Towards image-guided radiotherapy of prostate cancer
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Citation for published version (APA):
Smitsmans, M. H. P. (2010). Towards image-guided radiotherapy of prostate cancer Amsterdam: The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital

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AUTOMATIC LOCALIZATION OF THE PROSTATE FOR ONLINE OR OFFLINE IMAGE-GUIDED RADIOTHERAPY

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INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY & PHYSICS 2004; VOLUME 60: PG 623-635
ABSTRACT

PURPOSE With higher radiation dose, higher cure rates have been reported in prostate cancer patients. The extra margin needed to account for prostate motion, however, limits the level of dose escalation, because of the presence of surrounding organs at risk. Knowledge of the precise position of the prostate would allow significant reduction of the treatment field. Better localization of the prostate at the time of treatment is therefore needed, e.g. using a cone-beam computed tomography system integrated with the linear accelerator. Localization of the prostate relies upon manual delineation of contours in successive transverse CT slices or interactive alignment and is fairly time-consuming. A faster method is required for online or offline image-guided radiotherapy, because of prostate motion, for patient throughput and efficiency. Therefore, we developed an automatic method to localize the prostate, based on three-dimensional (3D) grey-value registration.

PATIENTS AND METHODS A study was performed on conventional repeat CT scans of 19 prostate cancer patients to develop the methodology to localize the prostate. For each patient, 8–13 repeat CT scans were made during the course of treatment. First, the planning CT scan and the repeat CT scan were registered onto the rigid bony structures. Then, the delineated prostate in the planning CT scan was enlarged by an optimum margin of 5 mm to define a region of interest in the planning CT scan that contained enough grey-value information for registration. Subsequently, this region was automatically registered to a repeat CT scan using 3D grey-value registration to localize the prostate. The performance of automatic prostate localization was compared to prostate localization using contours. Therefore, a reference set was generated by registering the delineated contours of the prostates in all scans of all patients. Grey-value registrations that showed large differences with respect to contour registrations were detected with a $\chi^2$ analysis and were removed from the data set before further analysis.

RESULTS Comparing grey-value registration to contour registration, we found a success rate of 91%. The accuracy for rotations around the left-right, craniocaudal, and anteroposterior axis was 2.4 degrees, 1.6 degrees, and 1.3 degrees (1 SD), respectively, and for translations along these axes 0.7, 1.3, and 1.2 mm (1 SD), respectively. A large part of the error is attributed to uncertainty in the reference contour set. Automatic prostate localization takes about 45 seconds on a 1.7 GHz Pentium IV personal computer.

CONCLUSIONS This newly developed method localizes the prostate quickly, accurately, and with a good success rate, although visual inspection is still needed to detect outliers. With this approach, it will be possible to correct online or offline for prostate movement. Combined with the conformity of intensity-modulated dose distributions, this method might permit dose escalation beyond that of current conformal approaches, because margins can be safely reduced.
Studies have demonstrated that increasing the radiation dose to the prostate increases the probability of disease control, particularly for patients suffering from advanced disease\(^1\)\(^-\)\(^3\). However, with the current methods of radiation delivery, increasing the radiation dose to the target will result in high dose to the surrounding tissues of the prostate gland. In current methods, that the position of the prostate and surrounding tissues is not known precisely for each radiation fraction, because of mobility of internal organs, this uncertainty is taken into account by taking a safety margin around the clinical target volume to guarantee that the entire prostate always receives the required daily dose. Therefore, many recent studies focus on position verification (offline and online) of the target just before and/or after treatment. Yan et al.\(^4\) developed an offline process for position verification, the adaptive radiotherapy (ART) system, using a composite drawing of the prostate generated from multiple computed tomography (CT) scans. Nederveen et al.\(^5\) performed online position verification using implanted gold markers in the prostate and an amorphous silicon flat-panel detector. Kitamura et al.\(^6\) developed a fluoroscopic real-time tumor tracking system and used gold markers to verify the position of the prostate. Bergström et al.\(^7\) performed online position verification of the prostate with a catheter containing markers at the start of a treatment fraction. Van den Heuvel et al.\(^8\) and Langen et al.\(^9\) tested the use of an ultrasound-based localization system that localizes the prostate before each treatment fraction and used gold markers to verify the position of the prostate. Studies that make use of limited delineations to quickly localize the prostate were performed by Hua et al.\(^10\) and Artignan et al.\(^11\), and these might be useful also for online position verification. In our investigations, we aim to develop an online image-guided radiotherapy (IGRT) system for high-precision radiotherapy of the prostate. This system will localize the target and normal tissues at the time of treatment, using a cone-beam CT (CBCT) system integrated with the linear accelerator (Jaffray and Siewerdsen\(^12\), Jaffray et al.\(^13\)). The CBCT system consists of an X-ray kilovolt source and an amorphous silicon flat-panel imager that are mounted on the accelerator perpendicular to the radiation beam direction. A CBCT scan is obtained within a few minutes before treatment in one single gantry rotation. Localization of the prostate and surrounding structures typically relies upon manual delineation of contours in successive transverse CT slices and is a
time-consuming process. This is unacceptable for online IGRT, because of short-term prostate motion and for patient throughput. Therefore, the aim of the study presented here is the development of a fully automated method for prostate localization to reduce the time interval between imaging and treatment. Such a method will be of great use, also to improve the efficiency of the offline ART process.

PATIENTS AND METHODS

PATIENT DATA

For this study, an existing data set from 19 patients, irradiated for prostate cancer at The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital, was used. Besides the planning CT, 8–13 repeat CT scans were made during the course of treatment for each patient. The CT scans were all made in treatment position (supine), approximately 30 min after treatment. The CT scans typically consist of 60 slices with 512 x 512 pixels, with a slice distance of 5 mm outside and 3 mm inside the region of the prostate.

DELINEATION OF PROSTATE AND SEMINAL VESICLES IN CT SCANS

The prostate and seminal vesicles (SV) were delineated on the transverse slices in the planning and repeat CT scans, using delineation software previously developed at The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital. The term ‘prostate’ or ‘prostate contours’ used in the rest of this article will refer to both the prostate and SV. The prostate contours were automatically registered by using a chamfer-matching algorithm (Van Herk et al.\(^{(14)}\)). In general, chamfer-matching requires that the features of interest in one scan are described by a collection of contour points, whereas the features in the other scan are reduced to a binary image, of which the distance transform is computed. Registration is performed by minimizing the root mean square difference (RMS) of the distance between the contour points of the first scan and the feature in the
Automatic prostate localization was based on the procedure proposed by Jaffray et al.\(^{(13)}\) An adapted flow chart of this procedure is shown in **Figure 1**.

**Figure 1.** Adapted flow chart of the automatic prostate localization procedure proposed by Jaffray et al.\(^{(13)}\). First, a bone registration of the planning computed tomography (CT) scan and the repeat CT scan was performed. This resulted in a transform that was used as the starting point for grey-value registration. Before grey-value registration, a region of interest was defined in the planning CT scan by using the delineation of the prostate plus a margin of 5 mm. This region was translated and rotated onto the repeat CT scan until it was registered. Registration was performed by minimizing a cost function. Optional filters were applied, to either the planning CT scan and/or the repeat CT scan. Then this process was repeated for registrations that used the bone registration as starting point, but with an additional rotation of the repeat CT scan by successively +5 and -5 degrees around the left-right axis. Of the three possible solutions, the registration that resulted in the lowest cost function value was chosen as the final grey-value registration.
First, the planning CT and the repeat CT scan were registered on bones. The prostate contour defined in the planning CT, enlarged with a margin of 5 mm, was used to select a region of interest in the planning CT that contained enough grey-value information for registration (Figure 2).

![Figure 2](image)

**Figure 2.** (a) A slice of a planning computed tomography (CT) scan. The black line represents the delineated contour of the prostate and the grey line represents the delineated contour of the prostate plus 5 mm margin. (b) A slice of the region of interest (delineated contour plus 5 mm margin) made out of the planning CT scan that will be registered to the repeat CT scans.

In initial tests, this margin appeared to be an optimum with respect to grey-value information and excluding bone from the os pubis and possible fecal gas in the rectum from the region of interest. Subsequently, this region of interest was registered to all repeat CT scans of a patient using a grey-value registration algorithm, for which only the pixels within this region of interest were used. That is, prostate localization required no delineation of the prostate in the repeat CT scans. The registration results were dependent on the cost function chosen, whether or not filtering was applied to the CT scans, and on the starting point for automatic grey-value registration. These aspects were all tested in this study (See following paragraphs).
COST FUNCTIONS

Five different cost functions that are frequently used for grey-value registration (e.g., Fei et al.\textsuperscript{15}) have been tested to develop the automatic registration procedure for the prostate. They are as follows: correlation ratio (CR), mutual information (MUI), normalized mutual information (NMUI), normalized cross correlation (NCC), and RMS. These cost functions express, each in their own way, the goodness of fit of the prostate as calculated from the pixel values of the scans. Registration of the repeat CT scan to the region of interest in the planning CT scan was performed by translating and rotating the repeat CT scan until the cost function was minimized. The best cost function to be used for grey-value registration was determined by counting the number of successful registrations and by determining the statistics of the difference between contour and grey-value registration for the successful registrations. A successful registration will be defined as described in the paragraph under the heading ‘Evaluation of registration results in terms of reliability: Outlier detection’. Tests were performed on a subset of 10 patients (randomly chosen), 5 scans (the first 5 scans) per patient, and for this purpose the CT scans were used without filtering.

FILTERS

One possible problem that could occur during automatic prostate localization is a variable amount of fecal gas in the rectum, which could mislead the registration algorithm. To test whether registration results improved when the gas regions were suppressed, two different filters have been tested on the same subset that was used for determining the cost function (\textbf{FIGURE 3}). One filter suppressed grey-values of gas, the ‘Suppress Gas’ filter, whereas the other filter replaced grey-values of gas by a tissue equivalent grey-value, the ‘Replace Gas by Tissue’ filter. For the ‘Suppress Gas’ filter, a binary mask was made, which first selected all pixels with a pixel value higher than -500 Hounsfield Units (HU) (halfway between the HU value of air and tissue), and these values were set to 1; all other pixel values (i.e., gas) were set to zero. Subsequently, a local minimum filter with a kernel size of 3 was applied to this binary image, which resulted in shrinkage of tissue structure by 1 pixel to exclude pixels that contain a mixture of gas and tissue (partial volume effect) to be sure to have all the gas suppressed. Then the new mask was applied to the original CT scan (\textbf{FIGURE 3A}), i.e., combined with the original mask
The zero pixel values in the new CT scan were ignored in the registration algorithm, and also the neighboring pixels were ignored for interpolation. The other filter, ‘Replace Gas by Tissue’, replaced all grey-values of -100 HU and smaller by a tissue-equivalent grey-value of -100 HU (Figure 3c). The value of -100 HU was chosen, because it is approximately the lowest pixel value that occurs in all tissues of the body. The filters were applied to none, one of the two, or both CT scans. The best filter to be used for grey-value registration was determined by counting the number of successful registrations for each filter used and by determining the registration accuracy.

**Figure 3.** CT images with fecal gas in the rectum. (a) Before filtering. (b) After applying the filter ‘Suppress Gas’. The pixel values of fecal gas were set to zero (i.e., the area with the white cross) and were ignored in the registration algorithm. (c) After applying the filter ‘Replace Gas by Tissue’. The pixel values of fecal gas were set to a ‘tissue-equivalent’ grey-value of -100 HU and were not ignored in the registration algorithm.

**Multiple Starting Points for Automatic Grey-Value Registration**

We observed that for some cases, automatic prostate localization failed with respect to contour registration. Main causes were large differences in rotations around the left-right (LR) axis and large differences in translations along the anteroposterior (AP) axis (See ‘Results’). This might be due to the choice of the offset value (offset = 4) in the grey-value registration algorithm that determines what initial rotation (degrees) and/or translation (mm) is tested for registration. This implies a risk of getting trapped in a local minimum. The offset was the same in all directions and optimized, in terms of registration results and speed of registration, in previous applications of
the registration algorithm. In an attempt to improve the robustness of the registration algorithm and to eliminate the risk of getting trapped in a local minimum, we studied the effect of changing the starting point for rotations around the LR axis without changing the offset value. No adaptations were made for translations, because a large rotation around the LR axis could imply a large translation along the AP axis. Tests were performed on the whole data set. As usual, a registration was done with the bone registration as starting point for automatic grey-value registration. Subsequently, the repeat CT scan was rotated around the LR axis by +5.0 and -5.0 degrees, respectively, with respect to the bone registration, and taken as the new starting point for a grey-value registration. The registration with the lowest cost function value out of these three was kept.

**EVALUATION OF REGISTRATION RESULTS IN TERMS OF RELIABILITY: OUTLIER DETECTION**

The reliability of automatic prostate localization was evaluated by calculating the differences for rotations and translations for each rotation and translation axis between grey-value registration and contour registration. For this purpose, an iterative $\chi^2$ outlier detection method (See ‘Appendix’) applied to the whole data set was used to detect outliers. The $\chi^2$ outlier detection method is based on the assumption that the errors have a normal distribution for the successful registrations and an unknown but much wider distribution for the outliers. By iteratively estimating the mean and standard deviation (SD) of the errors, a distinction was made between successful registrations and outliers, using the 95% confidence value of the $\chi^2$ distribution as a threshold.

**EVALUATION OF REGISTRATION RESULTS IN TERMS OF ACCURACY**

For all successful automatic registrations, the mean difference $\mu_p$ and standard deviation $\sigma_p$ with respect to contour registration was calculated for each rotation and translation axis. First, for each rotation and translation parameter $p$ (around or along the LR axis, the craniocaudal axis (CC), and the AP axis, respectively, where $p = R_{LR}, R_{CC}, R_{AP}, T_{LR}, T_{CC},$ or $T_{AP}$), the
difference between automatic grey-value registration (AGR) and automatic contour registration (ACR) of a registration \( i \) of patient \( j \) was calculated by \( \Delta p_{i,j} \) (Eq. 1):

\[
\Delta p_{i,j} = p_{i,j}(AGR) - p_{i,j}(ACR)
\]

Then, for each parameter \( p \) and for each patient \( j \), the mean, \( \mu_{p,j} \), and standard deviation, \( \sigma_{p,j} \), of all these differences between AGR and ACR of all successful registrations \( m_j \) of a patient were calculated. The mean difference between AGR and ACR, \( \mu_p \) (Eq. 2), for all patients \( n \) for a parameter \( p \) was calculated by averaging all the means per patient for that parameter \( \mu_{p,j} \), by:

\[
\mu_p = \frac{1}{n} \sum_{j=1}^{n} \left( \mu_{p,j} \right)
\]

(Eq. 2)

The standard deviation \( \sigma_p \) (Eq. 3) for a parameter \( p \) of all patients was calculated by:

\[
\sigma_p = \sqrt{\sum_p^2 + RMS_p^2}
\]

(Eq. 3)

In this equation, \( \Sigma_p \) (Eq. 4) is the standard deviation for a parameter \( p \) for the difference between AGR and ACR calculated over the mean values \( \mu_{p,j} \) of each patient and RMS\(_p\) (Eq. 5), which is the root mean square value calculated over the standard deviations \( \sigma_{p,j} \) of each patient:

\[
\Sigma_p = \sqrt{\frac{\sum_{j=1}^{n} \left( \mu_{p,j} - \mu_p \right)^2}{n-1}},
\]

(Eq. 4)
Evaluation of registration results in terms of accuracy: Volume overlap

The accuracy of grey-value registration was also evaluated by determining the percentage of volume overlap of the registered prostates in both grey-value registrations and contour registrations. For the grey-value registrations, contours were overlaid on the scans by using the grey-value registration transform. The influence of intraobserver variation in contour delineations on the volume overlap was studied (for the same set of scans) by determining the volume overlap of two contour drawings (A and B) delineated by one observer on the same CT scan. For practical reasons (amount of delineation work), this was done on a subset of 6 patients (randomly chosen), 8 scans (the first 8 scans) per patient. The volume overlap \((A \cup B)\) of the contours of the prostate was expressed as a percentage of the volume of the encompassing contour \((A \cup B)\) by \((A \cap B) / (A \cup B) \times 100\%\). Grey-value registration outliers and corresponding contour registrations were excluded.

Results

Automatic prostate localization: An example

An example of a transverse, sagittal, and coronal view of a successful grey-value registration (Figure 4A-C), using the correlation ratio cost function and filtering the planning CT scan with the 'Replace Gas by Tissue' filter, showed that the delineated contours of the planning CT scan, which are superimposed on the repeat CT scan using the grey-value registration
transform, follow the delineated contour of the repeat CT scan, indicating that automatic prostate localization is accurate. The transverse, sagittal, and coronal views of an outlier (Figure 4d-f) show that the overlaid contour of the planning CT scan is not registered to the contour of the repeat CT scan. Because of large compression of the SV as a result of fecal gas in the rectum, there is no unique fit causing the registration algorithm to get caught in a local minimum.

**Figure 4.** Results of automatic prostate localization using grey-value registration. A transverse, sagittal, and coronal view is shown of the repeat CT scan of a successful registration (a–c) and a registration that was detected as an outlier (d–f). The white lines represent the delineated contour of the repeat CT scan; the black lines in panels a–c and the grey lines in panels d–f show the delineated contour of the planning CT scan superimposed on the repeat CT scan, using the transformation for this grey-value registration. Contour information of the repeat scans was not used for grey-value registration.

**DETERMINATION OF BEST REGISTRATION PROCEDURE: COST FUNCTIONS**

For each cost function, the number of successful registrations was determined (Table 1). Other tests, when applying filters to the CT scans, showed similar results. Using the CR cost function resulted in 88% successful registrations, whereas MUI, NMUI, NCC, and RMS were
successful in, respectively, 82%, 85%, 82%, and 82% of the cases. For each cost function, the standard deviations of the differences between grey-value registration and contour registration for all rotation and translation axes were also calculated (Table 1). It shows that the accuracy of NMUI was worse compared to the accuracy of CR, especially for rotations around the LR axis and translations along the AP axis. NCC and RMS show even worse results. MUI was comparable in accuracy to CR. A test in which only those registrations were used that were successful for all cost functions showed even better accuracy for the CR cost function compared to the other cost functions. Because CR had the largest number of successful registrations, and it was one of the most accurate cost functions, the CR cost function was selected for further tests on the whole data set.

Table 1. Number (N) and percentage (%) of successful registrations (out of 40 scan pairs) for automatic prostate localization for the cost functions CR, MUI, NMUI, NCC, and RMS. Also, SDs are shown of differences between grey-value registrations and contour registrations per cost function (successful registrations only) for rotations (degrees) around and translations (mm) along the LR, CC, and AP axis. The correlation ratio cost function was chosen for further tests.

<table>
<thead>
<tr>
<th>Cost function</th>
<th>N</th>
<th>%</th>
<th>Rotations (1 SD, degrees)</th>
<th>Translations (1 SD, mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LR</td>
<td>CC</td>
</tr>
<tr>
<td>CR</td>
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<td>88</td>
<td>3.2</td>
<td>2.0</td>
</tr>
<tr>
<td>MUI</td>
<td>33</td>
<td>82</td>
<td>3.0</td>
<td>2.3</td>
</tr>
<tr>
<td>NMUI</td>
<td>34</td>
<td>85</td>
<td>4.4</td>
<td>2.4</td>
</tr>
<tr>
<td>NCC</td>
<td>33</td>
<td>82</td>
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<td>2.5</td>
</tr>
<tr>
<td>RMS</td>
<td>33</td>
<td>82</td>
<td>4.6</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Abbreviations. CR = correlation ratio; MUI = mutual information; NMUI = normalized mutual information; NCC = normalized cross correlation; RMS = root mean square difference; LR = left-right; CC = craniocaudal; AP = anteroposterior; SD = standard deviation.
DETERMINATION OF BEST REGISTRATION PROCEDURE: FILTERS

The number of successful registrations slightly increased when applying the filters ‘Suppress Gas’ and ‘Replace Gas by Tissue’ (Table 2). In the registration algorithm, the CR cost function was used. Other tests, using the other cost functions, showed similar results. The number of successful registrations increased when a filter was applied. Applying the filters to either the planning CT scan or the repeat CT scan or to both CT scans showed hardly any difference in terms of more or less successful registrations. The standard deviations of the differences between grey-value registrations and contour registrations for all rotation and translation axes and for each filter used were also calculated (Table 2).

<table>
<thead>
<tr>
<th>Filter type</th>
<th>Applied to</th>
<th>N</th>
<th>%</th>
<th>Rotations (1 SD, degrees)</th>
<th>Translations (1 SD, mm)</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LR</td>
<td>CC</td>
</tr>
<tr>
<td>No filter</td>
<td></td>
<td>34*</td>
<td>85*</td>
<td>2.5*</td>
<td>1.7*</td>
</tr>
<tr>
<td>Supress Gas</td>
<td>Planning CT</td>
<td>35</td>
<td>88</td>
<td>3.2</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Repeat CT</td>
<td>36</td>
<td>90</td>
<td>4.7</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Both</td>
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<td>88</td>
<td>3.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Replace Gas by Tissue</td>
<td>Planning CT</td>
<td>36</td>
<td>90</td>
<td>2.3</td>
<td>1.3</td>
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<td>Repeat CT</td>
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<td>88</td>
<td>2.9</td>
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<tr>
<td></td>
<td>Both</td>
<td>36</td>
<td>90</td>
<td>2.6</td>
<td>1.4</td>
</tr>
</tbody>
</table>

ABBREVIATIONS. LR = left-right; CC = craniocaudal; AP = anteroposterior; SD = standard deviation.
* These numbers differ from the numbers in Table 1, because the data in Table 2 were obtained with a slightly different registration algorithm.
The ‘Replace Gas by Tissue’ filter was more accurate than the ‘Suppress Gas’ filter, no matter which scan was filtered. Filtering the planning CT scan resulted in a better accuracy compared to filtering the repeat CT scan or filtering both CT scans, when the ‘Replace Gas by Tissue’ filter was applied. Based on these results, it was decided to use the ‘Replace Gas by Tissue’ filter for filtering the planning CT scans for the whole data set, while leaving the repeat CT scans unfiltered.

DETERMINATION OF BEST REGISTRATION PROCEDURE:
MULTIPLE STARTING POINTS

Using a single starting point for registration, frequency distributions (Figure 5) of the differences between automatic prostate localization and localization using contours showed that the main causes for outliers were large differences in rotations around the LR axis and large differences in translations along the AP axis. When multiple starting points (rotating the repeat CT scan around the LR axis by +5, 0, and -5, degrees and taking the result with the lowest cost function value) were used, the number of successful registrations increased, and the frequency distributions slightly improved (data not shown). Out of 211 registrations, the increase was from 188 to 191 successful registrations, which is an increase of the success rate by 2%: from 89% to 91%. The accuracy of grey-value registration with multiple starting points also slightly increased (data not shown). With this method, one registration took about 45 s on a 1.7 GHz Pentium personal computer, instead of 20 s when a single starting point was used. Based on these results, it was decided to use multiple starting points for the automatic prostate localization method.
**FIGURE 5.** Frequency histograms of differences between grey-value registrations and contour registrations. The black bars indicate the successful registrations, and the grey bars the outliers that were found by the $\chi^2$ outlier detection method. (a–c) Differences in rotations ($\Delta R$ in degrees) around the left-right (LR), craniocaudal (CC), and anteroposterior (AP) axis, respectively. (d–f) Differences in translations ($\Delta T$ in mm) along the LR, CC, and AP axis, respectively.

**GREY-VALUE REGISTRATION RESULTS: RESULTS OF THE COMPLETE DATA SET**

As mentioned, the success rate for automatic grey-value registration was 91% out of 211 registrations. Out of 19 patients, 8 patients had no outliers, 4 patients had 1 outlier, 5 patients had 2 outliers, and 2 patients had 3 outliers. The worst patient had 3 outliers out of 10 scans. The averages and standard deviations (SDs) calculated from **Eq. 2** and **Eq. 3**, of the differences between the grey-value registrations and contour registrations for all rotation and translation axes were determined for all successful registrations (**TABLE 3**). The averages were around zero. For rotations, the accuracy around the LR, CC, and AP axis was 2.4 degrees (1 SD), 1.6 degrees (1 SD), and 1.2
degrees (1 SD), respectively. For translations, the accuracy along the LR, CC, and AP axis was 0.7 mm (1 SD), 1.3 mm (1 SD), and 1.2 mm (1 SD), respectively.

| TABLE 3. Averages and SDs of the differences of the 91% successful grey-value registrations compared to the contour registrations. The tabulated values express the differences in rotations (degrees) around and translations (mm) along the LR, CC, and AP axis. |
|------------------|------------------|------------------|
|                  | Rotations (degrees) | Translations (mm) |
|                  | LR    | CC    | AP    | LR    | CC    | AP |
| Average          | -0.3  | -0.3  | -0.1  | 0.1   | 0.0   | 0.1 |
| SD               | 2.4   | 1.6   | 1.3   | 0.7   | 1.3   | 1.2 |

**ABBREVIATIONS.** LR = left-right; CC = craniocaudal; AP = anteroposterior; SD = standard deviation.

**GREY-VALUE REGISTRATION RESULTS: VOLUMETRIC EVALUATION**

The accuracy of grey-value registration and contour registration expressed in terms of volume overlap with respect to the encompassing volume is shown in **TABLE 4**. The mean volume overlap for grey-value registration was 76% (5%, 1 SD), and for contour registration 77% (5%, 1 SD). The mean volume overlap obtained from the intraobserver study, where the volume overlap of two contour drawings delineated by one observer on the same CT scan was calculated, was 81% (6%, 1 SD).
### Table 4

Averages and SDs of percentage volume overlap of prostate contours with respect to the encompassing contour (subset: 6 patients, 8 scans per patient). In the two middle columns, the results are shown for grey-value registrations and contour registrations, respectively. In the last column, the results of the intraobserver variation study are shown, in which the volume overlap of two contour drawings of the prostate, delineated by one observer on the same CT scan, was evaluated.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Grey-value registration*</th>
<th>Contour registration†</th>
<th>Intraobserver</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77%</td>
<td>79%</td>
<td>86%</td>
</tr>
<tr>
<td>2</td>
<td>79%</td>
<td>80%</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>76%</td>
<td>76%</td>
<td>81%</td>
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<td>70%</td>
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<td>78%</td>
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<td>81%</td>
<td>81%</td>
</tr>
<tr>
<td>6</td>
<td>71%</td>
<td>72%</td>
<td>76%</td>
</tr>
<tr>
<td>Average</td>
<td>76%</td>
<td>77%</td>
<td>81%</td>
</tr>
<tr>
<td>SD</td>
<td>5%</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

**Abbreviations.** SD = standard deviation; CT = computed tomography.

* Outliers were excluded; † The corresponding contour registrations were also excluded.

### Discussion

We developed an automatic method for prostate localization based on grey-value registration of CT scans. The method has a success rate of 91% and an execution time of 45 s on a 1.7 GHz Pentium personal computer. The time required for automatic prostate localization is much shorter than the time required for prostate delineation (and registration) and the speed is appropriate for online purposes. Applying this method to CBCT scans, we would expect the same results as for conventional CT scans. First test results on CBCT scans are encouraging (Smitsmans et al. (16)). The higher resolution of the CBCT scans in the CC direction is an advantage. However, the signal-to-noise ratio in CBCT scans is poorer. Overall, these differences
seem to cancel out, resulting in a similar performance of the registration algorithm.

**Evaluation of the method: Success rate**

The success rate of the grey-value registration method, 91%, is reasonable. Taking into account that we use a 95% confidence value in our $\chi^2$ outlier detection method, we would expect already 5% of the registrations to be flagged as failures, even when all registrations were successful. This means that we may assume that the success rate is actually higher than 91%, because the success rate depends on the $\chi^2$ outlier detection constraints and on inaccuracies in the reference set. If the method is implemented clinically, registrations will be assessed by visual inspection, because no contour registration will be available to serve as a reference. In a test, an observer assessed a set of 30 registrations, of which 20 were failures and 10 were successful cases according to the $\chi^2$ outlier detection method. Two of the 10 successful cases were borderline cases in the $\chi^2$ outlier detection method. The observer was instructed to indicate a registration as a failure if there was two or more pixels difference in overlap of the prostate, based on all views. The observer assessed 15 cases out of the 20 failures as successful, whereas 5 were rejected. Out of the 10 successful cases, 9 were assessed as successful and 1 as a failure. This failure was one of the two successful cases that were borderline cases in the $\chi^2$ outlier detection method. This subjective assessment test showed that the automatic prostate localization method performs well and indicates that the success rate is actually higher than 91%. If, in the clinic, a registration is visually assessed as a failure, the registration will be adjusted manually, either by grey-value alignment of the CBCT scan and the planning CT scan or by registering the drawn contour of the planning CT scan manually to the prostate in the CBCT scan (similar to ultrasound-based methods).

**Evaluation of the method: Failures**

Failures occurred mostly when there were large differences for rotations around the LR axis and large translations along the AP axis between grey-value registration and contour registration. Many of these outliers had large rectum filling differences that resulted mainly in rotation of prostate and SV
around the LR axis and sometimes distortion of the SV, which could influence the registration results. Laxating the patient on a daily basis during the first few weeks of treatment before making a CT scan is one way to overcome this problem. Improvement was obtained by using multiple starting points around the LR axis in the grey-value registration method, which suggests that there is a risk of getting trapped in a local minimum when the prostate is highly rotated and/or distorted.

**EVALUATION OF THE METHOD: ACCURACY**

The differences between the grey-value registration method and contour registration method showed that the mean values were about zero. This means that there are no systematic registration errors. In our study, the contour registrations were used as 'golden standard' to evaluate the performance of grey-value registration, with the assumption that the prostate behaves as a rigid body. Deurloo et al.\(^{(17)}\) 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 at the tip of the SV, 1.5 mm (1 SD). Taking the contour registrations as golden standard is therefore reasonable, because prostate deformations are small. The accuracy of the successful registrations in our study for translations was for all axes better than 1.3 mm (1 SD). For rotations, the accuracy around the LR axis was poorest, 2.4 degrees (1 SD), compared to an accuracy better than 1.6 degrees (1 SD) for the other two axes. The large standard deviation found for rotations around the LR axis is probably due to the impact of delineation errors in the reference set, as demonstrated by the volume overlap study. The mean volume overlap obtained from the intraobserver study (in which the volume overlap of two contour drawings delineated by one observer on the same CT scan was evaluated) was 81% (6%, 1 SD). Compared to the mean volume overlap for grey-value registration and contour registration, 76% (5%, 1 SD) and 77% (5%, 1 SD), respectively, the difference is small. Rasch et al.\(^{(18)}\) found that the volume overlap problem could be attributed mainly to delineation differences that occur at the apex, on the anterior side of the prostate, and at the tip of the SV. Therefore, and because the SV are usually included in the treatment in our clinic, we did not consider evaluating volume overlap from prostate only. In the intraobserver study, data of 6 patients, 8 scans per patient were used (e.g., ~30% of patient population and ~20% of scan population). These data seem to represent the study population well, because the standard errors of the means are smaller than 1% (6%/\(\sqrt{48}\) for
the worst case). These results indicate that the accuracy of grey-value registration is not poorer than registration on delineated contours, whereas intraobserver variation of the delineated contours contributes significantly to the observed misregistration. Another study performed at our institute, by Artignan et al.\(^{(11)}\), confirmed that the interobserver variation of delineations of the whole prostate resulted in large rotation errors around the LR axis for contour registration.

**MARGINS**

One of the overall goals of the project was to correct for patient and target motion and to reduce the margin between clinical target volume (CTV) and planning target volume (PTV). To estimate the potential margin reduction, we used the margin recipe as defined by Van Herk et al.\(^{(19)}\), based on a division in systematic and random errors. They expressed the PTV margin \(M\) as

\[
M = 2.5 \Sigma + 0.7 \sigma
\]

in which \(\Sigma\) is the square root of the quadratic sum of SDs of all preparation (systematic) errors, and \(\sigma\) is the square root of the quadratic sum of SDs of all execution (random) errors. Table corrections will be performed to eliminate random and systematic translation errors for each treatment fraction. Random and systematic errors for rotations of the prostate, and especially around the LR axis, will be eliminated by choosing the best fitting plan, according to the position of the prostate around the LR axis before each treatment. We may assume that systematic errors will be largely eliminated when using the proposed image guidance system. Therefore, we assume that the SDs presented in Table 3 are an upper bound for the remaining random errors. The results of this study are an overestimation of the error, because the SDs are differences between grey-value registrations and contour registrations that contain the delineation errors of two contours: one of the planning CT scan and one of the repeat CT scan. Assuming perfect systematic corrections and using the overestimated SDs as random errors, the required margin for the prostate between CTV and PTV would be 0.5 mm (0.7 x 0.7 mm) in the LR direction, 0.9 mm (0.7 x 1.3 mm) in the CC direction, and 0.8 mm (0.7 x 1.2 mm) in the AP direction. Here it is assumed that rotational errors can be neglected, because of the round shape of the prostate. Because of the rotation error, an extra margin should be added at the SV. For example, a rotation error around the LR axis of 2.4 degrees (1 SD) causes a motion of the tips of the SV of 1.3 mm along the AP axis (assuming a rotation point for registration in the middle of the prostate, a distance of the rotation point to the tips SV of
4.5 cm, and an angle of 45 degrees between the ‘prostate + SV’ vector and the AP axis). The margin needed in the AP direction at the top of the SV including the translation error along the AP axis and only the rotation error around the LR axis would then be 1.1 mm \( (0.7 \times \sqrt{(0.8 \text{ mm})^{2}+(1.3 \text{ mm})^{2}}) \). When all rotation errors are added up, the margin should be roughly twice as big at the tips of the SV as at the prostate only. Although the time between imaging and actual treatment in the image guidance system is drastically reduced when the proposed method for prostate localization is implemented, it is still necessary to define another extra margin to take into account possible prostate displacements in the short time between plan selection and actual delivery (short-term intrafraction motion). Also, a margin would be required for delineation errors in the planning CT scan.

FINDING THE BEST REGISTRATION ALGORITHM

The five different cost functions that were tested to find the best registration algorithm had a comparable success rate. The best accuracy was obtained by using the CR or MUI cost function. CR was chosen for further analysis, because its success rate was higher than that of MUI. A possible explanation for the better performance of CR is that CR assumes a one-to-one correspondence of the pixel values of the two scans (which is the case in our study), whereas MUI also can register scans with an arbitrary pixel value correspondence. It is also known that MUI depends strongly on the population of the grey-value cross histograms of the two scans and is therefore more vulnerable to noise when small image regions are used. For this reason, MUI probably more frequently gets caught in a local minimum. Fei et al.\(^{(15)}\) found that MUI resulted more frequently in local minima than CR, which is consistent with the results of this study. The influence on the registration algorithm of gas present in the rectum, especially in the planning CT scan, was minimized by applying a filter to the CT scans. The filters ‘Suppress Gas’ and ‘Replace Gas by Tissue’ both improved the success rate. The best accuracy was obtained by applying the ‘Replace Gas by Tissue’ filter to the planning CT scan. It has been pointed out by Lebesque et al.\(^{(20)}\) that the volume of the rectum decreases while the treatment proceeds. This might explain why applying a filter to the planning CT scan improves the accuracy of the registration results, because this CT scan is the reference scan for all registrations. Further improvement of the registration algorithm was achieved by using multiple starting points of the repeat CT scan for rotation around the LR axis, because there is a risk of
getting trapped in a local minimum (See also section ‘Evaluation of the method: Failures’ in ‘Discussion’). The success rate improved by 2%, although the time for one registration increased from about 20 s to 45 s on a 1.7 GHz Pentium personal computer. The longer registration time is still considered acceptable for online registration purposes.

COMPARISON AND RELATION TO OTHER STUDIES

The offline ART localization method developed by Yan et al.\(^4\) uses a composite drawing of the prostate from multiple CT scans for position localization. Our grey-value registration algorithm for prostate localization could be a useful tool in this method. The automatic grey-value registration method eliminates the need for repeated delineation and facilitates practical implementation of the offline ART method. The method presented by Nederveen et al.\(^5\), who use gold markers for automatic online position verification by using a marker extraction kernel, shows an accuracy of 0.6 mm (1 SD) to localize the markers on portal images. Although the method is fully automatic and accurate, drawbacks of this method are that the localization is only in 2D, insertion of markers is invasive for the patient, and theoretically markers are subject to migration. The real-time tumor tracking system developed by Kitamura et al.\(^6\) shows a discrepancy between the center of mass of the delineated prostate and the implanted marker of 1.1 mm (1 SD) in LR direction, 3.4 mm (1 SD) in CC direction, and 2.4 mm (1 SD) in AP direction. The accuracy for translations of our grey-value registration method is smaller. Therefore, our method seems to be more accurate in all directions. If only slight marker migration is assumed, most likely their larger error is mainly due to larger delineation errors. To fix the marker positions, Bergström et al.\(^7\) used a urethra catheter containing markers to localize the prostate at the time of treatment by using portal images. Adjustments down to 1 mm could be detected and verified. This method has provided until now position corrections in only AP direction and only 2D information. Other drawbacks of this method are that it is also invasive for the patient, because of the insertion of the urethra catheter at each treatment fraction, and theoretically the catheter may also move during treatment. The ultrasound-based prostate localization system tested by Van den Heuvel et al.\(^8\) uses two roughly perpendicular online ultrasound images (transverse and sagittal) that were manually registered to the contour of the planning CT scan. Electronic portal imaging and implanted gold markers were used to verify the ultrasound method. The residual errors after
ultrasound repositioning in LR, CC, and AP direction were -0.4 mm (4.3 mm, 1 SD), -2.6 mm (5.4 mm, 1 SD), and +2.5 mm (5.7 mm, 1 SD), respectively. A similar study, performed by Langen et al.\(^9\), reported differences in LR, CC, and AP direction between the ultrasound system and marker alignments of 1.6 mm (3.1 mm, 1 SD), 2.7 mm (3.9 mm, 1 SD), and 0.2 mm (3.4 mm, 1 SD), respectively. The accuracy obtained by our method on CT data is much better than the accuracy reported by Van den Heuvel et al.\(^8\) and Langen et al.\(^9\), probably because of the better image quality of CT scans. It would be interesting to test our grey-value method on ultrasound data. Hua et al.\(^{10}\) presented a method that localized the prostate (without SV) by identifying the anterior, posterior, left and right extent curves (projections of the prostate contours onto the sagittal and coronal planes) from delineations of the prostate on five transverse slices. These extents were fitted to the extents of the planning CT scan. To verify the method, prostate center of gravity displacements were calculated from a complete contour stack drawn by a physician. The differences obtained between these two methods were in LR, CC, and AP directions: 0.0 mm (0.4 mm, 1 SD), -0.4 mm (1.9 mm, 1 SD), and 0.0 mm (0.7 mm, 1 SD), respectively. Compared to the accuracy of our method, their accuracy for translations in LR and AP direction is slightly better, but in the CC direction slightly worse. Artignan et al.\(^{11}\) localized the prostate by defining a total of six contours in the transverse, sagittal, and coronal planes. Compared to that for registrations in which the whole prostate was delineated, the accuracy for translations and rotations (calculated as the square root of the quadratic sum) was 1.7 mm (1 SD) and 3.9 degrees (1 SD), respectively. The accuracy obtained by our method, also calculated as the square root of the quadratic sum, was 1.9 mm (1 SD) for translations and 3.1 degrees (1 SD) for rotations. The small differences between the two methods might be due to delineation errors. Both the methods presented by Hua et al.\(^{10}\) and Artignan et al.\(^{11}\) are alternative ways to localize the prostate before treatment that reduce the time interval between imaging and treatment. Nevertheless, the method presented in this paper is completely automatic, and it is a more convenient way to localize the prostate. Recently, Court and Dong\(^{21}\) performed a similar study as ours, but with only 2 patients (quantitatively) and considering translations only. Their results are consistent to ours.
CONCLUSIONS

We developed and validated a method for prostate localization based on grey-value registration that is suitable for online IGRT. The method is as accurate as contour registration. The advantage of the automatic registration method is that it can be used online, because delineating the prostate in the repeat CT scans is not needed anymore. Choosing a plan and treating the patient will be possible in a few minutes. The method provides an increased confidence in targeting just before treatment and, combined with the conformity of intensity modulated dose distributions this might permit dose escalation well beyond that of current approaches.
The $\chi^2$ outlier detection method is described in the flow chart in Figure A1. The original data set consists of the errors (differences) found between grey-value registration and contour registration for each rotation and translation parameter for all registrations of all patients. The sum of the normalized squared errors is called the $\chi_{i,j}^2$ value of a registration of a patient (Eq. A1).

$$\chi_{i,j}^2 = \sum_{p=LR}^{AP} \frac{(\Delta p_{i,j} - \mu_p)^2}{\sigma_p^2}$$  \hfill (Eq. A1)

$\Delta p_{i,j}$ (Eq. 1) is the difference between automatic grey-value registration and automatic contour registration for parameter $p$ of a registration $i$ and a patient $j$; $p$ expresses rotation and translation axes: the LR, CC, and AP axis, for which $p = R_{LR}, R_{CC}, R_{AP}, T_{LR}, T_{CC},$ or $T_{AP}$, respectively; $\mu_p$ is the mean value, and $\sigma_p$ is the standard deviation for a parameter $p$ calculated over all registrations of all patients.
The shape of a $\chi^2$ distribution depends on the number of degrees of freedom (df) and therefore also the 95% confidence value of the corresponding $\chi^2$ distribution. Because it is not known whether the six parameters are independent, the number of df has to be estimated. To do this, a normalized cumulative probability histogram was made of all the $\chi^2$ values, and a cumulative $\chi^2$ distribution was fitted through this histogram (Figure A2). The fitted df determines the 95% confidence interval of the fitted $\chi^2$ distribution, and according to this value, outliers can be rejected from the data set. This whole process is repeated for the new data set. After a few iterations, the new data set does not change anymore, and all outliers are rejected from the original data set. A final estimate of the mean, standard deviation, and df of the remaining data set is then obtained.

**Figure A2.** Histogram fit of the normalized cumulative probability of the data by a cumulative $\chi^2$ distribution. On the horizontal axis, the $\chi^2$ values are plotted, and on the vertical axis, the normalized cumulative probability is plotted. The dotted line represents the histogram data. The straight line represents the fitted $\chi^2$ distribution through the histogram data.
REFERENCES


