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AUTOMATIC PROSTATE LOCALIZATION ON CONE-BEAM CT SCANS FOR HIGH PRECISION IMAGE-GUIDED RADIOTHERAPY

MONIQUE H. P. SMITSMANS, JOSIEN DE BOIS, JAN-JAKOB SONKE, ANJA BETGEN, LAMBERT ZIJP, DAVID A. JAFFRAY, JOOS V. LEBESQUE, AND MARCEL VAN HERK

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ABSTRACT

PURPOSE Previously, we developed an automatic three-dimensional (3D) grey-value registration (GR) method for fast prostate localization that could be used during online or offline image-guided radiotherapy. The method was tested on conventional computed tomography (CT) scans. In this study, the performance of the algorithm to localize the prostate on cone-beam CT (CBCT) scans acquired on the treatment machine was evaluated.

PATIENTS AND METHODS Five to 17 CBCT scans of 32 prostate cancer patients (332 scans in total) were used. For 18 patients (190 CBCT scans), the CBCT scans were acquired with a collimated field of view (FOV) (cranio-caudal). This procedure improved the image quality considerably. The prostate (i.e., prostate plus seminal vesicles) in each CBCT scan was registered to the prostate in the planning CT scan by automatic 3D grey-value registration (normal GR) starting from a registration on the bony anatomy. When these failed, registrations were repeated with a fixed rotation point locked at the prostate apex (fixed apex GR). Registrations were visually assessed in 3D by one observer with the help of an expansion (by 3.6 mm) of the delineated prostate contours of the planning CT scan. The percentage of successfully registered cases was determined from the combined normal and fixed apex GR assessment results. The error in grey-value registration for both registration methods was determined from the position of one clearly defined calcification in the prostate gland (9 patients, 71 successful registrations).

RESULTS The percentage of successfully registered CBCT scans that were acquired with a collimated FOV was about 10% higher than for CBCT scans that were acquired with an uncollimated FOV. For CBCT scans that were acquired with a collimated FOV, the percentage of successfully registered cases improved from 65%, when only normal GR was applied, to 83% when the results of normal and fixed apex GR were combined. Grey-value registration mainly failed (or registrations were difficult to assess) because of streaks in the CBCT scans caused by moving gas pockets in the rectum during CBCT image acquisition (i.e., intrafraction motion). The error in grey-value registration along the left-right, craniocaudal, and anteroposterior axes was 1.0, 2.4, and 2.3 mm (1 SD) for normal GR, and 1.0, 2.0, and 1.7 mm (1 SD) for fixed apex GR. The systematic and random components of these SDs contributed approximately equally to these SDs, for both registration methods.

CONCLUSIONS The feasibility of automatic prostate localization on CBCT scans acquired on the treatment machine using an adaptation of the previously developed three-dimensional grey-value registration algorithm, has been validated in this study. Collimating the FOV during CBCT image acquisition improved the CBCT image quality considerably. Artifacts in the CBCT images caused by large moving gas pockets during CBCT image acquisition were the main cause for unsuccessful registration. From this study, we can conclude that CBCT scans are suitable for online and offline position verification of the prostate, as long as the amount of nonstationary gas is limited.
INTRODUCTION

Rapidly emerging technologies, such as commercially available cone-beam computed tomography (CBCT) image-guided radiotherapy (IGRT) systems, provide the opportunity to localize target volumes in a few minutes before each treatment fraction. Particularly for moving targets such as the prostate, knowledge of the precise position would improve the accuracy of treatment. Many recent studies have focused on position verification (offline and online) of the prostate to improve treatment accuracy. More accurate delivery of the prescribed dose would allow reduction of the safety margin around the clinical target volume (CTV). This treatment field margin accounts for mobility of the patient and the target volume, to guarantee that the entire prostate always receives the prescribed dose. Reducing the margin spares more surrounding normal tissue and therefore provides an opportunity for dose escalation. Escalating the dose has been proven to increase the probability of disease control; in addition, by reducing the margins normal tissue complications may decrease.

A CBCT-IGRT system (Elekta Synergy, Elekta, Crawley, UK) was installed in our clinic, and has been in clinical use since July 9, 2003 (Figure 1).

Figure 1. The prototype cone-beam computed tomography (CBCT) image-guided radiotherapy (IGRT) system (Elekta Synergy) implemented at The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital. The CBCT-IGRT system consists of a kilovolt (kV) X-ray source and an amorphous silicon flat panel kV imager, mounted in a retractable fashion on the linear accelerator perpendicular to the radiation beam direction. A CBCT scan can be acquired in a single gantry rotation in a few minutes, before each treatment fraction, to localize the prostate.
The system consists of a retractable kilovolt (kV) X-ray source and an amorphous silicon flat panel imager mounted on the linear accelerator perpendicular to the radiation beam direction. A CBCT scan can be obtained in 2–4 min (depending on the acquisition mode) requiring a single gantry rotation just before (or after) each treatment fraction.

For online IGRT of the prostate, localization of the prostate on the CBCT scans should be fast. Methods for prostate localization and registration based on manual delineation of contours on successive transverse CT slices\(^{(2,8-9)}\) or interactive alignment\(^{(6-7)}\) are fairly time-consuming, whereas methods based on implanted markers\(^{(3-5)}\) are invasive for the patient, and besides, markers might be subject to some migration that will result in errors. In addition, markers are implanted in the prostate gland and not in the seminal vesicles, which means that if the seminal vesicles are part of the target volume and they move relative to the prostate gland, this movement will not be registered by the markers.

To reduce the time interval between imaging and treatment, and to improve patient throughput, we developed a fast, automatic three-dimensional (3D) grey-value registration method for prostate localization\(^{(10)}\), which is comparable to another method developed independently, described by Court and Dong\(^{(11)}\). The algorithm we developed previously is a rigid registration algorithm (three translations and three rotations, no shape changes). It is based on the assumption that the prostate does not change shape significantly relative to its motion as a whole, as found by Deurloo et al.\(^{(15)}\) for a comparable patient group. The 3D grey-value registration method was tested and validated on conventional repeat CT scans. However, the image quality of CBCT scans differs from that of conventional CT scans. The CBCT scans have a higher resolution in the craniocaudal (CC) direction, which is an advantage, whereas the contrast-to-noise ratio of CBCT scans is lower, reducing the visibility of soft tissue structures such as the prostate. Other factors that influence the image quality of CBCT scans are acquisition time (slow-moving gantry) and intrafraction motion, which causes reconstruction artifacts. Therefore, the purpose of this study was to test and validate the use of the automatic 3D grey-value registration method to localize the prostate on our clinical CBCT scans.
PATIENTS AND METHODS

PATIENT DATA
For this study, we used one conventional planning CT scan and between 5 and 17 CBCT scans from 32 patients (332 CBCT scans in total) that were irradiated for prostate cancer at The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital.

PLANNING CT DATA
The planning CT scans were made in the treatment position (supine) and consisted of approximately 60 slices, each with 512 x 512 pixels (0.9 mm x 0.9 mm), with a slice distance of 5 mm outside and 3 mm inside the region of the prostate. In this study, the planning CT scans were downsized to 256 x 256 pixels (1.8 mm x 1.8 mm). (At the time of investigation, export of CT scans in our institute was limited to images with 256 x 256 pixels for reasons of data transfer capacity; therefore it was not possible, at that time, to export CT scans consisting of images with 512 x 512 pixels.) The prostate and seminal vesicles (SV) in the planning CT scan were delineated by a radiation oncologist and defined the CTV\(^{16}\). For this article, we use the term prostate to refer to the CTV and the term CTV contours to refer to the delineated contours of the CTV. The term prostate gland will be used to refer to the prostate only (i.e., prostate without SV).

CONEBEAM CT DATA
The CBCT scans were acquired on a prototype CBCT-IGRT system (Elekta Synergy) with the patient in treatment position before a treatment fraction. The acquisition parameters of the projection images for the CBCT scans were: 130 kV, 80 mA, 25 ms per projection. The applied dose for each CBCT scan was 3–4 cGy within the body. Approximately 630 projection images were acquired per CBCT scan and the total acquisition time of a CBCT scan was 4 min on the prototype system. Reconstruction of a CBCT scan took approximately 60 s on a 2.8 GHz personal computer (note: in future systems, CBCT acquisition will be about 2 times faster and reconstruction will be ready as soon as all images are acquired). The CBCT scans were reconstructed using in-house developed software, based on the Feldkamp-Davis-Kress algorithm\(^{17}\). To reduce the influence of scatter\(^{18-19}\) a
simple scatter correction algorithm was applied during reconstruction of all CBCT scans, which assumes scatter to be homogeneously distributed in the image. The field of view (FOV) of the acquired projection images was 25.6 x 25.6 cm² at the isocenter plane. By using a partially displaced kV detector, a reconstructed FOV of 40.0 x 40.0 cm² was achieved. For 18 patients (190 CBCT scans), reduction of scatter was achieved by collimating the FOV in the CC direction from 25.6 cm to 10.0 cm. Therefore, the reconstructed CBCT scans consisted either of 400 x 400 x 256 voxels (uncollimated FOV) or 400 x 400 x 100 voxels (collimated FOV), with a voxel dimension of 1.0 x 1.0 x 1.0 mm³.

GREY-VALUE REGISTRATION OF THE PROSTATE

BRIEF DESCRIPTION OF THE PREVIOUSLY DEVELOPED 3D GREY-VALUE REGISTRATION PROCEDURE
The automatic 3D grey-value registration algorithm developed previously was used to register the prostate in the CBCT scan to the prostate in the planning CT scan. The algorithm assumes that the prostate behaves approximately as a rigid body (three translations, three rotations, no shape changes). The start position of the algorithm was a registration of the bony anatomy. For grey-value registration, the CTV contours were expanded with a 5 mm margin, and used to generate a 3D CTV shaped region of interest (ROI) in the planning CT scan. Any gas in the rectum was filtered from the ROI. All CBCT scans of a patient were registered to the ROI using the previously developed algorithm, for which only the pixels within this ROI were used (i.e., prostate localization required no delineation of the prostate in the CBCT scans). Grey-value registration was based on maximizing the correlation ratio. The algorithm used multiple start positions of the CBCT scan with respect to the bony anatomy registration (i.e., the CBCT scan was rotated about the left-right axis by +5, 0, and -5 degrees, respectively). Of these three grey-value registrations, the one with the highest correlation ratio was selected.
ADAPTATIONS TO THE PREVIOUSLY DEVELOPED 3D GREY-VALUE REGISTRATION ALGORITHM

Two adaptations were made to the previously developed 3D grey-value registration algorithm. The first adaptation involved creation of the ROI. In the previous study, initial tests showed that a 5 mm margin was the optimum value to retain enough grey-value information and to exclude the pubic bone from the ROI. However, part of the pubic bone was sometimes still included in the ROI. This could influence grey-value registration of the prostate. Therefore, the first adaptation to the previous algorithm was that grey-values of the pubic bone were removed from the ROI. In addition, calcifications located at the inner border of the prostate that might be subject to movement relative to the prostate were also removed from the ROI. The second adaptation of the 3D grey-value registration algorithm was that the resolution of the scan with the lower resolution (the planning CT scan) was adjusted to that of the scan with the higher resolution (the CBCT scan). With this adaptation, all grey-value information of the CBCT scans could be used for registration. A single 3D grey-value registration (with adaptations) took approximately 30 s on a 2.0 GHz personal computer.

FALLBACK PROCEDURE

A fallback procedure for prostate localization on CBCT scans was developed in case 3D grey-value registration (GR) (= normal GR) fails. In this procedure, 3D GR was repeated in an adapted form. It was assumed that there was negligible organ motion for the apex, as was found in previous studies\(^{(21)}\), and that, after bony anatomy registration, the apex would be in the same relative position in the planning CT and CBCT scans. In the fallback method, the prostate was therefore fixed at the apex during registration (= fixed apex GR, i.e., the apex of the prostate was used as a rotation point for 3D grey-value registration; three rotations, no translations). The fixed rotation point was defined at the center of gravity of the most caudal prostate contour delineation (in the apex) of the planning CT scan. As the delineation error at the prostate apex is known to be 3.5 mm (1 SD) in CT data\(^{(22)}\), the accuracy of prostate localization by using fixed apex GR may be slightly influenced by the inaccuracy in the choice of this point, although this is a secondary effect. After the scans were registered on bony anatomy, this point was also known in the CBCT scan. The fixed apex GR method was applied only to those registrations for which normal GR failed. Running the fallback procedure took an extra 20 s on a 2.0 GHz personal computer.
STUDY OUTLINE

For initial tests, we wanted to verify the performance of the grey-value registration algorithm on CBCT scans by comparing the results of grey-value registration to contour registration, as was done in the study previously performed on conventional CT scans\(^{(10)}\). In that study, the CTV contours of repeat CT scans were automatically registered to the CTV contours of the planning CT scan\(^{(21)}\) and used as a reference for evaluating the grey-value registrations.

Unfortunately, in the current study, delineating the prostate on the CBCT scans appeared to be inaccurate because of the poorer contrast-to-noise ratio and the presence of image artifacts, especially in the earlier CBCT scans. However, the image quality of the CBCT scans was considered sufficient to assess the registrations visually (See next paragraph). In the absence of suitable contours, the error in grey-value registrations was quantified by calculating the error in position of a clearly defined calcification inside the prostate gland (if present), which served as a natural marker as described below.

VISUAL ASSESSMENT OF GREY-VALUE REGISTRATIONS

All registrations were assessed by visual inspection by one experienced observer to simulate clinical practice once the method will be implemented on the treatment machine. If a registration after normal GR was assessed as not successful, the fixed apex GR method was applied and the registration was assessed again. For this purpose, expanded CTV contours of the planning CT scan by 3.6 mm were used (i.e., 2 pixels in the 256 x 256 planning CT images). The expanded CTV contours were overlaid on the registered CBCT scan and the observer was instructed to assess a registration as successful if the prostate fitted within the expanded CTV contours. Assessment was based on all slices in three views: transverse, coronal, and sagittal. The visibility of the prostate in the CBCT scans was similar in all views. However, in some CBCT scans, the prostate was not always completely visible in each slice, which could usually be attributed to the presence of artifacts such as streaks in the reconstructed images. Despite the presence of these artifacts, grey-value registrations of the prostate could be assessed sufficiently while slicing through the registered scans in 3D.
A Pearson chi-squared test (at a 95% confidence level) was performed on the assessment results to determine whether there was a significant difference in the percentage of successfully registered cases for grey-value registration of CBCT scans acquired with collimated or uncollimated FOV; this was done for the results when normal GR alone, or the combined normal and fixed apex GR method was applied.

**DETERMINATION OF REGISTRATION ERRORS**

The errors in grey-value registration for the normal as well as the fixed apex GR method were determined by calculating the difference in position of 1 clearly defined calcification inside the prostate gland between planning CT scan and registered CBCT scan (typically there was 1 calcification per patient; if more than 1 were present, the most clearly defined calcification was used). Such calcifications served as natural markers, and were present in 12 patients, 127 CBCT scans. The relative positions of the calcifications in the planning CT and CBCT scans after registration were marked by an observer. The position of a calcification was marked on the planning CT grid, with a spatial resolution of 1 pixel (1.8 mm) and 1 slice (3.0 mm). Calcifications located at the inner-border of the prostate gland were not included in this study, as they might be part of, or close to, a lymph/blood vessel for which the relative position to the prostate might change. For this analysis, the calcifications inside the prostate were filtered from the ROI before registration (note: calcifications at the inner-border were already removed by a filtering step in the adapted grey-value registration method). Other tests (data not presented) showed that the calcifications could be used as independent verification of grey-value registration: because of their small size (compared with the rest of the prostate) they had negligible influence on grey-value registration. Both registration methods (normal and fixed apex GR) were independently applied to the scans of the selected patients (i.e., with calcifications). Only registrations that were assessed as successful for both GR methods were used to determine the registration error of the normal GR and fixed apex GR method (9 patients, 71 successful registrations). The registration errors were expressed as a mean and standard deviation (SD) for each of the 3 axes. The systematic and random components of these SDs were also calculated.
RESULTS

AUTOMATIC PROSTATE LOCALIZATION ON CBCT SCANS
BY 3D GREY-VALUE REGISTRATION: AN EXAMPLE

FIGURE 2 gives an overview of slices of a CBCT scan in which the prostate is registered to the planning CT scan. Transverse (2-I), coronal (2-II), and sagittal (2-III) image sets are shown. The coronal and sagittal slices show the reduced FOV in the CC direction. This procedure improved the image quality considerably. All (a) images show the whole CBCT slice in a particular view, illustrating the good image quality. The same slices of the CBCT scan are shown in all (b) and (c) images, fused with the planning CT scan after grey-value registration of the prostate. The (b) images show split views at the prostate gland and the (c) images show split views at the SV. To illustrate the split view at the SV in the coronal (2–IIc) view, another slice of the CBCT scan was selected. The top-left and bottom-right part of these images represent the planning CT scan; the top-right and bottom-left part of these images represent the CBCT scan.

The images show the difference in image quality of the CBCT scan and the conventional CT scan, which is a result of different acquisition and reconstruction methods. The prostate in the CBCT images is clearly visible in all directions, despite the lower contrast-to-noise ratio of the CBCT scans, compared to that of the conventional CT scans. The fused images show that the outline of the registered prostate in the CBCT scan agrees with the prostate outline in the planning CT scan. The (d), (e), and (f) images are identical to the respective (a), (b), and (c) images, except that the CTV contours of the planning CT scan were superimposed on these images. Note that the CTV contours were not used for registration, while for assessment of the registrations the expanded CTV contours were used. The registration results as seen in the images are typical, i.e., for most cases the prostate coincided within the CTV contours.
FIGURE 2. Overview of slices of a cone-beam computed tomography (CBCT) scan in which the prostate is registered to the planning CT scan. Transverse (2-I), coronal (2-II), and sagittal (2-III) image sets are shown. All (a) images show the whole CBCT slice in a particular view. The same slices of the CBCT scan are shown in all (b) and (c) images, fused with the planning CT scan after grey-value registration of the prostate. The (b) images show split views at the prostate gland and the (c) images show split views at the seminal vesicles (SV). To show the split view at the SV in coronal (2-IIc) view, another slice of the CBCT scan was selected. The top left and bottom right part of these images represent the planning CT scan; the top right and bottom left part of these images represent the CBCT scan. The (d–f) images are identical to the respective (a–c) images, except that the contours of the planning CT scan are superimposed on these images (contours were not used for registration).
VISUAL ASSESSMENT OF REGISTRATIONS

Visual assessment of the normal grey-value registrations of the patient group with CBCT scans acquired with a collimated FOV in the CC direction (18 patients, 190 CBCT scans) showed that 65% of the registrations were successfully registered (124 cases) (Table 1), i.e., the registered prostate fitted within the expanded CTV contours of the planning CT scan. For the patient group with CBCT scans acquired with an uncollimated FOV in CC direction (14 patients, 142 CBCT scans), 56% of the registrations were assessed as successfully registered (80 cases). The p value of the Pearson chi-square test, to determine whether there was a significant difference in the percentage of successfully registered cases for grey-value registration of CBCT scans acquired with collimated or uncollimated FOV, calculated for the normal GR assessment results, was p = 0.098. The registrations that were assessed as unsuccessful using the normal GR method were registered again by using the fixed apex GR method. For the patient group with CBCT scans acquired with a collimated FOV, 50% of the unsuccessful cases were now assessed as successfully registered, whereas for the patient group with CBCT acquired with an uncollimated FOV, this was 31% (Table 1).
TABLE 1. Visual assessment results of normal GR followed by fixed apex GR for the unsuccessful normal GR resulting in the combined percentage successfully registered cases. A division was made for registrations with CBCT scans acquired with collimated or uncollimated FOV.

<table>
<thead>
<tr>
<th>GR method</th>
<th>CBCT collimated FOV</th>
<th>CBCT uncollimated FOV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal GR</td>
<td>65%</td>
<td>56%</td>
</tr>
<tr>
<td>Fixed apex GR*</td>
<td>50%</td>
<td>31%</td>
</tr>
<tr>
<td>Combined</td>
<td>83%</td>
<td>70%</td>
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</table>

ABBREVIATIONS: GR = grey-value registration; CBCT = cone-beam computed tomography; FOV = field of view.
* Applied only to the unsuccessful normal GR

By combining the results of the two registration methods (normal and fixed apex GR), 83% of the CBCT scans acquired with a collimated FOV were assessed as successfully registered, whereas for the CBCT scans acquired with an uncollimated FOV, this was 70% (TABLE 1). The Pearson chi-square test was applied to the combined normal and fixed apex assessments to determine whether there was a significant difference in the percentage of successfully registered cases for grey-value registration of CBCT scans acquired with collimated or uncollimated FOV. The resultant p value was 0.0006.

For the patient group with CBCT scans acquired with a collimated FOV, FIGURE 3 shows for each patient the number of registrations (black bars) and the number of unsuccessful registrations when normal grey-value registration alone (grey bars) or the combined normal and fixed apex GR method (white bars) has been applied. Grey-value registration mainly failed (or registrations were difficult to assess) because of streaks in the reconstructed images of the CBCT scan caused by motion of gas pockets in the rectum during CBCT image acquisition.
FIGURE 3. Results of combining normal grey-value registration (GR) and fixed apex GR for the patient group with cone-beam computed tomography scans acquired with a collimated field of view: the number of registrations per patient (black bars), the number of unsuccessful registrations after normal GR (grey bars), and the number of unsuccessful registrations after the combined normal and fixed apex GR method (white bars).

FIGURE 4 shows the impact of a large moving gas pocket during image acquisition on the reconstructed CBCT image quality (i.e., streak artifacts). Images 4(Ia–Id) show examples of projection images in which a large moving gas pocket emerges in the rectum over a time span of 17 s at the position where the prostate would be projected in the image. Image 4–II shows the reconstruction result on a transverse slice of the CBCT scan: from this image, it is clear that the prostate is not detectable.
**Figure 4.** The impact of a large, moving gas pocket during cone-beam computed tomography (CBCT) image acquisition on the CBCT reconstruction result. 4(Ia-IId) Projection images (PI) showing a large, moving gas pocket (bright structure) emerging in the rectum in a time span of 17 s at a position where the prostate would be projected in the projection images. (4-II) The reconstruction result, showing the streak artifacts in a transverse slice of the CBCT scan.

**Registration errors**

The errors in registration, of the normal and fixed apex grey-value registration method, on CBCT scans, along the left-right (LR), CC, and anteroposterior (AP) axes, are shown in Table 2. The mean errors are close to zero. For normal GR, the mean deviation in the CBCT scan of the calcification with respect to the planning CT scan in AP direction was largest, -0.9 mm, whereas for the LR and CC axes, the mean deviation was smaller than 0.5 mm. For the fixed apex GR, the mean deviation was smaller than 0.5 mm for all axes. The deviations were comparable for both methods and ranged between 1.0 and 2.4 mm (1 SD); the SDs for fixed apex GR were slightly smaller. Table 2 shows that the systematic and random components of the SDs contributed approximately equally to these SDs, for both registration methods.
**Table 2.** The registration errors (in mm) of normal and fixed apex GR of the prostate using CBCT scans, expressed as a mean and standard deviation, along the LR, CC and AP axes. The systematic and random components of these SDs are also shown. The registration errors were determined from the position of a clearly defined calcification inside the prostate in planning CT and CBCT scans after registration. Only registrations that were assessed as successfully registered (i.e., the prostate fitted within the expanded clinical target volume contours for both methods) were used (9 patients, 71 registrations).

<table>
<thead>
<tr>
<th></th>
<th>Normal GR</th>
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<th>Fixed apex GR</th>
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<tr>
<td></td>
<td>TLR</td>
<td>TCC</td>
<td>TAP</td>
<td>TLR</td>
</tr>
<tr>
<td>Mean</td>
<td>0.2</td>
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<td>0.1</td>
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<tr>
<td>Σ</td>
<td>0.7</td>
<td>1.6</td>
<td>1.8</td>
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<tr>
<td>σ</td>
<td>0.8</td>
<td>1.8</td>
<td>1.5</td>
<td>0.8</td>
</tr>
<tr>
<td>SD</td>
<td>1.0</td>
<td>2.4</td>
<td>2.3</td>
<td>1.0</td>
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</tbody>
</table>

**Abbreviations.** GR = grey-value registration; (CB)CT = (cone-beam) computed tomography; SD = standard deviation; T = translation; LR = left-right; CC = craniocaudal; AP = anteroposterior; Σ = systematic error; σ = random error.

**Discussion**

The performance of the previously developed grey-value registration algorithm for prostate localization\((10)\) was evaluated using CBCT scans. For CBCT scans that were acquired with a collimated FOV, the percentage of successfully registered cases, based on visual assessment, improved from 65% when only normal grey-value registration was applied to 83% when the results of normal and fixed apex GR were combined. The errors in grey-value registration (1.0 – 2.4 mm, 1 SD) determined from the position of a clearly defined calcification in the prostate gland, are sufficiently small to reduce treatment field margins. The error in grey-value registration is somewhat larger than for registration of implanted markers, the accuracy of the latter being less than 1 mm (1 SD)\((3-4)\). However, as mentioned previously, markers might be subject to some migration and, in addition, when the SV are part of the target volume, movement of the SV relative to the prostate gland will not be registered by the markers.
VISUAL ASSESSMENT OF REGISTRATIONS

Assessment of the registration results by visual inspection was performed to simulate clinical practice, when the method will be implemented at the treatment machine. The viewing tool used for the inspection enabled simultaneous viewing of the scans in 3D and interactive slicing. This provided a very sensitive tool for assessment of the registrations. The expansion of the CTV contours by 3.6 mm, which aided visual assessment of the registrations, seems quite generous and will generally only be reached at the tips of the SV because of rotation errors or shape changes. Deurloo et al.\textsuperscript{(15)} reported a shape variation of 0.5 mm (1 SD) at the caudal side of the prostate, 0.9 mm (1 SD) anterior and posterior of the prostate, and 1.5 mm (1 SD) at the tips of the SV, for a comparable patient group. In our study, we noticed that the majority of the successfully registered prostates coincided within the CTV contours (not expanded), and that the expanded CTV contours were used primarily to account for deformations of the SV.

CBCT scans acquired with a collimated FOV in the CC direction had a considerably better image quality than CBCT scans acquired with an uncollimated FOV. This most likely explains the difference in the percentage of successfully registered cases for CBCT scans acquired with a collimated and uncollimated FOV, 83\% and 70\%, respectively, for the combined normal and fixed apex GR procedure. The Pearson chi-square p value for the combined normal and fixed apex GR procedure, to determine whether there is a significant difference in the percentage of successfully registered cases for grey-value registration of CBCT scans acquired with collimated or uncollimated FOV, was $p = 0.006$, whereas the Pearson chi-square p value calculated for the normal GR procedure alone was $p = 0.098$. The percentage of successfully registered cases using CBCT scans (83\%) was lower than that of conventional CT scans, which was 91\%\textsuperscript{(10)}. This result is reasonable, taking into account the fact that the contrast-to-noise ratio of the CBCT scans is still poorer than that of conventional CT scans. Part of the difference might be explained by the difference in the definition of a successfully registered case. In this study, visual inspection determined whether a registration was successful or not, whereas in the previous study, grey-value registrations were compared with contour registrations.

Grey-value registration on CBCT scans mainly failed (or registrations were difficult to assess) because of streaks in the CBCT scans. These were caused by large, moving gas pockets in the rectum during CBCT image acquisition. Improvement of the outcome for CBCT scans is likely achieved if
the amount of gas in the rectum could be reduced. A possible solution would be to prescribe a mild laxating diet for the patients to reduce the amount of rectal filling in the planning CT scan and in the CBCT scans (of the first few treatment fractions). This would probably also reduce the amount of (possibly moving) gas in the rectum, which would improve the image quality of the reconstructed CBCT scans. In addition, intrafraction motion would be reduced.

**REGISTRATION ERRORS**

The mean deviation of the calcifications for normal and fixed apex GR were smaller than 0.5 mm for all axes, except for the AP axis for normal GR: -0.9 mm. The registration errors determined from the position of clearly defined calcifications in the prostate gland along the LR, CC, and AP axes were 1.0, 2.4, and 2.3 mm (1 SD) for the normal, and 1.0, 2.0, and 1.7 mm (1 SD) for the fixed apex GR method. The registration errors were larger than that of the previous study\(^{10}\): along the LR, CC, and AP axes, these errors were 0.7, 1.3, and 1.2 mm (1 SD) for translations, and 2.4, 1.6, and 1.3° (1 SD) for rotations, respectively. Part of the differences might be explained by the accuracy of marking the positions of the calcifications, which was determined by the spatial resolution of the planning CT scan (i.e., 1.8 mm x 1.8 mm, with a slice thickness of 3 mm). Another explanation for the differences might be the difference in definition of a registration error. In this study, only one point, the calcification in the prostate gland, was used to determine the error in grey-value registration. Although a registration could be assessed as successful, this single point could be more subject to deformations of the prostate (e.g., because of rectum filling). This might also be an explanation for the smaller SDs for fixed apex GR than for normal GR, although normal GR was visually slightly more accurate. Therefore, fixed apex GR was only used as fallback, even though the SDs in CC and AP directions were slightly smaller than those of normal GR. In the previous study, grey-value registrations were compared with contour registrations to determine their accuracy. Both grey-value registrations and contour registrations were performed as rigid body registrations, which cannot detect deformations of the prostate. If however, implanted markers were used for verification of the grey-value registration procedure, similar results probably would be found, as described previously for the calcifications. Registration errors would possibly become smaller, and the percentage of successfully registered cases would most likely increase if the amount of moving gas in
the rectum of the patients could be reduced during CBCT image acquisition, which causes reconstruction artifacts.

**MARGINS**

The margin between the CTV and planning target volume (PTV) that we use in our clinic for prostate treatment is 1.0 cm. To estimate the margin for prostate treatments during online IGRT, the margin recipe as defined by Van Herk et al.\(^{(23)}\) could be used. The PTV margin (M) is expressed as: \(M = 2.5 \sigma + 0.7 \sigma\), in which \(\sigma\) represents the SD of all systematic errors combined, and similarly \(\sigma\) for all random errors. For an online IGRT process, table corrections would be performed to eliminate random and systematic translation errors for each treatment fraction. The idea is to also eliminate random and systematic rotation errors, around the LR axis, by choosing the best fitting patient specific plan from a set of predefined treatment plans (See the following section), according to the position of the prostate around the LR axis just before each treatment. We therefore assume that systematic and interfraction random errors will be largely eliminated when using the online image-guidance system. The required margin between CTV and PTV to account for the systematic and random errors in grey-value registration could be calculated by using the SDs of the measured calcification displacements. Using the margin recipe as mentioned previously, these margins would be for normal grey-value registration (\textit{Table 2}) 2.3 mm in the LR direction \((M_{LR} = (2.5 \times 0.7 + 0.7 \times 0.8) \text{ mm})\), 5.3 mm in the CC direction \((M_{CC} = (2.5 \times 1.6 + 0.7 \times 1.8) \text{ mm})\), and 5.6 mm in the AP direction \((M_{AP} = (2.5 \times 1.8 + 0.7 \times 1.5) \text{ mm})\). The margins for the combined normal and fixed apex GR procedure are expected to be similar as the registration errors for fixed apex GR are comparable to those of normal GR. Here it is assumed that rotation errors for the prostate can be neglected because of the round shape of the prostate. To account for rotation errors at the SV, the margin should be approximately twice as large at the tips of the SV than at the prostate\(^{(10)}\). Although the time between imaging and actual treatment in the image-guidance system is drastically reduced when the method for automatic prostate localization is implemented on the treatment machine, it is still possible for prostate displacements to occur in the short time between plan selection and actual delivery. Therefore, it is necessary to define an additional margin to take intrafraction motion into account. It is probably not necessary to define an additional margin in all directions for delineation.
errors of the prostate in the planning CT scan, because studies have demonstrated that CT-derived prostate volumes are larger than magnetic resonance image derived prostate volumes, especially towards the SV and the apex of the prostate \(^{(22)}\), and the margins for delineation errors are thus implicitly taken into account.

The margins calculated to account for errors in grey-value registration are quite large (the largest margin was 5.6 mm in AP direction), although from visual assessment it appeared that for most cases the prostates in the CBCT scans were very well registered (i.e., within the expanded CTV contours by 3.6 mm), and even coincided within the CTV contours. A possible explanation for this discrepancy between the calculated margin and the visual assessment results could be that if the prostate is slightly deformed, this could lead to large deviations in the positions of the calcifications, whereas the rigid-body grey-value registration would still be able to align the outer prostate border, and the result would be visually assessed as a successful registration. In addition, such a registration would lead to a correct irradiation as well, as long as the whole prostate is the target. This finding may also explain the slightly smaller SDs found for fixed apex GR, whereas visually the registration quality often is somewhat poorer than that of normal GR.

**FUTURE DIRECTIONS**

We are evaluating the grey-value registration algorithm on CBCT data from the Princess Margaret Hospital (Toronto, Ontario, Canada). A laxating diet was prescribed to the patients and three markers were implanted in the prostate gland. With these data, the accuracy of grey-value registration of the prostates, even without calcifications, will be evaluated, as well as the validation of rotations.

Future work will focus on how to deal with registration failures. Registration failures could be adjusted manually either based on grey-value or color overlays of the prostates, or by registering the CTV contours of the planning CT scan to the prostate in the CBCT scan (comparable to ultrasound-based methods). If a CBCT registration is impossible to assess because of image artifacts in the CBCT scan caused by moving gas in the rectum during image acquisition, possible solutions would be to repeat the CBCT after degassing the patient, to deliver that particular fraction in the conventional way (e.g.,
registered on bony anatomy in combination with the 1.0 cm margin, as used currently), to omit the fraction, or to treat the patient during the whole treatment the conventional way. We are investigating the effect of prescribing tablets of magnesium oxide to the patients on a daily basis during treatment in combination with a diet, which has a laxating effect and should minimize the amount of gas (and feces) in the rectum.

Our group is investigating implementation of the grey-value registration procedure in an offline adaptive radiotherapy protocol[24] that could reduce the systematic error in prostate (and rectum) position[2,25]. In the adaptive radiotherapy process, repeat CBCT scans will be used to determine the mean position of the prostate (and rectum) during the course of radiotherapy treatment. As mentioned previously, delineating the prostate on CBCT scans appeared to be inaccurate (especially on the earlier scans) and use of the grey-value registration procedure is therefore required. However, if delineating the prostate on CBCT scans is feasible, automatic grey-value registration with adaptive radiotherapy will save an extensive amount of delineation time.

For online IGRT, when a grey-value registration is assessed as successful, we would like to use the values found for prostate rotation and translation (with respect to the planning CT scan) for couch adjustment (i.e., to account for translation of the prostate relative to the planning isocenter). These values could also be used to select a best fitting patient specific plan from a set of predefined treatment plans (database) to account for prostate rotation[10,26]. To generate these patient-specific plans, we intend to rotate the CTV contours around the LR axis (e.g., -10° → +10°, with a 1° interval step size), because this is the main rotation axis. If we assume that movement of the prostate is the direct result of movement of the rectal wall neighboring the prostate, we could, as a first-order approximation, rotate the delineated rectum to the same extent as the prostate. This approximation is obviously not correct for the complete rectum, but one might expect that it provides a reasonable description for the rectal wall receiving the highest dose. Further investigation is therefore needed. We estimate that the time required to generate these plans during treatment preparation would be in the order of a few minutes, whereas their selection before treatment would take only a few seconds. For online IGRT, the time between imaging and treatment has to be short to minimize the possibility for prostate movement or shape changes. The total delay between imaging and treatment during online IGRT after implementation of the grey-value registration procedure on the treatment machine would be: approximately 2 min for acquisition and
reconstruction of the CBCT scan (on future CBCT-IGRT systems), approximately 30-60 s to register the prostate using the grey-value registration procedure, a few minutes to assess the registration, and a few seconds to select a patient-specific plan from a set of predefined treatment plans (database). Although the time between imaging and treatment would be drastically reduced when using the online IGRT system, further investigation is needed to investigate how much the prostate can move and change shape during this time\(^{(27)}\). Therefore, in all cases, the precise margin to be used for prostate treatment during offline or online CBCT-IGRT has to be reevaluated, taking registration errors, correction errors, and short-term intrafraction movement into account.

**CONCLUSIONS**

The feasibility of automatic prostate localization on CBCT scans acquired on the treatment machine using an adaptation of the previously developed 3D grey-value registration algorithm has been validated in this study. The percentage of successfully registered cases was 83\% for the combined normal and fixed apex grey-value registration procedure. The errors in grey-value registration, determined from the position of a clearly defined calcification in the prostate gland, ranged from 1.0 to 2.4 mm (1 SD). Collimating the FOV during CBCT image acquisition improved the CBCT image quality considerably. Artifacts in the CBCT images caused by large moving gas pockets during CBCT image acquisition were the main cause for unsuccessful registration. From this study, we can conclude that CBCT scans are suitable for online and offline position verification of the prostate, as long as the amount of nonstationary gas is limited.
REFERENCES


