteristics of the 390 patients evaluated in this study are shown in Table 1. The low and intermediate seed strength cohorts were well balanced with respect to risk categorization. The low seed strength cohort had a higher proportion of patients treated with hormonal therapy (26% vs. 15%, $p = 0.0120$), with

Table 1
Patient baseline characteristics

Characteristics	All patients	Low seed strength cohort	Intermediate seed strength cohort	p-Value[a]
Number of patients	390	142	248	
Source strength (U)	0.494 (0.387–0.572)	0.398 (0.387–0.414)	0.494 (0.494–0.572)	<0.0001
Age (y)	64 (48–79)	64 (48–77)	64 (48–79)	0.3381
Prostate-specific antigen (ng/mL)	6.0 (0.4–14)	5.8 (0.4–13)	6.1 (0.7–14)	0.2806
Gleason score, n (%)	≤6 = 376 (96)	≤6 = 136 (96)	≤6 = 240 (97)	0.6096
	7 = 14 (4)	7 = 6 (4)	7 = 8 (3)	
Clinical stage, n (%)	T1 = 204 (52)	T1 = 65 (46)	T1 = 139 (56)	0.1817
	T2 = 182 (47)	T2 = 75 (53)	T2 = 107 (43)	
	TX = 4 (1)	TX = 2 (1)	TX = 2 (1)	
Risk group, n (%)	Low = 323 (84)	Low = 123 (88)	Low = 200 (82)	0.1099
	Inter. = 62 (16)	Inter. = 17 (12)	Inter. = 45 (18)	
Patients treated with hormonal therapy, n (%)	75 (19)	37 (26)	38 (15)	0.0120
Needles per implant	25 (14–38)	29 (18–38)	23 (14–33)	<0.0001
Seeds per implant	102 (56–152)	113 (80–152)	95 (56–141)	<0.0001
Prostate volume on TRUS (mL)	45.3 (15.8–84.6)	45.7 (19.3–74.4)	45.1 (15.8–84.6)	0.8330
Air kerma strength/cubic centimeter	0.010 (0.005–0.031)	0.09 (0.005–0.020)	0.011 (0.006–0.031)	<0.0001
Followup (y)	6.1 (0.1–10.7)	8.3 (0.9–10.7)	5.0 (0.1–8.1)	<0.0001

Inter. = intermediate; TRUS = transrectal ultrasound.

Data are represented as median (range).

[a] Student's t test was used to compare patient characteristics.

a total of 75 patients in the total patient population treated with neoadjuvant androgen deprivation therapy for a median duration of 4 months (range, 1−15 months). Despite the prostate volumes being similar between the two cohorts, fewer needles (median needles, 23 vs. 29; $p < 0.0001$) and fewer sources (median sources, 95 vs. 113; $p < 0.0001$) per implant were used in the intermediate source strength cohort compared with the low strength cohort.

Dosimetric analysis

The postoperative dosimetry of the patient populations are summarized in Table 2. The median D_{90} and V_{100} were significantly higher in the intermediate strength cohort of patients, with only 14% of patients treated in the intermediate strength cohort having a D_{90} lower than 140 Gy and 22% of patients with a V_{100} lower than 90% compared with 46% ($p < 0.0001$) and 52% ($p < 0.0001$), respectively, in the cohort of patients treated with lower strength sources. In addition, implants with higher strength sources achieved a higher median V_{150} and V_{200} in the postoperative dosimetry.

Rectal toxicity

The rectal postoperative dosimetry identified a larger proportion of patients with an RV_{100} higher than 1 cc (volume of postimplantation CT rectal volume in cubic centimeters receiving 100% of the prescribed dose) in the lower strength cohort compared with the intermediate strength cohort, as summarized in Table 3. Despite the better postoperative dosimetry, the only cases of rectal bleeding requiring cauterization (10 patients) and of a rectovesical fistula (1 patient) occurred in patients from the intermediate strength cohort.

Urinary toxicity

A higher incidence of catheterization was identified in patients implanted with low strength sources, as illustrated in Table 4. A univariate analysis examining patient and implant characteristics that are associated with urinary retention identified the number of seeds, number of needles, and prostate volume as factors correlated with catheterization (Table 5). However, the multivariate analysis did not identify any of these factors as being correlated with catheterization. Also, there were no significant differences in the incidence of prolonged catheterization or patients requiring a transurethral resection of prostate between the low and intermediate seed strength cohorts (Table 4).

Outcomes

Patients had a median followup of 6.1 years in this study, with longer followup in the cohort of patients with low strength sources (8.2 vs. 5.0 years). Figure 1 illustrates the Kaplan−Meier curves for biochemical relapse-free survival, demonstrating no statistically significant difference between these two cohorts of patients. Although there were 19 deaths in the low strength cohort (compared with 7 in the intermediate strength cohort), only 3 of these were owing to prostate cancer (compared with none in the intermediate strength cohort).

Discussion

This study confirmed that using sources of higher strength can be advantageous owing to more efficient utilization of resources in our patient population (9, 10). Despite patients having similar prostate volumes in our study, the number of seeds per implant decreased from a median of 113 seeds to 95 seeds, whereas the number of needles per implant decreased from 29 to 23 needles. We also identified a lower incidence of catheterization in patients with intermediate strength sources. This would be consistent with previous studies that have suggested that the decreased trauma from fewer needles being used in an implant can decrease the risk of urinary retention (14) and urinary morbidity (15). In this study, the two cohorts were well balanced with respect to the factors that predict for a higher risk of urinary retention (baseline IPSS scores, diabetes, and prostate volumes) (16, 17).

This study identified better quality implants in the intermediate source strength cohort compared with the low source strength cohort, as reflected by a higher D_{90} and

Table 2
Postoperative dosimetry of implants based on CT on Day 28 after the implant

Parameters	All patients ($n = 388$)	Low seed strength cohort ($n = 141$)	Intermediate seed strength cohort ($n = 247$)	p-Value
D_{90} (Gy)	152.6 (57.0−274.2)	139.6 (80.3−182.5)	160.0 (57.0−274.2)	<0.0001[a]
$D_{90} < 140$ Gy (%)[b]	26	46	14	<0.0001
V_{100} (%)	90.7 (58.6−100)	86.1 (60.0−98.5)	93.4 (58.6−100)	<0.0001[a]
$V_{100} < 90$% (%)[b]	33	52	22	<0.0001
V_{150} (%)	53.9 (12.7−97.4)	46.5 (12.7−76.1)	58.2 (26.3−97.4)	<0.0001[a]
V_{200} (%)	25.4 (3.7−86.8)	20.9 (3.7−46.7)	27.9 (11.5−86.8)	<0.0001[a]

D_{90} = minimum dose covering 90% of postimplantation CT prostate volume; V_{100}, V_{150}, and V_{200} = percentage of the postimplantation CT prostate volume covered by 100%, 150%, and 200% of the prescription dose, respectively.

Data are represented as median (range).

[a] Student's t test was used to compare cohorts.

[b] Independent tests of proportions was used to obtain p-values.

Table 3
Dose to rectum

Parameters	All patients ($n = 388$)	Low seed strength cohort ($n = 141$)	Intermediate seed strength cohort ($n = 247$)	p-Value
RV_{100} (cc)	0.91 (1.24)	1.33 (1.44)	0.66 (1.03)	<0.0001[a]
$RV_{100} > 1$ cc (%)[b]	30	47	21	<0.0001
$RD_{1\,cc}$ (Gy)	146.1 (44.3)	161.9 (47.8)	137.1 (39.5)	<0.0001[a]
$RD_{1\,cc} > 145$ Gy (%)[b]	44	61	33	<0.0001

RV_{100} = volume of postimplantation CT rectal volume in cubic centimeters receiving 100% of the prescribed dose; $RD_{1\,cc}$ = minimum dose covering 1 cc of postimplantation CT rectal volume.

Data are represented as mean (standard deviation).

[a] Student's t test was used to compare cohorts.

[b] Independent tests of proportions was used to obtain p-values.

smaller proportion of patients in this cohort with a D_{90} lower than 140 Gy [18]. The higher postoperative dosimetry may partially be owing to the higher air kerma strength per cubic centimeter in the intermediate source strength cohort compared with the low source strength cohort (0.11 U/cc vs. 0.09 U/cc, $p < 0.0001$). However, it should be noted that the dosimetry from the low strength source cohort would suggest that the dosimetry for this cohort of patients was particularly poor, as it was worse than the dosimetry from experienced centers using low strength sources [14]. The poor dosimetry in this cohort of patients was likely because of the inexperience of the brachytherapists at the time and the utilization of loose sources. With respect to experience, our brachytherapists currently have 6 years, on average (range, 4–10 years), of experience with prostate brachytherapy. However, at the time of the implants, particularly for the low-activity cohort, the physicians performing implants would have had less than 4 years of experience with implants using the current technique. It should be noted that our center transitioned to stranded sources by the time the program had switched to using intermediate strength sources for implants, which can be associated with a lower rate of seed loss that can potentially compromise the quality of an implant.

Despite the use of fewer sources and needles in the cohort of patients treated with intermediate strength sources, the postoperative dosimetry was not found to be compromised. Previously, there have been concerns that higher strength sources are more susceptible to operator error [4] owing to a greater impact on dosimetry with loss of sources or source misplacement. However, our study identified significantly higher D_{90} and V_{100} in the intermediate strength cohort of patients and significantly fewer patients in this cohort having suboptimal dosimetry. This study also demonstrated more inhomogeneity in patients treated with intermediate strength sources, similar to other studies that have demonstrated higher V_{150} and V_{200} with higher strength sources [11].

The increased dose inhomogeneity present with higher strength sources has raised concerns about the possibility of an increased risk of toxicities [11]. In particular, there have been concerns that late urinary toxicities could potentially be worse in this cohort of patients because of the increased V_{150} and V_{200} for this cohort. Fortunately, our review has not identified a significantly different rate of late urinary toxicities between the two cohorts of patients. This study did identify a higher incidence of late rectal toxicities in the intermediate seed strength despite having dosimetric parameters that would predict for a lower risk of late rectal toxicity in the overall cohort of patients (i.e., RV_{100}, RV_{150}, and $RD_{1\,cc}$) [19]. This raises the concern that potentially the differences in seed strength could have contributed to these differences. A review of the postoperative dosimetry of the patients experiencing these significant complications identified parameters that would predict for a higher risk of complications in these 11 patients ($RV_{100} = 2.16$ cc and $RD_{1\,cc} = 172.2$ Gy).

Some explanations can be provided for the increased rectal toxicity that was identified in the intermediate strength cohort despite the improved rectal dosimetry in the overall cohort. Although the cohort of patients with the higher strength sources have improved rectal dosimetry as a population, it should be noted that individual patients with sources deposited a bit closer to the rectum would have a greater increase in the rectal dose than with lower strength sources. Thus, although these differences may not be appreciated in comparisons between the two cohorts, it could place a higher risk of rectal toxicity for individual patients with a higher strength of sources. In fact, this was identified with the 11 patients suffering significant

Table 4
Urinary toxicity after brachytherapy implant

	Overall	Low seed strength	Intermediate seed strength	p
Catheterization, n (%)[a]	76 (19)	38 (27)	39 (17)	0.0013
Prolonged catheterization[a] (>3 wk)	8	4	4	0.6891
TURPs[a]	3	2	1	0.8064

TURP = transurethral resection of prostate.

[a] Independent tests of proportions was used to obtain p-values.

Table 5
Univariate analysis of factors for catheterization

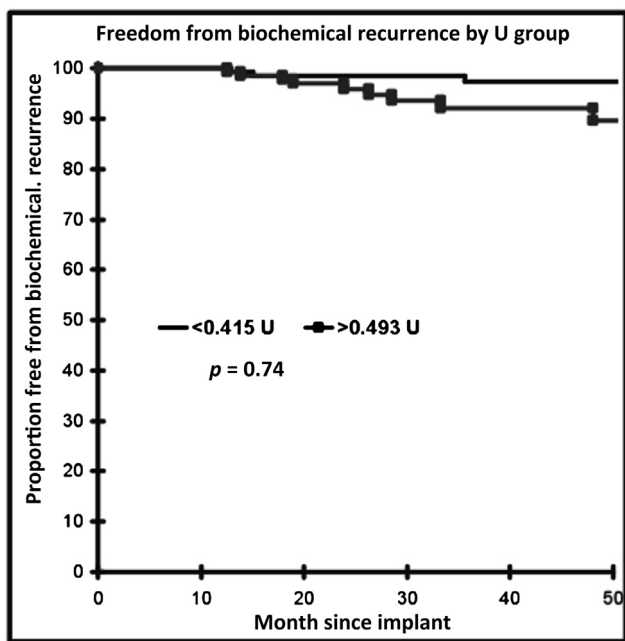| Factors	Odds ratio	95% CI	*p*-Value
Baseline IPSS	1.04	0.99−1.09	0.0825
Diabetes	1.87	0.80−4.33	0.1464
Prostate volume	1.03	1.01−1.05	0.0028
Number of seeds	1.02	1.01−1.04	0.0008
Number of needles	1.06	1.00−1.12	0.0486
Strength of sources (<0.415 U)	1.61	0.98−2.66	0.0611

CI = confidence interval; IPSS = International Prostate Symptom Score.

complications demonstrating higher rectal doses and overall dosimetry (i.e., higher D_{90} and V_{150}) on their postoperative dosimetry compared with patients not developing rectal complications. These findings are also consistent with previous reports identifying hotter postoperative dosimetry in patients developing rectal complications [20]. Also, it should be noted that these dosimetric assessments were taken at one point in time. It is possible that during the course of treatment, a patient's anatomy may change (i.e., owing to bladder filling, rectal distention, or prostatic edema) that can lead to changes in the dose distribution. These changes in anatomy may lead to more significant changes in the cohort of patients with intermediate strength sources because of the greater inhomogeneity that is present in this cohort, particularly with larger volumes of

Fig. 1. Freedom from biochemical recurrence by source strength. Kaplan−Meier curves of freedom from biochemical recurrence for 390 consecutive patients treated with prostate brachytherapy stratified by source strength. Solid line indicates patients with low seed strength (<0.415 U [0.327 mCi], median strength 0.405 U [0.319 mCi]) and boxed line indicates patients with intermediate seed strength (>0.493 U [0.388 mCi], median strength 0.494 U [0.389 mCi]).

tissue receiving 150% or 200% of the prescribed dose. Ideally, MRI−CT fusion would have allowed for more precise dosimetry to ensure that the differences in dosimetry were not owing to contouring variability. It is also possible that the implant geometry and preplanning algorithms used in planning the distribution of sources at our institution affects the rectal dosimetry to a greater extent for higher strength sources. Thus, although the finding of increased toxicity in the cohort of patients with improved dosimetric parameters is counterintuitive, there are plausible explanations to explain these differences.

The main purpose of this study was to confirm that the ultimate outcomes of patients treated with higher strength sources were not being compromised. There were no significant differences with respect to biochemical failure, prostate cancer mortality, or overall mortality between the two cohorts of patients. Although these early results are encouraging, longer followup will be necessary to confirm these results. One would not expect there to be significantly worse outcomes with respect to prostate cancer control in patients treated with higher strength sources. In fact, an argument could be made for improved tumor control owing to larger volumes of tissue receiving high doses of radiation (i.e., V_{150} or V_{200}) and an improved tumoricidal effect from this escalated dose. But this potential advantage must be weighed against the increased potential risk of toxicities, particularly given the significant differences identified in this study for rectal toxicities, despite other factors predictive of rectal toxicity being similar between the two groups.

In reviewing the outcomes of the two cohorts in this study, it is important to recognize the limitations of this study. The dosimetric analyses allowed for an understanding of how the implant characteristics were different between the two cohorts, although it should be recognized that these dosimetric parameters are subjective and contouring variability in delineating the prostate and critical structures could affect these results [21]. The toxicity and outcomes data were limited by their retrospective nature and the limited followup for some patients. In particular, retrospective reviews may underestimate low-grade toxicities that may not be captured retrospectively. However, the greatest limitation in this study may have been the potential confounding effect of a learning curve [14], as patients treated in the intermediate seed strength cohort were implanted by more experienced physicians, which could have affected the dosimetry and quality of implants between the two cohorts. These concerns prevent definitive conclusions from being made from this study, although this retrospective review was able to make observations and generate hypotheses based on its findings.

Conclusion

Our institution changed its practice in 2002 by increasing the strength of ^{125}I sources used for its prostate

brachytherapy implants. This transition was driven by the theoretical benefits that were identified in a planning study (6) and were subsequently confirmed in a dosimetric study (7). The present study continues to demonstrate that this change in practice did not compromise the clinical outcomes of patients, as our dosimetric, toxicity, and outcomes measures demonstrate that the higher strength sources led to comparable, if not better, outcomes than patients implanted with lower strength sources. This information will also be useful to other radiation oncologists who are considering a change in their source strength or have already undertaken such a change.

Acknowledgments

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