

# Impact of edema and seed movement on the dosimetry of prostate seed implants

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## ABSTRACT

This article summarizes current knowledge concerning the characterization of prostatic edema and intra-prostatic seed movement as these relate to dosimetry of permanent prostate implants, and reports the initial application to clinical data of a new edema model used in calculating pre- and post-implant dose distributions. Published edema magnitude and half-life parameters span a broad range depending on implant technique and measurement uncertainty, hence clinically applicable values should be determined locally. Observed intra-prostatic seed movements appear to be associated with particular aspects of implant technique and could be minimized by technique modification. Using an extended AAPM TG-43 formalism incorporating the new edema model, relative dose error RE associated with neglecting edema was calculated for three I-125 seed implants (18.9 cc, 37.6 cc, 60.2 cc) performed at our center. Pre- and post-plan RE average values and ranges in a 50 × 50 × 50 mm<sup>3</sup> calculation volume were similar at ~2% and ~0–3.5%, respectively, for all three implants; however, the spatial distribution of RE varied for different seed configurations. Post-plan values of D90 and V100 for prostate were reduced by ~2% and ~1%, respectively. In cases where RE is not clinically negligible as a consequence of large edema magnitude and / or use of Pd-103 seeds, the dose calculation method demonstrated here can be applied to account for edema explicitly and there by improve the accuracy of clinical dose estimates.

**Key words:** Brachytherapy dosimetry, edema, I-125 seed prostate implant, seed movement

## Introduction

Since its development by Holm and colleagues a quarter century ago,<sup>[1]</sup> transperineal interstitial permanent prostate brachytherapy (TIPPB) has emerged as a highly effective, resource-efficient, and popular treatment for localized prostate cancer.<sup>[2]</sup> A review of recent literature focusing on long-term outcomes<sup>[3]</sup> concludes that durable biochemical control rates above 90% for low-risk disease and above 80% for intermediate-risk disease can be achieved in both

the academic and community hospital setting. However, such favorable outcomes are highly dependent on implant quality as a tumoricidal dose of radiation must be delivered to the target. In implant programs where quality is notably lacking, reported control rates are reduced significantly by about 20%.<sup>[3]</sup>

In contemporary practice, implant quality assessment relies on dose-volume quantifiers estimated from image data acquired after the operative procedure. Because of the importance of these quantifiers, current practice guidelines issued by American Association of Physicists in Medicine (AAPM)<sup>[4]</sup> and Groupe Européen de Curiethérapie of the European Society for Therapeutic Radiation Oncology (GEC-ESTRO)<sup>[5]</sup> recommend that post-implant dosimetry be performed for all TIPPB patients. Dose should be calculated using the TG-43 formalism at a single time point lying within a radionuclide-dependent time interval chosen to mitigate the effects of edema. GEC-ESTRO recommends waiting until edema subsides before calculating dose; however, this approach might not yield accurate dosimetry for Pd-103 and Cs-131 implants. AAPM recommends an “optimal” time interval within which to calculate dose; however, the recommended interval does not accommodate the full range of variation

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in edema dynamics reported clinically. Neither AAPM nor GEC-ESTRO guidelines address the possibility of seed movement within the prostate apart from that induced by edema (herein referred to as “seed movement”) during the course of radiation delivery.

This article provides an overview of the impact of edema and seed movement on the dosimetry of prostate implants and reports the initial clinical application of a new edema model developed for the purpose of refining implant dose calculations using an extended TG-43 formalism. First, a brief description of the pre-planning approach to TIPPB taken at our center is presented. This is followed by a review of edema and seed movement literature as it pertains to implant dosimetry. Then, the new edema model<sup>[6]</sup> is applied to calculate dose distributions for selected I-125 implants done at our center. Results are reported in terms of parameter *RE*, which quantifies the dosimetric error which occurs when edema is neglected and dose is calculated after edema has resolved, and in terms of changes in dose parameters  $V_{100}$ ,  $V_{150}$ ,  $V_{200}$ , and  $D_{90}$ . The impact on dosimetry of varying edema magnitude and of using Pd-103 instead of I-125 seeds is also briefly examined. The article concludes by summarizing current practices aimed at mitigating the impact of edema and seed movement on dosimetry and indicating possible future means to include these effects explicitly in clinical dose calculations.

## Materials and Methods

### Transperineal interstitial permanent prostate brachytherapy technique

At our center, permanent I-125 seed implants have been used as monotherapy treatment for low-risk or low-tier intermediate-risk prostate cancer since 1998. The dose prescribed is 145 Gy,<sup>[4]</sup> and a pre-planning approach is taken that makes use of a set of 5-mm-thick transrectal ultrasound (TRUS) images acquired approximately 4 weeks before implantation. The treatment planning process involves defining a planning target volume (PTV) by adding 3 mm margins to the prostate contours anteriorly and laterally and a 5-mm margin at the apex, and visualizing the urethra using aerated gel. Needle locations are chosen from among those on a standard template grid falling no more than 2

mm outside the prostate contour at mid-gland. A custom plan is created manually for each patient to meet the dose-volume objectives given in Table 1 using a fixed seed strength of  $\sim 0.5$  U for all patients.

Needle spacing on the template grid and seed spacing within the needles are not strictly constrained by “rules;” however, these are made as uniform as planning objectives will allow. The approach taken to seed strength selection and seed placement, which can be characterized as falling somewhere between the modified uniform and peripheral loading schemes,<sup>[7-9]</sup> is based on clinical and dosimetric considerations summarized in <sup>[10]</sup>. A typical treatment plan for an average-sized prostate gland is illustrated in Figure 1.

Currently, implants are done with pre-loaded needles containing stranded seeds and post-implant dosimetry is performed on the day of implant (day 0) for all patients. A pelvic computed tomography (CT) scan having 3 mm slice thickness is obtained to visualize the prostate, seeds, and surrounding anatomical structures. A urinary catheter inserted in the operating theater typically remains in place for imaging to delineate the path of the urethra. Figure 2 illustrates day 0 post-implant dosimetry for the patient whose planned dosimetry is shown in Figure 1.

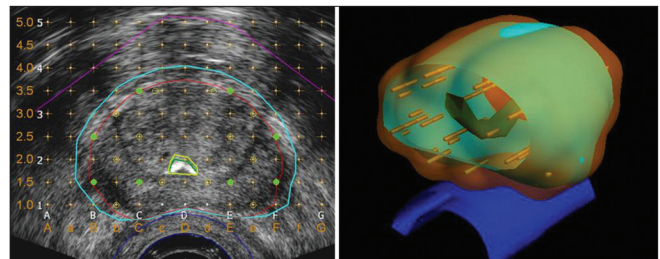


Figure 1: Pre-plan images for a 37.6-cc prostate implanted at our center with 0.5 U I-125 seeds. Left panel: Transrectal ultrasound image near mid-gland overlaid with contours delineating prostate (red), PTV (light blue), urethra (green), and rectum (dark blue). Also shown are the template grid, and seed (light green filled circles) and needle (yellow circles) locations. Right panel: 3D rendering of the 145 Gy isodose surface (translucent orange) covering the PTV (light blue). The prostate apex is at the front. Note that seed spacing in the needles is not uniform

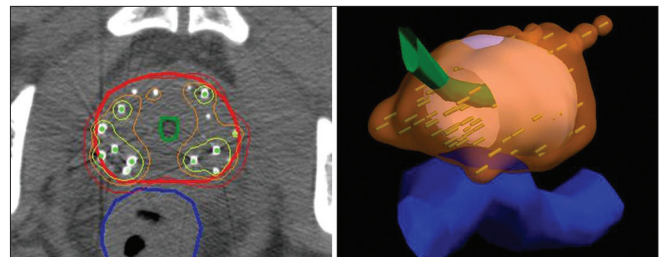


Figure 2: Post-plan images for the 37.6-cc prostate whose corresponding pre-plan images appear in Figure 1. Left panel: CT image near mid-gland overlaid with contours delineating prostate (red), urethra (green), and rectum (dark blue). Also shown are isodose lines corresponding to 100% (red), 150% (orange), and 200% (yellow) of the prescribed dose of 145 Gy. Right panel: 3D rendering of the 145 Gy isodose surface (translucent orange) covering the prostate (pink). The prostate apex is at the front

**Table 1: Dose-volume objectives used for transperineal interstitial permanent prostate brachytherapy treatment planning**

Dose parameter	Objective (%)
PTV $V_{100}$	>98
PTV $V_{150}$	≤65
PTV $V_{200}$	≤25
PTV $D_{90}$	120–130
Urethra $D_5$	<215 Gy
Rectum $D_{1cc}$	<145 Gy

While not routinely used at our center, magnetic resonance imaging (MRI) is employed occasionally to plan a supplementary implant when post-implant dosimetry for the initial implant reveals inadequate dose coverage. In this situation, T2-weighted MR images are registered with ultrasound and CT images from the initial implant to facilitate identification of the supplementary implant PTV.

### Edema and seed movement literature

The Medline® database of indexed medicine and health sciences literature was searched to identify pertinent articles. For prostate edema, the keywords “prostate implant,” “edema,” and “dosimetry” were used in the search strategy. For seed movement in prostate and periprostatic tissue, the keywords “prostate implant,” “seed movement,” “seed displacement,” and “dosimetry” were used. Key articles were then chosen from the search results and supplemented by references selected from those cited therein.

Each article’s core content was then summarized and the summaries organized to create an overview of current knowledge concerning the impacts of edema and seed movement on prostate implant dosimetry.

### Anisotropic edema model

A model for spatially anisotropic edema that resolves linearly with time was developed at our center<sup>[6]</sup> based on serial MRI measurements made on days  $-1$ ,  $0$ ,  $\sim 14$ , and  $\sim 28$  to characterize the edema for a group of  $N = 40$  prostate implant patients.<sup>[11]</sup> The model is briefly described here for completeness. Its main parameters are the maximum relative edema magnitude

$$\Delta = \frac{V_{\max} - V_s}{V_s} \quad \dots(1)$$

and the period over which the edema resolves,  $T$ . Here  $V_{\max}$  is the prostate volume associated with maximum edema and  $V_s$  is the prostate volume with no edema. The assumptions upon which the model is built are:

(i) that edema resolves with time according to (see Section “Prostatic edema”)

$$f_i(t) = (1 + \Delta(1 - t/T))^{\alpha_i}; \quad t < T; \quad i = \{x, y, z\} \quad \dots(2)$$

where  $\alpha_x = 0$ ,  $\alpha_y = \alpha_z = 1/2$  are quantifiers of the directional contributions to edema volume subject to the constraint  $\alpha_x + \alpha_y + \alpha_z = 1$ , and  $f_i(t) = 1$  for  $t \geq T$ ; and

(ii) that a seed implanted at location  $\vec{r}^s$  follows the movement of its surrounding tissue in all three Cartesian directions without further migration, i.e.

$$r_i^s(t) = r_i^s \cdot f_i(t); \quad i = \{x, y, z\} \quad \dots(3)$$

In the presence of edema, the cumulative dose from a seed to a calculation point located at  $\vec{r}$  relative to the seed, measured after the edema has resolved ( $t \rightarrow \infty$ ), can be expressed by extending the TG-43 formalism<sup>[4]</sup> for a point source as follows:

$$D(\vec{r}) = S_K \cdot \Lambda \cdot r_0^2 \cdot \bar{\phi}_{an} \int_0^\infty |\vec{r}(t)|^{-2} \cdot g(|\vec{r}(t)|) \cdot e^{-\lambda t} dt \quad \dots(4)$$

where  $S_K$  is the air-kerma strength of the seed,  $\Lambda$  the dose-rate constant,  $r_0$  the reference distance (usually 1 cm) for dose calculation,  $\bar{\phi}_{an}$  the average anisotropy constant,  $\lambda$  the time constant for radionuclide decay, and  $g(r)$  is the radial dose function accounting for additional dose fall-off beyond the geometrical reduction. Substituting Equations (2) and (3) into Equation (4) and evaluating the integral enables the dose around a single seed to be calculated in the presence of edema for specified values of  $\Delta$  and  $T$ . The total dose  $D_\Sigma$  to a calculation point is obtained by summing over all seeds in the implant.

The relative error arising from neglect of edema when calculating dose at any given point, expressed in percent, has been defined by Chen *et al.*<sup>[12]</sup> as

$$RE(\vec{r}) = 100 \times \frac{D_\Sigma(\vec{r})_{no-edema} - D_\Sigma(\vec{r})_{edema}}{D_\Sigma(\vec{r})_{edema}} \quad \dots(5)$$

With this definition,  $RE$  is always positive and indicates that the dose estimate obtained when edema is neglected overestimates the dose obtained when edema is considered.

### Relative dose error due to edema

Some potential implications for the clinical dosimetry of I-125, Pd-103, and Cs-131 implants in the presence of edema described by the above model were previously reported<sup>[6]</sup> using a reference configuration of seeds defined by the Radiological Physics Center (RPC) for the purpose of credentialing institutions participating in North American prostate brachytherapy clinical trials. In the present work, the edema model is applied for the first time to selected clinical implants.

For three prostates implanted with 0.5 U I-125 seeds (Oncura model 6711) and having volumes of 18.9 cc, 37.6 cc, and 60.2 cc,  $RE$  given by Equation (5) was calculated for both pre- and post-implant dose distributions for a single edema period  $T = 28$  d, and relative edema magnitudes  $\Delta = 0.2, 0.4, 0.6$ , and  $1.0$ . For pre-plans,  $RE$  represents the dose error associated with edema for a “virtual” implant in which the geometrical arrangement of seeds is exactly as planned. All  $RE$  calculations were done in a  $50 \times 50 \times 50$  mm<sup>3</sup> volume centered on the seed distribution using 1 mm grid spacing. Seed coordinates exported from the clinical treatment planning system (VariSeed v8.0, Varian Brachytherapy, Charlottesville, VA, USA) were used to place seeds exactly on grid positions for the pre-plans, and to snap seeds to the nearest grid position for post-plans after

applying a transformation (using Equations (2) and (3) with  $\Delta = 0.2$  and  $T = 28$  d) to estimate seed positions at time  $t > T$  from those measured on day 0 ( $t = 0$ ). Mean values of  $RE$  were determined for the entire calculation volume and for the upper 10% of  $RE$  values in the volume. Dose parameters  $V_{100}$ ,  $V_{150}$ ,  $V_{200}$ , and  $D_{90}$  for PTV (pre-plan) or prostate (post-plan) were then calculated using the CERR software platform (<http://www.cerr.info/about.php>) using structure contours exported from VariSeed. Calculations were repeated for the 37.6 cc prostate with the exact same seed configuration but using Pd-103 seeds (Theragenics model 200) of strength 2.5 U instead in order to obtain comparative data for a hypothetical Pd-103 implant. By way of further comparison, corresponding results for the isotropic edema model of Chen *et al.*,<sup>[12]</sup> adapted to reflect the time resolution of edema described in Equation (2), were also obtained.

## Results and Discussion

### Prostatic edema Characterization

The swelling of prostatic and peri-prostatic tissue that accompanies a TIPPB procedure is understood to be caused by mechanical insult associated with needle introduction. In a small study involving  $N = 28$  implant patients, Eapen and colleagues<sup>[13]</sup> found a statistically significant correlation between acute urinary toxicity and the total number of peri-urethral needle insertions / manipulations performed. A plausible explanation for their finding is that edema magnitude is directly related to the number of needle manipulations and the ensuing edema is responsible for the observed urinary toxicity.

As demonstrated,<sup>[12]</sup> edema can have a considerable influence on prostate implant dosimetry, depending on its magnitude and time course and, for post-implant dosimetry, on the timing of post-implant imaging. The influence of edema on dosimetry also depends to a large extent on the radionuclide selected for treatment. In general, the influence of edema becomes greater as the half-life of the radionuclide becomes shorter<sup>[14]</sup> because a larger fraction of the treatment dose is delivered when the prostate is in an edematous state. Therefore, it is important to accurately quantify edema for dosimetric assessment purposes. In that regard,<sup>[11]</sup> contains an extensive review of edema magnitude, time course, and spatial isotropy measurements reported in the literature. The summary following is drawn from that review.

The combination of pre-implant TRUS and post-implant CT images has been used most often to measure edema characteristics. When derived from prostate contours delineated on these images, average relative edema magnitude obtained within 24 h after implant for different groups of patients ranged from  $\sim 0.15$  to  $\sim 0.65$ , and

when derived from contours delineated on (pre- and post-implant) TRUS images alone ranged from 0.05 to 0.30. CT alone has also been used to infer relative edema magnitude from measured changes in inter-seed distances,<sup>[15]</sup> as have orthogonal film pairs. For these approaches, average relative edema magnitude obtained within 24 h ranged from  $\sim 0.20$  to  $\sim 0.50$ . More recently, in some centers, MR images have been registered with CT to improve contouring accuracy for post-implant dosimetry purposes, while TRUS images have continued to be used to determine pre-implant prostate volumes. Average relative edema magnitude obtained within 24 h after implant from TRUS/MR contours ranged from 0.08 to 0.45. Only two published studies have made use of MRI alone to measure relative edema magnitude and both indicate a value  $\sim 0.2$  within 24 h of implant.<sup>[11]</sup> Such large variation in observed edema magnitudes can be partly attributed to technical factors such as number of seed trains used, seed insertion method, presence of stranding material, and patient tissue mechanical properties. However, a second and perhaps equally important contributor to this variation is measurement uncertainty, which the literature collectively indicates is imaging-modality specific. For the contour-based measurement method, MRI is expected to yield the most accurate results and CT the least accurate.

The time course of prostatic edema has also been measured using various combinations of TRUS, CT, radiographic, and MR images. Some studies indicate that edema resolves inverse exponentially with time, others that it resolves linearly, and still others that it does not follow a discernable trend. Average edema half-life (defined as the time interval over which edema magnitude falls to 50% of its maximum value) reportedly varies from 9.3 to 30 days. Half-lives for individual patients span a wider range from 4 to 170 days. Measurements made at our center based on sequential MRI<sup>[11]</sup> are consistent with linear time resolution of edema having a half-life of 15 days, as shown in Figure 3.

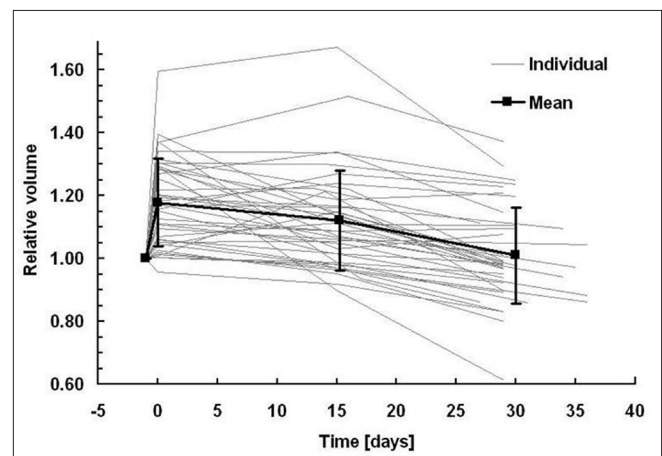


Figure 3: Relative prostate volume versus time for  $N = 40$  implant patients (gray lines) and the group mean (black line) measured using serial MRI on days 0, 1, 15, and 30.<sup>[11]</sup> Error bars represent one standard deviation in individual patient values



Prostate relative dimension measurements are quite rare. The three studies that report numerical data are in excellent agreement and indicate that the edematous prostate expands very little, if at all, in the L–R direction and substantively (and nearly equally) in the A–P and S–I directions.<sup>[11]</sup>

### **Mitigation of dosimetric effect**

Current practice guidelines from the AAPM<sup>[4]</sup> and GEC-ESTRO<sup>[5]</sup> recommend that post-implant dose be calculated using the TG-43 formalism at a single time point chosen to mitigate the effect of edema.<sup>[16,17]</sup> For I-125 implants, most centers calculate dose either on day 0 or on day 30 for reasons of practicality and/or convenience. Given the range of edema half-lives reported in literature, day 0 is not ideal and day 30 might not be optimal insofar as mitigation of the effect of edema is concerned. Several approaches have been developed to address this shortcoming:

- Increase the seed strength using either a fixed factor (1.1–1.15 has been suggested<sup>[18,19]</sup>) or a nomogram to obtain prostate size-dependent factors;<sup>[20]</sup>
- Place all needles prior to loading them and plan treatment intraoperatively,<sup>[21]</sup> thereby ensuring adequate dose coverage for the edematous prostate;
- Model edema in space and time (see e.g. Section “Anisotropic edema model”) and use the model to extend the TG-43 dosimetry formalism,<sup>[6,12,22]</sup> as is done here in Equation (4).

The first two approaches, while providing compensation for edema, do not improve the accuracy of dose calculations. The last approach which is followed in Section “Relative dose error due to edema” under “Results and Discussion,” does.

### **Intra-prostatic seed movement Characterization**

The question of whether seeds placed within and adjacent to the prostate move over the course of radiation delivery, apart from movement associated with edema, has been studied by several groups. At present, investigators appear equally divided in reporting the presence or absence of seed movement sufficient to affect dosimetry. Many of those reporting significant seed movement have noted that the observed movement could be associated with specific features of the implantation technique.

Fuller and colleagues<sup>[19]</sup> used orthogonal films and CT obtained on day 1 and orthogonal films obtained 3–12 months later to measure the prevalence of migration of loose and stranded (IBt InterStrands) seeds for  $N = 60$  patients. Seed migration was defined as the separation of a seed from the main seed cluster by  $>1$  cm. Using this definition, 0.49% of the seeds were found to migrate on or before day 1 and an additional 0.27% later; migration distances were not reported. Stranded seeds were found

to migrate less frequently than loose seeds, although the dosimetric consequences were described as modest.

McLaughlin *et al.*<sup>[23]</sup> employed CT/MRI fusion dosimetry on days 0 and 14 to study the impact of edema on dosimetry of stranded seeds (Oncura RapidStrand) for  $N = 28$  patients. Z-axis compression of strand length and a tendency toward an inferior shift of strands were observed for many patients. The magnitude of these seed movements was such that the authors concluded they had a greater impact on post-implant dosimetry than did prostate edema. A disclaimer is made that results might not apply to loose seeds.

Pinkawa *et al.*<sup>[24]</sup> used CT imaging on days 1 and 30 to measure the displacement of loose and stranded seeds (Oncura RapidStrand) with respect to pelvic bony anatomy for  $N = 51$  patients. Seeds near the prostate apex were stable over time relative to bone, but those near the prostate base moved inferiorly an average distance of 3.8 mm while the base itself moved an average distance of 3.5 mm inferiorly. Displacements were found to be greater in the inferior and posterior directions for stranded seeds versus loose seeds. The authors claim their analysis shows seed displacement to be another important factor besides edema in explaining dosimetric changes after permanent seed implantation; however, the analysis does not appear to clearly separate these two factors.

Crook’s group at Princess Margaret Hospital<sup>[25]</sup> applied CT/MRI fusion on days 0, 7, and 30 to study the movement of loose and stranded seeds (Biocompatibles VariStrand) and the impact on dosimetry for  $N = 40$  patients. Seed losses of 1.1% and 0.6% were observed in the stranded and loose seed cohorts, respectively; the urinary tract was identified as the primary site of loss. In both cohorts, dosimetric quality parameters showed the largest deterioration from pre-plan values on day 0 and gradual improvement as edema resolved. For some patients, significant caudal movement of strands with time was observed.

Usmani *et al.*<sup>[26]</sup> observed the movement of 232 seed strands (Oncura RapidStrand) with respect to implanted gold fiducial markers on CT between day 0 and day 30 for  $N = 10$  patients. Strand movements were found to be consistent with those caused by edema resolution, with 84% of strands migrating  $<5$  mm in any direction. The authors concluded that no clinically significant patterns of mean migration were identified.

Finally, Vassiliev and co-investigators<sup>[27]</sup> observed the movement of 72 peri-urethral strands (Biocompatibles VariStrand) with respect to penile bulb and base of prostate on day 0 and day 30 CT supplemented with day 30 MRI for  $N = 10$  patients. The mean displacement of peri-urethral stranded seeds relative to prostate did not exceed 1 mm in any direction and only two strands were displaced more than 4 mm.

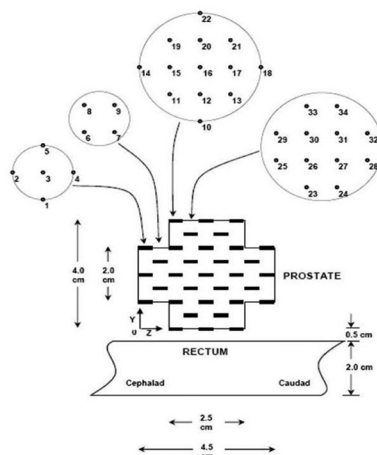
### Mitigation of dosimetric effect

Several investigators reporting dosimetrically significant seed/strand movements within prostate (apart from those associated with edema) point to the technical aspects of implant technique as possible explanations for the observed movements. Saibishkumar *et al.*<sup>[25]</sup> note that puncturing the bladder wall when introducing a needle likely increases the risk of seed loss via the urinary tract. Likewise, McLaughlin *et al.*<sup>[23]</sup> and Pinkawa *et al.*<sup>[24]</sup> suggest that placing a strand proximal to the prostate apex into the levator ani muscle could result in subsequent inferior movement of the strand when the muscle contracts. If the hypothesized seed movement mechanisms are correct, then modification of implant technique to avoid them seems most appropriate.

If dosimetrically significant intra-prostatic seed movements cannot be mitigated through modification of implant technique, then it might be possible to account for them using dynamical dosimetry.<sup>[28,29]</sup> In this approach, imaging is performed at multiple time points after the implant and dose is calculated based on the measured dynamics of the seed configuration. One obvious drawback is the added time and expense involved.

### Relative dose error due to edema

For comparison purposes, a reference *RE* distribution was calculated for a configuration of seeds defined by the Radiological Physics Center to credential institutions participating in North American prostate brachytherapy clinical trials. Figure 4 depicts the reference seed configuration and Figure 5 the associated distribution of *RE* values in the  $50 \times 50 \times 50 \text{ mm}^3$  calculation volume for I-125 seeds (Oncura model 6711) obtained using the anisotropic edema model with  $\Delta = 0.2$  and  $T = 28 \text{ d}$ . These edema parameters reflect average clinical values measured for patients implanted at our center.<sup>[11]</sup> A number of features



**Figure 4: Radiological Physics Center (North America) reference case #2 incorporates 81 seeds in a geometrical pattern inside a virtual prostate volume. This figure is available online at: [http://rpc.mdanderson.org/rpc/credentialing/Prostate%20Brachytherapy%20QA\\_Ref\\_Cases.pdf](http://rpc.mdanderson.org/rpc/credentialing/Prostate%20Brachytherapy%20QA_Ref_Cases.pdf) (accessed 31 October 2011)**

of the *RE* distribution are evident. First, the median *RE* value is small, being just over 2%. This is a consequence of radionuclide half-life and dose fall-off with distance, edema magnitude, and edema half-life. Second, *RE* ranges from near 0% to about 3.5%. This variation occurs because the effect of edema is minimal very close to a seed and increases in a directionally dependent manner at greater distances from it. Third, the greatest impact of edema is seen near the periphery of the seed configuration in the central sagittal slice. This feature arises from the spatially anisotropic nature of the edema, which is negligible in the left–right direction (*x* axis) and of equal magnitude in the anterior–posterior (*y* axis) and superior–inferior (*z* axis) directions (see Equation (2)).

Figures 6–8 present the distributions of *RE* values calculated for post-implant dose distributions for the 18.9 cc, 37.6 cc, and 60.2 cc prostates, using the same edema parameters as for the reference seed configuration of Figure 4. In comparison with Figure 5, the *RE* distributions for actual implants display both similarities and differences. *RE* median values and ranges for all three prostates are very close to those for the reference seed configuration, and larger values of *RE* continue to be seen surrounding the periphery of the seed configuration in the central sagittal slice. However, the *RE* distributions in the central axial and coronal slices, and throughout the calculation volume, clearly exhibit some degree of variation from implant to implant. This variation apparently stems from differences in the seed configurations.

A summary of volume-averaged *RE* values for all of the clinical seed configurations as well as the Radiation Therapy Oncology Group (RTOG) reference seed configuration appears in Figure 9. In addition to the average over the full calculation volume, the average over the highest 10% of *RE* values in the volume is presented. For comparison, the value of *RE* obtained using the isotropic edema model of Chen *et al.*<sup>[12]</sup> adapted for linear time resolution (see Equation (2)) is also shown. It can be seen that for I-125 seeds and the edema model parameters characterizing the implant technique at our center, both the RTOG reference seed configuration and the isotropic edema model yield average *RE* values in the calculation volume not too different from those for the clinical implants obtained using the isotropic edema model.

Table 2 summarizes the influence of edema on implant dose parameters as determined using the edema model. For the clinical pre- and post-plans done using I-125 seeds,  $D_{90}$  values for PTV and prostate are reduced, but by no more than 2.5%. Corresponding  $V_{100}$  values are likewise reduced, typically by  $\sim 0.5\%$  but by no more than 1.7%. By comparison,  $D_{90}$  values for the simulated Pd-103 implant created by using the mid-sized prostate I-125 seed locations

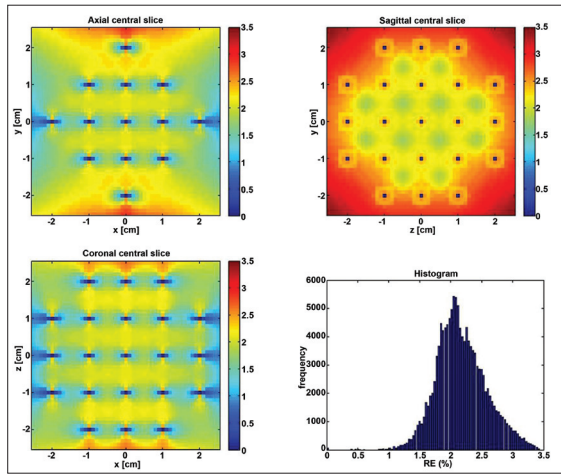


Figure 5: Percent relative dose calculation error  $RE$  (see Equation (5)) for a reference configuration [see Figure 4] of I-125 seeds (Oncura model 6711), obtained using the anisotropic edema model of "Materials and Methods" with  $\Delta = 0.2$  and  $T = 28$  d. These edema parameters reflect clinical values measured at our center. Panels depict planar distributions in central axial, sagittal, and coronal slices through the seed configuration, and the frequency distribution in the full calculation volume

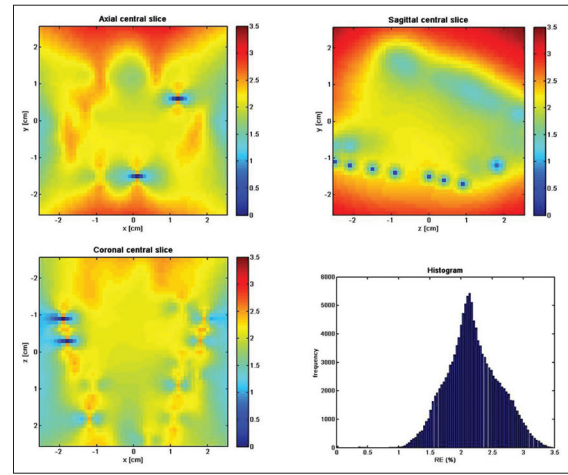


Figure 6: Relative dose error  $RE$  (%) for a post-implant distribution of I-125 seeds treating an 18.9-cc prostate, obtained using the anisotropic edema model with  $\Delta = 0.2$  and  $T = 28$  d. Panels depict planar  $RE$  distributions in central axial, sagittal, and coronal slices through the seed configuration, and the frequency distribution of  $RE$  in the full calculation volume

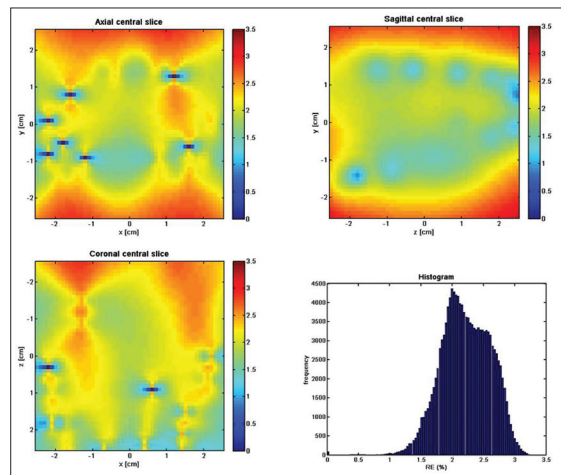


Figure 7: Relative dose error  $RE$  (%) for a post-implant distribution of I-125 seeds treating a 37.6-cc prostate, obtained using the anisotropic edema model with  $\Delta = 0.2$  and  $T = 28$  d. Panels depict planar  $RE$  distributions in central axial, sagittal, and coronal slices through the seed configuration, and the frequency distribution of  $RE$  in the full calculation volume

and scaling the seed strength are reduced by 7.5% for the pre-plan and 6.6% for the post-plan.

Finally, Figure 10 illustrates how volume-averaged  $RE$  values change with increasing edema magnitude for I-125 and Pd-103 implants. At small values of  $\Delta$ ,  $\langle RE \rangle$  increases nearly linearly with  $\Delta$  for both radionuclides and is considerably greater for Pd-103 than for I-125. The latter feature is explained by the shorter half-life and steeper dose fall-off with distance of Pd-103. Thus, it can be seen that the effect of edema on dosimetry can be minimized by using I-125 seeds and by refining implant technique so that the number of needle manipulations and consequently the maximum edema magnitude is reduced.

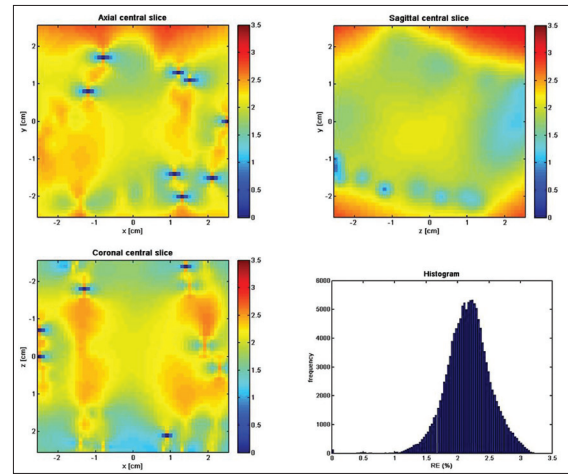


Figure 8: Relative dose error  $RE$  (%) for a post-implant distribution of I-125 seeds treating a 60.2-cc prostate, obtained using the anisotropic edema model with  $\Delta = 0.2$  and  $T = 28$  d. Panels depict planar  $RE$  distributions in central axial, sagittal, and coronal slices through the seed configuration, and the frequency distribution of  $RE$  in the full calculation volume

In circumstances where the effect of edema is deemed not to be negligible from the clinical standpoint, the dose calculation approach outlined in Section "Anisotropic edema model" can be used to explicitly account for edema in either pre- or post-implant dosimetry. One way to accomplish this would be to measure  $\Delta$  and  $T$  for a cohort of patients treated with a given technique and then apply the average values prospectively to dosimetry for all patients treated with that technique, as illustrated here. Although edema parameters are expected to differ somewhat from patient to patient, it can be argued that using population-averaged parameter values yields more accurate dosimetry than neglecting edema entirely. Another approach would be to try and establish relationships between edema parameters and surrogate variables, such as number of needle manipulations or prostate volume, and to select

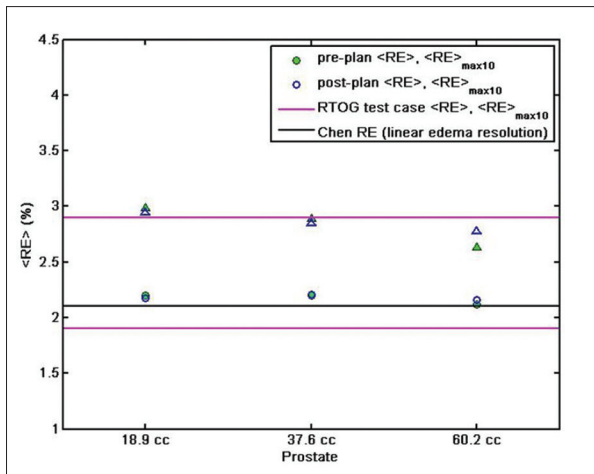


Figure 9: Summary of average RE values for all clinical I-125 seed configurations, obtained using the anisotropic edema model with  $\Delta = 0.2$  and  $T = 28$  d. Averages over the full calculation volume and over the highest 10% of values in the volume are shown. Corresponding values for the RTOG reference seed configuration (magenta lines) and for the isotropic edema model of Chen et al.<sup>[12]</sup> adapted for linear time resolution (black line) are also shown for comparison

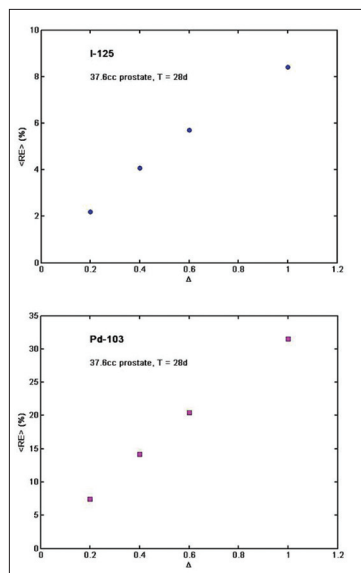


Figure 10: Calculation volume-averaged RE values as a function of the maximum relative edema parameter  $\Delta$  for the 37.6-cc prostate post-implant seed configuration, obtained using the anisotropic edema model with  $T = 28$  d. Upper panel: I-125 seeds; lower panel: Pd-103 seeds

edema parameters for each patient individually based on those relationships.

### Summary and Conclusions

A survey of indexed literature indicates that reported population-averaged values for prostatic edema maximum relative magnitude vary from 0.1 to 0.7 and for edema half-life they vary from 9.3 to 30 d. Furthermore, the time resolution of edema has been variously reported as being inverse exponential, linear, and having no discernable pattern. For the most part, these studies relied on a combination of imaging modalities, primarily US and CT, to measure edema characteristics. Recently, our center used serial MRI to make similar measurements for our implant patient population. An average edema maximum relative magnitude of 0.2 that resolved linearly in time with an average half-life of 14 d and a spatially anisotropic distribution of edema were found. The broad range of values associated with earlier measurements is likely due in part to uncertainties associated with contour definition and seed localization.

A second literature survey looking at intra-prostatic seed movement apart from that caused by edema indicates that investigators are equally divided in detecting or not detecting seed movement sufficient to affect dosimetry. Many of those reporting such movement note that it appears to be associated with specific technical aspects of the implant procedure such as puncture of the bladder wall or placement of the proximal end of a seed strand into the levator ani muscle. These observations suggest that seed movement could be effectively limited by modification of implant technique.

To date, approaches to compensate for the effect of edema on dosimetry have included increasing seed strength, introducing all needles prior to intraoperative treatment planning and needle loading, and timing post-implant imaging to minimize dosimetry error estimated using a simplified model for edema. Although the latter approach is currently recommended by AAPM and GEC-ESTRO practice guidelines, many centers routinely perform post-implant dosimetry on day 0 or day 30 for reasons of practicality

Table 2: Target structure (PTV or prostate) dose parameters calculated including edema

Prostate volume (cc)	Seed type / model	Plan type	${}^pV_{100} [\delta]$ (%)	${}^pV_{150} [\delta]$ (%)	${}^pV_{200} [\delta]$ (%)	${}^pD_{90} [\delta]$ (%)
18.9	I-125 / 6711	Pre	99.4 [-0.2]	68.6 [-2.8]	28.5 [-1.7]	127.0 [-2.2]
31.7	I-125 / 6711	Post	91.5 [-1.7]	38.3 [-2.7]	12.5 [-1.0]	101.9 [-2.1]
37.6	I-125 / 6711	Pre	99.3 [-0.2]	68.1 [-2.8]	31.1 [-1.8]	127.5 [-2.3]
38.5	I-125 / 6711	Post	95.1 [-0.6]	62.6 [-2.3]	26.5 [-2.0]	113.7 [-2.2]
60.2	I-125 / 6711	Pre	99.5 [-0.2]	66.6 [-2.8]	25.7 [-1.9]	126.3 [-2.5]
67.9	I-125 / 6711	Post	96.4 [-0.5]	56.0 [-3.0]	22.2 [-1.7]	114.4 [-2.2]
37.6	Pd-103 / 200	Pre	98.3 [-0.8]	68.6 [-5.9]	39.6 [-6.4]	118.2 [-7.5]
38.5	Pd-103 / 200	Post	89.7 [-2.5]	59.0 [-5.2]	32.4 [-6.1]	99.6 [-6.6]

Values in square brackets denote differences from TG-43 values, Prostate volume calculated from ultrasound (pre-plan) or CT (post-plan) image contours,  ${}^p$ denotes the target structure: PTV for pre-plan and prostate for post-plan,  $\delta$  = dose parameter including edema (%) - dose parameter excluding edema (%)



and convenience. None of these approaches provides a direct means to correct dosimetry for the effect of edema.

In this work, a new anisotropic edema model incorporating locally measured edema parameters ( $\Delta = 0.2$ ,  $T = 28$  d) was used to calculate the relative dose error *RE* associated with neglecting edema for three I-125 seed implants done at our center. Pre- and post-plan *RE* average values and ranges in a  $50 \times 50 \times 50$  mm<sup>3</sup> calculation volume were similar at  $\sim 2\%$  and  $\sim 0\text{--}3.5\%$ , respectively, for all three implants; however, the spatial distribution of *RE* varied for the different seed configurations. Additional *RE* calculations done for a reference configuration of seeds and for an isotropic edema model were in good agreement. Corresponding reductions in post-plan dose parameters  $D_{90}$  and  $V_{100}$  for the clinical implants were  $\sim 2\%$  and  $\sim 1\%$ , respectively.

Although the magnitude of *RE* values calculated here for I-125 implants done at our center is relatively small, it increases with edema magnitude and can be substantially greater when Pd-103 seeds are used. In cases where *RE* is deemed not to be negligible, the dose calculation method described here can be applied to explicitly account for edema in both pre- and post-implant dosimetry, thereby improving the accuracy of clinical dose estimates used in implant quality assessment.

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