Physics Contribution

Edema and Seed Displacements Affect Intraoperative Permanent Prostate Brachytherapy Dosimetry

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Summary

The positions of seeds on intraoperative transrectal ultrasonography and C-arm cone beam computed tomography were automatically linked for a large group of 699 permanent prostate implants. The corresponding displacements and the effects on dosimetry were calculated, intraoperatively and on day 30. Edema seemed to cause systematic dose differences between the intraoperative dosimetry and the day 30 dosimetry, which can be compensated for using a simple equation. The largest seed displacements were observed near the rectal wall, probably induced by the transrectal ultrasound probe.

Purpose: We sought to identify the intraoperative displacement patterns of seeds and to evaluate the correlation of intraoperative dosimetry with day 30 for permanent prostate brachytherapy.

Methods and Materials: We analyzed the data from 699 patients. Intraoperative dosimetry was acquired using transrectal ultrasonography (TRUS) and C-arm cone beam computed tomography (CBCT). Intraoperative dosimetry (minimal dose to 40%-95% of the volume [D40-D95]) was compared with the day 30 dosimetry for both modalities. An additional edema-compensating comparison was performed for D90. Stranded seeds were linked between TRUS and CBCT using an automatic and fast linking procedure. Displacement patterns were analyzed for each seed implantation location.

Results: On average, an intraoperative (TRUS to CBCT) D90 decline of 10.6% ± 7.4% was observed. Intraoperative CBCT D90 showed a greater correlation (R² = 0.33) with respect to Day 30 than did TRUS (R² = 0.17). Compensating for edema, the correlation increased to 0.41 for CBCT and 0.38 for TRUS. The mean absolute intraoperative seed displacement was 3.9 ± 2.0 mm. The largest seed displacements were observed near the rectum, probably induced by the transrectal ultrasound probe.

Conclusions: Intraoperative CBCT D90 showed a greater correlation with the day 30 dosimetry than intraoperative TRUS. Edema seemed to cause most of the systematic difference between the intraoperative and day 30 dosimetry. Seeds near the rectal wall showed the most displacement, comparing TRUS and CBCT, probably because...
Introduction

International guidelines have recommended dosimetry for permanent $^{125}$I prostate implants 1 month after the implantation procedure, when prostate swelling from edema has resolved (1-4). The dosimetry at day 30 correlates with the clinical treatment outcome (1, 5-7). However, it is difficult to predict the day 30 dosimetry during the implantation procedure (4, 8-13). Factors such as contouring and registration inaccuracies (14), edema (15), transrectal ultrasound (TRUS) probe-induced deformation (16), and difficult localization of implanted seeds using TRUS (13) can lead to a hampered estimate of the delivered dose to the prostate and organs at risk (17). Edema affects dosimetry already during the implantation procedure (18).

Furthermore, during implantation, the seeds can move, which cannot be accurately visualized using TRUS (12, 13, 19). Therefore, TRUS-based live procedures have limited capability of capturing the final positions of the seeds. An accurate intraoperative identification of all final seed positions will potentially lead to a better prediction of the day 30 dosimetry.

In the present study, we analyzed the systematic patterns of edema and seed displacements. This is only feasible if the data processing is fully automated. Therefore, we developed an automated registration method that links the stranded seeds between the different image sets of the permanent prostate implants (20).

The purpose of the present study was to assess the intraoperative edema, quantify the seed displacements, and evaluate the corresponding effects on the dosimetry. We compared intraoperative C-arm cone beam computed tomography (CBCT)—based seed localization and dosimetry with standard TRUS-based observations, using our automated procedure. We quantified the geometric and dosimetric consequences of intraoperative edema and the differences in seed localization between TRUS and CBCT for 699 patients and related these findings to the day 30 dosimetry.

Methods and Materials

Patients

From October 2007 to June 2012, 740 patients with prostate cancer who had undergone $^{125}$I seed implantation were eligible for the present study. The prescribed dose was 145 Gy for the patients receiving monotherapy (81%). Patients receiving a boost after external beam radiation therapy (19%) were prescribed 110 Gy. Excluded were those patients who had not received a standard treatment or who had undergone transurethral resection of the prostate before implantation. Of the 740 patients, 41 had an incomplete image data set, leaving 699 cases available for analysis.

Implantation procedure

A preplan was made using a treatment planning system (TPS; Variseed, version 7.1-8.0.2; Varian Medical Systems, Inc, Palo Alto, CA) approximately 2 weeks before the implantation procedure to determine the appropriate source strength and number of seeds to order.

In the operating room, 4 fiducial gold markers, ø1.0 × 5.0 mm (Heraeus GmbH, Hanau, Germany) were placed using 2 needles. Using the left needle, the markers were placed near the base and apex, and using the right needle, the markers were placed near the midplane and base of the prostate. The fiducial markers showed improved visibility compared with the seeds, facilitating (rigid) image registration.

Subsequently, the preplan was adjusted to the actual prostate size and shape at the moment of implantation using a TRUS scan (Falcon 2101 EX and Flex Focus 400; BK Medical, Herlev, Denmark) with 5-mm spaced slices.

The periphery of the prostate was implanted with stranded seeds clockwise, viewed from the observer, as shown in Figure 1A. After placing all the peripheral needles, the seeds were deposited. The position of the deposited strands was manually determined using transversal and sagittal TRUS imaging, the seeds were individually digitized. The dose distribution was updated, and the number and location of the seeds to be placed posteriorly was planned, placed, and recorded. The planning was repeated for the central positions, and the implant was finished.

A final dose distribution was calculated using the pre-implant TRUS contours (Table 1). On average, 72 ± 8 seeds were implanted. Stranded seeds with a strength of 0.419 to 0.876 U and dimensions of 0.8 × 4.6 mm were used (IBt 1251L, Seneffe, Belgium; IBt-Bebig I25.S06, Berlin, Germany; Bard STM1251, Murray Hill, NJ). Spacing between seeds was equidistant (10 mm center to center) in most strands. Strands with varying spacing were applied mainly to the central locations (3 and 4 in Fig. 1A). Next, a new TRUS scan was taken with 2.5-mm spaced slices and minimal pressure to the rectal wall to limit deformation of the prostate. The prostate was contoured again on this TRUS data set. The TRUS probe was removed, the legs of the patient were lowered, and a CBCT scan with 2.5-mm spaced slices was acquired (Siemens Arcadis Orbic 3D; Siemens Medical Systems, Erlangen, Germany). The CBCT scan was acquired approximately 5 minutes after the postimplant TRUS scan.
acquisition and <10 minutes after finishing the implant. The CBCT and TRUS data sets were registered using the fiducial gold markers, and the dosimetry was evaluated. If deemed necessary, the implant was adapted by placing remedial seeds (21).

Postimplant dosimetry was performed at day 30 using CT (Brilliance CT Big Bore; Philips Healthcare, Best, The Netherlands) to obtain the seed positions. For cases in which an implant had been adapted in the operating room, an additional postplan was created. In this postplan, the source strength of the remedial seeds was set to 0, omitting the dose contribution of the remedial seeds. The present study focused on the intraoperative effects and how these translated to the day 30 dosimetry. Therefore, the contribution of the remedial seeds was omitted from the day 30 dosimetry. Thus, the currently reported values of intraoperative CBCT-based dosimetry and the dosimetry at day 30 do not correspond to the actual values we achieved.

The dosimetry at day 30 was based on the seed locations on the day 30 CT scan and the preimplant contours on the TRUS scan. Registration of both data sets was done by matching the fiducial gold markers using the least squares method of the TPS. If needed, the registration was manually adjusted. This method closely resembles the method proposed by Bowes (22), with the major difference that we used fiducial gold markers for the registration instead of the urethra. A detailed description of our procedure has been previously published (21).

### Analysis

The intraoperative dosimetry was compared with the day 30 dosimetry. In addition to a direct comparison, we determined the relationship between the edema-compensated intraoperative dosimetry and the day 30 dosimetry. The effect of edema on the minimal dose to 90% of the volume (D90) was

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**Table 1** Overview of analyses and data sources

<table>
<thead>
<tr>
<th>Item</th>
<th>Contours</th>
<th>Seed positions</th>
<th>Registration</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative TRUS</td>
<td>TRUS before implantation*</td>
<td>TRUS intraoperatively</td>
<td>NA</td>
<td>Edema, dosimetry, and displacements</td>
</tr>
<tr>
<td>Intraoperative CBCT</td>
<td>TRUS after implantation†</td>
<td>CBCT after implantation‡</td>
<td>Least squares minimization§</td>
<td>Edema, dosimetry, and displacements</td>
</tr>
<tr>
<td>Day 30</td>
<td>TRUS before implantation</td>
<td>CT day 30</td>
<td>Least squares minimization§</td>
<td>Edema, dosimetry</td>
</tr>
</tbody>
</table>

* Intraoperatively acquired before implantation.
† Intraoperatively acquired immediately after implantation.
‡ Intraoperatively acquired after postimplant TRUS.
§ Rigid registration using fiducial gold markers.

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**Fig. 1.** (A) Implantation order: 1, periphery (circles); 2, posterior (crosses); 3, central right and left (triangles); 4, central posterior (square). (B) Linking of seeds from cone beam computed tomography (circles) to transrectal ultrasonography (stars), viewed caudally. The corresponding seeds in both distributions are linked by orange lines.
compensated for by the inverse square law ($r/r_{ref}$)$^2$ and attenuation ($r/r_{ref}$)$^{0.7}$ using an equation proposed by Moerland (23).

$$D_{90\,\text{comp}} = D_{90} \left( \frac{r}{r_{ref}} \right)^{2.0+0.7}$$ (1)

where $r$ is the mean distance of all seeds to their center of mass (COM). The compensated $D_{90}$ ($D_{90\,\text{comp}}$) was plotted against the $D_{90}$ of day 30 (reference, $r_{ref}$). $V_x$ (percentage of volume receiving the minimal $x\%$ of the prescribed dose) does not scale with the radius. No compensation for $V_x$ was determined.

The seed positions obtained by intraoperative TRUS were linked and registered to the seed positions acquired by CBCT imaging using a strand-based algorithm that has previously been described and evaluated in detail (20). The registration of the TRUS- and CBCT-based seeds allowed for translation and rotation. A typical result of the automated linking procedure is shown in Figure 1B. All seeds in the CBCT distribution were linked to seeds in the TRUS distribution. The displacements are visualized.

The differences in the linked seed positions (ie, displacements) were analyzed. The TRUS-based seed positions were taken as the reference to analyze the seed displacements. In Figure 2, the reference seed positions of all implants, plotted together, cluster at specific locations. These locations resemble the coordinates of the commonly used holes in the implantation template. The $X$ (left–right) and $Y$ (anteroposterior) coordinates of all seeds were plotted, and 19 clusters were identified. The seed positions were attributed to 1 of the clusters using K-means clustering (24).

The prostate was subdivided into 4 transversal slices (Fig. 2). The slices coincided with the positions of the seeds in the strands containing 4 seeds, which were the most common. For each slice, the seeds were visualized by plotting all the seed positions as dots, with colors showing displacements in the craniocaudal direction. Per cluster, the mean resulting in-plane displacement, in that slice, was depicted as a vector.

Next, the individual clusters were displayed sagittally (Fig. 3). Each cluster was subdivided in the $Z$ (craniocaudal) direction in the number of seed positions in that cluster. The centers of the seed clusters were determined visually, and the seeds were assigned to these seed clusters using K-means clustering. For each needle, all corresponding seed clusters were analyzed. Each seed position was shown as a dot in the $Z$–$Y$ plane, with the color representing the length of the (3-dimensional) displacement. The mean $Z$–$Y$ displacement of each seed cluster was visualized as a vector. The analyses and corresponding data sources are listed in Table 1.

**Results**

**Dosimetry**

Dosimetric data for 699 patients were obtained at day 0 using TRUS and CBCT and at day 30 using CT. The
dosimetric results are summarized in Table 2. On average, a decline of 10.6% ± 7.4% (standard deviation, percentage of the prescribed dose) for D90 and 5.1% ± 5.2% for V100 was observed in the operating room comparing the CBCT-acquired dosimetry with the TRUS-acquired dosimetry. On day 30, D90 was 1.8% ± 8.5% lower than intraoperatively using TRUS and 8.7% ± 8.0% greater than intraoperatively using CBCT. The day 30 dosimetry showed, on average, a 2.6% ± 3.1% lower V100 compared with TRUS and a 2.4% ± 4.5% greater V100 compared with CBCT.

Figure 4 shows the correlation of the intraoperative dosimetry with the day 30 dosimetry. The intraoperative D90 (based on TRUS and CBCT) was compared with the day 30 D90. The correlation of the D90 TRUS dosimetry showed an $R^2$ of 0.17. The CBCT dosimetry correlation showed an $R^2$ of 0.33. In the lower row of the subfigures, D90 was compensated for edema and attenuation were compensated using Equation 1. Compensating for edema by applying Equation 1, the correlation ($R^2$) increased to 0.38 and 0.41 for the TRUS- and CBCT-based D90, respectively. For all correlations, a $P$ value $<<10^{-6}$ was found. For the compensated situation, the linear regression slope was 0.89 for the TRUS-based and 1.01 for the CBCT-based dosimetry compared with the day 30 values.
Displacement

In total, 49,722 seeds were linked between TRUS (reference) and CBCT. An average displacement (vector length) of 3.9 ± 2.0 mm was observed. Relative to the COM, the standard deviation of the displacements was 1.8 mm in the left–right, 2.1 mm in the anteroposterior, and 3.4 mm in the craniocaudal direction. The relative distance to the COM (\( \left| r/r_{ref} \right| \)) was 1.01 ± 0.04 for TRUS and 1.04 ± 0.04 for CBCT compared with day 30. After scaling the distribution to account for edema, the mean displacement vector length decreased from 3.9 to 3.7 mm.

Table 2 Dosimetry at days 0 and 30

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intraoperative (day 0)</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TRUS</td>
<td>CBCT</td>
</tr>
<tr>
<td>D(_{50})</td>
<td>154 ± 9</td>
<td>148 ± 10</td>
</tr>
<tr>
<td>D(_{60})</td>
<td>139 ± 7</td>
<td>131 ± 9</td>
</tr>
<tr>
<td>D(_{80})</td>
<td>125 ± 5</td>
<td>119 ± 8</td>
</tr>
<tr>
<td>D(_{90})</td>
<td>118 ± 5</td>
<td>107 ± 8</td>
</tr>
<tr>
<td>D(_{90}) comp.</td>
<td>122 ± 13</td>
<td>119 ± 15</td>
</tr>
<tr>
<td>D(_{95})</td>
<td>113 ± 5</td>
<td>101 ± 9</td>
</tr>
<tr>
<td>V(_{100})</td>
<td>99.5 ± 1.1</td>
<td>94 ± 5</td>
</tr>
<tr>
<td>V(_{150})</td>
<td>44 ± 10</td>
<td>37 ± 10</td>
</tr>
<tr>
<td>UD(_{50})</td>
<td>119 ± 6</td>
<td>116 ± 10</td>
</tr>
<tr>
<td>V(_{\text{Prostate}}) (cm(^3))</td>
<td>39 ± 11</td>
<td>39 ± 11</td>
</tr>
</tbody>
</table>

Abbreviations: CBCT = cone beam computed tomography; CT = computed tomography; D\(_x\) = minimal percentage of prescribed dose to x% of the prostate; D\(_{90}\) comp. = minimal dose to 90% of the prostate, with edema compensated for using Equation 1; TRUS = transrectal ultrasonography; UD\(_{50}\) = Minimal percentage of prescribed dose to 30% of the urethra; V\(_x\) = percentage of volume receiving minimal x% of the prescribed dose.

Data presented as mean ± standard deviation.

The least displacement was observed in the central seed clusters of needles 4 to 7, with a mean displacement of 3.1 ± 1.5 to 3.4 ± 2.0 mm. The most displacement was observed in needles 12, 13, and 19. The clusters in needle 19 presented with a mean displacement of 5.1 ± 3.0 mm; the basal cluster displacement equaled 4.5 mm. The outer clusters in needle 12 and 13 showed displacements of 4.6 ± 2.2 mm. Seeds displaced depending on their position. In the outer ring (needles 2–9), the seeds displaced predominantly caudally (Fig. 3).

Discussion

The present study is the first to show the displacement of seeds and the dosimetric consequences during the implantation procedure for a large group of patients (n = 699). The size of the group allowed the investigation of the systematic displacement patterns of seeds.

Differences in dosimetry were observed for the intraoperative acquisitions with TRUS and CBCT and the postoperative dosimetry at day 30 (Table 2). The systematic difference in D\(_{90}\) can be attributed to the presence of edema. A simple model compensating for the inverse square law and attenuation (Eq. 1) seems to explain the systematic difference between day 0 and day 30 (Fig. 4). Furthermore, after compensating for the edema, the CBCT-based dosimetry showed a better correlation for D\(_{90}\) at day 30 than did the TRUS-based dosimetry (Fig. 4). However, this improved correlation does not allow for individual, CBCT-based dosimetry predictions for day 30.

Random differences were not reduced after edema compensation. The simple spherical model cannot compensate for the nonuniform displacements shown in Figures 2 and 3 and decreased the mean displacement by only 0.2 mm. Also, stranded seeds might, because of strand rigidity, respond differently to prostatic edema in the craniocaudal direction than in the lateral directions. We have previously shown that this effect is fairly limited (25). However, loose seed implants could show slightly different edema. Consequently, residual displacements would still affect the dosimetry, just as would seed identification, contouring, registration uncertainties, and movement in the implantation channels.

Using the linking method (20), we linked the seed positions in the TRUS and CBCT data sets and quantified the corresponding displacements. A rigid registration between the TRUS and CBCT data sets minimized the distance between the seeds. The minimization of the distance between the seeds in both data sets could have resulted in an overcompensation of the displacement patterns. For example, if all the seeds would show displacement in the caudal direction, this would have been compensated for by an equal translation. This was verified by comparing the seed positions with the prostate contours. The physician contoured the prostate before and after implantation. We evaluated whether the seeds were displaced between TRUS and CBCT by
comparing the seed distribution and the most basal contour. We did not find indications for systematic shifts.

Figures 2 and 3 show the left—right symmetry of the displacement patterns. The pattern of displacements, as visualized by the vectors, was continuous, with the neighboring clusters showing similar displacement.

Displacements originate from multiple underlying mechanisms. Among others, the following were found to play a role. The first factor was the pressure of the ultrasound probe on the prostate. This pressure was minimized but does still deform the prostate, as shown previously by Liu et al (16). Seeds near the rectum (probe) will displace to the posterior near the prostate base and to the anterior near the prostate apex. TRUS probe-induced prostate deformation affects the seeds’ positions and the prostate shape. Liu et al (16) reported that dosimetry changes due to TRUS probe removal mainly resulted from changes in seed position and, to a lesser extent, contour changes. The second factor was that the posterior needles, placed close to the rectum, were intentionally placed at an angle, using the beveled needle tip, to follow the prostate—rectum interface. The TPS did not allow angles for strands on the real-time TRUS images. For the CT image data sets, angles were allowed. This amplifies the effect of the ultrasound probe. Finally, the presence of edema will move seeds away from the COM.

Edema is difficult to predict but it results in considerable consequences on the dosimetry during the implantation procedure. This effect has also been observed by other groups that compared the dosimetry shortly after implantation with the day 30 dosimetry (26, 27). The amount of edema observed in the present study agreed well with the results from an earlier study in which we reported a spherical volume change of 12%, corresponding to an \( \frac{\tau}{\tau_{ref}} \) of 1.04 (25). The contoured prostate volumes (Table 2) did not show this amount of edema. This could
have been caused by the different slice spacing of the data sets and the tendency to contour an additional slice to ensure full target coverage. The wider slice spacing (5 vs 2.5 mm) of the preimplant TRUS scan could have led to an overestimation of the volume and might have hidden the volume increase due to the presence of edema.

The use of stranded seeds might lead to an underestimation of edema in the craniocaudal direction. Loose seeds might show more edema, but this would not challenge the qualitative observations.

The anterior—lateral outer ring of seeds displaced caudally. In contrast, the central and outer posterior seeds displaced cranially. This could be an indication that the implantation (Fig. 1A) order affects the displacements. However, comparing the left and right needle positions (Fig. 3), we did not observe differences between the earlier and later placed seeds. Therefore, we do not believe that the displacement of seeds is directly related to the order of implantation.

Published data have indicated that underdosage occurs predominantly at the base of the prostate (8, 28, 29). Edema, needle divergence, and the caudal displacement of the (outer) seeds could result in underdosage in that region. If seeds have been not accurately identified during the implantation procedure, the underdosage will remain unnoticed. This could result in underdosage at day 30. An adaptive brachytherapy procedure that includes CBCT might thus help to improve the dosimetry. Further investigation of the consequences of adaptive brachytherapy is needed for verification.

The implantation technique could be slightly modified to anticipate the intraoperative displacement patterns. The observed divergence of the needles could possibly be lowered by implanting the needles in a slightly convergent geometry. The displacements caused by TRUS probe removal could be anticipated by placing the seeds near the prostate base slightly more anteriorly than planned. The seeds in the outer anterior ring could be implanted slightly deeper. However, these suggestions depend on the implantation technique, model of seeds and strands, and the use of loose or stranded seeds.

Currently, interest in focal treatments is increasing. Particularly for small lesions, accurate seed placement is important (30); thus, knowing the displacement properties could help in such procedures. In addition to implantation technique enhancements, the TPS should allow for the registration of nonparallel needles during the implantation procedure.

Conclusions

We visualized the intraoperative systematic displacements for a large group of implants (n = 699) using an automated analysis of 49,722 seeds on TRUS and CBCT. The magnitude and orientation of displacements of seeds differ considerably for various positions in the prostate. Seeds close to the rectal wall showed the most displacement, probably resulting from TRUS probe—induced prostate deformation. Seeds close to the base showed more divergent displacements than seeds close to the apex. The corresponding dosimetry was assessed. The intraoperative systematic difference in D90 seems to be predominantly caused by edema. Compared with TRUS, the intraoperative CBCT-based D90 showed a greater correlation with the day 30 dosimetry. Automated analysis is a prerequisite for the results we obtained for this large group.

References


