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Treating prostate cancer
how tight can the prostate safely be irradiated using gold markers?: developing a comprehensive simulation method to determine margins

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Treating prostate cancer: How tight can the prostate safely be irradiated using gold markers?

Developing a comprehensive simulation method to determine margins.

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Abstract

A commonly used recipe to determine CTV to PTV margins used in the radiotherapy of prostate cancer is the Van Herk margin recipe. The study done by Van Herk et. al. considers translations of the CTV and observer variation, but no rotation and deformation. Using implanted gold markers as guidance for correction during treatment, the uncertainties due to translational movement become zero, and only observer variation, rotation and deformation remain as sources of uncertainty. Therefore there was a need for a study which incorporates these uncertainties, which is done here.

CTVs (prostate and seminal vesicles) are contoured by three observers in the planning CT and by one observer in eight follow-up CT scans using triangulated surfaces (meshes), for twenty patients. Rectums are also delineated with use of meshes. Treatments plans are developed with a five beam IMRT technique, aligning the 100% isodose with the PTV and minimizing the distance between the 95% isodose and the PTV. After evaluation an elastic body spline deformation model (based on Gaussian forces) is chosen to use for image registration, creating deformation fields of the follow-up scans to the planning CT using the CTV and rectum as constraints. These deformation fields are used to deform and accumulate the dose distributions for all follow-up CT scans. Meshes are generated from the 95% isodose surfaces.

A distance tool is developed in Matlab which determines the distance between meshes. Because one and the same mesh is used to delineate all CTVs, distance mappings (from CTV to 95% isodose) can be constructed combining all twenty patients. A method is developed to incorporate observer variation, using the delineations of the three observers, into the distance mappings.

Three patient setup protocols (using implanted gold markers, the patients bony anatomy and external skin markers) are simulated by aligning the CT scans accordingly. For the goldmarker protocol initially a margin of 0 mm is used. The distance of the CTV to the 95% isodose of the accumulated dose gives an impression of what margin should have been used to get no underdosage. Incorporating observer variation this resulted in requiring non-uniform margins. For the seminal vesicles (SV) a margin of 7 mm was found, for the apex region 6 mm for the posterior part (rectum side) of the CTV 2 or 3 mm margin and for the rest 4 or 5 mm margin. These absolute values are mere indications and should be validated. The effect of observer variability on the accumulated dose at rectal side of the CTV is small with respect to the anterior side of the prostate, whereas the movement of both sides is similar. It also became clear that the observer variability is a large source of error for the apex region, while the error due to displacement there is small. For the seminal vesicles it showed that movement is the main source of error. A 5 mm uniform margin is applied for the GM protocol. The resulting accumulated doses confirm the need for the non-uniform margins. For the bony anatomy and skin marker protocol only a 0 mm margin is applied. The results showed that larger margins would be needed using these protocols. It was also noted that the CTV possibly showed a systematic movement towards the rectum during treatment, for instance due to increasing laxation.

Future studies should be done to determine the absolute values needed, for each of the non-uniform margins. These studies should entail evaluating possible underdosage applying these margins, and analyzing the accumulated dose in the rectum (wall).
Contents

1 Background: Why is there a need for a new margin assessment? .................................................. 5
  1.1 General introduction to External Beam Radiation Therapy .......................................................... 5
  1.2 Patient setup protocols and the Van Herk margin recipe .............................................................. 8

2 Simulation of dose accumulation: Describing a new approach ................................................... 12
  2.1 Simulation of treatment trajectory and dose planning ................................................................. 13
  2.2 Linking CTVs: meshes, a new contouring method ................................................................. 13
  2.3 Three-dimensional deformation models ...................................................................................... 15
  2.4 Margins: distance of CTV to an isodose of the accumulated dose distribution ......................... 15
  2.5 List of deliverables ...................................................................................................................... 16

3 The road to margin recommendations .......................................................................................... 17
  3.1 List of realization steps .................................................................................................................. 17
  3.2 Setup of contouring and protocol simulation .............................................................................. 17
  3.3 Choosing and evaluating deformation models ............................................................................ 18
  3.4 Developing Matlab distance tools to calculate underdosage mappings and interobserver variability. ................................................................................................................... ...................... 18
  3.5 Developing treatment plans ......................................................................................................... 19
  3.6 Developing strategy to incorporate observer variability into margin assessments...................... 19

4 Results ............................................................................................................................................ 22
  4.1 Observer variation ....................................................................................................................... 22
  4.2 Margin assessments ..................................................................................................................... 23

5 Discussion and conclusions .............................................................................................................. 27

Bibliography ....................................................................................................................................... 29

Appendix A: The Van Herk margin recipe .......................................................................................... 30

Appendix B: Automated mesh adaptation .......................................................................................... 32
  B.1 General information ..................................................................................................................... 32
  B.2 Visual quality check ..................................................................................................................... 33

Appendix C: Deformation models ....................................................................................................... 34
  C.1 General ......................................................................................................................................... 34
  C.2 Choosing a deformation model .................................................................................................... 34
Chapter 1

Background: Why is there a need for a new margin assessment?

1.1 General introduction to External Beam Radiation Therapy

Prostate cancer

Prostate cancer is together with lung cancer the most occurring form of cancer encountered with males, and it is the most frequent tumor for the age group above 65 years. The incidence and mortality incline rapidly with age. In The Netherlands in 2005, the incidence of prostate cancer among all ages was 115 per 100.000 persons, for the age group above 70 years this was 794 per 100.000. Mortality rates were 32 per 100.000 for all age groups and 387 per 100.000 for the age group above 70 years.

Among others, the projected relative and absolute increase of elderly in The Netherlands in coming years will lead to an increase of cases of prostate cancer. In 2005 in the age group above 50, there were 9.404 cases of which 2.779 persons died as a result. The projected numbers for this age group for 2015 are 14.945 cases with 3.039 deaths (KWF, 2004).

Treatment of prostate cancer can be divided into three areas. The tumor can be surgically removed, it can be irradiated by implanted radioactive seeds - radiation from the inside, so-called brachytherapy - and the tumor can be irradiated by means of external beams - radiation from the outside, external beam radiation therapy. This study will focus on external beam radiation therapy.

External beam radiation therapy

The field of external beam radiation therapy (EBRT) consists, just as brachytherapy, of treating oncologic patients with ionizing radiation. When sufficient radiation dose is delivered to malignant tumor cells, DNA is damaged and these cells eventually die (Fig. 1.1a). Unfortunately, this also applies to cells of healthy tissue. Therefore, main challenges in the design of treatment techniques are found in maximizing radiation dose to just the tumor volume while simultaneously minimizing radiation dose to tumor surrounding tissues (Fig. 1.1b). Here, accuracy in dose delivery-geometrically and dosimetrically-is of great importance.
Chapter 1  Background: Why is there a need for a new margin assessment?

Figure 1.1: a) DNA damage by ionizing radiation. After DNA is damaged in the tumor area, cell division will lead to cells with a smaller chance of survival. In that way the tumor cells will die eventually if the treatment is successful. b) Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP). Both TCP and NTCP represent a probability as function of radiation dose; while the TCP is a measure to indicate the treatment success, the NTCP represents the negative side effects of radiation to healthy surrounding tissue. Here, dose delivery should be done with high precision: underdosage decreases the TCP, while overdosage increases the NTCP.

To describe the specific parts within a patient that should receive a certain radiation-dose, ICRU (ICRU, 1993) defined the planning- and clinical target volume as follows:

Clinical Target Volume (CTV): "Tissue volume that contains the gross tumor volume (GTV) which is the gross palpable or visible/demonstrable extent and location of the malignant growth, and/or subclinical microscopic malignant disease, which has to be eliminated. This volume has to be treated adequately in order to reach the aim of therapy: cure or palliation."

Planning Target Volume (PTV): "The PTV is a geometrical concept, and it is defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all possible geometrical variations and inaccuracies in order to ensure that the prescribed dose is actually absorbed in the CTV."

So one radiates a larger area than the CTV itself to ensure coverage. In case of prostate cancer the CTV and PTV are represented schematically in fig. 1.2. This figure also shows the organ at risk (OAR); in this case this is the rectum. An OAR is defined as healthy tissue located near the CTV, which cannot receive too much radiation.

Notice that the whole prostate gland is considered as CTV. Using CT as image modality it is impossible to distinguish between the tumor and healthy tissue. This is however not the only reason why the whole of the prostate is considered as CTV, in many cases the cancer cells have spread in the prostate. There are cases of prostate cancer where the seminal vesicles are included in the CTV, this means that the cells are also present in the seminal vesicles. In this study both the prostate and the seminal vesicles are subject of investigation, so that a wider range of types of prostate cancer are considered.
Chapter 1  Background: Why is there a need for a new margin assessment?

Figure 1.2: (a) Overview of the male reproductive system. The prostate gland is about the size of a walnut and surrounds the neck of a man's bladder and urethra - the tube that carries urine from the bladder. It is partly muscular and partly glandular, with ducts opening into the prostatic portion of the urethra. The seminal vesicles are attached to the prostate and partly surround the ductus deferens – the tube that carries sperm cells from the testicles into the part of the urethra located in the prostate. The seminal vesicles produce the largest portion of the seminal fluid, a fluid that carries sperm. It also adds substances - vitamin C e.g. - that are important for the nutrition and mobility of the sperm cells (Junqueira, 1984). The prostate glands also secrete a fluid that forms part of the seminal fluid. This fluid contains a substance that regulates the liquidity of the semen. During male climax, the muscular glands of the prostate help to propel the fluids produced by the prostate and seminal vesicles, in addition to sperm that was produced in the testicles, into the urethra. The semen then leaves the body out through the tip of the penis during ejaculation. (b) Frontal view of the prostate and seminal vesicles. Notice the location of the apex and the base. (c) Schematic representation of the regions of interest as defined by ICRU (ICRU, 1993). Here, a transversal slice of the male pelvic area shows the prostate P, seminal vesicles S, and rectum R. Here both seminal vesicles and prostate are considered to be the Clinical Target Volume (CTV); the rectum is considered to be the organ at risk (OAR). A margin is put around the CTV to account for geometric uncertainties; this results in the Planning Target Volume (PTV = CTV + margin). Notice that for this case, the PTV partly coincides with the OAR.

Treatment trajectory

The treatment trajectory for a patient being treated for prostate cancer with external beam radiotherapy (EBRT) consists of two phases: the preparation phase and the treatment phase. These phases are illustrated in fig. 1.3. During the preparation phase, first the patient's anatomy is visualized, usually by means of a CT scan. The CT image-set is transferred to the treatment planning system (TPS). A common used TPS is Pinnacle3. A treatment planning system is a piece of software that simulates an actual irradiation. Using the electron density information of the CT images, the TPS can calculate the absorbed dose in the patient for a virtual beam set-up. To do so, it uses a model of the actual linear accelerator (LINAC), the machine that radiates the patients. Before the actual treatment planning, first the radiation oncologist determines the clinical target volume (CTV) and the organs at risk (OAR) by contouring them with use of a CT scan and/or MR image. In this study only CT scans are considered.
After selecting the proper beam setup according to protocol, the radiation dose is calculated. When the radiation oncologist is satisfied by the calculated dose distribution, the virtual settings are transferred to the LINAC and the patient can be treated. During the treatment phase, the patient is irradiated using the settings determined during the preparation phase. The patient is irradiated during multiple sessions, or fractions. To ensure that the patient’s CTV is at the right position each time, several setup protocols can be used. These will be discussed in the next section.

**Figure 1.3:** Overview of the treatment trajectory for a patient being treated for prostate cancer with external beam radiotherapy (EBRT). The total treatment process consists of two phases: the preparation phase and the treatment phase. The patient’s CTV is contoured in a CT-scan. Software that simulates the radiation is used to determine a proper radiation plan. The software used here is Pinnacle3. The patient is irradiated during multiple fractions, in this example 35 times. Several setup protocols can be used for proper alignment of the patient during radiation.

### 1.2 Patient setup protocols and the Van Herk margin recipe

**Treatment uncertainties**

As mentioned in the previous section, the CTV is radiated with a margin to ensure that the CTV receives sufficient dose. If no margin would be applied, uncertainties would cause an underdosage of the tumor. The main uncertainties are the setup error (how is the patient’s body positioned during treatment?), organ motion error (motion of the organ within the body) and observer variability. The setup error entails the error in the position of the bony anatomy of the patient in reference to the room. Causes of this error can be e.g. a variation of relaxation of the patient during multiple fractions. The organ motion is the motion of the organ with respect to the bony anatomy. As seen in fig. 1.2, the prostate is located near the bladder and rectum, the contents of which may change from day to day. Therefore, its position can change from fraction to fraction because of filling and emptying of the
bladder and rectum. Many studies have already been done that quantify motion of the prostate and seminal vesicles during treatment as well as the setup error. The observer variability is the variability in the delineation of different observers contouring the same CTV, combined with the variability of the same observer delineating different CTVs. If an observer delineates what he believes is the CTV, and he is off a fraction, this will lead to an error during treatment. The observer variability is a measure for this error. Many studies have been done to quantify observer variability using multi 2D delineation on CT in the prostate region (e.g. Remeijer, 1999)

These errors can be divided in systematic (preparation) and random (execution) errors. Except for the observer variability, this is only systematic of nature, because it does not change after treatment planning.

We now define:

\[ \sum_{set} = \text{SD of systematic setup error.} \]
\[ \sum_{org} = \text{SD of systematic error component of organ motion (translation only).} \]
\[ \sum_{io} = \text{SD of observer variability.} \]
\[ \sigma_{set} = \text{SD of random setup error.} \]
\[ \sigma_{org} = \text{SD of random error component of organ motion (translation only).} \]

Setup protocols

In this study, only online correction protocols are considered, no offline. The simulation of offline correction protocols would take a lot of time. Whereas one of the aims of this study is analyse the gold marker setup protocol, which is more and more used with an online correction.

The skin marker (SM) protocol uses external alignment. Markers are placed on the skin (e.g. tattooed points) and with use of external lasers the patient can be positioned. This is already an online procedure because each time the patient is treated during a fraction, the patient will be aligned with the use of these skin markers and external lasers. Lead markers are temporarily attached to the tattooed markers so that they are visible on the planning CT scan. This way the position of the CTV with respect to the external markers can be assessed, but only during the preparation phase. All the above mentioned treatment uncertainties are significant using this protocol.

The bony anatomy (BA) protocol uses the bony anatomy to align patients. First the patient is aligned using the SM protocol. Using EPID (Electronic Portal Imaging Device) as an imaging modality, the patient’s actual position during a treatment fraction can be determined. The prostate and SV are not visible on EPID images because these are made of soft tissue. The bony anatomy however can be distinguished. This EPID image can now be compared with the original planning CT. This indicates the difference between the position of the bony anatomy of the patient – with respect to the skin markers - during preparation phase and the treatment phase. If the EPID images are used to adjust the patient’s position each fraction – so an online protocol – the systematic setup error \( \sum_{set} \) and the random setup error \( \sigma_{set} \) are reduced. But the error due to organ motion and interobserver variability are still significant.

The gold markers (GM) protocol uses implanted gold markers as guidance for correction. The gold markers are implanted in the prostate. These markers are visible on EPID images, in contrast to the prostate itself. This makes it possible to determine the location of the CTV during each treatment fraction. The same yields for the GM protocol as for the BA protocol. First the patient is aligned using the SM protocol. The EPID image can be compared with the original planning CT, on which the gold markers are also visible. This indicates the difference between the position of the CTV during preparation phase and the treatment phase, the position with respect to the external skin markers. So using this protocol, the position of the CTV can be determined each fraction, and by changing the position of the treatment table this CTV can be moved in the correct position. If used online, this
Chapter 1  Background: Why is there a need for a new margin assessment?

means that only the contouring of the doctor is still a significant source of error. All the other errors mentioned above are reduced. If using this protocol the above mentioned errors are reduced this much, the question arises if there are errors which were discarded originally because they were too small in comparison, but will start to play a role now.

The Van Herk margin recipe and the need for a new one

The CTV to PTV margin is necessary to account for errors. So that, despite geometrical uncertainties and delineation errors, the CTV still receives adequate dose when the PTV is considered target volume during treatment preparation and actual treatment. The errors can be assessed by analyzing delineations, CT images and EPID images. But what relationship is there between errors and an appropriate margin?

The Van Herk margin recipe (van Herk, 2000) is commonly used as a tool to derive appropriate margins. This recipe is the result of an analytical study. This study represents the CTV as a sphere, and it describes its displacements in a homogenous dose field with penumbral. These displacements of the sphere are a result of the systematic and random errors and include no rotation or deformation, solely translation. The translations are assumed to have a Gaussian probability distribution. Because only translation is considered, margins in six directions can be derived. Van Herk aligns the 95% isodose with the PTV in the planned dose distribution. When the cumulative dose over all treatment sessions is considered, van Herk et al. showed that to ensure a minimum dose to the CTV of 95% of the prescribed dose for 90% of the patients, the following CTV to PTV margin should be maintained:

\[ m_{ptv} = 2.5 \sum + 0.7 \sigma, \]  

(1.1)

with \( m_{ptv} \) the CTV to PTV margin, \( \sum \) the total SD of the systematic error

\[ \sum = \sqrt{\sum_{set}^2 + \sum_{arg}^2 + \sum_{io}^2}, \]  

(1.2)

and \( \sigma \) the total SD of the random error

\[ \sigma = \sqrt{\sigma_{set}^2 + \sigma_{arg}^2}, \]  

(1.3)

For more information on the Van Herk margin recipe see Appendix A.

Using results found by Van Herk for the errors (Appendix A), and using eq (1.1), an appropriate margin for the online SM protocol would be 13 mm, for the online BA protocol it would be 11 mm, and for an online GM protocol 9 mm.

So for the GM protocol only the observer variability is a source of error in the Van Herk formula. However, when uncertainties are reduced this much, other sources of error come into play. These uncertainties are for instance organ deformation, rotation effects and inaccuracies in the correction procedure. Because the conventional way of correction is a simple translation, a margin around the CTV will always be necessary.

Stroom et. al. (Stroom, 1999) did a similar study as Van Herk did to derive margins. The CTV is not approximated by a sphere, but delineated structures are used (prostate only). Stroom et. al. considers translation and rotation, which however, are assumed to have a Gaussian probability distribution. It is unclear what dose distributions are used.
In the study described in this paper, contoured CTVs, and planned dose distributions calculated with an IMRT technique, are used to simulate dose accumulation in the CTV. By linking the anatomic regions of the prostate and seminal vesicles for a patient for multiple fractions, and patients among, organ translation, rotation and deformation are accounted for. The assumption that the probability distributions are Gaussian does not have to be applied, because measured data is used. This also yields for the penumbra in the dose distribution. Because of the usage of triangulized surfaces and image registration, it is possible to make margin assessments for each region of the CTV, not only in six directions. The 100% isodose is aligned with the PTV. This means that the 95% isodose is at a certain distance of the PTV, creating a ‘natural’ margin. By simulating the setup procedures inaccuracies in the correction procedure are considered.
Chapter 2

Simulation of dose accumulation: Describing a new approach

In general, the aim of this study is to derive margin recommendations by simulating the actual accumulated dose. That is to say, the total dose received by a patient over treatment, and its distribution. If one has this accumulated dose distribution, one is able to say whether or not the CTV has received enough dose throughout treatment. And one could assess which margin should have been applied to gain full coverage of the CTV.

To get to this accumulated dose, several things have to be simulated. Such as the patient’s anatomy during a treatment fraction, and the setup protocols which are used. The radiation plan developed in the preparation phase is used throughout treatment. So if one has information about the position of the patient’s anatomy during treatment, one knows the coverage of the CTV during this fraction.

If one has these dose distributions in, and around the CTV for each fraction, one can accumulate these distributions to assess the effect of the total treatment. This is shown schematically in fig. 2.1.

However, if one wants to add these dose distributions, one has to label each anatomic region of the CTV in every fraction, in order to be able to define which part of the CTV in a certain fraction corresponds to the same part in another fraction. And because this study uses more than one patient, the anatomic regions of CTVs of different patients also have to be linked. If each anatomic region is labelled, the accumulated dose in this region can be calculated because for each fraction the dose in that region is known. This labelling is done by using template meshes as contouring structures, this is discussed in section 2.2.

Using this method, uncertainties as setup error, organ movement, organ deformation and organ rotation are accounted for. However, observer variation is also a large uncertainty. Especially when the
goldmarker setup protocol is used, as explained in section 1.2. This study also considers observer variation in its margin assessment. This is discussed in section 3.6.

## 2.1 Simulation of treatment trajectory and dose planning

Of each patient nine CT- scans are made, of which one scan is the planning CT. The other eight scans represent the patient’s anatomy during treatment, these scans are made at random moments during the treatment phase of the patient. The number of patients used is twenty. The nine CT scans represent a whole treatment course, whereas a total treatment consists of 30 to 35 fractions. There are not more scans than nine made, because more scans would lead to too much workload and it would be more burden for the patients. It is believed that nine CT scans show the movement of the body and organs in a sufficient way. And with using twenty patients, any possible deviation of the true body and organ movement, will cancel out. The helical CT scans used have a resolution of 1.5 mm in the z-direction (transverse slices).

The simulation of the setup protocols is done in Pinnacle³. The external markers used with the SM protocol are visualized on the CT scans by placing lead markers on the tattooed dots while making the CT. The scans are aligned manually in such a way that the lead markers coincide. The BA protocol is simulated by automatic alignment. The scans are aligned on bony anatomy using the density information given by the grey values of the CT. The GM protocol is simulated in a similar way. With this protocol the scans are aligned in such a way that the goldmarkers coincide as best as possible.

To develop radiation treatment plans a five beam IMRT (Intensity Modulated Radiotherapy) technique is used. The IMRT technique is a relatively new technique, with which one can steer the desired dose distribution more accurately. Five beams are used because this is commonly used by radiotherapy departments. More details about the radiation plan used are found in section 3.5.

## 2.2 Linking CTVs: meshes, a new contouring method

Using the research version of Pinnacle³, it is possible to contour with the use of triangulized surfaces, also known as meshes. Nowadays, contouring is commonly done multi-2D. That is to say, a doctor delineates in one single view (transverse for instance). And he or she scrolls through the slices while contouring on each slice.

![Figure 2.2: An example of a 3D mesh-contoured CTV, reconstructed in Matlab software. The bulk represents the prostate and the pointy structures at the right side are the seminal vesicles. The colour corresponds with the height of the mesh. The mesh consist of points, connected in such a way that the mesh surface is build up out of triangles.](image-url)
Chapter 2  Simulation of dose accumulation: Describing a new approach

Figure 2.3: a) Transverse view of the prostate region. Using the multi-2D delineation procedure, radiotherapists draw curves in transverse view, slice by slice. The slice thickness in this example is 1.5 mm, this is also the slice thickness of all CT’s used throughout the project. The prostate and SV are delineated together. b) Sagittal view of the delineation done with the multi-2D method described under a). The result is a non fluent structure, and possible deviations detected in sagittal or coronal view can only be corrected in transverse view. c) The same sagittal view as shown in b), but now the CTV is delineated with the use of the mesh (3D). This structure is more fluent, and one can use tools to adapt the mesh in all views, also coronal. In this way, information from all views can be used for correct contouring.

The usage of meshes has two advantages. First, it is possible to delineate in three dimensions, which makes for more accurate delineation (fig. 2.3). Second, using the same mesh for different delineations it is possible to link structures. In fig. 2.2 an example of a CTV-mesh is shown. In this study, to incorporate observer variability in the process, three specialized observers delineated the CTV for each patient in the planning CT.

As mentioned before, using the mesh, it is possible to link structures. Each point of a certain mesh grid is labelled. If one uses the same (template) mesh to delineate two meshes, one has to pay attention that the same points of the meshes are located at similar anatomic regions. Now if point number $x$ in mesh number one represents an anatomic region in organ one, the same point number $x$ in mesh number two represents a similar anatomic region in organ two. In this way the surfaces of the CTV delineated in all nine CT scans per patient can be linked. And patients among each other can also be linked by using the same template mesh for delineation. An example of how the CTVs of two patients are linked is shown in fig. 2.4.

Figure 2.4: Patchwork CTV meshes. a) Prostate of patient one. All mesh points situated in a certain region are given a certain colour. b) Prostate of patient two. The same mesh is used to delineate the CTV, and the mesh points kept their colour. In this way, one can see how the same mesh points represent the same anatomical region for different patients.
All contouring done in this project is done with the use of 3D meshes. Not only the CTV is delineated this way, also the bladder and rectum are. This makes way for analysis of the organs at risk. This is for future work and is beyond the scope of this study. One in three delineations of the CTV are done with the direct use of a template mesh. Two in three delineations are done using other meshes, after which the template mesh is wrapped around these other meshes using an automated adaptation technique. This is because of practical reasons. The bladder and rectum are also contoured with the use of this technique. This automated adaptation is proposed by M. Kaus et al. (Kaus, 2003) and is implemented in the version of Pinnacle$^3$ used in this project. It automatically adapts a mesh around an already delineated structure, or it adapts a mesh on the basis of grey values in the CT. Only the bladder is delineated with automatic adaptation based on grey values. The rectum is delineated by using a template mesh which is adapted around a delineation already done. It is important that the template mesh needs to be positioned and formed closely to the target volume, bearing in mind which points need to represent which region. This is to prevent large displacement of the mesh vertices by rigid alignment such as rotation. More on this is found in Appendix B, and section 3.2.

2.3 Three-dimensional deformation models

For each patient, three delineations of the CTV are done in the planning CT. The template mesh is wrapped around all these meshes, if they weren’t template meshes already. For each patient, one of the three structures is copied to the eight other CT’s. This structure is now used to delineate the CTV in these CT scans. In this way the surfaces of the CTVs are linked. However, to make a margin assessment, the accumulated dose has to be calculated for the whole space. And by linking the surfaces, it is only possible to accumulate dose values which belong to surface points.

If two mesh surfaces with different shapes are linked, and a point on the second surface is shifted a centimetre with respect to the same point in the first surface, what is the shift of a voxel (small volume unit) near this surface? To know this, one has to use a mathematical model which describes the deformation of one volume to another using only knowledge about the displacement of the surface points. So using a deformation model it is possible to ascertain image registration, that is to say, describing which voxel in one image corresponds to which voxel in another image. Another way of describing the function of a deformation model is that it describes how an image should be deformed so that it matches another image. Because one is interested in the accumulated dose, one can also deform the dose distributions using the deformation model which is determined on basis of the mesh deformation. This is also less time consuming than deforming the actual image. In this study the dose distributions of the eight follow-up CT scans are deformed (warped) to the planning CT in such a way that the CTVs and rectums match. The rectum is also used for the deformation so that future work regarding the rectum is possible. Several deformation models are available in the version of Pinnacle$^3$ used in this project. More information on deformation models can be found in Appendix C and section 3.3.

2.4 Margins: distance of CTV to an isodose of the accumulated dose distribution

After the dose distributions in the follow-up CT scans are deformed, they are accumulated. Projecting the accumulated dose on the planning CT shows which region received which dose, accumulated over treatment. It is possible to recognize any possible underdosage. If one uses a CTV to PTV margin of 0 mm, one can establish the underdosage. The distance of the CTV mesh surface to a isodose line of interest gives an estimate of what margin should be used in order to get no underdosage, and a lowest possible dose around the CTV.
According to ICRU (ICRU, 1993) a margin is sufficient if 99% of the CTV volume receives 95% of the prescribed dose. Therefore the 95% isodose is the isodose surface of interest. In this study, first the accumulated dose is calculated with the use of a zero millimetre margin. Then the distance of each surface point of the CTV template mesh to the 95% isodose surface is calculated. This is done for twenty patients, and for the GM, BA and SM protocol. This gives an indication of what margin should be applied, using each protocol. For the GM protocol an actual margin is applied for validation. Especially considering the GM protocol it is important to incorporate the observer variability. This is also done in this study.

Calculating the distance between surfaces is not possible in Pinnacle\(^3\). For this, Matlab software is developed.

### 2.5 List of deliverables

In this section the list of deliverables of this project are given.

For twenty patients combined, and using a newly developed distance mapping technique (section 3.4 and Appendix D):

- A 3D calculation and representation of observer variability.

For twenty patients combined, using an appropriately defined treatment plan (section 3.5 and Appendix E), using a newly developed method of incorporating observer variability (section 3.6 and Appendix F) and also using the newly developed distance mapping technique, the following:

- A 3D calculation and representation of underdosage mapping for the CTV. For the skin marker (SM) setup protocol with usage of 0 mm margin.
- A 3D calculation and representation of underdosage mapping for the CTV. For the bony anatomy (BA) setup protocol with usage of 0 mm margin.
- A 3D calculation and representation of underdosage mapping for the CTV. For the gold marker (GM) setup protocol with usage of 0 mm margin, and with usage of an appropriate margin.
- Margin recommendations for the online GM protocol.
Chapter 3

The road to margin recommendations

3.1 List of realization steps

In order to make margin assessments as described in the list of deliverables in section 2.5, several steps have to be taken.

The list of these realization steps is:

- Setup of protocol simulation and contouring.
- Choosing and evaluating deformation models
- Developing Matlab distance tools to calculate underdosage mappings and observer variability.
- Developing treatment plans.
- Developing strategy to incorporate observer variability into margin assessments.

3.2 Setup of contouring and protocol simulation

As described in section 2.2 and Appendix B, the template mesh has to be positioned close to the target in order to minimize rigid translation. A visual check of this procedure is also found in Appendix B.

During the contouring phase it became clear that there was a need for a guideline regarding the delineation of the seminal vesicles (SV). For each patient two spheres are created, each with their centre at the base of a seminal vesicle. The radius of each sphere is 2 cm. The guideline is that the observers are not allowed to delineate the SV outside these spheres, so that the length of each delineated vesicle is 2 cm. Vesicles that were shorter than 2 cm were delineated as a whole.

It also became clear that delineation on CT scans already matched on goldmarkers was preferable. After copying the CTV and rectum to the follow-up scans, these structures were moved and adapted again so that they contour the CTV and rectum in these follow-up scans. Using the goldmarker matched CT’s, the copied structures were already more or less in place. If one would have to move the CTV and rectum separately, the chances are that these structures are displaced with respect to one another. This becomes a problem in the CTV-rectum transition region. Here, the mesh points of the two structures lie close to one another, and big shifts would result in errors using the deformation model. Also the thinning process, which is used in the deformation, may cause incorrect deformation. So using the goldmarker matched CT scans, the CTV and rectum keep aligned. It is also considered, that in all delineations, the rectum and CTV must not have an overlap. This would also result in errors in the deformation process.

Several Pinnacle3-scripts were developed. These include the creation of lists of relevant regions of interest (ROI’s), such as the CTV for each observer, rectum, bladder and goldmarkers. There are also scripts made for automatic CT matching on bony anatomy and goldmarkers. And for automatically wrapping the template mesh around the delineation of each observer.
3.3 Choosing and evaluating deformation models

The following subjects are discussed in more detail in Appendix C.

The Pinnacle3 software offers the possibility to choose from six deformation models: Thin Plate Spline, Wendland 31, Wendland 32, Elastic Body Spline (EBS) Davis, EBS Gauss and Todds EBS Gauss. After a theoretical and practical evaluation of the models, the EBS Gauss deformation appeared to be the most suitable for this study. This model treats the structures used as bodies with elastic behaviour, on which Gaussian shaped forces are exerted on to make the deformation possible. The Poisson’s ratio – which is a measure for the compressibility of the material – can be varied. Using a Poisson’s ratio of 0.5 means that the material is incompressible. Because in this study volume change occurs (which is contradictory to incompressibility) a Poisson’s ratio of 0.3 is used. It was found that using the value of 0.5 the deformation showed abnormal behaviour. The model assumes a constant density and stiffness. Note that in the end we are interested in margins, and distances of isodose surfaces to the CTV surfaces. The mesh points are used as constraints in the deformations, so the surface is always deformed correctly, and the errors of areas near the surface are smaller than the errors of the areas far away from the surface. Because the isodose of interest is often near the CTV surface (especially using the GM protocol), the isodose is in the area with less errors.

It was found that with large displacements errors occur in the deformation. Because the bladder volume can vary during treatment, which would lead to large displacements, the bladder is not used in the deformation. Because a final analysis on the bladder is not an objective, the exclusion is permitted.

A dosegrid box is a three-dimensional structure which limits the calculation of the dose distributions. If a dosegrid box is used, only the dose within this grid is calculated. Often, a small dosegird box is used to reduce computation time. This is possible if one is only interested in the dose distribution in a certain area. However, it is experimentally found that using a small dosegrid box in the deformation process, the process shows abnormal behaviour, so a big dosegird box is needed.

Pinnacle3 offers the option of thinning; reducing the number of mesh points used in the deformation. This particular thinning process suggests however that problems may arise using multiple structures. This is not found experimentally. Because it is unclear what the drawbacks are of this thinning process, the delineation of the CTV and rectum in the follow-up scans is done using goldmarker matched CT scans. In this way the CTV and rectum do not have to be translated after they are copied, which means that they do not move with respect to one another in the transition CTV-rectum region. This is as well desirable in general.

The accumulation of all the deformed dose distributions gives the total accumulated dose distribution in a patient after treatment. This accumulation is also validated using several example situations.

3.4 Developing Matlab distance tools to calculate underdosage mappings and interobserver variability.

Using meshes, it is possible to calculate distances between structures without for instance having the structures to be approximated by spheres. In this realization step a distance tool is developed which can calculate the distance of a mesh to another mesh for each mesh point. This distance is the distance of a mesh point of the first mesh to a point on the surface of the second mesh. This second point is most of the time not a mesh point on the surface of the second mesh, but a point on the surface of the second mesh lying in between mesh points.

To find this point, originally, a method was developed which begins with finding the three nearest mesh points on the second surface. This method however was deemed insufficient.
A second method was developed which starts with finding the nearest mesh point on the second surface, and uses all mesh triangles of which this point is part of. This method generated smaller errors, and was considered accurately enough for this project. More on the (in)efficiencies of these methods can be found in Appendix D.

After the distance to the nearest point is calculated, one wants to establish if this point is situated inside or outside the primary mesh. To do this, a method is used which uses the total solid angle of the mesh triangles viewed from the selected point (Oosterom, 1983). This sum is zero if the point lies outside the closed mesh surface, and is $4\pi$ if it lies inside.

The distance tool is evaluated by using an example of a CTV receiving an accumulated dose using the SM protocol and a margin of 0 mm (Appendix D). The evaluation showed that there were no significant errors using the tool. This example also illustrates that the distance tool using meshes is also a mapping technique, because distances can be determined and displayed locally.

### 3.5 Developing treatment plans.

The goals in developing an appropriate treatment plan are that the plan has resemblances for different patients, and that the dose distribution is in such a way that the accumulated dose in the CTV may not be higher than if one would have used a clinical plan. To achieve these goals, it is desirable that the 95% isodose is located at a fixed minimum distance from the PTV. If the isodose is close to the PTV, one sees to it that if the CTV moves during treatment, it will receive less dose at the edges than if a clinical plan would have been used, which results in an overestimation of the margins. And because the distance is fixed, the starting conditions for each patient is comparable.

The treatment plans are made using the Intensity Modulated Radiation Therapy (IMRT). One feature of this technique is that it uses objectives. An objective can be for instance a desired minimum or maximum dose value in a certain structure. To realize the fixation of the 95% isodose a structure is made, 1.5 mm from the PTV, using an objective for the maximum dose. In this way, the dose gradient outside the PTV is made steeper. The result of this tightening, is that higher dose values are found in the PTV. This is not desirable, and therefore the second step taken is an artificial cut-off of the dose distribution to 100% of the prescribed dose in the PTV, 80 Gy in our case. An example case can be found in Appendix E.

After evaluation, it appeared that in the apex region an underdosage occurred, already in the treatment plans. To change this, two more structures are made with each another objective (Appendix E).

After a final IMRT treatment plan protocol was developed, the planned dose distributions of the twenty patients were evaluated (Appendix E) using the distance mapping technique. It was found that the mean over patients of the distances of the PTV to the 95% isodose is 6 mm to 7 mm in concave areas around the seminal vesicles as well as the side of the prostate where the rectum is located. The left side, right side and back side (anterior) show distances of 5 mm to 6 mm, and the tips of the seminal vesicles, the apex and the top (cranial) part of the CTV shows distances of 3 mm to 4 mm. The standard deviation over patients shows values of 0 mm to 1 mm for the tips of the seminal vesicles, and the apex, the top, sides and back parts of the CTV. The concave regions around the seminal vesicles and the part of the prostate where the rectum is located shows values of 1 mm to 2 mm.

### 3.6 Developing strategy to incorporate observer variability into margin assessments

To incorporate the total observer variation – systematic observer variation and intraobserver variation– into margin assessments, one can make use of the delineations done by the three different observers.
For each observer a radiation plan is calculated, and for each of these plans the accumulation process is applied. For each patient a main observer is appointed, and for the deformation processes used in the accumulation based on the other observers, the CTV and rectum (constraints) of the main observer is used.

Now we have three accumulated dose distributions, based on three different delineations. To incorporate the effect of observer variability into the margin assessment process, one can calculate the distances of the 95% isodose surfaces of these three dose distributions to a, to be determined, ‘true’ position of the CTV. And using these values instead of using the distance of the 95% isodose to CTV, based on one observer, so using the dose distribution based on an observer and the CTV of this same observer.

To determine this ‘true’ position of the CTV, one can use the average of the three delineations. The spread over patients of the distances of the delineations to their average, however, is always smaller than the spread of the distances to the true position. Let’s say that the true position is the average of infinite delineations, in general the three delineations lie closer to their own average than the true position, because the true position differs from the average of the three. This phenomenon is described quantitively in several articles and papers (Remeijer, 1999; de Boer, 2001). A more general approach, however, is given in Appendix F.

To compensate for this inaccuracy, one wants to make a better estimate of the spread of the distances to the true position. One could use not the average of the three delineations, but an average of the ‘other two’ delineations. So for instance, for calculating distances one can use the isodose calculated on basis of observer one, and then calculate the distance to the average of the two delineations done by observer two and three. This however, gives an overestimation of the spread of distances (Appendix F).

After some calculation (Appendix F) it appears that one has to use a weighted average in order to approximate the correct spread. If one wants to calculate the distance using the isodose based on observer one, the correct way is using the equation

\[
 d_{correct} = x_{iso,1} - \frac{\sqrt{6} - 2}{\sqrt{6}} x_{CTV,1} + x_{CTV,2} + x_{CTV,3},
\]

with \(d_{correct}\) the distance, \(x_{iso,1}\) the position of the isodose calculated on basis of observer one and \(x_{CTV}\) the three delineations done by the observers. The same can be applied for the observers two and three.

An example of using different averages is given in fig. 3.1. This graph shows a cumulative distribution of distances of an averaged CTV mesh point (in the apex) to the 95 % isodose of the accumulated dose distribution, using the GM protocol and a margin of 0 mm. These distances are a measure of what margin should have been used in order to get no underdosage. If one would now assess the margin needed for the apex region, so that 100 % of the patients are covered, one would get different results for different averaging methods. Using the average of all three delineations, one would recommend a margin of 6 mm. This is however too small. Using the other two delineations one would recommend 11 mm, this is too big however, as described above and as shown in Appendix F. Using the weighted average, a margin of 8 mm would be recommended so that 100 % of the patients get full coverage in the apex region. This is the correct averaging method.
Figure 3.1: Cumulative graph showing distances of a mesh point, situated in the apex, to 95% isodoses of the accumulated dose, using the GM protocol and a margin of 0 mm.
Chapter 4

Results

4.1 Observer variation

The standard deviation (SD) of the total observer variation (intraobserver and systematic differences) is given by (Remeijer, 1999)

\[
S_{obs}^2 = \frac{1}{N_p} \sum_{p=1}^{N_p} \left( \frac{1}{N_o} \sum_{o=1}^{N_o} \left( x_{p,o} - \frac{1}{N_o} \sum_{o=1}^{N_o} x_{p,o} \right)^2 \right)
\]  

(4.1)

with \(N_p\) the number of patients, \(N_o\) the number of observers, and \(x_{o,p}\) the delineation of observer \(o\) for patient \(p\). In fig. 4.1 \(S_{obs}\) is shown, projected on a template mesh, for twenty patients and three observers. The tips of the seminal vesicles (SV) show low values for the SD, this is because during the delineation process, it was agreed to delineate the SV so that they have a length of 2 cm. We also see that at the rectal side the SD is 1 mm or smaller. This is probably because the transition CTV-rectum can be distinguished more clearly. The cranial and anterior side show values of 2 mm. The largest observer variation can be found in the apex region, with values of the SD of 3.5 mm. This region is hard to distinguish on CT images.

![Image of seminal vesicles](image_url)

**Figure 4.1:** The standard deviation of the total observer variation over twenty patients using three observers projected on a template mesh. The values in the legend are given in cm.
4.2 Margin assessments

The computation time for calculating dose distributions in Pinnacle\(^3\) (planned, for each follow-up CT and accumulated) is eight days, using a 1.3 GHz processor, for twenty patients, three protocols and one margin. The computation time for calculating distances with Matlab tools for one isodose, three protocols, one margin and twenty patients is 70 minutes using a 3 GHz processor.

The distance mappings discussed in this section are projections of distances on a template mesh. These distances are the mean, SD, 90 percentile or 100 percentile of the distances of the CTV to the 95\% isodose of the accumulated dose. This accumulated dose can be calculated using varying setup protocols and varying margins. There is also an option of incorporating observer variation or not. Distance values are given in cm; negative values indicate that the 95\% isodose is located inside the CTV, so indicating underdosage. The population includes 20 patients, and three observers, so sixty single analyses combined.

The 90 percentile is determined in the following manner. First the minimum value over all mesh points over all delineations over all patients is determined. Then this patient is excluded from the analysis. Then this is repeated, so that the two ‘worst’ patients of the twenty are discarded. There are three delineations and three accumulated doses per patient, so all these are not considered anymore for these two patients. The disadvantage of this is that for different protocols different patients could be discarded. Also, the ‘worst’ patient is singled out because of one mesh point, with the lowest value. It could be that the other mesh points of this patient do not carry the lowest values, but are discarded anyway. The advantage is that if one would assess a margin based on the 90 percentile calculated in this way, the margin would be sufficient to cover 90 percent of the patients.

Gold marker protocol

In fig. 4.2 the 90 percentile distance mapping is shown using the GM protocol and a margin of 0 mm, including observer variation. This mapping suggests that different margins would be needed for the apex region (6 mm) and the SV (7 mm). The rest of the prostate is divided in two parts; the rectal part would suffice with a 2 or 3 mm margin, whereas the anterior part would need a margin of 4 or 5 mm.

If one reviews the same mapping, but now excluding observer variation (Appendix G), the apex shows distances around -1 mm, the SV -5 mm, and the rectal part, as well as the anterior part of the prostate, +2 mm. This indicates that the main cause of the underdosage of the SV is the movement of the SV, and that a main cause of the underdosage in the apex region and the anterior part of the prostate is observer variability.

The mean of the distances for GM, using 0 mm and including observer variation (Appendix G) shows resemblance with the mean of the planned dose distributions (Appendix E). This indicates that the displacement of the CTV in the follow-up CT’s, with respect to the planning CT, is evenly distributed (over patients, and over CT scans) in all directions.

The 100 percentile mapping, including observer variation (Appendix G), shows no significant difference with the 90 percentile graph, except for the SV and the apex. The SV show distances of -8 mm and the apex -7 mm.

In fig. 4.3 the 90 percentile distance mapping is shown, using the GM protocol, including observer variability, but now applying a margin of 5 mm (same objectives for the treatment plans). For the main part of the CTV no underdosage occurs. For the apex region and seminal vesicles one sees negative values. This was to be expected on basis of the 90 percentile using 0 mm margin (fig. 4.2). So bigger margins would be required for these regions. If one compares these figures some more, one sees that the purple areas in fig. 4.3 resemble the red areas in fig. 4.2. Except for a part of the rectal region of
the prostate. The rectum is closer to the PTV using a 5 mm margin than using a 0 mm margin. This results in a positioning of the 95% isodose closer to the PTV in the planned dose distribution using a 5 mm margin, in the rectal area of the prostate, because the objective on the rectum (maximum dose) becomes more important. Looking at the 100 percentile using 5 mm margin (Appendix G), it shows no differences with respect to the 90 percentile (both including observer variation), except for the apex region and seminal vesicles. The negative values found in these areas are more negative for the 100 percentile.

In Appendix G the 90 percentile, using 5 mm margin and excluding observer variation can be found. If one compares the 90 percentile including and excluding observer variation, one sees that no underdosage occurs at the apex region and even in the seminal vesicles. The observer variation has no influence at the rectal side, but we see clear differences at the anterior side.

**Bony anatomy and skin marker protocol**

In fig. 4.4 the 90 percentile distance mapping is shown using the BA protocol and a margin of 0 mm, including observer variation. This mapping also suggests non-uniform margins. For the BA protocol a margin of 14 mm for the SV, 11 mm for the apex and 7 mm for the bulk would be needed.

If one examines the same mapping, but now excluding observer variation (Appendix G), it strikes that the anterior part of the CTV shows positive values. Using the BA protocol, excluding observer variability, only the organ motion with respect to the bony anatomy gives cause for any underdosage. Given the fact that positive values can be found at the anterior part and negative at the posterior part for the 90 percentile, the idea arises that there could be a systematic underdosage at the rectum side of the prostate because of a systematic decrease of rectum filling during treatment (because of increasing laxation for instance). The comparison of the mean over all patients and over all delineations (which is the same if one includes or excludes observer variation) with the mean of the planned dose distributions can give information about systematic behaviour. This is applicable to movement of the CTV due to varying rectum filling. Comparing the mean using the BA protocol (Appendix G) with the mean of the planned dose (Appendix E), the anterior part shows similar values, whereas the rectal side shows values of 5 mm for the BA protocol and 7 mm for the planned dose distributions. This could indicate a systematic movement of the CTV to the rectum side, during treatment. The same yields for the SM protocol. This can be validated by examining the change in rectum volume and CTV positioning during treatment for these twenty patients.

The 90 percentile using the SM protocol, 0 mm and including observer variation is shown in fig. 4.5. The figure suggests that there is a systematic movement of the CTV to the cranial side. This is however not the case if one examines the mean (Appendix G). The values of -15 mm at the cranial side are the results of the worst patient within the 90 percentile. The two patients which were discarded to obtain the 90 percentile had the two lowest values overall. These were values of -18 mm in the seminal vesicles. The values shown at the cranial side of the prostate, are the values of the worst patient (of the twenty) for that region.
Chapter 4  Results

Figure 4.2: Distance mapping of 90 percentile for GM protocol using 0 mm margin and including observer variability. The legend is given in cm.

Figure 4.3: Distance mapping of 90 percentile for GM protocol using 5 mm margin and including observer variability. The legend is given in cm.
Figure 4.4: Distance mapping of 90 percentile for BA protocol using 0 mm margin and including observer variability. The legend is given in cm.

Figure 4.5: Distance mapping of 90 percentile for SM protocol using 0 mm margin and including observer variability. The legend is given in cm.
Chapter 5

Discussion and conclusions

The margin assessment technique as used in this project gives spatial information about accumulated dose distributions. Geometrical uncertainties (translations, rotations, deformations) are included to derive the distributions. Simulating different setup protocols shows the effect of the difference in uncertainties between protocols on the accumulated dose in the CTV. The technique also allows to assess the effect of the observer variability.

The usage of the 90 percentile, as it is calculated, has some disadvantages. Cases which are outliers in certain regions of the CTV are discarded, but for the other regions the outliers still determine the outcome for those other regions. Another disadvantage is that it displays an extremity (which also yields for the 100 percentile). Cumulative graphs such as fig. 3.1 would complement the evaluation. These graphs (for instance for eight mesh points, the six directions and two in the seminal vesicles) would show the behaviour of the population more adequately.

Still several conclusions can be drawn on basis of these percentiles. A main conclusion is that using goldmarkers as a guidance for correction during the setup procedure, smaller CTV to PTV margins would be needed than using the BA or SM protocol. Several more conclusions can be drawn because the effect of observer variability can be included or excluded. Observer variability is of varying importance for the three different protocols. Comparing the 90 percentile, including and excluding observer variability for the GM, BA and SM protocol, the observer variability has the largest effect using the GM protocol. Using the BA protocol it has a lesser influence, and for the SM protocol it has a small relative effect, only at the apex it remains a significant source of uncertainty. Focussing on the GM protocol, the effect of observer variability on the accumulated dose at rectal side of the CTV is small with respect to the anterior side of the prostate, whereas the movement of both sides is similar. It also became clear that the observer variability is a large source of error for the apex region, while the error due to displacement there is small. For the seminal vesicles it showed that movement is the main source of error. The total errors for each of these regions differed from one another resulting in a need for non-uniform margins. Different margins would be needed for the seminal vesicles, apex, the bulk of the CTV and the rectal side of the CTV (in order of largest to smallest margin needed).

The positioning of the 95% isodose is closer to the PTV in the planned dose distribution using a 5 mm than using a 0 mm margin, because of the objective on the rectum. However, the assessment of the non-uniform margins still yields after applying a margin of 5 mm. To obtain the absolute values of each of these margins, one has to apply certain values and see whether or not underdosage occurs. After the calculation of a treatment plan, the next step is to calculate the resulting dose distribution in the patients simulating the use of the lead leaves shaping the radiation beams. This next step is not considered in this study, and to obtain absolute margin values this step should be taken, because it may enlarge the distance between the 95% isodose and the PTV in the planned dose, which would result in smaller margins.

What is also to be considered determining final margin values is the effect of resulting dose distributions on the rectum. The more accurately steering the dose into the CTV by using the GM protocol instead of the BA or SM protocol, and by using smallest margins as possible, could have two advantages. The first advantage is that one can escalate the delivered dose in the CTV, which would
lead to better treatment results regarding the cancer (Peeters, 2006), the other advantage is that less dose could be delivered in the rectum, which would lead to a reduction of rectum related complications. To assess if, and to what extent, one can make use of these advantages, one has to have information about the effect of margins used on the delivered dose in the rectum.

For the bony anatomy protocol it was found that it might be the case that a systematic movement occurs towards the rectum during treatment, which might be the result of a increasing laxation. This can be validated by examining the change in rectum volume and CTV positioning during treatment for these twenty patients.

The data produced in this study can be used to perform many other studies. Such as the rectum dose evaluation, and systematic volume change in the rectum as mentioned above. But also the relationship between rectum volume, bladder volume and CTV movement, and deformation and volume change of the prostate and seminal vesicles itself. These studies would give more insight into the radiation process of prostate cancer. They could lead to changes in treatment plan development and changes in treatment protocols which could enhance the treatment success and reduce complications for the patient.
Bibliography


Appendix A

The Van Herk margin recipe

General characteristics of uncertainties

In general, systematic (preparation) and random (treatment) errors have a different effect on cumulative dose distributions. This is illustrated in fig. A1.

![Figure A1](image)

**Figure A1:** Schematic drawing of the impact of geometrical deviations on the dose distribution described in a coordinate system that is fixed relative to the CTV. (A) Treatment execution (random) deviations lead to blurring of the dose distribution. (B) Treatment preparation (systematic) deviations lead to a (unknown) shift of the cumulative dose distribution relative to the CTV.

The systematic errors have a larger influence on the received dose of the CTV. These are made once during the preparation phase and continue to exist throughout the treatment. The random errors however cause a blurring of the dose.

Van Herk’s margin assessment

The dose distribution is chosen as a uniform field with a Gaussian penumbra. The CTV is represented by a sphere, and the errors are assumed to have a Gaussian distribution. Because of the mathematical description (in Gaussian terms) it is possible to treat the process shown in fig. A1 in a probabilistic manner. That is to say, a smallest possible margin can be given, for which at least a certain percentile
of dose is delivered to a certain percentile of patients. The percentile of dose can be ascertained from the blurred dose distribution, and the percentile of patients via the probability density function (Gaussian curve) of the systematic error. This probability density function shows what the chances are that a patient is biased with a certain systematic error. From this it can be derived how much the margin should have been to have full coverage. The Gaussian curves of the systematic and random errors are described by their standard deviation (SD).

To ensure a minimum dose of 95% for 90% of the patients, Van Herk found after some algebra

\[ m_{ptv} = 2.5\Sigma + 0.7\sigma, \]  

(A.1)

with \( m_{ptv} \) the CTV to PTV margin, \( \Sigma \) the total SD of the systematic error

\[ \Sigma = \sqrt{\Sigma_{set}^2 + \Sigma_{org}^2 + \Sigma_{io}^2}, \]  

(A.2)

with and \( \sigma \) the total SD of the random error

\[ \sigma = \sqrt{\sigma_{set}^2 + \sigma_{org}^2}, \]  

(A.3)

and

- \( \Sigma_{set} \) = SD of systematic setup error.
- \( \Sigma_{org} \) = SD of systematic error component of organ motion.
- \( \Sigma_{io} \) = SD of observer variability
- \( \sigma_{set} \) = SD of random setup error.
- \( \sigma_{org} \) = SD of random error component of organ motion.

Table A1 gives an overview of values of uncertainties as obtained by Van Herk et al. This table gives standard deviations of uncertainties in three directions. For each direction a margin can be calculated. If one applies the rolling ball algorithm (morphological dilation) (Stroom, 1997) to the CTV to obtain a uniform margin, the margin should be used, which is the margin for a direction with the largest value. For the SM protocol all the uncertainties play a role. Applying eq. (A.1) to the values in table A1 (for SI direction the maximum uncertainty is taken) for the SM protocol, the direction with the largest margin is the SI direction. This margin is 13 mm. If one does the same for the online BA protocol, where the total setup error is reduced, the SI direction is also the direction which needs the largest margin. Applying eq (A1) gives a CTV to PTV margin of 11 mm. For the online GM protocol, where only the observer variation is a source of uncertainty, the SI direction is again the direction with the largest margin. This margin is 9 mm. So these margins should be maintained if one uses a uniform margin, according to Van Herk.

Table A1: Overview of prostate irradiation uncertainties (standard deviations of translations) as obtained by different studies from the group Van Herk et al.

<table>
<thead>
<tr>
<th>Treatment execution (random errors (mm))</th>
<th>Treatment preparation (systematic errors (mm))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
</tr>
<tr>
<td>Target volume delineation (2)</td>
<td></td>
</tr>
<tr>
<td>Organ motion (5)</td>
<td>0.9</td>
</tr>
<tr>
<td>Setup error (6)</td>
<td>2.0</td>
</tr>
<tr>
<td>Total SD (quadratic sum)</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* These values are due to the larger uncertainty in target volume delineation near the apex and the seminal vesicles.

\* These values are estimates of the systematic error without the use of a correction protocol.
Appendix B

Automated mesh adaptation

B.1 General information

The automated adaptation proposed by M.R. Kaus et. al. (Kaus, 2003) describes the automatically adaptation of a mesh around an already delineated structure, or the adaptation of a mesh on the basis of grey values in the CT. The adaptation around a delineated structure treats the structure as a binary mask, which means that all the voxels inside the structure all have one certain value, whereas all the voxels outside the structure have value zero. The adaptation is a three-step procedure:

First step
The template mesh is rigidly aligned with the target. This rigid alignment involves rotation, scaling and translation. The parameters describing this alignment are calculated by optimizing the alignment of the normals of the mesh triangles with the local gradient vectors of the image.

Second step
At each triangle centre, a point in the image or on the surface of the binary mask is found. This is done in such a way that there is an optimal trade-off between the distance and the inner product of the normal of the triangle centre and the image gradient at the location of the chosen point.

Third step
The third step is mesh reconfiguration. The positions of the mesh vertices are recalculated by minimizing the trade-off between the so-called external energy and internal energy. The external energy drives the triangle centres toward the detected points in the target image. These are the points found in the second step. However, one does not want all the points of the original template to change position randomly with respect to each other. The internal energy restricts the movements of the mesh vertices with respect to each other, so that one keeps a proper distribution of the mesh vertices on the mesh surface.

The parameters describing these steps and trade-offs are organ dependent. In this study, for each organ, settings were used which were predefined in Pinnacle.

The CTVs are contoured with the use of automated adaptation based on an already delineated structure. During step one, the rigid alignment makes use of the image gradients at the locations of the mesh vertices. Using a binary mask, this gradient is zero, and if not, it is unclear how it is calculated. It is also possible that using a binary mask, step one still makes use of the image grey values. If the binary mask represents a structure which is also distinguishable in the CT image this is not a problem.

The aim of using the template mesh is to link CTVs. So it is imperative that the mesh vertices represent the same anatomical regions of different CTVs. Therefore, certain mesh points need to be at a certain region. So after positioning the template mesh close to the target structure, large displacements as rotation in step one are undesirable, especially when it is unclear how this is done. The conclusion is that the template mesh needs to be positioned and formed closely to the target
volume, bearing in mind which points need to represent which region. This is to prevent large
displacement of the mesh vertices by rigid alignment in step one.

B.2 Visual quality check

In this section the effect of the automatic mesh adaptation on the displacement of the mesh points is
visualized by means of an example. This is shown in fig. B1. This figure shows a mesh, and the same
mesh after it’s wrapped around itself. It shows a decrease of mesh point density. Although there are
only small displacements, one still has to consider the effect of this on the final projection of all
patients on the template mesh. It means that a margin assessed for a single point is the margin assessed
for a region around that point.

Figure B1: CTV meshes, the bulk is the prostate and the vesicles are the pointy structures. The
view is from above (cranial side). a) The original delineation, using the template mesh for
contouring. b) The template mesh wrapped around the mesh shown in a) using automatic
adaptation. The slight decrease of density gives an idea of the displacement of the mesh points.
Appendix C

Deformation models

C.1 General

The goal in image registration is to find a transformation function $u(x) : \mathbb{R}^3 \rightarrow \mathbb{R}^3$ that translates every voxel of a secondary image $I_s(x) : \mathbb{R}^3 \rightarrow \mathbb{R}$ (each voxel in space has a grey value assigned to it) to its corresponding voxel in a fixed primary image $I_p(x) : \mathbb{R}^3 \rightarrow \mathbb{R}$. An interpolation transformation function or displacement field $u(x)$ based on point-landmarks must fulfil the constraint

$$u(p_i) = q_i,$$

where $p_i \in \mathbb{R}^3$ constitute a given set of point-landmarks in the primary image, and $q_i \in \mathbb{R}^3$ are the corresponding point-landmarks in the secondary image. For a parametric basis function the displacement field can be expressed as

$$u(x) = \sum_{i=1}^{N} c_i U(r) + Ax + b,$$  \hspace{1cm} i = 1, \ldots, N, \hspace{1cm} (C.2)$$

where $Ax + b$ is an $\mathbb{R}^3 \rightarrow \mathbb{R}^3$ affine transformation, $N$ is the number of point-landmarks, $c_i \in \mathbb{R}^3$ are the coefficients, and $U(r)$ is the basis function depending on the Euclidian distance $r = |x - p_i|$ from $x$ to $p_i$. A transformation is affine when parallelism and collinearity are preserved. Three points are collinear when they lie on a straight line. Examples of affine transformations are translation, rotation, scaling, reflection and shearing. The summation of the basis functions in eq. (C.2) describes the non-affine part of the transformation. The choice of the basis function $U(r)$ determines the characteristics of the displacement field away from the point-landmarks. Inserting eq. (C.2) into eq. (C.1) results in a system of linear equations, which can be solved to calculate the coefficients $c_i$ and the components of the affine transformation, $A$ and $b$.

In our case the point-landmarks are the mesh vertices of the CTV and rectum meshes, and the transformation function describes the volumetric deformation of the follow-up CT scans to the planning CT. Matlab routines are used to confirm that the mesh vertices and connections remain intact and remain in the same order after copying the mesh to other scans and after manipulation (rotation, deformation).

C.2 Choosing a deformation model

In the version of Pinnacle$^3$ used in this project one can choose among several deformation models. There are six options which can be divided into three groups:
1. Thin-Plate Spline deformation model: The 3D TPS function is $U_{TPS}(r) = r$ (Bookstein, 1989). The name "thin plate" refers to a physical analogy involving the bending of a thin sheet of metal orthogonal to the plate, while taking a shape in which it is least bent. The TPS model produces transformations which are globally distributed.

2. Wendland function deformation models, Wendland 31 and Wendland 32: With the TPS model a single point-landmark pair can influence the whole image. It has been argued that TPS has difficulties describing local deformations if the point-landmarks are not well distributed over the image to prevent deformations in regions where no changes are desired. Other basis functions are proposed (Fornefett, 2000) for image registration, called Wendland functions, with:

$$U_{W_{31}} = (1 - (r/a))^4 (4(r/a) + 1),$$  \hspace{1cm} (C.3)

and

$$U_{W_{32}} = (1 - (r/a))^6 \left[35(r/a)^3 + 18(r/a) + 3\right],$$  \hspace{1cm} (C.4)

which produces local transformations that are zero for $r > a$. The support radius $a$ determines the spatial range of influence induced by a particular point-landmark pair. The deformation induced by mapping $p_i$ to $q_i$ is zero outside of a spherical image region around $p_i$ with radius $a$. These functions are not physically motivated.

3. Elastic Body Spline (EBS) deformation models, EBS Davis, EBS Gauss and Todds EBS Gauss: The EBS is a physically motivated model, which may be advantageous over the application of the Wendland transformations for registering follow-up data of the same subject. The EBS is an analytical solution to the Navier equation. It describes the deformation of elastic bodies under the influence of externally applied forces. A parametric representation of the deformation of the form (C.2) with an analytical solution of the Navier equation can be derived if forces are centered at the positions of the point-landmarks to elastically deform the image in a way that the prescribed corresponding point-landmarks are preserved. In case of EBS Davis the forces are polynomial or rational of nature (Davis, 1997), and in case of EBS Gauss, these forces are Gaussian of nature. It is unclear what Todds EBS Gauss entails, and in what way it differs from the ‘normal’ EBS Gauss. Because of this, and because this model yielded abnormal deformations in some experiments, the Todds EBS Gauss model is not considered any further. The advantage of EBS Gauss over EBS Davis is that it can cope with more local deformations because the Gaussian forces decrease faster than the forces used by Davis et al. This ability of deforming more locally is important in this study because of the local nature of the deformation of the rectum and seminal vesicles.

The analytical solution of the Navier equation, using Gaussian forces, leads to the EBS Gauss function (Kohlrausch, 2005)

$$U_{EBS}(r) = \frac{1 + \nu}{8\pi Y(1 - \nu)} \left\{ \Phi_1(\xi) I + \Phi_2(\xi) e_r e_r^T \right\}$$

with

$$\Phi_1(\xi) = \frac{1}{\sqrt{2\sigma}} \left\{ \frac{(3 - 4\nu) \text{erf}(\xi)}{\xi} - \frac{\exp(-\xi^2)}{\xi^2 \sqrt{\pi}} + \frac{\text{erf}(\xi)}{2\xi^2} \right\},$$  \hspace{1cm} (C.5)

$$\Phi_2(\xi) = \frac{1}{\sqrt{2\sigma}} \left\{ \frac{\text{erf}(\xi)}{\xi} + \frac{3 \exp(-\xi^2)}{\xi^2 \sqrt{\pi}} - \frac{3 \text{erf}(\xi)}{2\xi^2} \right\},$$

where $\xi = r/\sqrt{2\sigma}$, $e_r = (p - q)/r$ is a unit vector pointing in the direction of $r$, and $\nu$ and $Y$ are the Poisson’s ratio and Young’s modulus controlling the compressibility and stiffness of the material.
Similar to the Wendland functions, the parameter $\sigma$ can be used to define the locality of the transformation. In the software however, only $\nu$ can be varied. So the deformation model assumes a constant density of the material, with a constant stiffness.

For a body compressed along the $y$–axis the Poisson’s ratio $\nu$ is given by

$$\nu = -\frac{\varepsilon_x}{\varepsilon_y} = -\frac{\varepsilon_z}{\varepsilon_y}, \quad \text{(C.6)}$$

with $\varepsilon_x$ and $\varepsilon_\nu$ the relative contraction or transverse strain (normal to the applied load), and $\varepsilon_y$ the relative extension strain (in the direction of the applied load). For a perfectly incompressible material, the Poisson's ratio would be exactly 0.5. In this study a Poisson’s ratio of 0.3 is used. More on this is found in section C. 3.

**Difference in ratio affine/non-affine parts of deformation models**

In order to obtain the most realistic transformation field one has to use as many point-landmarks as possible. It turned out however, that the delineation of the skin could not be done in a reproducible manner. This means that the organs have no reference to which they displace or deform. If the CTV has an internal movement, the model does not know if the whole body has moved, or just the CTV within the body, or a mixture of the two. The model has to choose in the amount of contribution of the affine part and in the amount of contribution of the non-affine part. It appeared that models decide that either the whole body has moved, or just the CTV within the body. This is illustrated in fig. C1. Note that the dose distribution is deformed and not the actual CT data. This is much faster, and in the end we are interested in the deformed and accumulated dose.

![Figure C1](image1)

**Figure C1**: Transverse views of a patient’s anatomy (planning CT) with dose distributions as a result of a two-beam radiation plan. The different coloured planes represent the magnitude of the locally absorbed dose in Gy. The blue contouring represents the CTV located in the planning CT. The yellow contouring represents the (unrealistically) displaced CTV in the secondary CT, but is now projected on the planning CT. Only the CTV is used for the deformations. **a)** Original dose distribution. **b)** Deformed dose distribution using the EBS Davis model. The secondary CTV is warped to the CTV in the planning CT. There is no frame of reference, and in this case the model interprets the displacement as a translation of the whole. **c)** Deformed dose distribution using the EBS Gauss model. In this case the model interprets the displacement as a non-affine deformation.

Because it is not desirable to describe internal translation by a translation of the whole body, the models which use just the translation part of the deformation are not used. These are the TPS and EBS Davis models.
Delineated structures used in the deformation

In this study, the CTV, rectum and bladder are delineated with the use of meshes. However, because large displacements can lead to inaccuracies in the deformation models, the bladder is not used in the deformation. These inaccuracies are illustrated in fig. C2. This figure shows a dose-volume histogram (DVH) of the CTV based on the situation as displayed in fig. C1c. The secondary CTV is moved six centimetre with respect to the original CTV. It shows that the DVH of the secondary CTV with the original dose distribution does not coincide with the DVH of the original CTV with the deformed dose distribution. The deformation model used in this example is EBS Gauss. Similar results were obtained using the other deformation models.

![Dose Volume Histogram](image)

**Figure C2:** A DVH based on the situation as displayed in fig. C2c. The yellow line represents the DVH of the secondary (yellow) CTV combined with the original dose distribution. The blue line represents the DVH of the primary (blue) CTV combined with the deformed dose distribution. If there were no inaccuracies in the deformation model, these lines would coincide. The model used in this example is EBS Gauss. Because of this the bladder is not used in the deformation, because large changes in bladder volume can occur.

Practical example

To make a choice among the final three deformation models (Wendland 31, Wendland 32 and EBS Gauss) a practical example is evaluated. The models Wendland 31 and Wendland 32 yielded similar results in several experiments. Therefore, in this example, only Wendland 31 and EBS Gauss are compared. Fig. C3 shows a more or less realistic deformation. This time the deformation is determined by both the CTV and rectum. The CTV is moved, and the rectum is moved. The rectum is also scaled. The DVHs show that EBS Gauss performed better. This was also the case with other examples.

Conclusion

The first part of this section consisted of a theoretical evaluation of the several deformation models. In this theoretical analysis it was concluded that the EBS Gauss model was the most suitable for this project. This was also concluded after a practical evaluation.
Appendix C Deformation models

Figure C4: a)-c) Sagittal views of a more or less realistic deformation. The radiation plan used involves a five-beam IMRT technique. The blue contouring represents the CTV in the planning CT, the yellow represents the displaced secondary CTV. The rectum is represented by an artificially introduced rod. The green one is the original primary rectum and the red one is the secondary rectum. The secondary rectum is scaled and moved. a) Original dose distribution. b) Deformed dose distribution using the Wendland 31 model. c) Deformed dose distribution using the EBS Gauss model.

d) and e) Dose volume histograms of the CTVs. The yellow lines represent the DVHs of the secondary (yellow) CTVs combined with the original dose distribution. The blue lines represent the DVHs of the primary (blue) CTV combined with the deformed dose distributions. d) The DVHs based on the deformation using the Wendland 31 model. The lines do not coincide. e) The DVHs based on the deformation using the EBS Gauss deformation model. The EBS Gauss model performs better in this example because the lines coincide more. Also the spatial distribution of the deformed and original dose distributions have more resemblance than using the Wendland 31 model. This can be seen in a)-c).

C.3 The Poisson’s ratio and volume change

If a material has a Poisson’s ratio of $\nu = 0.5$ this material is considered incompressible. So a volume change is not possible. In this study however, per patient, the rectum volume varies. This could also be the case for the CTV, especially regarding patients who receive hormonal therapy, which can cause the prostate to shrink during treatment. It is believed that the contradiction of incompressibility and volume change lead to unpredictable and abnormal behaviour of the deformation model. An example of this is given in fig. C5. Other examples showed large disturbances of the dose field in the CTV region, halving local dose values. In this study a Poisson’s ratio of $\nu = 0.3$ is used. This is an estimate.
Appendix C Deformation models

Figure C5: Transverse views of a patient’s anatomy with dose distributions as a result of a two-beam radiation plan. The blue contouring represents the CTV located in the planning CT. The yellow contouring is the secondary CTV, scaled to smaller proportions. Only the CTV is used for the deformations. a) Original dose distribution. b) Deformed dose distribution using the EBS Gauss model with $\nu = 0.49$. The dose distribution shows abnormal ‘lobs’, at the anterior and posterior side. c) Deformed dose distribution using the EBS Gauss model with $\nu = 0.3$. The distribution of the original dose distribution in the secondary CTV resembles the distribution of the deformed dose distribution in the original CTV.

C.4 The need for a big dosegrid box

The dosegrid box is a structure which restricts the dose calculation to a certain region. This box is used because it reduces computation time, and one is often only interested in the dose distribution in certain regions. However, if one uses a small dosegrid box during the deformation, the deformation model shows abnormal behaviour. This is illustrated in fig. C6.

Figure C6: The same situation as in fig. C1. The model used is EBS Gauss. The green dotted line represents the dosegrid box. a) Original dose distribution. b) The deformed dose distribution using a large dosegrid box. c) The deformed dose distribution using a small dosegrid box. One can see that this distribution differs significantly from the distribution displayed in b).
C.5 Thinning

To reduce computation time Pinnacle\(^3\) offers the option to reduce the number of points used in the deformation. These points are denoted as \(p_i\) and \(q_i\) as used in eq. C.1. This thinning process starts to determine the mesh point with the largest displacement, so \((p_i - q_i)_{\text{max}}\). After this, all points \(p_j\) which are located in a sphere around \(p_i\), with radius \((p_i - q_i)_{\text{max}}\), are discarded. Then the largest displaced point is determined among the remaining group of points, and the discarding process is repeated. This iterative process suggests that problems could occur using multiple structures.

If two structures are used in the deformation which are adjacent, and one structure has a larger displacement than the other in this transition region, the thinning process would imply that the local deformation of the other structure is discarded. This is applicable in the region where the two structures lie close together. This is however not suggested by the experiment in fig. C7.

![Figure C7](image)

**Figure C7:** Zoomed-in transverse views of a patient’s anatomy and dose distributions as a result of a two-beam radiation plan. The contours are all spheres with a radius of 1 cm, each mesh consisting of 259 points. The blue and green contourings are the original primary structures, and the yellow and red are the secondary structures. **a)** Original dose distribution. **b)** Deformed dose distribution using all structures. The model used is EBS Gauss with 30 points as target number for the points used after the thinning is applied. One would expect, on basis of the thinning process, that the displacement of the red sphere with respect to the green sphere would discard the displacement of the yellow sphere with respect to the blue sphere. It appears however that this is not the case.

In this study, the CTV and the rectum are used in the deformation. These structures have parts which lie close together. These organs are copied to the follow-up scans and put in place separately. If however, these structures have to be moved over large distances, the chances are that the structures are displaced with respect to each other. This is also to be expected because it is difficult to identify corresponding regions of the rectum. This is undesirable in general, but also because it is unclear what the drawbacks are of the thinning procedure. To reduce this effect it is decided to delineate the structures in goldmarker matched CT scans. Using these scans, the organs do not need to be translated after being copied. The CTVs used have 962 mesh points, the rectums have 980 points. The target number for the points used after the thinning is applied in this study is 70 for both organs. This was the default value in Pinnacle\(^3\).
Appendix D

The development of a distance tool

To determine the distance of one mesh to another, for each mesh point, two methods were developed using Matlab software.

First method

The first method begins with, for a certain mesh point, determining the three nearest mesh points of the other mesh. It is now believed that the point closest to the starting mesh point is located in the triangle spanned by the three mesh points found on the other mesh. Now, this point is found in the following manner. The middle point of the triangle is determined, so we have four points. Then the three nearest of these four are determined. This can be repeated. It was found experimentally that after five iterations the situation does not change significantly after another iteration.

The drawback of this method is that the triangle spanned by the primarily selected three mesh points does not need to be part of the (other) mesh. This means that if one locates the closest point in this surface, this point is not located in the mesh surface. Another drawback is, that even if the three originally selected points form a triangle which is part of the mesh, the nearest point need not to be part of this triangle, but could be situated for instance in a neighbouring triangle. This is illustrated by the experiment in fig. D1c.

Second method

It was found that this method was insufficient, therefore a second method was developed. This method starts with finding the nearest mesh point on the other surface. After this, all existing mesh triangles are selected of which this point is part of. For each of these triangles the middle point is determined, and then the triangle is selected of which the middle point is closest to the point on the first surface. This leads to a higher probability that the correct triangle is selected. Then the iterative process as described in the first method is applied on this triangle to find the nearest point. The result using the second method is shown in fig. D1d.

One of the drawbacks of the first method was that initially a wrong triangle could be selected. Using the second method, it is more likely that the correct triangle is selected. The next step however is the first step of the iterative process. But the first step in this process is analogue to the initial selection step of method one. So the same mistake can be made again, except on a smaller scale. Or in other words, after initially selecting the correct triangle, while searching within this triangle one could select the wrong three initial points. That is why in fig. D1d the red dot does not lie completely on top of the green spot. This effect is however considered secondary, en especially when the distance between the mesh surfaces is large, negligible.
Appendix D  The development of a distance tool

Figure D1: In this experiment, for each mesh point of the green mesh, the closest point on the surface of the blue mesh is sought. Ideally, the closest points would coincide with the green mesh points, because the structures are similar. These points are indicated with the red (half) circles. a) Two structures with the same dimensions, one structure has more mesh points than the other. b) Zoomed in view. The mesh point of the green mesh in the black dotted circle is the point of interest in this example. c) Result using the first method. The three blue points nearest the green point of interest constitute a triangle located to the right of the green point. After the iterative process the point is found as indicated by the red half circle. d) Result using the second method. The closest blue point is the one right and above of the green point. The correct triangle is selected, and the nearest point is found with the iterative process. There is still an error, this is due to the iterative process.
Appendix D  The development of a distance tool

Tool evaluation using a patient example

So now a tool is developed which can determine the nearest point on another mesh surface, and can
determine whether this point is located inside or outside the original mesh surface. To evaluate this
tool, a practical example is shown in fig. D2. This figure shows a CTV and a 95 % isodose surface of
the accumulated dose distribution using the SM protocol, and a distance map.

Figure D2: a) Side view in Pinnacle³ of a patient’s CTV with an isodose surface. The yellow
surface is the rendered CTV mesh, the blue structure is the non-rendered isodose mesh. The
isodose surface is the 95% isodose of the accumulated dose using the SM protocol and a margin of
0 mm. Because no margin is used, underdosage is expected. Here we see that the seminal vesicles
and the part of the prostate at the rectum side did not receive enough dose. In this case, this seemed
to be caused by a varying rectum filling. b) Distance mapping of the situation described in a). The
CTV is reconstructed in Matlab, and for each mesh point the distance to the isodose surface is
calculated. This distance corresponds to the colour, and is given in cm. The colour transitions are
smooth because of interpolation. Notice the line where the isodose intersects the CTV in a), and
the region of 0 cm distance in b). Negative values indicate that the 95% isodose is situated inside
the CTV, so indicating underdosage.
Appendix E

Developing treatment plans

In this Appendix the development of an appropriate treatment plan is described. For a normal plan, three objectives are used, a minimum dose value for the PTV, a maximum dose value for the PTV, and a maximum dose value for the rectum. Here, to make the dose gradient steeper and to locate the 95% isodose at a fixed distance from the PTV, initially an extra structure is created 1.5 mm outside the PTV, with a maximum dose value objective. This enlarges the dose in the PTV, and therefore an artificial cut-off is applied, to 100% of the prescribed dose, which is 80 Gy in our case. This is illustrated in fig. E1.

![Initial steps in treatment plan development. Sagittal views of the PTV and dose distributions. The white coloured surface represents a minimum of 104% of the prescribed dose, the purple surface the 100% and the red represents a minimum of 95%. The light blue structure is the PTV. The bar on the right side indicates the scale in cm. Here, a margin of 0 mm is used, so PTV = CTV. a) Normal plan with three objectives. b) Dose distribution after adding the objective on the extra structure. c) Dose distribution after an artificial cut-off to 100%.](image)

Using this initially developed plan, it was found that underdosage already occurred in the treatment plan in the apex region. This had two causes. The first cause was the resolution of the dose grid. This resolution was 4 mm in all directions. The dose distributions shown in the figures are the dose distributions after interpolation of this dose field with a coarse resolution. The mesh of the 95% isodose surface is generated on basis of the coarse grid. Now the resolution in the z-direction (from the inferior side of the prostate, apex, to the superior side) is reduced to 1.5 mm. The effect of this change is shown in fig. E2b. It appeared that there was no need for a change in resolution in the other directions.

The second cause was the area of dose calculation. The algorithm which is used to calculate the dose distribution, using the objectives, restricts the area where high dose values are allowed (unless they are countered with objectives for maximum dose) more or less to structures with an objective for
minimum dose values. This is because there is no need for minimum dose values outside these structures, so the dose is allowed to drop. In the apex region, this leads to calculations which result in a positioning of the 95% isodose close to the PTV. Now an extra structure is created, which is slightly bigger than the PTV, with a minimum objective of 0.001 Gy. The effect of this is shown in fig. E2c. After adding this extra objective, it was found that (undesirable) higher dose values were found at larger distances from the PTV, in regions other than the apex region. Therefore a third extra structure is made with a maximum objective to reduce these values. This had no effect on the dose distribution in the apex area.

![Image of treatment plans](image)

**Figure E2:** Countering the underdosage in the apex region. Sagittal views of the apex. The purple area represents 100% of the prescribed dose, the red surface represents a minimum of 95%. The light blue structure is the PTV, the dark blue structure is the mesh generated from the 95% isodose (edge of red area). The bar on the right side indicates the scale in cm.  

a) The dose distribution and generated 95% isodose mesh using the initially developed plan.  
b) After reducing the resolution of the dose grid to 1.5 mm in the z-direction (bottom to top in figure).  
c) After changing the resolution and adding a structure larger than the PTV with a minimum objective.

To evaluate the calculated treatment plans for all twenty patients, the distance mapping technique is used which is developed earlier. Fig. E3. shows a template mesh with a projection of the mean over patients of the distances of the PTV to the 95 % isodose of the planned dose distributions. Fig. E4 shows the standard deviation.
Figure E3: Projection of the mean of distances of PTV to 95% isodose for the planned dose, using a margin of 0 mm. The legend is given in cm.

Figure E4: Projection of the standard deviation of distances of PTV to 95% isodose for the planned dose, using a margin of 0 mm. The legend is given in cm.
Appendix F

Using weighted average to compensate for usage limited number of observers

Given \( N_o \) observers with delineations \( x_{o,p} \), with the true position of the CTV as origin. The spread of the delineation of an observer (intraobserver variation) can be written as

\[
\sigma^2(x_o) = \frac{1}{N_p-1} \sum_{p=1}^{N_p} \left( x_{o,p} - \frac{1}{N_p} \sum_{p=1}^{N_p} x_{o,p} \right)^2 , \quad (F.1)
\]

with \( N_p \) the number of patients and \( x_{o,p} \) the delineation of observer \( o \) for patient \( p \). It is assumed that the intraobserver variation is the same for each observer. Systematic differences between observers is allowed, this does not effect eq. (F.1). Because the true position is unknown, one has to use an average of the delineations as reference. For observer one:

\[
\sigma^2 \left( x_1 \right) = \frac{\alpha \sum_{i=2}^{N_o} x_i + N_o \alpha x_o}{\alpha + N_o - 1}, \quad (F.2)
\]

with \( \alpha \) a parameter to be chosen. If one chooses \( \alpha = 1 \) (using all delineations for the average), and using the general property

\[
\sigma^2 \left( \sum_{o=1}^{N_o} a_o x_o \right) = \sum_{o=1}^{N_o} a_o^2 \sigma^2(x_o) , \quad (F.3)
\]

with \( a_o \) scalars, then (F.2) can be written as \( [(N_o-1)/ N_o]\sigma(x_i) \). So using all delineations in calculating the average leads to an underestimation of the spread. If one chooses \( \alpha = 0 \) (using all the other delineations for the average), then (F.2) can be written as \( [N_o/(N_o-1)]\sigma(x_i) \). So that leads to an overestimation of the spread. To find the correct weighted average one needs to solve the equality

\[
\sigma^2 \left( x_1 \right) = \sigma^2 \left( x_1 \right) \quad (F.4)
\]

Again, using eq. (F.3), this leads to

\[
\frac{1}{(\alpha + N_o - 1)} \left( (N_o - 1)^2 + (N_o - 1) \right) \sigma^2(x)_1 = \sigma^2(x)_1, \quad (F.5)
\]
Appendix F  Using weighted average to compensate for usage limited number of observers

And this is true for

\[ \alpha = \sqrt{N_o(N_o - 1)} - N_o + 1. \]  \hspace{1cm} (F.6)

In our case \( N_o = 3 \), and according to eq. (F.6), \( \alpha = \sqrt{6} - 2 \).
Appendix G

Distance mapping figures

In this Appendix several distance mappings are shown.

For the GM protocol:
- 0 mm margin. 90 percentile excluding observer variability, 100 percentile including observer variability, mean over patients and delineations, standard deviation over patients and delineations.
- 5 mm margin. 90 percentile excluding observer variability and 100 percentile including observer variability.

For the BA and SM protocol:
- 0 mm margin. 90 percentile excluding observer variability and the mean over patients and delineations.
Figure G1: Distance mapping of 90 percentile for GM protocol using 0 mm margin and excluding observer variability. The legend is given in cm.

Figure G2: Distance mapping of 100 percentile for GM protocol using 0 mm margin and including observer variability. The legend is given in cm.
Figure G3: Distance mapping of the mean over patients and delineations for GM protocol using 0 mm margin. The legend is given in cm.

Figure G4: Distance mapping of the standard deviation over patients and delineations for GM protocol using 0 mm margin and including observer variability. The legend is given in cm.
Figure G5: Distance mapping of 90 percentile for GM protocol using 5 mm margin and excluding observer variability. The legend is given in cm.

Figure G6: Distance mapping of 100 percentile for GM protocol using 5 mm margin and including observer variability. The legend is given in cm.
Figure G7: Distance mapping of the 90 percentile for BA protocol using 0 mm margin and excluding observer variability. The legend is given in cm.

Figure G8: Distance mapping of the 90 percentile for SM protocol using 0 mm margin and excluding observer variability. The legend is given in cm.
Figure G9: Distance mapping of the mean over patients and delineations for BA protocol using 0 mm margin. The legend is given in cm.

Figure G10: Distance mapping of the mean over patients and delineations for SM protocol using 0 mm margin. The legend is given in cm.