Towards image-guided radiotherapy of prostate cancer
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Discussion
GENERAL

It was the main purpose of this thesis to develop a method for reliable and accurate prostate localization that could be used for online or offline image-guided radiotherapy (IGRT). The thesis describes the steps that were taken to achieve this goal.

CHAPTER 2 describes the developed automatic grey-value registration method for prostate that was tested on diagnostic quality computed tomography (CT) scans. In CHAPTER 3 an adapted method is provided to be used on cone-beam CT (CBCT) scans, which have a somewhat poorer image quality. CHAPTER 4 describes how a dietary protocol improves the registration results of the developed method for CBCT scans. The developed method was found to be reliable to be implemented in an offline radiotherapy protocol using CBCT scans and is now in clinical use\(^1\).

The other objectives of this thesis were to investigate related effects of marker-based and ultrasound-guided prostate localization techniques on the accuracy of prostate treatment. When prostate localization is based on marker registration the residual error at the position of the seminal vesicles (SV) was found to be large, as described in CHAPTER 5. CHAPTER 6 addresses the effect of probe pressure on prostate displacement, which is an error source when ultrasound-based imaging is used for prostate localization.

In this chapter, the results are discussed and future directions in prostate localization techniques and treatment will be described.

ADVANCES IN IMAGE-GUIDED RADIOTHERAPY

The objective of IGRT is to verify the proper positioning of the patient just prior to the delivery of radiation dose. IGRT is becoming essential as dose distributions become more complex using intensity modulated radiotherapy (IMRT). The past decade, ‘image-guided’ radiotherapy has become the
magic word in treatment of cancer with external beam radiotherapy and several methods have been developed to achieve the goal of IGRT.

Several correction protocols are nowadays used to correct for interfraction prostate motion, like bony anatomy registration, registration based on implanted markers, transabdominal ultrasound guidance and in-room CT imaging techniques. All these techniques have their advantages and disadvantages compared to the developed grey-value registration method for prostates on CBCT scans, as described in this thesis, which will be outlined below.

ADVANCES IN INTERFRACTION DISPLACEMENT CORRECTION

BONY ANATOMY REGISTRATION

The introduction of the electronic portal imaging device (EPID), which became commercially available in the early 90’s of the past century, reduced the workload for treatment setup verification in the clinic. The EPID could replace the use of film to localize the anatomy of a patient with respect to the field edges.

The EPID makes megavolt (MV) images of the patient and visualizes the bony anatomy of the patient. The bony anatomy is nowadays still frequently used for registration and provides information to re-position the patient after initial set-up. Bony anatomy registration is accurate and fast and was frequently used in offline and online prostate treatment protocols. One of the major disadvantages of using bony anatomy for repositioning is that the prostate can move with respect to the bony anatomy. Assessments with either implanted markers or CT scans showed a poor correlation of prostate position and bony anatomy\(^{(2-4)}\).

The prostate displacement data as presented in Chapter 4 (Table 3), showed also differences e.g., in rotations around the LR axis (\(R_{LR}\)), between grey-value registration of the prostate and bony anatomy registration: 2.5 degrees systematic and 4.8 degrees random (nondiet group). One may assume that these values are actually higher as part of the data (17%) could not be used due to poor image quality. The dependency of the grey-value registration algorithm on image quality of CBCT scans could be reduced by
applying a dietary protocol to the patients (Chapter 4). The reason for that was that the amount of moving gas during acquisition of the scans significantly reduced. Even with a dietary protocol, bony anatomy based methods are considered inadequate to correct for prostate motion.

MARKER BASED REGISTRATION METHODS
To overcome the forementioned problem of bony anatomy registration, many institutes nowadays use fiducial markers that are implanted in the prostate gland for registration. Like bony anatomy registration, registration on fiducial markers is accurate and fast and is suitable for offline and online correction protocols. Implanted fiducial markers can be detected by planar and volumetric imaging, for which the latter is gaining in popularity, as it is becoming more efficient and interuser variability in the registration process can be reduced\(^{(6)}\).

The stability of markers in the prostate gland has been studied frequently. The limited interuser variability and marker stability make markers an ideal surrogate to detect prostate position and rotation\(^{(6-9)}\). However, the accuracy of markers as surrogates for the position of the entire prostate gland has been questioned, mostly because of possible deformation of the prostate at the time of treatment delivery\(^{(10-11)}\). In Chapter 5 we studied the effect of rotation correction when markers are used. For the SV we found that rotation correction hardly reduced their displacement compared to translation correction only. This illustrates deformation of the SV relative to the prostate gland that is not captured by the position of the markers.

An endorectal balloon in combination with markers is sometimes used to immobilize the prostate gland, as a surrogate for targeting, and to improve rectal dosimetry. However, recent studies show that the impact of endorectal balloons on localization and immobilization are minimal and do not decrease the systematic and random errors associated with day-to-day variations in prostate position\(^{(12)}\). It would, however, have a positive effect on decreasing the dose to the posterior side of the rectum, potentially leading to less rectal complications\(^{(13-14)}\).

TRANSABDOMINAL ULTRASOUND
The use of transabdominal ultrasound has rapidly spread in radiotherapy departments because of its clinical efficiency to perform daily image guidance. However, it has been associated with significant interuser
variability due to poor image quality\textsuperscript{(15-16)}. The main reasons why institutes nowadays use transabdominal ultrasound are its efficiency and low costs compared to other image-guidance systems.

In \textbf{CHAPTER 6}, we studied the effect of probe pressure on prostate displacement and image quality. We found a strong correlation between probe pressure (quantified by probe displacement) and prostate displacement. In addition, to get good quality images some probe pressure needs to be applied. Between 1.0 and 2.0 cm of probe displacement was needed to get good quality images when using our 3D ultrasound probe. When compared to prostate positioning on CT or implanted markers its accuracy has been found limited\textsuperscript{(17-20)} and a systematic shift was found of about 3 mm\textsuperscript{(18)} which is in accordance with our data for 1 cm probe pressure. Some groups correct for this systematic shift by shifting all patients by 3 mm\textsuperscript{(21)}. Differences found between ultrasound and CT alignments or between ultrasound and implanted markers vary from group to group. Dosimetric consequences of the differences between ultrasound and CT alignment have been reported\textsuperscript{(22)}. Alignment on transabdominal ultrasound provided acceptable prostate coverage in 90\% of patients and CT alignment for 100\%. For the SV, full dose coverage was achieved in 70\% of cases with ultrasound and 80\% with CT alignment.

\textbf{IN-ROOM CT IMAGING}

Several in-room volumetric CT imaging solutions exist today. Daily CT-imaging can be performed either with an in-room kilovolt (kV) CT-scanner on rails\textsuperscript{(23-25)}, kV\textsuperscript{(26-29)} or MV\textsuperscript{(30-31)} CBCT or MV fan-beam CT (tomotherapy)\textsuperscript{(32-34)}. At the time that research for this thesis started, around 2002, in-room CT imaging devices were about to be implemented in several institutes. Studying the applicability of a kV CBCT device, mounted on the accelerator\textsuperscript{(35-36)}, to be used for online or offline IGRT of the prostate, was the main subject of this thesis.

Each of the in-room CT imaging modalities seem to have certain advantages and drawbacks. With these imaging techniques bony anatomy, implanted fiducials, or soft tissue like the prostate gland can be detected. One of the advantages of kV CBCT is that it provides good image quality at low imaging dose, but a disadvantage is that it may be prone to metal artifacts and shadowing compared to MV CT\textsuperscript{(37-38)}. Good image quality is important for soft tissue image-guidance. In addition, CT provides information about anatomic variations of other structures that cannot be visualized with
markers, such as the rectum and bladder. Because the prostate can be visualized on CT scans, prostate localization could potentially be performed directly on the prostate gland itself. However, like on ultrasound images, interpreting and determining the exact location of the prostate gland can be challenging as has been shown in this thesis. But, the advantage of CBCT scans is that registration is done automatically. The use of CBCT scans instead of conventional CT scans provides the opportunity to correct fast and online for prostate displacement, which takes too much time with for example the CT on-rails systems. And, with the CT on rails systems there is a potential for prostate motion (i.e., an error source) between CT imaging and positioning on the treatment machine.

VOLUMETRIC ALIGNMENT METHODS
With the previously described volumetric imaging techniques, different techniques can be used for alignment, such as using the entire grey-scale anatomy, or using contours from the planning CT scan to align on the prostate, or to delineate the prostate also on the follow-up scans and register them to the planning CT scan\(^{39}\). To be able to correct online for prostate displacement the algorithm should be fast. For online purposes contouring takes too much time and, in addition, it is very prone to delineation variation\(^{28}\). When using the grey-value registration method (\textit{Chapters 2, 3 and 4}), one has to take into account that it still requires a human observer to assess the registration results and subjectivity of the assessment may be of influence. In addition, the developed method is a rigid registration algorithm, as is contour registration. In case of deformation of prostate and SV the algorithm will search for the best fit for both. This may cause underdosage in part of the prostate or SV. When applying the grey-value registration algorithm in combination with CBCT scans, one has to take into account that a dietary protocol is required to guarantee a high reliability. However, the use of a dietary protocol is also important to reduce intra-fraction prostate motion (see below). Correcting for interfraction motion by means of the developed grey-value registration, and the steps that were taken to implement it in an adaptive radiotherapy (ART) protocol in our clinic, will be outlined in the next paragraph.

CLINICAL IMPLEMENTATION IN AN ADAPTIVE RADIOTHERAPY PROTOCOL
ART for prostate positioning was first described by Yan et al.\(^{40}\). It is a procedure in which the impact of systematic errors on the accuracy of
treatment is decreased by collecting information and correcting for systematic errors during the first few fractions. Yan et al.\textsuperscript{(40)} described offline ART for the prostate based on repeat CT data. Offline ART requires that the used registration technique is accurate. In addition, an online protocol requires also that the registration method is fast.

Our developed grey-value registration algorithm is nowadays implemented in our clinic in an offline ART protocol\textsuperscript{(1)}. As a result of increased insight, we went through 3 different protocols:

**THE FIRST PROTOCOL**

In the first protocol, the patient is scanned during the first 5-6 days. Registrations, based on bony anatomy, are performed and possible online corrections are applied. After 5-6 days scanning each CBCT scan was registered to the planning CT scan by means of grey-value registration of the prostate. The registration results were used to transform the planning CT contours to the prostate position at the respective days of scanning. A new average prostate contour plus an average rectum contour based on the position of the prostate and rectum on these days is constructed. We choose to follow this procedure to save time and because delineating the prostate on the CBCT scans was not considered possible due to the relatively poor image quality. The average prostate and rectum contours are used for replanning the patient. During the first week of radiotherapy, the margin used around the prostate was 10 mm. After replanning, the margin was reduced to 7 mm. This offline protocol was based on the results published by Hoogeman et al.\textsuperscript{(41)} and Nuver et al.\textsuperscript{(42)}

**THE SECOND PROTOCOL**

The previous protocol was recently adapted into a second protocol to reduce replanning time (2 hours or more) and to minimize the amount of scans that had to be replanned. The decision whether a new plan was required is now dependent on the position of the average prostate and the following conditions. When the translations were <1 mm and the rotations <6 degrees, the plan was not adapted. When translations were >1 mm and rotations were <6 degrees, only an isocenter displacement was performed (without replanning). For those cases where rotations were >6 degrees, a new plan is required. The rectum is no longer adapted. This offline protocol is nowadays in clinical use.
THE THIRD PROTOCOL

Requirements of daily imaging for our hypofractionation trial (16 fractions of 4.9 Gy vs 39 fractions of 2.0 Gy) gave rise to a third adaptation of the protocol as grey-value registration with visual assessment takes too much time online. In addition, with this protocol it is possible to correct for the position of the SV in case of large rotations (Chapter 5). Therefore, studies in our institute are nowadays conducted with implanted fiducial markers in the prostate gland. In the third protocol the patient is scanned on all days but registrations are now performed on the markers (instead of using bony anatomy registration) and possible corrections are applied online. The average prostate and SV position is still, offline, after 5-6 days, determined by using grey-value registration. The conditions whether a new plan is required are adapted into: when rotations are <6 degrees the plan is not adapted, when rotations are >6 degrees a new plan is required.

The use of a combined registration procedure (third protocol) does overcome some of the disadvantages of grey-value registration alone or marker registration alone. The combined procedure is faster as no visual inspection of the registration is required and can therefore be used online. In addition, when grey-value registration is used solely, there is some ambiguity about the accuracy of the grey-value registration algorithm at the prostate apex. The visibility at the apex is limited, which could be an argument that the registration algorithm is mostly driven by registration of the SV. Although the accuracy of grey-value registration on CBCT scans was determined to be satisfactory, the determination of the accuracy was based on calcifications (Chapter 3). The combined registration procedure would overcome this visibility problem at the apex as for prostate gland registration marker registration is used. In addition, the combined registration procedure would improve the irradiation of the prostate gland and SV as a whole. That is, as we found that for marker-based correction strategies alone the impact of small marker localization errors and registration errors on rotation correction may not be ignored when SV are part of the target volume (Chapter 5).
ADVANCES IN INTRAFRACTION DISPLACEMENT CORRECTION

Most correction protocols, as described before, are used to correct for interfraction prostate displacement. Recent studies also focus on correcting for intrafraction prostate displacement. This can be achieved by using electromagnetic transponders\(^{(43-44)}\) or the CyberKnife Robotic Radiosurgery System with implanted markers\(^{(45-46)}\).

ELECTROMAGNETIC TRANSPONDERS

With regard to the electromagnetic transponders, they are implanted in a way similar to metallic markers. The stability of the transponders is equal to that of metallic markers\(^{(47)}\). Electromagnetic tracking and correction is performed continuously throughout the time the patient is on the treatment couch. However, the net effect of correcting for intrafraction motion if certain thresholds are exceeded is questionable. The majority of excursions of the prostate gland will have a random nature and will only result in smearing out of the dose distribution, that requires very small additional margin if intrafraction correction protocols are used.

CYBERKNIFE

The CyberKnife Robotic Radiosurgery System is a system that may be the model for the next generation of radiosurgery units. It combines continuous image-guidance technology with a compact linear accelerator that has the flexibility to move in three dimensions according to the treatment plan. The CyberKnife system is designed to track, detect and correct for tumor and patient movement in real time, during the procedure. This enables the delivery of precise, high dose radiation typically with sub-millimeter accuracy. One of the unique features of this unit is that the CyberKnife linear accelerator is attached to a commercial robot to provide greater movement and achieve angles that fixed gantries cannot attain. A disadvantage is that it only can correct on bone or markers due to lack of volumetric images. Therefore, it is less suitable to correct for e.g., SV displacement.
FUTURE DIRECTIONS

Current research to correct for organ motion during the course of radiotherapy has its focus on developing procedures and registration algorithms that are reliable and efficient. Some of the limitations of the developed grey-value registration method as described in this thesis is that it is dependent on image quality of the CBCT scans and that it is a rigid registration algorithm. Since the introduction of the CBCT system in 2004, image quality of CBCT scans is an issue and has been studied exhaustively. Its quality has been improved but still improvements of CBCT image quality could be achieved by understanding and correcting the effects of ghosting, scatter, beam hardening and motion (See below). In the light of image quality, the development of an integrated MRI scanner with the linear accelerator is one of the future directions. Image quality of an MRI scan is superb over that of CT scans and CBCT scans. However, the costs of such a system are enormous.

Improvements in CBCT image quality will benefit future development of registration techniques that focus on deformable registration and deformation correction of prostate and SV. However, closer to clinical implementation are correction strategies based on rotation correction. Increased knowledge of the exact location of the tumor in the prostate will have its advances in subboosting, and correction strategies based on rotation correction could then easily be applied. These insights and improvements will inevitably result in adaptations to the well-known Van Herk margins recipe or the developed margins recipe by Stroom et al. and/or the development of new margin recipes. All these topics will be more extensively outlined in the next paragraphs.

IMPROVEMENTS IN CONE-BEAM CT IMAGE QUALITY

Ghosting in flat panel imagers is an effect which is extensively studied and described for MV images, but the same effects occur for kV images. Ghosting is caused by incomplete readout: the measured intensities in a projection image are actually higher for a certain frame. For example, in the first projection image an air region is the field which causes a high intensity in the kV image. In subsequent images, when the air region is covered by
the patient, the higher intensity is still present in that image. In the reconstruction of all kV images these higher intensities result in so-called ‘radar’ artefacts or ‘rings’.

Scatter\textsuperscript{(62-65)} is a well known effect that occurs in any material that is being irradiated. Scatter adds noise to the CBCT projection image which results in a poorer image quality of the CBCT scan compared to the diagnostic CT scan. Scatter causes so-called ‘cupping’ artefacts, i.e., due to interaction of the photons with the irradiated patient, the intensity in the middle part of the projection image is higher compared to the intensity at the edges of the image. This results in a reconstruction of a patient that has a darker center area (i.e., the reconstruction algorithm ‘thinks’ that the patient is thinner in the middle).

Beam hardening means that high density materials absorb more low energetic photons which results in a beam with more high energetic photons. These high energetic photons interact less with the irradiated body which results in higher measured intensities in the kV image. Improvements in CBCT image quality with regard to beam hardening seems to be almost negligible\textsuperscript{(64)}.

Ghosting and scatter artefacts can be corrected for by proper software algorithms. The effects of ghosting and scatter correction on CBCT image quality are shown in Figure 1. Hardware adjustments to reduce scatter artefacts are a bowtie filter, decreasing the field of view (Chapter 3) and/or applying a grid on the EPID at cost of reducing the signal-to-noise ratio. Image quality can also be improved by increasing the imaging dose.

However, in our system, motion distortion during acquisition of the projection images results in streaks in the reconstructed CBCT scan. An example of a software adaptation to correct for motion during scanning caused by moving gas is the Flatex algorithm\textsuperscript{(66)}. This algorithm uses only part of the acquired projection images (acquired during 360 degrees gantry rotation) to reconstruct the CBCT scan. By selecting only those projection images acquired either during the first, middle or last 180 degrees in which no motion was detected, a CBCT scan could be reconstructed with reduced streak artefacts and sharper tissue-to-air boundaries, as shown in Figure 2.
FIGURE 1. Examples of cone-beam CT images at the level of the prostate (a-c) and intensity profiles (d-e). a) Uncorrected: one obviously can see the ring artefact (ghosting, pointed by the white arrow) and the lower image intensity in the middle of the patient (scatter artefact), b) After ghosting correction: the ring artefact is no longer present c) After scatter correction: the lower image intensity in the middle of the patient is no longer present. d,e) Intensity profiles, taken at the white lines of images b) and c), of ghosting (d) and scatter corrected (e) images: the black line represents the uncorrected image and the grey line the corrected image.
Figure 2. The impact of a large moving gas pocket during cone-beam CT (CBCT) image acquisition of the pelvic region on the CBCT reconstruction result. A transverse (a) and sagittal (b) slice of the reconstruction result, showing streak artifacts and ambiguous air(gas)-to-tissue boundaries. Images c) and d) show the transverse and sagittal slices after applying the Flatex algorithm: streak artifacts are reduced and a sharp tissue-to-air interface is restored.

Deformable Registration and Deformation Correction

Deformation correction, with or without the use of deformable registration methods\(^{67}\), could solve the problem of deformed organs during the course of radiotherapy treatment. With deformable registration a deformation field is determined, which can be applied in several ways to correct for prostate motion and/or deformation. Prostate motion and/or deformation correction could be achieved by repositioning, replanning or adaptation of the plan by changing the multileaf collimator (MLC) leaf positions.
Godley et al.\(^{(68)}\) used deformable registration for replanning in an ART procedure to correct for large deformations in prostate cancer treatment. The obtained deformation fields from planning CT and scans on the treatment days was used to deform the delivered dose to match the planning CT, which was used for replanning in the ART procedure. Van Kranen et al.\(^{(69)}\) developed a deformable registration method that can be used in an ART procedure to correct for anatomy changes during radiotherapy of head-and-neck cancer patients. They demonstrated the feasibility of plan adaptation for systematic deformations based on an average anatomy measured with deformable registration. Validation showed that plan adaptation on an average anatomy led to higher local setup accuracy for bony anatomy.

Methods that rely on the adaptation of the MLC leaf-positions are described by, for example, the following groups. Court et al.\(^{(70)}\) used a slice-by-slice registration to calculate the final leaf positions. The shift within a slice could then be projected to a shift of the corresponding MLC leaf pair for each treatment segment for each gantry angle. Mohan et al.\(^{(71)}\) calculated the new leaf positions by deforming the reference image to the image of the day and deformed the intensity distribution accordingly in an online strategy. From the differences in the projected contours in the beam’s-eye-view (BEV) of the target and normal structures drawn on the images of the day and on the planning images, a set of deformation vectors were derived and used for intensity deformation. A leaf sequencing procedure then produced the beam apertures (i.e., leaf-positions) to be used for the day of treatment. Fu et al.\(^{(72)}\) accounted for interfractional target motion and deformation by adapting the original IMRT leaf positions. The leaf positions for each subfield were automatically adjusted, based on the position and shape changes of target projection in the BEV. Feng et al.\(^{(73)}\) used deformable registration in an online correction strategy by adjusting the treatment apertures. They used the 3D geometric transformation matrix to morph the treatment apertures. The segments were deformed in one step eliminating the approximations associated with leaf sequencing.

However, most of the above described methods are elaborate. Therefore, nowadays research focuses on faster and even more accurate methods to determine the amount of deformation by means of deformable registration.
Different kinds of correction strategies to correct for prostate and SV motion are currently being developed and implemented in the clinic\(^\text{(74)}\). The first IGRT correction strategies typically only corrected for translations by shifting the treatment table\(^\text{(75)}\). Correcting for prostate rotation around the main rotation axis, the LR axis\(^\text{(41)}\), could not be achieved with the table as the rotations are normally too large to correct for with a tilt-and-roll table\(^\text{(76-77)}\). With ART, correcting for large rotations is possible\(^\text{(40,42)}\). However, ART only compensates for systematic errors and significantly increases the workload because it necessitates replanning. Therefore, fast and online correction methods are preferred for rotation and deformation. Likely, the first methods to be implemented focus on rotation corrections only, as correcting for deformations is still quite difficult.

Wu et al.\(^\text{(78)}\) describe a method to correct online for the rotational component in the sagittal plane only by rotating the collimator angles for lateral beams. Intensities can be modified online with the calculated transformation parameters or with a quick reoptimization. However, the SV were excluded in this study, as non-rigid organ motion cannot be corrected for with this online method, and have to be corrected for in an offline protocol. Rijkhorst et al.\(^\text{(79)}\) developed a strategy to correct for rotation of prostate and SV motion together by means of gantry and collimator angle adjustment which can be used for offline and online IGRT protocols. This method is based on rotation correction around the dominant motion axis, the LR axis, and assumes that prostate and SV move together as a rigid object\(^\text{(39)}\). With this method of compensating for prostate rotations, safe and straightforward implementation of margin reduction and/or improved local control through dose escalation is achievable.

Current radiotherapy involves treatment of the entire prostate (and SV). More knowledge is becoming available of the exact location of the tumor inside the prostate. One way to obtain the exact tumor location is by combining two imaging modalities, diffusion weighted imaging and dynamic contrast-enhanced MRI, which was studied by Groenendaal et al.\(^\text{(80)}\) They quantified whether the two imaging modalities were consistent in what voxels they determine as being suspicious of tumor tissue. However, large variation in consistency between the two imaging modalities was found. In the future, one may choose to give an extra boost to that part of the prostate where the dominant tumor focus is located\(^\text{(81)}\). For that purpose, rotation correction based on markers will be beneficial, because the position of the
boosted part is located closer to the marker configuration than the SV, and, as the boosted part is mainly inside the prostate gland it will be less prone to deformation, and more affected by rotation of the prostate gland \(^{(82)}\).

**MARGINS**

Reduction of margins is the way to reduce side-effects of irradiation. Especially in case of hypofractionation, when higher doses per fraction are delivered. The balance between irradiating the tumor and avoiding irradiation of any organs at risk (OARS) becomes a question of the size of treatment margins around the clinical target volume (CTV). The correction strategies as described in the previous paragraph give rise to many studies on reduction of the margins, which is an ongoing challenge for tumor sites with large internal and/or interfractional motion and where sensitive OARS are located close to the tumor.

**UNIFORM MARGIN REDUCTION**

More precise localization of the prostate allows safe reduction of the margins around the CTV. This was shown by, Nuver et al. \(^{(42)}\), who developed an offline ART procedure, as described previously in the first protocol, to reduce the margins uniformly from 10 mm to 7 mm around prostate and SV. Wu et al. \(^{(78)}\) stated that with their online IGRT strategy, including correction for rotational organ motion, for prostate only, a minimum margin of 3 mm around the prostate was necessary with ideal image registration. However, additional margins will be needed to correct for deformations, e.g., in case SV are involved in the treatment. Rijkhorst et al. \(^{(83)}\) compared four different correction strategies for prostate plus SV, from online setup to full motion correction. They showed that with online corrections for both translations and rotations, treatment margins of 4 mm were sufficient in 15 of 19 patients, whereas the remaining four patients had an underdosed CTV volume <1%. In addition, the online corrections resulted in similar or lower doses to the rectum and bladder. Care should be taken not to reduce the margins too much as the residual error for a given IGRT technique as well as the available organ motion data has to be taken into account \(^{(84)}\).

**NON-UNIFORM MARGIN REDUCTION**

Correcting for deformations is becoming more and more an issue in prostate cancer treatment for high risk patients, i.e., when SV are included in the
target, and the associated margin design as well. As the forementioned methods mainly use uniform margins for prostate and SV, many studies now investigate the applicability of non-uniform margins. Meijer et al.\textsuperscript{(85)} used deformable registration to warp the delivered dose distributions back to the dose in the planning CT scan. On the basis of the geometric extent of the underdosed areas, a set of anisotropic margins was derived to ensure a minimal dose to the CTV of 95% for 90% of the patients. The margins, when aligning the patient to implanted gold-markers, were 3 mm for the prostate and 8 mm for the SV. Van der Wielen et al.\textsuperscript{(86)} also determined deformation of the prostate and SV relative to intraprostatic fiducial markers by means of a deformable registration method. They found considerable SV displacement with respect to the prostate gland. Mutanga et al.\textsuperscript{(87)} used this information, together with measurement and intra-fraction displacement errors, to derive margins for prostate and SV by tracking voxels inside the planned dose distribution. They stated that margins could be reduced to 4 mm for the prostate gland and to 7 mm for the SV to guarantee adequate dose coverage. Liang et al.\textsuperscript{(88)} used a binary image mask for rigid image registration to determine daily organ motion. They found that when including the SV in the treatment, margins of 4.5 mm to the SV and 3 mm to the prostate are recommended for IMRT with prostate-only guidance. The smaller margins for the SV found by Liang et al.\textsuperscript{(88)} may be attributed to differences in registration technique, or may be due to differences in patient protocol, like dietary prescriptions, which is, however, not clear from their paper. Another study on non-uniform margin design for prostate and SV was presented by Van Kranen et al.\textsuperscript{(89)} Where previously developed margin recipes\textsuperscript{(58-59)} were based on rigid objects and which assume that all objects move in the same direction, their study focused on margin design for deformable and differential moving targets. For example, for uniform differential moving objects they showed that the margin for a 90% coverage for the systematic component in the Van Herk margin recipe, depends on the amount of differential moving objects and on the correlation between these objects. Based on this work, we explained in \textsc{Chapter 5} the adaptations to the Van Herk margin recipe, for the SV, which could be considered as two differential moving objects. More insight in the kind of motion and/or deformation of individual moving objects will be necessary to develop appropriate margins for all kinds of movements.
REFERENCES


21 Private communication De Meerleer G.


