Investigating the dosimetric and tumor control consequences of prostate seed loss and migration

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Purpose: Low dose-rate brachytherapy is commonly used to treat prostate cancer. However, once implanted, the seeds are vulnerable to loss and movement. The goal of this work is to investigate the dosimetric and radiobiological effects of the types of seed loss and migration commonly seen in prostate brachytherapy.

Methods: Five patients were used in this study. For each patient three treatment plans were created using Iodine-125, Palladium-103, and Cesium-131 seeds. The three seeds that were closest to the urethra were identified and modeled as the seeds lost through the urethra. The three seeds closest to the exterior of prostatic capsule were identified and modeled as those lost from the prostate periphery. The seed locations and organ contours were exported from Prowess and used by in-house software to perform the dosimetric and radiobiological evaluation. Seed loss was simulated by simultaneously removing 1, 2, or 3 seeds near the urethra 0, 2, or 4 days after the implant or removing seeds near the exterior of the prostate 14, 21, or 28 days after the implant.

Results: Loss of one, two or three seeds through the urethra results in a D_{90} reduction of 2%, 5%, and 7% loss, respectively. Due to delayed loss of peripheral seeds, the dosimetric effects are less severe than for loss through the urethra. However, while the dose reduction is modest for multiple lost seeds, the reduction in tumor control probability was minimal.

Conclusions: The goal of this work was to investigate the dosimetric and radiobiological effects of the types of seed loss and migration commonly seen in prostate brachytherapy. The results presented show that loss of multiple seeds can cause a substantial reduction of D_{90} coverage. However, for the patients in this study the dose reduction was not seen to reduce tumor control probability.

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I. INTRODUCTION

Low dose-rate (LDR) brachytherapy is a radiation therapy modality that has enjoyed increased popularity in the treatment of low-grade prostate adenocarcinoma. By inserting radioactive seeds directly into the prostate, brachytherapy techniques are better able to spare healthy tissue compared with external beam radiotherapy. However, once implanted, the seeds are vulnerable to loss and movement. Factors that may influence the likelihood of seed movement include seed shape, implanted location and stranded versus loose seeds.¹

Seeds are most commonly lost in two ways: through the urethra or embolized in the lungs. Nag *et al.* have reported that approximately 9% of patients experience loose seed loss through the urethra.² These are typically seeds implanted too near to the prostatic urethra or implanted within the bladder. The time course for this type of seed loss tends to occur during first few days following implantation.² Seeds are also commonly found embolized within the lungs. Authors have reported 21%–29% of LDR patients will have loose seeds migrate to the lungs.^{3,4} These seeds may be seen on chest radiographs. It is thought that seeds implanted near the exterior

of the prostate migrate into the prostatic veins, which carry them from the prostate into the lungs. The time course for this type of seed loss seems more variable, ranging from day one to one month.³ Furthermore, loose seeds that remain within the prostate are also vulnerable to movements. Seeds are seen to become shifted toward the perineum.¹ As the seed is dropped and the needle withdrawn, it is thought that a vacuuming action occurs and the seeds are moved slightly toward the perineum. Seeds lost through the urethra will affect the dose to the central gland, those lost in the vasculature will affect the peripheral dose and those that migrate within the gland will shift dose intensity in an unintended way. In all these cases, the resulting dosimetry may be less than optimal.

Quantifying the dosimetric and radiobiological effects of seed loss and migration is important because they produce alterations in the dose distribution that can affect the clinical result. Ideally, these effects would be determined using post-implant dosimetry. However, for practical reasons many brachytherapists choose to perform the follow-up scan the same day as the implant.⁵ Therefore, seeds destined for loss will still be in place during the scan. Additionally, since the acquired CT slice thickness is similar to the size of the seeds; small axial displacements may not be visualized.

The goal of this work is to explore the dosimetric and radiobiological effects of the types of seed loss and migration commonly seen in prostate brachytherapy. The results may be useful to clinicians, since they provide a fairly realistic picture of the impact that the problem of seed loss following implantation may have. This work is unique in that it provides a comprehensive evaluation of seed loss and migration, assessing not only their impact in dosimetric terms but also in terms of radiobiological response, for the three most commonly used isotopes.

II. MATERIAL AND METHODS

Five patients were selected on the grounds of their uniform clinical characteristics and their clinical data were used in this study. The range of prostate volumes was 21.3–37.0 cc with the average being 31.1 cc. These patients are representative of *medium* sized patients treated at our facility. The seed implants were all planned using a modified peripheral loading scheme. The number of seeds used ranged from 61 to 101. For each patient, three treatment plans were created, each using a different radioisotope. Treatment plans were created using ¹²⁵I seeds (BARD, BrachySource model, Covington, GA) to a dose of 145 Gy; ¹⁰³Pd seeds (Theragenics, model 200, Buford, GA) to a dose of 125 Gy; and ¹³¹Cs seeds (Iso-Ray, CS-1 Rev2, Richland, WA) to a dose of 115 Gy. All implants used loose seeds. Transrectal ultrasound (TRUS) images were used for treatment planning on the Prowess Panther 3D Brachy Pro (Prowess, Concord, CA). Volumes for the prostate, urethra, rectum, and bladder were drawn by a physician. Once the plans were created, the three seeds that were closest to the urethra were identified and modeled as the seeds lost through the urethra in this analysis. The three seeds closest to exterior of prostatic capsule were identified and modeled as the seeds that will be lost from the prostate periphery.

The seed locations and organ contours were exported from Prowess and used by in-house software to perform the dosimetric and radiobiological evaluation. Seed loss through the urethra was simulated by removing 1, 2, or 3 seeds near the urethra. Seed loss was simulated by removing simultaneously the selected seed(s) in each case 0, 2, or 4 days after the implant. Similarly, seeds lost from the prostate periphery were simulated by removing 1, 2, or 3 seeds near the exterior of the prostate 14, 21, or 28 days after the implant. Seed selection was done with the assumption that the seeds nearest to the urethra or prostate periphery were most likely to be lost. The time course for seed loss used is consistent with times given in literature reports.^{2,3} This work uses $D_{\min}$, D_{50} , D_{80} , D_{90} , V_{100} , and V_{150} for the dosimetric evaluation. These dose quantifiers are commonly used clinically and recommended by American Association of Physicists in Medicine (AAPM) Task-Group (TG) 64.⁶ The radiobiological evaluation made use of response probabilities to the tumor and organs at risk and were calculated using equations recommended in AAPM TG-137.⁷ The biological parameters used in the study are those recommended by King *et al.*⁸ In addition to seed loss, seeds are also commonly seen to be *vacuumed* or *pulled* toward the perineum when the needle is withdrawn. This effect was simulated by applying a small uniform shift to all seeds. All seeds were shifted based on the assumption that each seed is equally susceptible to this effect.

The radiobiological response to the treatment was calculated using the linear-quadratic model. The physical dose was calculated from the AAPM TG-43 formalism, using the seed strengths and coordinates from Prowess.⁹ Then, the organ contours for each ultrasound image slice were exported from Prowess. Based on the physical dose and type of tissue present in each voxel, the response probability was calculated. The value of tumor control probability (TCP) is based on a calculation of biologically effective dose (BED), which is calculated using the following equation:^{10–12}

$$BED_{\text{tum}} = D_{\text{eff}} \left\{ RBE + \left[\frac{2R_0\lambda}{(\mu - \lambda)(\alpha/\beta)_{\text{tum}}} \right] * A * (B - C) \right\} + \frac{K}{\lambda} \ln \left(\frac{K}{RBE * R_0} \right), \quad (1)$$

where

$$A = \frac{1}{1 - e^{-\lambda T_{\text{eff}}}},$$

$$B = \frac{1 - e^{-2\lambda T_{\text{eff}}}}{2\lambda},$$

$$C = \frac{1 - e^{-T_{\text{eff}}(\mu + \lambda)}}{\mu + \lambda}.$$

In the above equations, R_0 is the initial dose rate and λ is the decay constant (for ¹²⁵I $\lambda = 0.01166 \text{ day}^{-1}$, ¹⁰³Pd $\lambda = 0.04079 \text{ day}^{-1}$, ¹³¹Cs $\lambda = 0.07144 \text{ day}^{-1}$). The α/β for the prostate was assumed to be 3 Gy and α component used was 0.3 Gy⁻¹.⁸ The sublethal damage repair constant (μ) was calculated by

$$\mu = \frac{\ln(2)}{T_{1/2}}. \quad (2)$$

TABLE I. Summary of the dosimetric and radiobiological parameters used in the analysis.

Parameters related to the isotopes			
Parameters/isotopes	I-125	Pd-103	Cs-131
Decay constant, λ (day ⁻¹)	0.01166	0.04079	0.07144
Relative biological effectiveness, RBE	1.45	1.75	1.45
Parameters related to prostate			
Repair half-life, $T_{1/2}$ (min)		16	
Sublethal damage repair constant, μ (h ⁻¹)		2.6	
Tumor repopulation factor, K (Gy/day)		0.0385	
α/β (Gy)		3.0	
α (Gy ⁻¹)		0.3	
Maximum normalized dose-response gradient, γ		6.45	

This factor accounts for the decrease in cell kill as the cell repairs damage. Here, a general repair half-life of 16 min was assumed, making $\mu = 2.6 \text{ h}^{-1}$.^{13,14} The tumor repopulation factor (K) accounts for the growth of new tumor cells during treatment and is calculated from Eq. (3).^{12,15} A K factor of 0.0385 Gy/day was used in this study.⁸

$$K = \frac{\ln(2)}{\alpha T_{\text{pot}}}. \quad (3)$$

The effective dose (D_{eff}) was calculated using Eq. (4). The effective treatment time (T_{eff}) was determined from Eq. (5). The endpoint for brachytherapy has been defined as the point where the rate of cell kill is equal to the tumor repopulation factor. For normal tissues it is assumed that $T_{\text{eff}} = \infty$, hence the effective dose is taken to be equal to the total physical dose accumulated over the lifetime of the seeds.

$$D_{\text{eff}} = D(1 - e^{-\lambda T_{\text{eff}}}), \quad (4)$$

$$T_{\text{eff}} = -\frac{1}{\lambda} \ln\left(\frac{K}{R_0^* \text{RBE}}\right). \quad (5)$$

The relative biological effectiveness (RBE) for ¹²⁵I, ¹⁰³Pd, and ¹³¹Cs used in this study were 1.45, 1.75 and 1.45, respectively.^{12,16} γ is the maximum normalized dose-response gradient. The values of γ used in this study were 6.45.⁸ Voxel response probability (TCP) was then determined using Eq. (6).¹⁷ The overall response probability for the tumor was calculated using Eq. (7). The response probability of the individual organs at risk was calculated by the relative seriality model. Equations (1)–(5) are equivalent to those in TG-137 with the addition of the RBE factor, implementing the original expression by Dale.^{9–11} RBE was included in this work because, for the energies of the isotopes used, the RBE differs from unity. Its inclusion is expected to improve the estimates of tumor control.

$$\begin{aligned} \text{TCP} &= \exp(-N_0^* \exp(-\alpha^* \text{BED})) \\ &= \exp(-\exp(e^* \gamma)^* \exp(-\alpha^* \text{BED})) \Rightarrow \\ \text{TCP} &= \exp(-\exp(e^* \gamma - \alpha^* \text{BED})), \end{aligned} \quad (6)$$

where N_0 is the number of the clonogenic cells of the tumor and it is related to the radiobiological parameter γ through the following expression:

$$N_0 = \exp(e^* \gamma),$$

where e is the base of the natural logarithm.

$$P_{\text{tum}}(D, V) = \prod_{i=1}^N \text{TCP}(D_i)^{\Delta v_i}, \quad (7)$$

where N is the number of voxels or sub-volumes in the tumor and Δv_i is their fractional volume in relation to the total volume of the tumor. A summary of the values of all the parameters used in the present analysis are presented in Table I.

III. RESULTS

The dosimetry of the original treatment plans is summarized in Table II. The treatment plans used in this work have dosimetry similar to typical clinical plans. Tables III–V show the dosimetric and radiobiological results for seeds lost through the urethra for Iodine-125, Palladium-103, and Cesium-131, respectively. Tables VI–VIII show the dosimetric and radiobiological results for seeds lost to the lungs for Iodine-125, Palladium-103, and Cesium-131, respectively. The radiobiological responses of the normal tissues adjacent to the prostate were not shown in these tables because loss of seeds can only result in a beneficial reduction of toxicity.

Figure 1 shows the effect of displacing the seeds toward the perineum on tumor control probability and prostate D_{50} , D_{90} , V_{100} , and V_{150} . For the plots in Fig. 1, the uncertainties in D_{50} and D_{90} were similar and around 20 Gy for all the points.

TABLE II. Summary of the dosimetric and response evaluation of the original treatment plans.

Isotope	D_{min} (Gy)	D_{50} (Gy)	D_{80} (Gy)	D_{90} (Gy)	V_{100} (%)	V_{150} (%)	TCP (%)
I-125	109 ± 10	296 ± 24	165 ± 12	153 ± 6	92.4 ± 6.0	44.0 ± 8.0	99.9 ± 0.0
Pd-103	91 ± 12	262 ± 29	140 ± 10	127 ± 9	89.7 ± 5.6	48.8 ± 7.1	99.9 ± 0.0
Cs-131	90 ± 8	265 ± 67	136 ± 5	125 ± 3	95.3 ± 1.3	42.3 ± 3.7	99.9 ± 0.0

TABLE III. Results of the dosimetric and radiobiological effect of central seed loss through the urethra for implants with I-125 seeds. The results are presented as a difference from original plans and the corresponding variations among the five patients are indicated by the standard deviations.

¹²⁵ I								
# Seeds lost		$D_{\min}$ (Gy)	D_{50} (Gy)	D_{80} (Gy)	D_{90} (Gy)	V_{100} (%)	V_{150} (%)	TCP (%)
Day 0	1	-1.4 ± 1.4	-4.0 ± 0.7	-3.7 ± 1.0	-2.8 ± 0.7	-1.8 ± 1.7	-2.0 ± 0.4	0.0 ± 0.0
	2	-4.4 ± 3.2	-7.7 ± 1.3	-7.0 ± 1.5	-5.9 ± 1.0	-4.2 ± 3.4	-3.3 ± 0.6	-0.1 ± 0.1
	3	-8.7 ± 4.3	-10.4 ± 2.1	-9.7 ± 1.3	-9.1 ± 2.7	-5.9 ± 4.0	-4.1 ± 0.7	-0.4 ± 0.3
Day 2	1	-1.4 ± 1.4	-3.9 ± 0.7	-3.5 ± 1.0	-2.7 ± 0.7	-1.7 ± 1.6	-1.9 ± 0.5	0.0 ± 0.0
	2	-4.2 ± 2.9	-7.5 ± 1.3	-6.7 ± 1.5	-5.6 ± 1.0	-4.0 ± 3.4	-3.2 ± 0.6	-0.1 ± 0.1
	3	-8.0 ± 4.0	-10.2 ± 2.0	-9.3 ± 1.4	-8.7 ± 2.6	-5.7 ± 3.9	-4.0 ± 0.7	-0.3 ± 0.4
Day 4	1	-1.4 ± 1.3	-3.8 ± 0.7	-3.4 ± 0.9	-2.6 ± 0.7	-1.6 ± 1.5	-1.9 ± 0.5	0.0 ± 0.0
	2	-4.0 ± 2.7	-7.4 ± 1.2	-6.5 ± 1.4	-5.4 ± 1.0	-3.9 ± 3.2	-3.1 ± 0.6	-0.1 ± 0.1
	3	-7.3 ± 3.8	-9.9 ± 2.0	-9.0 ± 1.4	-8.4 ± 2.5	-5.5 ± 3.8	-4.0 ± 0.7	-0.3 ± 0.3

TABLE IV. Results of the dosimetric and radiobiological effect of central seed loss through the urethra for implants with Pd-103 seeds. Details as in Table II.

¹⁰³ Pd								
# Seeds lost		$D_{\min}$ (Gy)	D_{50} (Gy)	D_{80} (Gy)	D_{90} (Gy)	V_{100} (%)	V_{150} (%)	TCP (%)
Day 0	1	-3.8 ± 2.8	-3.8 ± 0.8	-2.4 ± 1.5	-2.3 ± 1.5	-1.7 ± 1.4	-1.1 ± 0.7	0.0 ± 0.0
	2	-9.1 ± 7.0	-6.7 ± 1.5	-5.3 ± 1.5	-4.9 ± 1.0	-3.6 ± 1.4	-2.4 ± 0.7	0.0 ± 0.0
	3	-10.0 ± 6.8	-9.7 ± 3.2	-7.4 ± 1.8	-7.6 ± 2.3	-5.2 ± 2.1	-3.5 ± 1.3	-0.1 ± 0.1
Day 2	1	-5.5 ± 3.2	-3.6 ± 0.8	-2.3 ± 0.7	-2.4 ± 0.7	-1.7 ± 0.9	-1.2 ± 0.3	0.0 ± 0.0
	2	-7.4 ± 4.9	-6.1 ± 1.5	-4.7 ± 1.2	-4.6 ± 1.1	-3.4 ± 1.3	-2.2 ± 0.7	0.0 ± 0.0
	3	-8.3 ± 4.9	-9.1 ± 2.3	-6.4 ± 1.5	-6.5 ± 1.7	-4.5 ± 1.8	-3.2 ± 1.2	-0.1 ± 0.1
Day 4	1	-4.6 ± 1.6	-3.3 ± 0.8	-2.1 ± 0.6	-2.1 ± 0.7	-1.5 ± 0.8	-1.1 ± 0.3	0.0 ± 0.0
	2	-6.3 ± 3.3	-5.9 ± 1.1	-4.1 ± 1.0	-3.8 ± 0.7	-2.8 ± 1.0	-2.0 ± 0.6	0.0 ± 0.0
	3	-7.0 ± 3.6	-8.5 ± 2.5	-5.8 ± 1.2	-5.7 ± 1.4	-4.1 ± 1.6	-2.9 ± 1.1	-0.1 ± 0.1

TABLE V. Results of the dosimetric and radiobiological effect of central seed loss through the urethra for implants with Cs-131 seeds. Details as in Table II.

¹³¹ Cs								
# Seeds lost		$D_{\min}$ (Gy)	D_{50} (Gy)	D_{80} (Gy)	D_{90} (Gy)	V_{100} (%)	V_{150} (%)	TCP (%)
Day 0	1	-2.8 ± 2.2	-4.4 ± 2.0	-3.4 ± 1.1	-2.9 ± 0.9	-1.3 ± 0.7	-5.2 ± 0.9	0.0 ± 0.0
	2	-7.7 ± 7.1	-8.0 ± 4.2	-6.0 ± 1.6	-5.9 ± 1.4	-3.2 ± 1.0	-6.4 ± 0.9	0.0 ± 0.0
	3	-10.6 ± 6.3	-11.7 ± 5.5	-8.8 ± 2.8	-8.5 ± 1.9	-4.9 ± 0.9	-7.6 ± 0.8	-0.1 ± 0.1
Day 2	1	-2.4 ± 1.6	-3.8 ± 1.8	-2.8 ± 0.9	-2.3 ± 0.8	-1.0 ± 0.5	-5.0 ± 0.9	0.0 ± 0.0
	2	-6.3 ± 6.0	-7.0 ± 3.6	-4.9 ± 1.1	-4.8 ± 1.0	-2.5 ± 0.7	-6.0 ± 0.9	0.0 ± 0.0
	3	-8.6 ± 5.3	-10.1 ± 4.8	-7.2 ± 2.2	-6.9 ± 1.4	-3.7 ± 0.7	-7.0 ± 0.8	-0.1 ± 0.1
Day 4	1	-2.1 ± 1.3	-3.3 ± 1.5	-2.3 ± 0.7	-1.9 ± 0.7	-0.9 ± 0.4	-4.8 ± 0.9	0.0 ± 0.0
	2	-5.3 ± 5.0	-6.0 ± 3.1	-4.1 ± 0.9	-4.0 ± 0.9	-2.0 ± 0.6	-5.7 ± 0.9	0.0 ± 0.0
	3	-7.2 ± 4.5	-8.8 ± 4.1	-6.2 ± 1.8	-5.6 ± 1.1	-3.0 ± 0.5	-6.6 ± 0.9	-0.1 ± 0.1

TABLE VI. Results of the dosimetric and radiobiological effect of peripheral seed loss for implants with I-125 seeds. Details as in Table II.

¹²⁵ I								
# Seeds lost		$D_{\min}$ (Gy)	D_{50} (Gy)	D_{80} (Gy)	D_{90} (Gy)	V_{100} (%)	V_{150} (%)	TCP (%)
Day 14	1	-0.5 ± 0.2	-3.3 ± 0.4	-1.3 ± 0.2	-1.3 ± 0.4	-0.7 ± 0.6	-1.8 ± 0.5	-0.1 ± 0.0
	2	-3.9 ± 6.6	-5.9 ± 1.1	-2.4 ± 0.5	-2.3 ± 0.7	-1.4 ± 1.2	-2.8 ± 0.6	-0.1 ± 0.1
	3	-5.1 ± 7.8	-9.2 ± 2.0	-3.7 ± 1.1	-3.5 ± 1.1	-2.1 ± 1.9	-4.1 ± 0.9	-0.2 ± 0.2
Day 21	1	-0.5 ± 0.2	-3.0 ± 0.4	-1.2 ± 0.2	-1.2 ± 0.4	-0.6 ± 0.5	-1.7 ± 0.5	0.0 ± 0.1
	2	-3.5 ± 5.9	-5.4 ± 1.0	-2.2 ± 0.5	-2.1 ± 0.7	-1.3 ± 1.1	-2.5 ± 0.5	-0.1 ± 0.1
	3	-4.6 ± 7.0	-8.5 ± 1.8	-3.4 ± 0.9	-3.2 ± 1.0	-1.9 ± 1.8	-3.8 ± 0.9	-0.1 ± 0.2
Day 28	1	-0.4 ± 0.2	-2.8 ± 0.4	-1.1 ± 0.2	-1.1 ± 0.3	-0.6 ± 0.5	-1.5 ± 0.5	0.0 ± 0.0
	2	-3.1 ± 5.3	-5.0 ± 0.9	-2.0 ± 0.4	-1.9 ± 0.5	-1.1 ± 1.0	-2.3 ± 0.5	-0.1 ± 0.1
	3	-4.2 ± 6.3	-7.8 ± 1.7	-3.1 ± 0.9	-2.9 ± 0.9	-1.7 ± 1.7	-3.4 ± 0.8	-0.1 ± 0.1

TABLE VII. Results of the dosimetric and radiobiological effect of peripheral seed loss for implants with Pd-103 seeds. Details as in Table II.

¹⁰³ Pd								
# Seeds lost		$D_{\min}$ (Gy)	D_{50} (Gy)	D_{80} (Gy)	D_{90} (Gy)	V_{100} (%)	V_{150} (%)	TCP (%)
Day 14	1	-6.5 ± 6.4	-2.3 ± 0.6	-0.7 ± 0.2	-0.6 ± 0.2	-0.5 ± 0.3	-0.7 ± 0.2	0.0 ± 0.0
	2	-6.7 ± 6.3	-4.0 ± 1.8	-1.2 ± 0.5	-1.1 ± 0.5	-0.7 ± 0.5	-1.1 ± 0.5	0.0 ± 0.0
	3	-9.3 ± 6.4	-6.3 ± 2.4	-2.0 ± 0.7	-1.7 ± 0.7	-1.2 ± 0.7	-1.8 ± 0.6	0.0 ± 0.0
Day 21	1	-5.5 ± 4.1	-1.7 ± 0.5	-0.5 ± 0.1	-0.5 ± 0.1	-0.3 ± 0.2	-0.5 ± 0.2	0.0 ± 0.0
	2	-5.6 ± 4.0	-3.0 ± 1.3	-0.8 ± 0.3	-0.8 ± 0.3	-0.5 ± 0.3	-0.8 ± 0.3	0.0 ± 0.0
	3	-7.4 ± 4.2	-4.7 ± 1.8	-1.4 ± 0.5	-1.3 ± 0.5	-0.8 ± 0.5	-1.2 ± 0.4	0.0 ± 0.0
Day 28	1	-4.7 ± 2.5	-1.3 ± 0.4	-0.3 ± 0.1	-0.4 ± 0.1	-0.2 ± 0.2	-0.4 ± 0.2	0.0 ± 0.0
	2	-4.8 ± 2.4	-2.3 ± 1.0	-0.6 ± 0.2	-0.6 ± 0.2	-0.4 ± 0.2	-0.6 ± 0.3	0.0 ± 0.0
	3	-6.0 ± 2.6	-3.6 ± 1.4	-1.0 ± 0.4	-0.9 ± 0.4	-0.6 ± 0.4	-0.9 ± 0.3	0.0 ± 0.0

TABLE VIII. Results of the dosimetric and radiobiological effect of peripheral seed loss for implants with Cs-131 seeds. Details as in Table II.

¹³¹ Cs								
# Seeds lost		$D_{\min}$ (Gy)	D_{50} (Gy)	D_{80} (Gy)	D_{90} (Gy)	V_{100} (%)	V_{150} (%)	TCP (%)
Day 14	1	-1.4 ± 1.1	-1.0 ± 0.4	-0.5 ± 0.3	-0.5 ± 0.1	-0.2 ± 0.0	-4.1 ± 0.9	0.0 ± 0.0
	2	-2.4 ± 1.3	-2.3 ± 1.1	-1.3 ± 1.2	-1.1 ± 1.2	-0.5 ± 0.1	-4.8 ± 0.8	0.0 ± 0.0
	3	-4.0 ± 2.1	-3.7 ± 1.8	-1.8 ± 0.7	-1.6 ± 0.5	-0.8 ± 0.2	-5.1 ± 0.9	0.1 ± 0.0
Day 21	1	-1.3 ± 1.1	-0.6 ± 0.2	-0.3 ± 0.2	-0.3 ± 0.1	-0.1 ± 0.0	-3.9 ± 0.9	0.0 ± 0.0
	2	-1.8 ± 1.3	-1.4 ± 0.6	-0.7 ± 0.3	-0.6 ± 0.1	-0.3 ± 0.0	-4.2 ± 0.9	0.0 ± 0.0
	3	-2.9 ± 1.4	-2.2 ± 1.1	-1.1 ± 0.4	-0.9 ± 0.3	-0.5 ± 0.0	-4.5 ± 0.8	0.0 ± 0.0
Day 28	1	-1.2 ± 1.1	-0.4 ± 0.1	-0.2 ± 0.1	-0.2 ± 0.1	-0.1 ± 0.0	-3.8 ± 0.8	0.0 ± 0.0
	2	-1.4 ± 1.0	-0.8 ± 0.4	-0.4 ± 0.2	-0.3 ± 0.8	-0.2 ± 0.1	-3.9 ± 0.9	0.0 ± 0.0
	3	-2.2 ± 1.1	-1.3 ± 0.6	-0.7 ± 0.3	-0.6 ± 0.1	-0.3 ± 0.0	-4.1 ± 0.8	0.0 ± 0.0

FIG. 1. Top: Tumor control probability as a function of distance displaced toward the perineum. Middle: D_{90} and D_{50} as a function of the distance displaced toward the perineum. Bottom: V_{100} and V_{150} as a function of the distance displaced toward the perineum. The curves have been averaged over all the five examined patients.

The uncertainties in V_{100} and V_{150} were also similar and around 10%. The uncertainty in the TCP plot varied most significantly around the inflection point and it was of the order of 20%. This uncertainty is due to differences in the TCP curves of the patients in addition to the locally high gradient.

IV. DISCUSSION

In the past, different research groups have investigated different elements of this problem. Gao and colleagues analyzed dosimetrically and radiobiologically the clinical data of 14 patients treated with Pd-103, who had a much larger range of prostate volumes and number of seeds used as well as a different pattern of seed migration.¹⁸ Beaulieu and colleagues studied the dosimetric impact of seed misplacement and migration of a prostate case of similar prostate size as that of the present analysis. Furthermore, seed misplacement and migration were simulated by a Monte Carlo method,

based on the measured displacement distributions from clinical post-implant cases.¹⁹ In the study by Su and colleagues, the variation of permanent prostate brachytherapy dosimetry as a function of seed detection rates was investigated for nine patients and I-125 implants with seed activities commonly employed in contemporary practice.²⁰

The results of this study show that the amount of dose lost is dependent on the number of seeds lost and the time at which they were lost. The location of the lost seeds (near urethra or prostate periphery) seems to have little effect on the magnitude of dose reduction, since seeds at both locations contribute similarly to the overall dose. For seeds lost through the urethra, since the loss typically occurs very quickly after the implant, the dose loss per seed is consistent among the isotopes. It should also be noted that approximately the same number of seeds were used for each patient's plans. The magnitude of seed loss effects may vary if the implant used stronger or weaker seeds. Indeed,

Beaulieu and colleagues have shown that very high activity seeds are more strongly affected by seed position inaccuracy.¹⁸ However, they reported that the importance of seed activity was minimal for the range of activities commonly used. Based on these findings, the results of this work are expected to be accurate even for implants with somewhat different seed strengths. The effect per seed lost being proportional to the seed strength. Based on the findings of this study, loss of one seed through the urethra results in a D_{90} reduction of 2%. Loss of two or three seeds results in a 5% and 7% loss, respectively. These results are similar to those by Su and colleagues, who studied dose coverage with incomplete seed detection. Su and colleagues reported that D_{90} was reduced by 5% when 5% of seeds were not detected.¹⁹ The relative reduction in V_{100} is similar to that of D_{90} . However, while the dose reduction is modest for multiple lost seeds, the reduction in tumor control probability was minimal.

Due to delayed loss of peripheral seeds, the dosimetric effects are less severe than for loss through the urethra. This is due to the fact that those peripheral seeds are characterized by lower strength/activities since a considerable time has elapsed from their initial placement and start of treatment. Additionally, the delay in loss results in differences between the isotopes. The effect was proportional to the half-life of the isotope. Contrary to the lower dose loss per seed, the reduction in TCP for seeds lost to the lungs was seen to be no different than the reduction caused by the seeds lost through the urethra.

Regarding the displacement of seeds toward the perineum, the results show that movement of 3 mm or less does not result in a major reduction in D_{90} . This magnitude of movement is similar to reports of commonly observed seed placement variation.²⁰ A 2 mm distal migration was found in this work to reduce D_{90} by 1.2%. This is comparable to the results by Gao and colleagues, who reported a reduction in D_{90} by 0.8% for a 2 mm random migration.²¹ While D_{90} is reduced for displacements greater than 3 mm, Fig. 1 shows that tumor control is unaffected until displacements greater than 8 mm. The normal tissue complication probabilities for the bladder, rectum and urethra varied little, even for large displacements. However, some have suggested that large inferior seed movement may increase the dose to the penile bulb, increasing the likelihood of sexual dysfunction.¹

Due to the fact that these patients are characterized by very similar clinical characteristics we believe that the number of the selected patients is adequate to give us a good picture of the impact of seed loss and migration on such type of patients. However, similar studies have to be performed for patient groups of different characteristics and especially different prostate volumes in order to provide more general conclusions.

The results of this work show that unanticipated seed loss may affect dose coverage to the prostate. However, the observed reduction in dose was not seen to adversely affect the estimated TCP. An explanation for this may be that common dose prescription levels which were determined by clinical experience are relatively overdosed, which negates the

effect of the relatively common occurrence of seed loss. Furthermore, it seems that the standard treatment plans are very robust against these types of dose delivery uncertainties. This is due to the fact that these dose distributions do not match the underlying radiosensitivity map of the clinical case, which makes them less conformal. Performing a treatment plan optimization using radiobiological objectives could result in a more conformal dose distribution to the target and OARs with the potential of reducing the overall dose, which should reduce toxicity. Such a dose distribution would be expected to better spare the OARs while being more vulnerable to uncertainties such as seed loss. While the reduction in TCP was not great for these patient plans, we believe that the information presented here may be useful for patients with compromised dosimetry before seed loss.

V. CONCLUSIONS

The goal of this work was to explore the dosimetric and radiobiological effects of the types of seed loss and migration commonly seen in prostate brachytherapy. The results presented show that loss of multiple seeds can cause a reduction of D_{90} coverage. However, for the patients in this study the dose reduction was not seen to reduce tumor control probability. The results of this work may be useful in making patient management decisions following seed loss.

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