Towards image-guided radiotherapy of prostate cancer

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Residual Seminal Vesicle Displacement in Marker-Based Image-Guided Radiotherapy for Prostate Cancer and the Impact on Margin Design

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ABSTRACT

PURPOSE The objectives of this study were to quantify residual interfraction displacement of seminal vesicles (SV) and investigate the efficacy of rotation correction on SV displacement in marker-based prostate image-guided radiotherapy (IGRT). We also determined the effect of marker registration on the measured SV displacement and its impact on margin design.

PATIENTS AND METHODS SV displacement was determined relative to marker registration by using 296 cone-beam computed tomography scans of 13 prostate cancer patients with implanted markers. SV were individually registered in the transverse plane, based on grey-value information. The target registration error (TRE) for the SV due to marker registration inaccuracies was estimated. Correlations between prostate gland rotations and SV displacement and between individual SV displacements were determined.

RESULTS The SV registration success rate was 99%. Displacement amounts of both SVs were comparable. Systematic and random residual SV displacements were 1.6 mm and 2.0 mm in the left-right direction, respectively, and 2.8 mm and 3.1 mm in the anteroposterior (AP) direction, respectively. Rotation correction did not reduce residual SV displacement. Prostate gland rotation around the left-right axis correlated with SV AP displacement ($R^2 = 42\%$); a correlation existed between both SVs for AP displacement ($R^2 = 62\%$); considerable correlation existed between random errors of SV displacement and TRE ($R^2 = 34\%$).

CONCLUSIONS Considerable residual SV displacement exists in marker-based IGRT. Rotation correction barely reduced SV displacement, rather, a larger SV displacement was shown relative to the prostate gland that was not captured by the marker position. Marker registration error partly explains SV displacement when correcting for rotations. Correcting for rotations, therefore, is not advisable when SV are part of the target volume. Margin design for SVs should take these uncertainties into account.
INTRODUCTION

Over the past decade, the development and clinical introduction of image-guided radiotherapy (IGRT) has made an improvement in the accurate treatment of prostate cancer\(^1\). By applying intensity-modulated RT in combination with offline or online image-guided setup correction protocols, toxicity can be reduced\(^2\). Presently, prostate setup correction protocols focus mainly on reducing the error caused by interfraction prostate motion\(^3\)–\(^6\), although more institutes these days are starting to study the effect of intrafraction prostate motion\(^7\)–\(^8\). Many different imaging techniques can be used, for example, ultrasound, portal imaging, megavolt computed tomography (CT), in-room CT, cone-beam CT (CBCT), in-room magnetic resonance imaging, and four-dimensional (4D) marker-based localization system like Calypso\(^1\). For prostate localization, registration techniques can be based on registration of implanted fiducial markers, delineations, or soft tissue\(^9\)–\(^11\).

To account for residual uncertainties in prostate motion and deformation after correction, a safety margin is generally used around the prostate during treatment planning. More accurate treatment allows for reduction of the margins to reduce toxicity. Recent studies show that margin reduction may be feasible\(^12\)–\(^14\). However, for prostate treatment that includes the seminal vesicles (SV), margin reduction is limited to a large extent by the mobility of the SV, because they may become deformed and/or move to a certain extent with respect to the prostate gland\(^9\)–\(^10\).

The use of fiducial markers in prostate cancer treatment is a well-known and accurate technique for correcting for setup error and organ motion\(^9\). Rotation correction based on marker positions can be done but is often ignored. If only translation corrections for marker positions are applied, the measured SV displacement originates from rotations, deformation, and registration errors. After corrections are made for rotations, measured displacement originates only from deformation and registration errors. Knowledge of residual displacement is required to ensure adequate treatment of the SV and to calculate appropriate (e.g., nonuniform) margins for prostate and SV. Therefore, the objectives of this study were to quantify the residual amount of SV displacement and to investigate the efficacy of marker-based rotation correction on SV displacement. In addition, the effect
of marker registration on the measured displacement and the effect on margin design were determined. Contrary to that of previous studies\(^{(9-10)}\), analysis in the present study was based solely on image registration, excluding potential delineation variations.

**PATIENTS AND METHODS**

**PATIENTS**

In a research study approved by the University Health Network Research Ethics Board (UHN REB 05-0037C), data from 13 patients who were irradiated for prostate cancer at Princess Margaret Hospital, Toronto, Canada, were acquired in a prospective trial of cone-beam image guidance for localized prostate cancer therapy. Patients were subjected to a laxative regimen. Analysis of data was carried out at The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital (NKI-AVL), Amsterdam, The Netherlands. Patients underwent transrectal implantation of three gold fiducial markers (Oroplata, Quebec, Canada), measuring 1 mm x 5 mm, under ultrasound guidance in the prostate gland (at the base, posterior midportion, and apex).

**DATA ACQUISITION**

For each patient, one planning CT scan and 6 to 35 CBCT scans (not all scans were available for analysis due to practical reasons) were acquired (total, 296 CBCT scans). The planning CT scans were made in the patient’s treatment position (supine) and consisted of approximately 70 slices, each with 512 x 512 voxels (0.94 mm x 0.94 mm), with a slice distance of 5 mm outside and 2 mm inside the region of the prostate. CBCT projection images were acquired on a linear accelerator (LINAC)-integrated kV CBCT scanner (Elekta Synergy release 3.1; Elekta, Crawley, UK), with the patient in treatment position, just prior to each treatment fraction. Reconstruction of the projection data, based on the Feldkamp-Davis-Kress algorithm\(^{(15)}\), was performed at NKI-AVL, using in-house developed software. Reconstructed
CBCT scans consisted of 400 x 400 x 256 voxels, with voxel dimensions of 1.0 x 1.0 x 1.0 mm$^3$.

**Fiducial Marker Registration**

Fiducial marker registration was begun by segmenting the markers in the planning CT scan by choosing a threshold value of ~300% of the density of water (3,072 HU). Then, the segmented markers were jointly registered to the markers in the CBCT scan, based on chamfer matching$^{(16)}$, obtaining translations, and rotations in three dimensions. The accuracy of marker registration, expressed as an average uniform fiducial registration error (FRE), was 0.24 mm, which is in accordance with the FRE found by Mutanga et al.$^{(17)}$. The FRE was calculated as the RMS value over all patients of the RMS values over all fractions of the random displacement errors determined in each direction. The FRE is needed to calculate the target registration error (TRE) (See below).

**SV Registration**

SV in the CBCT scans were individually registered to the corresponding SV in the planning CT scans, using in-house-developed software (an adapted version of the Elekta Synergy system). For that, a 3D rectangular region of interest (~three slices in the craniocaudal (CC) direction in the middle of the SV) was defined. SV registration was based on grey-value information, using an adapted version of the previously described grey-value registration method for the prostate$^{(11)}$: only left-right (LR) and anteroposterior (AP) translations ($T_{LR}$ and $T_{AP}$) were optimized. Also, two different start positions for SV registration were used: either marker registration with or without rotation correction. Each SV registration was visually assessed by an experienced observer in the transverse and sagittal planes. In case of registration failure, registration was repeated with the difference that after marker registration, a manual pre-match was performed on the SV before grey-value registration of the SV.

The accuracy of the adapted grey-value registration method may be assumed to be better than 1.8 mm in AP and 0.7 mm in LR directions (both 1 standard deviation (SD) systematic)$^{(11)}$. This is because only two rather than six parameters (three translations and three rotations) were fitted, and
because the visibility of the vesicles in the CBCT images is better than the prostate gland because the former are embedded in fatty tissue. The accuracy, however, may become slightly worse as the grey-value registration method will try to find a compromise in the presence of deformations. This effect, however, is assumed to be small as only a small part of the SV is considered.

**Residual SV Displacement and Statistical Analysis**

Residual SV displacement was determined for both methods, with and without rotation correction of the markers, relative to the center of mass of the prostate gland. Group means ($\mu$), systematic errors ($\Sigma$), and random errors ($\sigma$, calculated as the RMS of the SD per patient) for $T_{LR}$ and $T_{AP}$ were determined for each individual SV.

To determine whether there were significant differences between the two methods, the data should be considered paired. We tested whether group means significantly deviated from zero (one sample t-test). Furthermore, we tested whether group means significantly differed between groups (paired samples t-test). To test for significant differences for paired data in systematic errors, the Wilcoxon signed-rank test was used, as described by Sandvik and Olsen, and the Wilcoxon signed-rank test was also used for the random errors.

Furthermore, we determined whether there were significant differences between right and left SV for both methods. We tested whether group means significantly deviated from zero, i.e., the position of the SV in the planning CT scan (one sample t-test). As the data were unpaired, significant differences in systematic errors were determined using Levene’s test, and to test significant differences in random errors, the Mann-Whitney test was applied.

SPSS version 15.0 software for Microsoft Windows (SPSS Inc., Chicago, IL) was used for statistical analyses. For residual SV displacement analysis, Bonferroni’s correction was applied to correct the p value for the number of parameters (two translations) used ($n = 2$), i.e., the p value used was $0.05/n = 0.025$. 
CORRELATIONS

To define appropriate margins for prostate and SV in case of nonrigid body motion of these structures, it is important to understand the behavior of SV displacement with respect to the prostate gland and with respect to each other. To describe the motion of SV relative to the prostate (and whether it is rigid or not), we determined the squared Pearson correlation coefficient ($R^2$) between the average prostate gland rotation (determined from the marker registrations) and the average residual SV displacement for each patient, as well as for the mutual average residual SV displacements.

TARGET REGISTRATION ERROR

It is important to realize that the accuracy of marker registration, the configuration of the markers themselves, and the configuration of the markers with respect to the SV could influence the observed residual SV displacement after fiducial marker registration. Previously, Fitzpatrick et al.\(^{(20)}\) published an algorithm (for rigid geometry) to calculate the expectation value of the target (in our study, the SV) registration error (TRE), which is the RMS error at any distance of the marker configuration, which is related to the FRE and configuration of the markers. If prostate and SV were rigid, the observed SV displacement would be purely this TRE. In reality, the observed SV displacement will be a combination of deformation and this TRE. In our study, the markers were registered using a chamfermatching algorithm that takes the marker shape and orientation into account. To estimate the TRE in this situation, the markers were described by two points on both ends.

To test the impact of marker registration uncertainty on SV displacement in the clinical data, we determined the correlation between the observed residual SV random displacement errors with and without rotation correction and the calculated expectation value of this TRE. That is, the RMS vector length of the observed AP and LR displacements was plotted against the expected TRE.
RESULTS

SV REGISTRATION

Figure 1 shows a registration result at the position of the SV after registration based on markers only and the registration result after applying the SV registration procedure. One can clearly see that the SV within the region of interest after SV registration are properly aligned in transverse and sagittal views.

The success rate for each individual SV as determined from the visual assessments was about the same: ~99%, with or without rotation correction of the markers.

RESIDUAL SV DISPLACEMENT

Displacement of the SV with respect to the prostate gland, with and without rotation correction of the markers, are displayed in Table 1. No significant differences in mean, systematic, and random errors were found between right and left SV, with and without rotation corrections. Therefore, the data are presented for both SV together.

Systematic and random errors were larger along the AP axis than the LR axis, independent of rotation correction. The systematic error (Σ) was 1.5 mm in the LR direction compared to 2.6 mm in the AP direction, without rotation correction. With rotation correction, errors were similar: 1.8 mm in the LR direction and 2.1 mm in the AP direction. The random errors (σ) for SV displacement with or without rotation correction were around 2.0 mm in the LR direction and around 3.0 mm in the AP direction. Except for the random $T_{LR}$ ($p = 0.001$), the differences between the two methods were not significant.
FIGURE 1. Split views of cone-beam CT (CBCT) and planning CT registration results of a SV in transverse (A and C) and sagittal (B and D) views. Panels A and B show the result after registration on markers only. The result after SV registration is shown in panels C and D. SV registration was performed within the region of interest (grey box) and assessed only for residual translations in the LR and AP directions (white arrows).
### TABLE 1. Residual seminal vesicle displacement.

<table>
<thead>
<tr>
<th></th>
<th>Without rotation correction</th>
<th>With rotation correction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( T_{LR} ) (mm)</td>
<td>( T_{AP} ) (mm)</td>
</tr>
<tr>
<td>Mean</td>
<td>-0.3</td>
<td>-0.1</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>( \Sigma )</td>
<td>1.9</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS.** \( \Sigma \) = systematic error; \( \sigma \) = random error; \( T \) = translation; LR = left-right; AP = anteroposterior; mm = millimeters.

**CORRELATIONS**

**CORRELATION BETWEEN PROSTATE GLAND ROTATION AND RESIDUAL SV DISPLACEMENT.**

In Figure 2, the correlation between the systematic error for rotations of the markers around the LR axis and the systematic error of the translation of the SV in the AP direction are shown. When no rotation correction was applied, a squared correlation coefficient, \( R^2 = 42\% \), was found, whereas the correlation with rotation corrections of the markers was very small: \( R^2 = 1.7\% \). The displayed lines were determined by linear regression. As the graphs for each individual SV were similar, the average was displayed in this graph. These results imply that some (42\%) of the systematic SV displacement variation can be explained by prostate rotations. For the other rotation axes, no correlations with the residual translations were found.

**CORRELATION OF MUTUAL RESIDUAL SV DISPLACEMENT.**

Figure 3 shows the correlation of the systematic error between the SV for translations in the AP direction (\( R^2 = 62\% \)), i.e., the differential displacement. Results are shown for the case in which no rotation corrections were applied. The data were similar with and without rotation correction. The other \( R^2 \) values are displayed in Table 2 and were almost zero.
FIGURE 2. Mean residual SV translation error along the AP axis as measured from SV registrations for each patient is plotted against mean prostate gland rotation error around the LR axis as measured by marker registration for each patient. Black squares/line = without rotation correction of the markers; grey triangles/line = with rotation correction of the markers.

FIGURE 3. Correlation between mean residual translation error along the AP axis of each patient between left and right SV (black squares/line) without rotation correction.
**TABLE 2.** $R^2$ values of mean displacement between right and left SV.

<table>
<thead>
<tr>
<th>Direction</th>
<th>SV&lt;sub&gt;left&lt;/sub&gt;</th>
<th>SV&lt;sub&gt;right&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>0.005</td>
<td>0.0001</td>
</tr>
<tr>
<td>AP</td>
<td>0.002</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**ABBREVIATIONS.** SV = seminal vesicle; LR = left-right; AP = anteroposterior.

**TARGET REGISTRATION ERROR**

For each patient, the TRE was estimated based on the marker configuration. Three of the 13 patients had a high TRE and also relatively large residual SV displacement. A correlation of an $R^2$ value of 34% between residual SV displacement for the data corrected for rotations and TRE was found. No correlation was found for the data not corrected for rotations. The larger TRE for some patients can be partly explained by the distance of the target (SV) to these markers. **Figure 4** shows a marker configuration for 1 of 3 patients with a high TRE compared to 1 of 10 patients with a ‘normal’ TRE (TRE values of 2.8 mm and 1.3 mm, respectively). One clearly can see that for the patient with high TRE, the SV are further away from the markers. A bad marker configuration, e.g., markers placed approximately on a line, results in an even larger TRE.
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**FIGURE 4.** Right-frontal-top and right-sagittal views of marker configurations in a patient with a high TRE (TRE = 2.8 mm (panels A and B)) and in a patient with a ‘normal’ TRE (TRE = 1.3 mm (panels C and D)). The three fiducial markers are shown in white, and the mid position of the SV is indicated by the rectangular light-grey region of interest. For visual reasons, body contours of the patient are shown.

**DISCUSSION**

SV displacement after marker registration was determined. For practical reasons, we determined translations only in LR and AP directions. By doing this, we ignored position variability in the CC direction, away from the prostate gland. This is reasonable when we assume adequate dose coverage of the SV in CC direction, i.e., during treatment, almost the entire SV is included, assumed to be 3 to 4 cm, while SV cancer invasion is known to be only in the first 2.0 to 2.5 centimeters of the vesicles\(^{(21)}\).

We found large residual SV displacements after correction for marker translation without correcting for rotations: they were largest in the AP
direction (2-3 mm for $\Sigma$ and $\sigma$). However, rotation correction hardly reduced SV displacement, illustrating that a large part of the motion of the SV relative to the prostate gland is not captured by the marker position. This finding implies deformation and/or inaccuracy in the marker registration. We found, however, that the mean AP displacement of the SV did correlate somewhat with the mean prostate gland LR rotation error ($R^2 = 42\%$), from which we may conclude that prostate and SV behaviors are at least partially rigid or that their motion can be attributed to a common source, i.e., rectum volume.

We also found that when the estimated TRE due to the marker registration error at the position of the SV was large, large residual SV displacements were found. In other words, inaccuracy of marker registration turns out to be significant when correcting for rotations. This effect can be explained because minute marker registration errors at the position of the markers can be greatly magnified at a distance from these markers, i.e., at the position of the SV.

From these observations, we may conclude that when SV are part of the target volume, it is not advisable to base rotation correction on the markers, as the determined rotations of the markers are not representative of the SV displacement.

We also studied the correlation of the motion of left and right SV. We found some correlation ($R^2 = 62\%$) between the SV for the systematic errors in AP displacement (Figure 3), while there was no correlation for LR displacement. These data are useful to define appropriate margins for SV. Some thoughts on margin design are described below.

**Studies about prostate and SV displacement and margins**

Deurloo et al.$^{(10)}$ found that for contour delineations-based correction strategies, residual deformation of the SV was small compared to interfracton displacement and that prostate and SV could be treated as a rigid body. Frank et al.$^{(6)}$ found that the variability in SV displacement appeared larger than the variability in prostate displacement with respect to bony anatomy. An AP margin of 1 cm for the SV might be inadequate for some cases (~14% of patients treated). Van der Wielen et al.$^{(9)}$ found considerable SV displacement with respect to the prostate gland relative to
intraprostatic fiducial markers, using a deformable registration method. However, that study did not evaluate the effect of marker registration errors. Based on this information, Mutanga et al.\textsuperscript{(17)} stated that margins could be reduced to 4 and 7 mm, respectively, for prostate gland and SV to guarantee adequate dose coverage. Meijer et al.\textsuperscript{(13)} found that an 8 mm margin for the SV was sufficient to guarantee adequate dose coverage. Liang et al.\textsuperscript{(22)} found that the magnitude of SV displacement in the AP direction was larger than for the prostate. A correlation $R^2$ of 0.7 was found, which indicates that other independent factors exist. A minimum margin of 4.5 mm to the SV was recommended for IMRT with prostate-only guidance. The smaller margins found by Liang et al.\textsuperscript{(22)} may possibly be attributed to the difference in registration technique. Liang et al.\textsuperscript{(22)} use a binary mask for image registration, whereas the others used contour delineations, although they were corrected for intraobserver variability, as in studies by Van der Wielen et al.\textsuperscript{(9)} and Mutanga et al.\textsuperscript{(17)}, and interobserver variability, as in studies by Frank et al.\textsuperscript{(6)} and Meijer et al.\textsuperscript{(13)}.

**SOME THOUGHTS ABOUT MARGIN DESIGN FROM OUR DATA**

To get an idea of the margins in the presence of SV motion/deformation toward the low-dose region for the case in which no rotation correction was applied, we used the margin (M) equation of $M = 2.15 \Sigma + 0.7 \sigma$ for a 2D dose distribution instead of the well-known margin equation $M = 2.50 \Sigma + 0.7 \sigma$ for a 3D dose distribution\textsuperscript{(23)}, as we assumed adequate dose coverage of the SV in the CC direction. Without rotation corrections, SV margins of 4.6 mm (range, 4.2-4.8 mm) and 7.6 mm (range, 7.0-7.9 mm) in the LR and AP direction will be required to correct for SV displacement in marker-based IGRT, after online correction of the markers. That margin equation\textsuperscript{(23)} and others\textsuperscript{(24)} for clinical tumor volume-to-planning target volume expansion, however, are valid only for rigid body motion and do not take into account possible deformations. In order to define appropriate margins for the nonrigid case, one needs to know the motion correlations as shown by Van Kranen et al.\textsuperscript{(25)} in an abstract about margin design for deforming and differentially moving targets. Lack of motion correlation implies that the factor for the systematic component in the margin recipe has to increase. If, in our study, we assume that the SV moves completely independently, e.g., acts in a nonrigid manner, then the probability that any SV is outside the margin is twice as high as the probability that a single SV is outside the margin. Then,
the systematic component of the margin recipe would need to change into 
2.45 $\Sigma$, which is equal to a 95% confidence level for a 2D dose 
distribution$^{(23)}$. The same holds for the 3D dose distribution: for the fully 
dependent (rigid) case, the well-known margin equation is $M = 2.50 \Sigma + 0.7 \sigma$, which will change into $M = 2.79 \Sigma + 0.7 \sigma$ for the fully independent 
(nonrigid) case$^{(23)}$.

To illustrate the effect of partially correlated motion on margins, consider the 
following. Assume a marker-based correction strategy (without rotation 
correction) with a margin of 5 mm. Correlation of motion does not affect the 
required margin for random errors. If the margin for random errors in the AP 
direction ($0.7 \times 3.0 = 2.1$ mm) is subtracted, then, what is left for the 
systematic error is 2.9 mm. In Figure 5, the mean residual error and the random 
error bars for each SV per patient are shown. If we draw lines at 2.9 
mm, then in more than half of the patients, one or two of the SV would fall 
outside, i.e., would be underdosed, while only 30% of the SV are 
underdosed. In other words, to ensure coverage of both SV at the same 
time, a larger margin is required than when individual SV are considered. In 
all margin calculations, we should note, however, that lack of required dose 
conformity may lower required margins$^{(28)}$.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Mean residual error and the random error bars for each SV per patient.}
\end{figure}
CORRECTION STRATEGIES FOR SV FOR MARKER-BASED CORRECTION PROTOCOLS

The question arises now, apart from margin design, what correction strategy would be appropriate when SV are part of the target volume while applying marker-based correction protocols? As pointed out in ‘Results’, we found some correlation between TRE and residual SV displacement variability for the data corrected for rotations: for 3 of the 13 patients with a high TRE, we found relatively large SV deformation. Even if we recalculate the residual SV displacement for the remaining 10 patients, no significant differences were found between the data with and without correcting for rotations. This means that rotation correction actually can make the SV position worse than without rotation correction, as very small inaccuracies in marker position have a high impact on the target registration error at the location of the SV. Our suggestion would therefore to apply caution when applying rotation correction based on marker-based correction strategies when SV are part of the target volume. Rotation correction for subboosting parts of the prostate gland, however, is important. For the SV, it would be better to use soft tissue image-guidance to actually detect the SV before treatment or in combination with an adaptive radiotherapy protocol. The development of combined correction protocols using marker registration and soft tissue registration of the SV is the subject of ongoing research.

CONCLUSIONS

This study shows that residual SV displacement in marker-based IGRT is quite large: 2 to 3 mm (1 SD) (systematic and random errors) in the AP direction. Correction for rotations barely reduced the SV displacement, suggesting deformation of the SV with respect to the prostate gland that is not captured by the marker position. In addition, the impact of small marker localization errors and registration errors on rotation correction cannot be ignored. Therefore, when the SV are part of the target volume, rotation correction based solely on markers is not advisable.
REFERENCES


