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<tr>
<td>ART</td>
<td>Adaptive Radiation Therapy</td>
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<tr>
<td>CBCT</td>
<td>Cone-beam Computed Tomography</td>
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<td>CTV</td>
<td>Clinical Target Volume</td>
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<td>DRR</td>
<td>Digitally Reconstructed Radiograph</td>
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<td>DVH</td>
<td>Dose Volume Histogram</td>
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<td>FOV</td>
<td>Field of View</td>
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<td>GTV</td>
<td>Gross Tumor Volume</td>
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<td>HU</td>
<td>Hounsfield Unit</td>
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<td>IGRT</td>
<td>Image Guided Radiation Therapy</td>
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<td>IMRT</td>
<td>Intensity Modulated Radiation Therapy</td>
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<tr>
<td>kVCT</td>
<td>kilovoltage Computed Tomography</td>
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<tr>
<td>MVCT</td>
<td>megavoltage Computed Tomography</td>
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<tr>
<td>NTCP</td>
<td>Normal Tissue Complication Probability</td>
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<td>OAR</td>
<td>Organ at Risk</td>
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<td>OBI</td>
<td>On-Board Imager</td>
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<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
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<td>RT</td>
<td>Radiation Therapy</td>
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<tr>
<td>SV</td>
<td>Seminal Vesicles</td>
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<td>TPS</td>
<td>Treatment Planning System</td>
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1 INTRODUCTION

A radiation course usually consists of several treatment fractions. Since organs are mobile, inter-fractional motion of the tumor leads to an uncertainty in its position during the treatment course. Localization and adjustment of the target position prior to dose delivery by using image guided radiation therapy (IGRT) results in a more accurate treatment. The principle of IGRT is to acquire an image prior to treatment and comparing this image with a reference image from dose planning and according to the latter adjusting the tumor position by isocenter correction. Various advanced imaging techniques used for IGRT are available today like transabdominal ultrasound (Langen et al. 2003, Fuss et al. 2004), implanted markers with kilovoltage (kV) or megavoltage (MV) X-ray images, kV computed tomography (kVCT) on-rail (Wong et al. 2005), kV or MV cone beam computed tomography (CBCT) (Jaffray et al. 2000/2002, Pouliot et al. 2005) and helical mega voltage CT (MVCT) (Kupelian et al. 2006).

In 2004 a Varian linear accelerator with an integrated imaging system, a so called On-Board Imager® (OBI) (Varian Medical Systems, Inc., Palo Alto, CA, USA) (Jaffray et al. 1999) was installed at the Karolinska University Hospital. The OBI offers both 2-dimensional (2D) X-ray imaging and 3-dimensional (3D) CBCT imaging. 3D CBCT images provide soft-tissue information, while for conventional 2D radiographs implanted markers are still required to localize the tumor. Additionally to tumor motion, deformation and shrinkage of the tumor and patient position setup errors may occur. Consequently, quite a large margin has to be applied around the tumor, which leads to increased irradiation of healthy tissue and organs at risk (OAR). The implementation of IGRT will make it possible to reduce the safety margin around the tumor and to escalate the dose to the planning target volume (PTV). Although IGRT has brought the opportunity of correcting for patient position setup errors and tumor motion, the technique does not always take into account the important occurrences of organ deformation and motion of OAR, since it often concentrates on target delineation. By adjustment of the dose plan according to inter-fractional motion of OAR and deformations of organs, also these phenomena could be eliminated. This modern treatment technique which includes modifying of the dose plan is known as adaptive radiation therapy (ART) (Yan et al. 1997/2000, Martinez et al. 2001). The opportunity at the Karolinska University Hospital of acquiring a CBCT scan at the time of treatment, offers the possibility to calculate the delivered dose distribution and to adapt a new plan based on the acquired CBCT scan.
ART is a wide concept and the strategies are usually divided into off-line and on-line ART. Off-line ART uses image feedback from a number of fractions for the ART process. With on-line ART the daily position and changes of the target and OAR of the patient is detected and the treatment plan is adjusted according to deviations from the approved planning dose distribution, while the patient is lying on the treatment couch. With intensity modulated radiation therapy (IMRT), it is possible to deliver a dose distribution that closely conforms the target shape. This means that target can receive a high dose while dose to OAR can be reduced. However, since the dose gradients around the target are large for IMRT plans, precise target and OAR localization becomes very important before treatment, to ensure accurate dose delivery. Application of a suitable ART method for IMRT patients is therefore of great interest.

At the Karolinska University Hospital prostate cancer patients have been treated with IGRT since June 2004 to correct for inter-fractional movements of the prostate due to changes in rectal and bladder filling. In this thesis an OBI is used to evaluate both this IGRT method for prostate cancer patients and an alternative on-line ART method. The first part, involving ten prostate cancer patients treated with IGRT, consists of the comparison of two different match applications used in image registration, the radiographic 2D-2D and the 3D-3D (CT-CBCT) match. The second part concerns daily dose verifications, dose plan reoptimization and normal tissue complication probability (NTCP) calculations of the OAR. In this study CBCT images of one IMRT prostate cancer patient acquired at 6 different treatment fractions are analyzed. To test the accuracy of using the CBCT images for dose calculations in the pelvic region, additional measurements on an Alderson phantom were executed. Finally some alternative ART methods for clinical implementation are considered.

1.1 ART METHODS

Since ART is a new technique, many groups are now focusing on developing suitable strategies for clinical use. Therefore, it could be of interest to give an overview of some of the suggested methods and also to state the present situation, i.e. are there ART methods used routinely or are they still under development. In figure 1 a rough structure of some radiation therapy methods to correct for geometrical differences between dose planning and dose delivery is illustrated.
Some radiation therapy (RT) methods to correct for geometrical differences between dose planning and dose delivery:

**Image Guided RT**
- Basic correction strategy: Isocenter correction

**Dose Guided RT**
- Basic correction strategy: Isocenter correction and dose recalculation

**Adaptive RT (ART)**
- Off-line ART
  - Correction strategies:
    - Indirect: Patient-specific PTV and OAR
    - Direct: Isocenter correction and off-line reoptimization for dose compensation

- On-line ART
  - Correction strategies:
    - On-line replanning/reoptimization
    - On-line modification of MLC, intensity distribution, etc.

*Figure 1:* Schematic presentation of some radiation therapy (RT) methods to correct for geometrical differences between dose planning and dose delivery.
As mentioned in the introduction, the technique of IGRT often concentrates on the inter-fractional motion of the tumor treated as a rigid body and therefore does not always take into account inter-fractional motion of OAR and deformations of target and OAR. However, IGRT techniques providing volumetric imaging of the tumor and surrounding tissue have given the opportunity of dose verification and patient specific adjustment of the dose plan in different ways. Kupelian et al. (2006) suggest an advanced use of the IGRT technique, which they describe as dose guided radiation therapy. The method would include on-line dosimetric evaluation and subsequent shift in the position of the patient not only on the basis of target location, but also on the basis of the on-line evaluation of OAR. The dose would be recalculated for different patient positions and the position that would ensure full coverage of the target and minimization of the OAR doses would be applied.

1.1.1 Off-line ART

Yan et al. (2000) suggested an off-line strategy for constructing a patient-specific planning target volume in adaptive treatment process for prostate cancer. A patient-specific bounding volume to correct for internal target motion was constructed using the convex hull of the first \( k \) days of CT measurements. The number of CT measurements needed for the construction of the bounding volume was determined using the dosimetric criterion that the maximum dose reduction in the clinical target volume (CTV) due to internal target motion was no more than a predefined tolerance when the bounding volume was applied for the remainder of treatment. The resulting PTV was constructed as the bounding volume plus a patient-specific setup margin. 4-6 portal images were acquired during the initial days of treatment to determine the patient-specific setup margin to correct for patient setup errors. The construction of the setup margin was based on the criterion that the maximum dose reduction to the PTV should be no more than a predefined tolerance to the remaining treatment fractions when applying the patient-specific setup margin. The results showed that for the 4-field-box technique, the PTV for prostate cancer treatment can be constructed after the first week of treatment, while for IMRT 2 weeks of daily CT measurements are required to achieve the same dosimetric criterion. Based on this patient-specific PTV, a new treatment plan can be designed. The PTV volume could be reduced significantly compared to the standard PTV due to safety margin reduction.
In 2001, 150 patients with prostate cancer were treated with the off-line strategy described above (Martinez et al. 2001). Either a conventional 4-field-box technique or IMRT was applied based on the level of dose escalation achievable and the risk of inaccurate targeting. The results showed that on average 5% more dose to the PTV could be delivered using the ART process with the 4-field-box technique and 7.5% more dose could be delivered with IMRT compared to the conventional treatment process with a generic PTV. The ART process was adapted as a standard of practice for prostate cancer treatment at the William Beaumont Hospital, Royal Oak, MI, USA. Since for prostate cancer patients late rectal bleeding may occur as a serious side effect of radiotherapy, Hoogeman et al. (2005) claimed that it is also of importance to use the imaging information of the first treatment days to correct for the changes in the shape of the rectum. Their group evaluated an off-line adaptive procedure on prostate cancer patients, who were treated with conformal radiotherapy. The method calculates an average prostate position and an average rectum shape based on the planning CT and the CT scans of the first four fractions. The treatment plan can then be adapted to conform the dose distribution to the average structures. The results of Hoogeman et al. showed that the systematic error of the position and shape of the rectum could on average be reduced by 43%. The systematic error in the position of the prostate could be reduced by a factor of 2. Recently, the same group determined a PTV margin reduction from 10 mm to 7 mm for this off-line adaptive method (Nuver et al. 2007).

An article with the first clinical results of the ART method described above is now in press (Nijkamp et al.). Pos et al. (2006) studied the feasibility of an adaptive radiotherapy technology for invasive bladder cancer. This method was similar to the method of Yan et al. (2000), with a gross tumor volume (GTV) encompassing all the GTV’s on the CT scans from the first treatment week including the planning CT scan. The PTV was then constructed as the total GTV plus a 1 cm uniform margin. Pos et al. found that a 40% reduction of the treatment volumes could be reached.

The off-line processes described above don’t include patient-specific variations in the planning dose calculation, but they construct a patient-specific PTV based on the interfractional movement of the organs and then according to the new PTV perform conventional replanning or IMRT reoptimization. Another method of off-line ART is to directly include patient-specific variations in the planning dose calculation. This method though, has been
limited to modelling and simulation studies (Löf et al. 1998, Wu et al. 2006, Birkner et al. 2003, Rehbinder et al. 2004).

Wu et al. (2006) developed an off-line dose compensation technique for IGRT. On-line matching was performed to correct for patient setup errors and inter-fractional rigid organ motion. The off-line part included dose distribution calculation for each fraction and deformable organ registration to accurately evaluate the cumulative dose distribution delivered to the CTV. If the cumulative dose distribution deviated significantly from the original goal, the deficit was made up using dose compensation. The dose compensation was given weekly or at the end of the treatment course. Wu et al. found this off-line compensation technique being effective for repairing dose deficits. Weekly dose compensation showed to be more biologically beneficial than the single dose compensation at the end of the treatment course.

1.1.2 On-line ART

On-line ART is based on 3D imaging prior to daily treatment fractions. The 3D images need to be registered with the reference 3D image to provide actual organ positions/deformations. The localization and deformation information from the image of the day provides appropriate treatment plan modification and accurate treatment delivery. With on-line ART, evaluation of the image and adjustment of the treatment plan are performed immediately after 3D imaging, i.e. prior to daily treatment delivery. Therefore, an accurate deformable image registration technique offering automatic organ contouring is an important contribution to on-line treatment plan modifications, since manually delineations are too time consuming. The time aspect is very important and the performance of on-line reoptimization must be fast and simple to avoid intra-fractional organ movements. Finding an appropriate automatic recontouring technique is still the largest challenge of on-line ART and hinders a clinical implementation.

As for off-line ART, different ways of performing on-line ART are possible. IMRT real-time replanning prior to a treatment fraction is probably the most advanced method of on-line ART, but additionally there are several intermediate possibilities (Court et al. 2005/2006, Mohan et al. 2005). Court et al. (2005) developed an on-line ART method, which according to changes in target shape and position modifies the multileaf collimator (MLC). The method
was compared with the simple couch-shift method, where the isocenter in the daily CT images was adjusted to mimic a couch shift. The ART method improved geometric coverage of the prostate and seminal vesicles (SV) compared with the couch-shift method. Additionally it reduced the dose to the rectum more than the couch-shift method. Although the algorithm works well when treating the prostate, it does not take into account in-slice shape changes and therefore is not appropriate for extremely large shape changes. The proposed ART technique has not been used as routine for patient treatments, since there are still some difficulties remaining. One of the difficulties is the adaptation of daily modification of treatment fields to the record and verification system.

1.2 THE OBI SYSTEM AND IMAGE REGISTRATION

The On-Board Imager (OBI) is an imaging system integrated with the linear accelerator. It consists of a kV X-ray source and a flat-panel kV detector mounted on two robotic arms, which are oriented at 90° from the MV treatment beam (figure 2). The OBI arms rotate with the gantry. There are three different methods of imaging employed: 2D radiographic imaging for patient set-up corrections, fluoroscopic imaging for tracking tumor motion during treatment and 3D CBCT for patient set-up and tumor position corrections or ART techniques. A CBCT image is acquired by rotating the gantry once. All selected slices are obtained from the 650 projections acquired within this single rotation. The 3D image is reconstructed by using a filtered back-projection technique. Two different acquisition modes are possible, full-fan and half-fan. The full-fan mode has a reconstruction field of view (FOV) of 24 cm with a source to imager distance (SID) of 150 cm and is used for head scans. The half-fan mode is used for body scans since it has a reconstruction FOV of 45 cm. When using the half-fan mode, half of the beam is cut off and the kV detector is shifted by 15 cm laterally. Half-fan and full-fan bowtie filters are used to correct for beam hardening effects to improve image quality and homogeneity.

Since the treatment plan is based on the images acquired with the conventional CT (reference images), one has to adjust the position of the tumor at the time of treatment according to the position on the conventional CT image to receive the planned dose to the tumor. By acquiring OBI images prior to treatment and then matching these with the reference images both target movement and setup errors can be corrected for. The images can be registered either according to bony anatomy, implanted gold markers or soft tissue. When the images
are registered, the required couch correction is displayed in lateral, vertical and longitudinal directions and in couch rotation. The couch can then be moved remotely according to these coordinates. Three different match applications are available, 2D-2D match, 2D-3D Marker Match and 3D-3D match, whereas all can be performed manually or automatically.

![Varian linear accelerator with an OBI system consisting of a kV X-ray source and a flat-panel kV detector mounted on two robotic arms. On the treatment couch the pelvic region of an Alderson phantom is visible.](image)

**Figure 2:** Varian linear accelerator with an OBI system consisting of a kV X-ray source and a flat-panel kV detector mounted on two robotic arms. On the treatment couch the pelvic region of an Alderson phantom is visible.

The 2D-2D match technique uses two orthogonal images acquired with the OBI prior to treatment. These are then matched with the reference images, the digitally reconstructed radiographs (DRRs) generated from the planning CT data. First the kV images are superimposed onto the DRRs and then the DRRs are moved to match corresponding structures in the kV images. Finally, the couch is moved to the right treatment position. The linear accelerator can also be used to acquire two orthogonal MV images or one MV image and one kV image used for matching. The time required for 2D-2D matching is less than 1 minute.
The 2D-3D Marker Match technique is based on the implanted gold markers. Since the soft tissue visibility is limited in the kV images, implanted gold markers are used as a surrogate for the tumor. The 3D planning CT image set is used as a reference image set. Two orthogonal kV images are acquired before each treatment fraction wherein the gold markers can be localized. The gold markers are detected on the reference CT and are then marked as crosses at the corresponding locations on the orthogonal kV images. Finally, the crosses are matched with the gold markers in the kV images and the couch is moved. The time to perform automatic 2D-3D Marker Match registration is about 1 minute.

The 3D-3D match technique uses the reference CT image and a CBCT image acquired with the OBI prior to a treatment fraction. The two 3D images are superimposed and matched in three different views, transversal, sagittal, and coronal. When matching the images, the CBCT image is moved to fit the structures of the planning CT image. Because the CBCT images provide soft tissue information, the images can be registered without the use of gold markers as surrogate. Another advantage of this match technique compared to the other two is that it is able to correct more accurately for rotation of organs. However, the 3D-3D match application (gantry rotation, reconstruction of the 3D image, registration and couch shift) is time consuming and may add up to 10 minutes to the treatment time which may result in intra-fractional motion of the organs.

1.3 PROSTATE CANCER TREATMENT TECHNIQUES AT THE KAROLINSKA UNIVERSITY HOSPITAL

The most common treatment for prostate cancer patients at the Karolinska University Hospital (~250 patients per year) is a combination of conventional external 4-field radiotherapy and high dose-rate Brachytherapy. The external radiotherapy consists of 25 fractions at 2 Gy and is given to the prostate and SV, while Brachytherapy treatment is divided into 2 fractions at 10 Gy and is only given to the prostate. Usually the patient receives external radiotherapy treatment the first 2.5 weeks followed by the first Brachytherapy treatment fraction. After a rest of 2 weeks the second Brachytherapy treatment fraction is delivered followed by 2.5 weeks of external radiotherapy. Another treatment method, used on patients having a prostate being too large to provide Brachytherapy or having tumor engagement in the SV, is the so-called dose escalated treatment (~60 patients per year). External radiotherapy is given to the prostate and SV over
39 fractions at 2 Gy. The dose escalated treatment is performed with a 5-field IMRT technique. IMRT requires accurate localization of the prostate before treatment and therefore all IMRT patients are treated with IGRT. The third treatment method applied for prostate cancer patients is the low dose-rate (LDR) Brachytherapy treatment. With this method low-risk patients are treated with implanted Iodine or Palladium seeds. The activity decays within 3 months and the biological effective dose (BED) given to the prostate is approximately 70-72 Gy.

To localize the prostate on the radiographs, gold markers are implanted to patients treated with IGRT. The PTV margins used for patients with implanted gold markers are 0.5 cm in all directions except for the SV, where a safety margin of 1 cm is applied. This is because the SV are very movable organs. For patients without gold markers implanted, i.e. patients treated with the combination of extern radiotherapy and Brachytherapy, a margin of 1.5 cm is used in all directions except in the posterior, where the margin is reduced to 1 cm.
2 MATERIAL AND METHODS

2.1 COMPARISON OF 3D-3D AND 2D-2D MATCH APPLICATIONS

The position of the prostate may vary due to changes in rectal and bladder filling and it is of importance to localize the target before or during each treatment fraction (Balter et al. 1995). At the Karolinska University Hospital some specific prostate cancer patients are treated with IGRT, i.e. kV images are acquired with the OBI in the treatment room and matched with the reference images. To visualize the prostate on the kV images, three gold markers are implanted in the prostate under trans-rectal ultrasound control. The patients are treated in the supine position with the legs fixed in an individually fabricated vacuum cushion. The patients are first positioned by aligning the tattooed marks on the skin with the laser beams. Then the 2D-2D matching program is applied, where the gold markers are aligned manually and the couch is moved, whereas the couch rotation coordinate is usually not applied.

In this study the clinically used 3D-3D and 2D-2D match applications were compared. Ten prostate cancer patients treated with IGRT were involved in the comparison. The therapist performed a manual 2D-2D matching, i.e. the orthogonal images acquired in the treatment room were registered with the DRRs according to the gold markers, and the couch was moved in lateral, vertical and longitudinal directions. Additionally, a CBCT image was taken at this adjusted patient position and a 3D-3D matching based on the implanted gold markers was performed. The coordinate output of the matching is therefore equivalent to the difference between the 2D-2D and 3D-3D match applications. The number of CBCT images taken per patient at different treatment fractions varied from 3-5. For each patient, in each direction it was tested whether the measured values showed a statistically significant systematic deviation. First a rough method called the Sign test was applied on all matching method difference data for each direction. The test showed statistically significant deviations. Therefore the more refined Wald test was performed to test whether the deviations were similar for different patients on whom measurements had been made. A detailed description of the tests can be found in the appendix A1.
2.2 DOSIMETRIC COMPARISON OF CBCT AND CT IMAGES

When introducing modern ART methods based on CBCT techniques, the possibility of exact dose calculations on CBCT images is crucial. The dose calculations are based on the electron density information contained in the CBCT images, which is in the form of Hounsfield Units (HU). Accurate dose calculation requires an accurate HU-to-electron-density relation on the CBCT images. To cover the pelvic region, there is a need of a large FOV and the half-fan geometry has to be implemented. Unfortunately, the use of half-fan geometry results in a large amount of scattered radiation with complicated scatter profiles. The scattered radiation, which also reaches the detector, cannot be distinguished from the primary radiation. This results in a misleading relationship between HU and electron density and the dose calculations cannot be accurately performed. Different methods have been investigated to reduce the scatter effects in CBCT imaging. One method is to apply corrections on the raw data by separating the scattered from the primary radiation. Scatter can be predicted by using for example Monte Carlo simulation (Jarry et al. 2006), empirical models (Spies et al. 2001) or scatter measurement approaches (Ning et al. 2004, Siewerdsen et al. 2006). Depuydt et al. (article in press) compared two post-reconstruction HU correction methods. Both methods showed to be effective to improve HU correlation between CBCT and CT.

In this work, the dose calculations based on CBCT images have been achieved using the HU/electron density curve calibrated for conventional CT images. Therefore, an investigation of possible dosimetric deviations between CBCT- and CT-plans is of importance. To simulate dose calculations of prostate cancer patients, a so called Alderson phantom (ATOM® Phantom, CIRS Tissue Simulation and Phantom Technology, Norfolk, VI, USA, www.cirsinc.com) was used for measurements (figure 2). The phantom is constructed to simulate a human body and is divided into several slices. It consists of a bone and a uniform soft tissue equivalent material. For our measurements only the pelvic region of the phantom was used. The phantom was first placed on the treatment couch. The couch was then moved according to the delineation of three radio opaque markers placed on the phantom and the lasers. The scanning was first performed with the conventional CT and then with the CBCT. The CBCT images were acquired in the half-fan mode. Then they were imported to the Eclipse treatment planning system (TPS) (Varian Medical Systems, Inc., Palo Alto, CA, USA) for dose calculations. Prior to dose calculations, the fictitious organs prostate and SV, bladder and rectum had to be drawn into the images. This was performed by manually
drawing the contours on the 2D slices. Since the CBCT scan consists of fewer slices than the
CT scan because of the longitudinal scan range of ~14 cm, the organs were first drawn into
the CBCT image, to make sure they were all properly included into the 3D image. Then they
were copied to the matched CT image. An optimization was performed on a standard IMRT
plan with included organ constrains for prostate cancer patients and the dose distribution was
calculated on the CBCT image. The optimized plan was then transferred to the CT image and
again a dose calculation was performed. The cumulative DVHs of the prostate and SV, bladder and rectum were obtained in the TPS. For comparison, DVHs of corresponding organs from the CBCT and CT images were plotted together.

2.3 CBCT STUDIES ON ONE PROSTATE CANCER PATIENT

The following studies involve one prostate cancer patient treated with the dose escalated
IMRT technique described in chapter 1.3. The patient did not receive any instructions of
emptying or filling the bladder or rectum before each treatment fraction. Manual 2D-2D gold
marker matching was performed and the couch was moved to the correct position without
applying couch rotation. At 6 different treatment fractions, within a time period of 16 days, a
CBCT image of the pelvic region was acquired immediately after the couch had been moved.
Later in Eclipse TPS the prostate and SV and the organs at risk, i.e. the bladder and the
rectum on all CBCT images were contoured manually by an oncologist. The entire bladder
and prostate and SV volumes were contoured. On all the images the rectum was contoured
from the rectosigmoid junction. The rectum was contoured to the second lowest slice since
the small anatomical structures were difficult to distinguish. Since the longitudinal scan
range of the conventional CT is larger than that of the CBCT, the corresponding anatomical
structure of the rectum was used as a caudal limit. In clinical routine at the Karolinska
University Hospital the rectum is usually contoured from the level of the upper limit of the
PTV to the level of the lower limit of the PTV. However, since also normal tissue
complication probability (NTCP) calculations were included in this work, the use of
anatomical boundaries of the rectum seemed to be more adequate. Further, the whole bladder
and rectum volumes were contoured and not just the bladder and rectum wall. Cheung et al.
(2007) found the shape of the dose volume histogram (DVH) and the dose wall histogram
(DWH) of the bladder being very similar and suggested that the whole-bladder DVH may be
simpler and better to use in clinical treatment planning than the bladder-wall DWH.
Concerning the rectum, it may be difficult to contour the rectal wall and in this study the DVH of the rectum including filling is investigated. However, the most correct way would be to analyze the DWH of the rectal wall.

2.3.1 Dose verification and quantification

The following study is using the opportunity of CBCT dose calculations based on electron density information to investigate the accuracy of the clinically used IGRT technique.

To verify the dose given at one treatment fraction, the real dose given to the target and the OAR should be reconstructed on the corresponding CBCT image and compared with the planned dose distribution on the CT image. This was performed by transferring the original IMRT plan from the approved dose plan to the 6 CBCT images and recalculating the dose distribution. In this work this process is called recalculation. Based on the recalculated dose distributions, the cumulative DVHs of the target and the OAR of the different fractions were plotted and compared. To visualize the inter-fractional deformation of the target, the structure of the prostate and SV of the reference CT and CBCT have been superimposed on the reference CT. To eliminate patient set-up errors, this was performed after matching the gold markers on the CBCT image with the corresponding ones on the CT image. Since rectum is one of the most critical organs for prostate cancer patients, this structure was also superimposed.

2.3.2 Normal tissue complication probability (NTCP) calculations

With modern radiation treatment techniques like 3D conformal radiotherapy and IMRT, it is not always obvious how the critical organs will be affected. However, a significant correlation between dose-volume parameters derived from DVH and clinically observed toxicity has been detected in several studies (Boersma et al. 1998, Cozzarini et al. 2003, Cheung et al. 2007). Models to predict radiation induced toxicity are therefore of great importance. Two of the more widely used NTCP models are the ones referred to as Lyman (-Kutcher-Burman) (LKB) (Lyman 1985) and the relative seriality (RS) model proposed by Källman et al. (Källman et al. 1992).
The LKB model describes the complication probabilities of uniformly irradiated parts of critical organs. The equations used are the following:

\[ NTCP(D, \nu) = (2\pi)^{-\frac{1}{2}} \int_{-\infty}^{t} \exp\left(-\frac{x^2}{2}\right) dx \]  

(1)

where

\[ t = \left(1 - \frac{D - TD_{50}(\nu)}{m \cdot TD_{50}(\nu)}\right)^2 \]  

(2)

and

\[ TD_{50}(\nu) = TD_{50}(1) \cdot \nu^{-n} \]  

(3)

The parameters used are:
- \( \nu \), the fraction of the organ irradiated uniformly;
- \( D \), the dose uniformly irradiated to the volume \( \nu \)
- \( TD_{50}(\nu) \), the dose which uniformly delivered over the volume \( \nu \) would cause a complication probability of 50%;
- \( TD_{50}(1) \), the dose which uniformly delivered over the whole organ would cause a complication probability of 50%;
- \( m \), a parameter representing the steepness of the dose-response curve;
- \( n \), the exponent of volume in the power law that relates the tolerance doses for uniform whole and uniform partial organ irradiation.

To incorporate the situation of a nonuniform irradiation of the critical organ, Kutcher and Burman (1989) gave a reduction scheme to reduce the DVH to an effective fractional volume uniformly irradiated to the maximum dose in the DVH with:

\[ \nu_{eff} = \sum_{i=1}^{k} \nu_i \left(\frac{D_i}{D_{max}}\right)^{1/n} \]  

(4)

and:
- \( k \), the number of bins in the differential DVH;
- \( \nu_i \), a subvolume in the DVH;
- \( D_i \), the bin dose;
- $D_{\text{max}}$, the maximum dose in the DVH.

With this reduction scheme, $D$ is replaced by $D_{\text{max}}$ and $\nu$ is replaced by $\nu_{\text{eff}}$ in the equations (1)-(3).

An organ can be divided into functional subunits (FSUs), which are arranged in series, in parallel or in a combination of series and parallel. When one FSU is damaged in a serial organ, the entire chain of FSUs is broken which results in a complication. The so called volume effect for these serial organs is small. For a parallel organ a significant fraction of the FSUs has to be damaged before any complications appear and the volume effect is large. The parameter $n$ represents the volume effect. When $n$ is near unity, the volume effect is large and the organ has a parallel architecture, when $n$ is near zero, the volume effect is small and the organ has a serial architecture.

$m, n$ and $TD_{50}$ are population-based parameters and have been reported by Burman et al. (1991) for different organs and end-points.

The RS model takes explicit account of the structure or architecture of an organ. The model describes the response of the whole organ to an arbitrary dose distribution $\{D_i, \Delta\nu_i\}$:

$$NTCP = \left[ 1 - \prod_{i=1}^{k} \left( 1 - NTCP(D_i) \right)^{\nu_i} \right]^{\frac{1}{\nu}}$$

(5)

as a function of the response of the whole organ to a homogeneous dose distribution:

$$NTCP(D_i) = 2^{-\exp\left( \frac{\gamma}{\nu} \left( 1 - \frac{D_i}{D_{50}} \right) \right)}$$

(6)

The parameters in this model are:
- $\gamma$, the maximum relative slope of the dose-response curve;
- $D_{50}$, the dose which uniformly distributed over the whole organ would give a 50% risk of complication;
- $k$, the number of bins in the differential DVH;
- $D_i$, the bin dose;

- $\Delta V_i = \frac{V_i}{V}$ where $V_i$ is the volume of each subvolume in the DVH and $V$ is the volume of the organ;

- $s$, the relative seriality factor, i.e. it describes how serial (for serial organs $s = 1$) or how parallel (for parallel organs $s \to 0$) the organ acts in its volumetric response to irradiation.

The main critical organs for prostate cancer patients are rectum and bladder. In this study NTCP calculations based on the differential reference CT DVH and the 6 differential fractional CBCT DVHs were performed for both rectum and bladder. The CBCT DVHs were normalized to 78 Gy under the assumption that the size of the patient was stable during the course of treatment. Then NTCP calculations were performed for every single CBCT DVH and for the reference CT DVH. The program BIOPLAN (BIOlogical evaluation of PLANs) developed by Sanchez-Nieto and Nahum (2000) was applied for the calculations.

The parameters used in this study for the endpoint late rectal bleeding of grade $\geq 2$ were the ones calculated by Rancati et al. (2004). Rancati et al. distinguished between late rectal bleeding of grade 1 and grade 2 by using a modified RTOG (Radiotherapy Oncology Group, USA) protocol, which is listed in table A3 in the appendix A2. Rancati et al. used DVH data from the whole rectum, regarded as a solid organ. Patients with rectal bleeding of grade $\geq 2$ were considered as bleeders, while the others were considered as non-bleeders. Late complications were defined as those developing more than 3 months after the completion of the therapy, or those starting prior to and remaining for longer than 3 months after the completion of therapy. In the present study additional NTCP calculations with grade 3 rectal bleeding used as an endpoint were performed. The parameters used to investigate the probability of severe rectal bleeding were calculated by Rancati et al. (2004).

To calculate the probability of developing late urinary toxicity in this study, the estimated parameter values for the LKB model of Cheung et al. (2007) were used. The endpoint used was late genitourinary toxicity of grade $\geq 1$. Cheung et al. defined late complications as those developing more than 3 months after the completion of the therapy. The grading system used for late genitourinary radiation side effects is tabulated in the appendix A2 (table A4).
2.3.3 Reoptimization of the dose plan

An accurate way of performing radiation therapy treatment would be to reoptimize the dose plan before each treatment session, based on the daily CBCT scan. This on-line ART technique would assure the most optimal doses to be delivered to the patient. The technique though is still too time consuming allowing for intra-factional motion and the image quality of the CBCT still too poor. In this study a retrospective reoptimization process was performed to compare the on-line ART technique with the IGRT technique. The IMRT plan of one selected CBCT image was reoptimized in Eclipse and the dose distribution was calculated. The same margin, i.e. 0.5 cm in all directions, was applied as for the reference target. For IMRT optimizations the dose guidelines recommended by RTOG are used as an upper limit. The cumulative DVHs of the prostate and SV and rectum and bladder based on the reoptimized dose plan were then plotted and compared with the corresponding cumulative DVHs based on the recalculated dose distributions and the reference DVHs.
3 RESULTS AND DISCUSSION

3.1 COMPARISON OF 3D-3D AND 2D-2D MATCH APPLICATIONS

Figure 3 shows a plot of the estimated mean values $m_p$ of the measured deviations between the 3D-3D and 2D-2D match application in lateral, vertical and longitudinal directions of ten patients together with the estimates of their standard deviations. In the table the mean $m_{overall}$ of all measured deviations, and the estimate of the standard deviation $S$ based on all patient measurements are listed. The definition of the quantities is in the appendix A1.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Long [cm]</th>
<th>Lat [cm]</th>
<th>Vert [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$m_{overall}$</td>
<td>-0.02</td>
<td>-0.12</td>
</tr>
<tr>
<td></td>
<td>$S$</td>
<td>0.12</td>
<td>0.13</td>
</tr>
</tbody>
</table>

**Figure 3:** Mean values plus/minus one standard deviation of measured deviations between 3D-3D (CT-CBCT) and 2D-2D (kV-kV) match in a given direction for ten patients with 3-5 measurements per patient. The table parameters have been zeroed based on 2D-2D gold markers registration.

$m_{overall}$ shows a small negative value in the lateral direction and agrees well with the miscalibration noticed on the quality assurance (QA) of the OBI during the last months (Djordjevic 2007). With the more rough statistical test the Sign test, the hypothesis of no systematic deviation between the 3D-3D and 2D-2D match application could be rejected at significance level less than 0.01, i.e. the probability that the hypothesis was falsely rejected is less than 0.01 in two directions. The result showed a significant systematic deviation in the
negative direction for the lateral direction and a significant systematic deviation in the positive direction for the longitudinal direction. However, in the vertical direction there is a risk of about 18% to falsely reject the same hypothesis. Since two directions showed systematic deviations, an additional more refined test was performed, the Wald test. With this test the hypothesis that the mean values for the measurements on the different patients are the same was rejected at significance level 0.01 for all three directions. Hence, the hypothesis that the systematic deviations are similar for all patients could not be accepted.

3.2 DOSIMETRIC COMPARISON OF CBCT AND CT IMAGES

Figure 4 shows a comparison between the differential CBCT and CT DVHs of the fictitious prostate and SV while figures 5, 6 and 7 show the cumulative CBCT and CT DVHs of the fictitious prostate and SV, rectum and bladder from an Alderson phantom. The peak of the CBCT DVH in figure 4 is shifted by 2.2% to higher doses. The shift of the CBCT DVH is also visible in figure 5 with a mean dose increase to the prostate and SV by 2.5% (table 1). Depuydt et al. (article in press) who compared two correction methods of HU in CBCT images also observed this shift to higher doses for their prostate cancer patient. They primarily related the dose deviation to differences in HU between the CT and CBCT image. Yoo et al. (2006) investigated the dosimetric feasibility of CBCT-based treatment planning. Their half-fan CBCT DVHs of a lung tumor of an inhomogeneous phantom showed a dose-increase of about 3% for the entire volume of the tumor.

HU measurements performed on the CBCT and CT image of the Alderson phantom showed that the HU for bone equivalent material was about 100-250 HU lower in the CBCT image compared to the CT image. On an average the HU values in the target region were also lower in the CBCT images than in the CT image, but not as much lower as in the bone equivalent structures. The lowering of the HU for bone in the CBCT image is primarily the reason for the prostate and SV receiving higher doses in the CBCT than in the CT image as observed in figures 4 and 5. The prostate is surrounded by bony structure and the radiation will be attenuated by the bones before it reaches the prostate. Since the HU for bone equivalent material are lower in the CBCT than in the CT image, it will seem like the electron density in bone is lower in CBCT images. Therefore, the attenuation of the planned treatment beams will be lower in CBCT images and the dose to the prostate and SV will be higher.
**Figure 4:** Absolute differential DVHs of prostate and SV from an Alderson phantom based on CT image (red line) and CBCT image (blue line).

**Figure 5:** Relative cumulative DVHs of prostate and SV from an Alderson phantom based on CT image (red line) and CBCT image (blue line).
Djordjevic (2007) performed HU uniformity and linearity measurements of the CBCT scanner used in this work for half- and full-fan mode and compared with the conventional CT. For the half-fan mode he also observed a lowering of the CBCT HU compared to the CT HU for bone and soft tissue equivalent material. However, a head sized phantom was used in his comparison.

In figure 6 the curves of the rectum agree very well except at the high dose region, where again a slightly shift of the CBCT DVH to higher doses is visible. An increase of 2.3% of the maximum dose to the rectum was measured (table 1). The high dose region of the rectum is located at the rectum-prostate interface, where the same effect as for the prostate and SV described above may cause this dose increase.

Figure 7 shows the DVHs of the bladder. The largest dose deviations are visible for lower doses. Here the CBCT DVH is shifted to the left to lower doses. At doses of about 40 Gy the CBCT DVH crosses the CT DVH and is shifted to higher doses. The high dose region of the bladder is located at the bladder-prostate interface and again the lowering of the CBCT HU in bone is most probably the reason for the CBCT DVH shift to higher doses.

![Figure 6: Relative cumulative DVHs of rectum from an Alderson phantom based on CT image (red line) and CBCT image (blue line).](image-url)
Figure 7: Relative cumulative DVHs of bladder from an Alderson phantom based on CT image (red line) and CBCT image (blue line).

Table 1: Relative dose deviations compared to mean prostate dose and maximum rectal and bladder dose on the CT image.

<table>
<thead>
<tr>
<th></th>
<th>$\Delta D_{\text{mean,prostate}}$ [%]</th>
<th>$\Delta D_{\text{max,rectum}}$ [%]</th>
<th>$\Delta D_{\text{max,bladder}}$ [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+2.5</td>
<td>+2.3</td>
<td>+1.6</td>
</tr>
</tbody>
</table>

Yang et al. (2007) evaluated the use of CBCT for dose calculations. They used a CIRS pelvic IMRT phantom to validate the CBCT-based dose calculation. A hypothetical target and sensitive structure at the centre of the phantom were created. The calculated dose of the CT image agreed with the dose of the CBCT image within 1.0%.

3.3 CBCT STUDIES ON ONE PROSTATE CANCER PATIENT

3.3.1 Dose verification and quantification

In figure 8 a) the cumulative relative CBCT DVHs of the prostate and SV from 6 treatment sessions are plotted together with the CT DVH of the reference prostate and SV for one patient. Figure 8 b) represents the high dose region of the DVHs in figure 8 a). A systematic deviation is observed, where the CBCT DVHs are shifted to higher doses with a maximum
mean dose increase to the prostate and SV of 1% (table 2). Depuydt et al. (article in press) also observed these shifts to higher doses for the same patient. This is the same phenomenon as observed for the phantom in section 3.2. The relatively small deviations visible in figures 8 a) and b) are primarily due to the deviations in HU between the CT and the CBCT image.

In table 2 the relative volume and dose deviations of the prostate and SV are listed. Some differences in volume between the fractions are visible. However, in the study of Deurloo et al. (2005) there was no observation of variations of the volume that were significantly different from the intra-observer variations of the volume. Fiorino et al. (1998) studied the intra-observer variability in contouring prostate and seminal SV on CT images and found an average percentage variation of the volume of ~5%. The volume deviations found for our patient with a mean deviation of -7.8% most probably result from the difficulties in contouring due to the limited soft tissue visualization in the CBCT images.

Figure 8 a): Cumulative relative DVHs of prostate and SV at planning moment and at 6 treatment fractions for one patient.
Figure 8 b): High dose region of prostate and SV DVHs for one patient.

Table 2: Relative volume and mean dose deviations compared to computed on reference CT for prostate and SV.

<table>
<thead>
<tr>
<th>Fraction</th>
<th>ΔVol [%]</th>
<th>ΔD_{mean} [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-3.2</td>
<td>+0.5</td>
</tr>
<tr>
<td>2</td>
<td>-13.6</td>
<td>+0.9</td>
</tr>
<tr>
<td>3</td>
<td>+4.5</td>
<td>+0.5</td>
</tr>
<tr>
<td>4</td>
<td>-11.4</td>
<td>+1.0</td>
</tr>
<tr>
<td>5</td>
<td>-12.5</td>
<td>+0.8</td>
</tr>
<tr>
<td>6</td>
<td>-10.7</td>
<td>+1.0</td>
</tr>
</tbody>
</table>

Figure 9 shows a slice from the middle region of the 3D structure of the prostate and SV. Since the SV are located above the prostate, this middle slice represents the superimposed prostate contours of the 6 CBCT images and the reference CT image. Figure 10 shows one slice from the upper part of the prostate and SV structure and therefore represents more the contours of the SV. In figure 9 the shape of the contours are comparable, i.e. there is no significant deformation of the prostate. Only a small shape variation of the prostate was also found by Deurloo et al. (2005). Figure 10 however shows large deviations between the superimposed contours. Significant deformations of the SV are visible in the image. Since this is a known phenomenon, the PTV margins at the Karolinska University Hospital have been changed. The old safety margin of 0.5 cm to the SV was increased to 1 cm. For the patient in this study though, the old margin was still used.
Figure 9: Transversal view of prostate contours of the 6 CBCTs (red) and of the reference CT (blue) superimposed on the CT image after gold markers matching.

Figure 10: Transversal view of prostate and SV contours of the 6 CBCTs (red) and the reference CT (blue) superimposed on the CT image after gold markers matching.

Figure 11 shows the cumulative relative DVHs of the rectum. Table 3 lists the relative volume and relative maximum dose deviations of the rectum. Exceeding the prescribed maximum dose to the rectum may result in late rectal complications. All the DVHs except
the one of fraction 3 show lower values above doses of ~60% compared to the DVH of the reference rectum. This is most probably due to the decrease in rectal volume as represented in table 3.

**Table 3:** Relative volume and maximum dose deviations compared to computed on reference CT for rectum.

<table>
<thead>
<tr>
<th>Fraction 1</th>
<th>Fraction 2</th>
<th>Fraction 3</th>
<th>Fraction 4</th>
<th>Fraction 5</th>
<th>Fraction 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔVol [%]</td>
<td>-15.6</td>
<td>-0.4</td>
<td>-15.0</td>
<td>-25.0</td>
<td>-21.5</td>
</tr>
<tr>
<td>ΔD$_{\text{max}}$ [%]</td>
<td>+0.1</td>
<td>+0.5</td>
<td>+1.0</td>
<td>+0.2</td>
<td>+0.3</td>
</tr>
</tbody>
</table>

The DVH of fraction 3 though shows higher values above doses of ~60% and larger rectal volumes than planned receive doses over ~100%. This is because the rectum seems to be more compressed which results in a larger part of the rectum located in the target field. For this specific patient in the 6 treatment fractions with CBCT images, the rectal volume was smaller than at the planning moment. The dose to the rectum did not exceed the planned dose to the rectum significantly at these fractions and the maximum dose to the rectum was about the same compared to the planned maximum dose (table 3).

![Figure 11: Cumulative relative DVHs of rectum at planning moment and at 6 treatment fractions.](image)

The dose guidelines used for IMRT optimization and recommended by RTOG are listed in table 4. The DVH of fraction 3 exceeds one of the dose constraints and receives a slightly
higher dose than 75 Gy to 15% of the rectal volume. The remaining rectal DVHs do not exceed any of the dose constraints.

### Table 4: RTOG P0126 Dose Guidelines

<table>
<thead>
<tr>
<th>Volume [%]</th>
<th>Dose [Gy]</th>
<th>Dose [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>80</td>
<td>102.6</td>
</tr>
<tr>
<td>25</td>
<td>75</td>
<td>96.2</td>
</tr>
<tr>
<td>35</td>
<td>65</td>
<td>83.3</td>
</tr>
<tr>
<td>50</td>
<td>60</td>
<td>76.9</td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>75</td>
<td>96.2</td>
</tr>
<tr>
<td>25</td>
<td>70</td>
<td>89.7</td>
</tr>
<tr>
<td>35</td>
<td>65</td>
<td>83.3</td>
</tr>
<tr>
<td>50</td>
<td>60</td>
<td>76.9</td>
</tr>
<tr>
<td>Target</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>82</td>
<td>105.1</td>
</tr>
<tr>
<td>≥98</td>
<td>78</td>
<td>100</td>
</tr>
</tbody>
</table>

In figures 12 and 13, the movement and the deformation of the rectum relatively to the implanted gold markers in the reference prostate is visible. The structures showed in figure 13 are comparable and the movement of the rectum is small. The largest inter-fractional deviations appear in the upper part of the rectum, where the difference in rectal filling results in rectal shape and volume variations (figure 13 a).

**Figure 12:** Sagittal view of the rectal structure of the 6 CBCTs (red) and the reference CT (blue) superimposed on the CT image after gold markers matching.
In this patient case no large rectal distentions were visible and the volumes receiving high doses were comparable with the planned high dose volumes or even smaller. However, for other patients the rectal volume may vary significantly. Kupelian et al. (2006) studied the variations in delivered doses to the prostate, rectum and bladder during a full course of image guided radiotherapy based on intraprostatic fiducials. They found significant daily variation in rectal and bladder doses, mostly because of variations in volume and shape of these organs. Based on recalculations performed on daily MVCT imaging they analyzed the delivered doses to the prostate, rectum and bladder for 10 patients for the entire course of treatment. Figure 14 shows the rectal DVHs for an entire course of treatment of one of the patients. Large variations of daily delivered doses are visible. The two most extreme cases are pointed out with black arrows and a transversal view of the corresponding MVCT is showed. The two MVCT images very clearly illustrate the large difference in rectal distention. Deflation of the rectum results in lower doses to the rectum (lower MVCT image), as was the case for our patient and distention of the rectum results in higher doses as planned to the rectum (upper MVCT image).

Figure 13: Transversal view of superimposed rectal structure (red: CBCT images, blue: reference CT image) with a) upper, b) central and c) lower part of the rectum.
Figure 14: Kupelian et al. 2006.

Figure 15 illustrates the cumulative relative DVHs of the bladder. Half of the DVHs are shifted to lower doses and half of them to higher doses. The DVHs of fraction 1 and 2 show the largest deviations compared to the DVH of the reference bladder. Table 5 shows large variations of the bladder volume with the largest inter-fractional variation between fraction 1 and 2. The decrease of the bladder volume in fraction 1 is large and the relative bladder volumes receive higher doses than planned. At the time of fraction 2 though, the increase in bladder volume is large and the doses given to the relative bladder volumes are much lower than planned.

Table 5: Relative volume and dose deviations compared to volume and maximum dose computed on reference CT for bladder.

<table>
<thead>
<tr>
<th>Fraction</th>
<th>ΔVol [%]</th>
<th>ΔD_{max} [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-31.4</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>+155.7</td>
<td>-0.3</td>
</tr>
<tr>
<td>3</td>
<td>-33.7</td>
<td>-0.3</td>
</tr>
<tr>
<td>4</td>
<td>+20.4</td>
<td>+0.3</td>
</tr>
<tr>
<td>5</td>
<td>+33.2</td>
<td>+0.5</td>
</tr>
<tr>
<td>6</td>
<td>-8.2</td>
<td>+0.5</td>
</tr>
</tbody>
</table>
Figure 16 shows a transversal view of the CBCT image from fraction 1 (left image) and fraction 2 (right image). The images illustrate the volume of the bladder (light blue color) overlapping the target volume (dark blue color). Since the bladder volume in fraction 1 is much smaller than in fraction 2, the relative bladder volume overlapping the target volume is much larger, which obviously results in larger doses to the relative bladder volumes. In fraction 2, where the bladder volume is very large, the relative volume overlapping the target volume is small and therefore the received doses to the bladder low. The DVH of fraction 3 shows lower doses than the DVH of fraction 1 although the volume of the bladder is slightly smaller in fraction 3. This demonstrates that not only the volume of the bladder decides the dose to the bladder but also the location of the bladder relative to the prostate and SV.

Figure 15: Cumulative relative DVHs of bladder at planning moment and at 6 treatment fractions.
The RTOG P0126 bladder dose-volume constraints in table 4 shows that the DVHs of fraction 1 and 6 exceed two of the restrictions and 25% respectively 35% of the bladder volume receive a higher dose than the prescribed 75 Gy respectively 65 Gy. Further, they lie very close to the remaining two constraints. The remaining DVHs are all within the recommended dose constraints.

3.3.2 Normal tissue complication probability (NTCP) calculations

The parameters used in the program BIOPLAN for late rectal bleeding of grade ≥2 and grade 3 are given in table 6. Rancati et al. (2004) calculated for the LKB model the volume parameter $n = 0.23$. When considering severe injury (grade 3) though, the rectum seems to have a more serial architecture ($n = 0.06$). Rancati et al. thought that probably the irradiation of relatively large volumes of the rectum at intermediate doses (40-60 Gy) may play some role in the formation of moderate bleeding, maybe due to a transient reduction of the repair capacity. However, when a small volume is irradiated at high doses (> 70 or 75 Gy), no severe bleeding is occurring due to a preserved repair capacity. When escalating the dose and a significant volume of the rectum is irradiated at high doses, the probability of severe bleeding increases. The volume receiving intermediate doses is therefore important for the probability of developing grade 2 bleeding. Limiting the volume receiving high doses (> 70 Gy) should decrease the risk of grade 3 bleeding.
Table 6: Estimated parameter values for the LKB and the RS model for late rectal bleeding of grade $\geq 2$ and grade 3 (Rancati et al. 2004).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Grade $\geq 2$</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LKB</td>
<td>RS</td>
</tr>
<tr>
<td>$D_{50}$ [Gy]</td>
<td>81.9</td>
<td>83.1</td>
</tr>
<tr>
<td>$m, \gamma$</td>
<td>$m = 0.19$</td>
<td>$\gamma = 1.69$</td>
</tr>
<tr>
<td>$n, s$</td>
<td>$n = 0.23$</td>
<td>$s = 0.49$</td>
</tr>
</tbody>
</table>

In table 7 the calculated NTCP values for developing grade $\geq 2$ and grade 3 bleeding are presented. The values of the RS model seem generally lower than the LKB values. For all fractions and for the reference rectum the probability of developing grade $\geq 2$ late rectal bleeding is low with a slightly higher probability for the reference rectum respectively the rectum in fraction 3 with NTCP values for the LKB model of 10.1% respectively 10.4% (table 7). When looking at the DVHs for the rectum in figure 11, section 3.3.1, one can see that the volumes receiving intermediate doses are the largest for reference rectum and fraction 3. This is consistent with the conclusions of Rancati et al. mentioned above. When comparing the values for developing grade $\geq 2$ bleeding with developing grade 3 bleeding for both models, the values for the latter are smaller except for the reference rectum and rectum in fraction 3. The DVHs for reference rectum and fraction 3 show significant larger volumes receiving high doses compared with the remaining DVHs.

Table 7: Calculated NTCP values for the reference rectum and for the rectum at 6 treatment fractions using the LKB and the RS model with the endpoint late rectal bleeding of grade $\geq 2$ and grade 3.

<table>
<thead>
<tr>
<th>3D-image</th>
<th>Grade $\geq 2$</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LKB [%]</td>
<td>RS [%]</td>
</tr>
<tr>
<td>Reference rectum</td>
<td>10.1</td>
<td>8.7</td>
</tr>
<tr>
<td>Fraction 1</td>
<td>7.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Fraction 2</td>
<td>6.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Fraction 3</td>
<td>10.4</td>
<td>9.1</td>
</tr>
<tr>
<td>Fraction 4</td>
<td>7.0</td>
<td>4.6</td>
</tr>
<tr>
<td>Fraction 5</td>
<td>7.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Fraction 6</td>
<td>7.4</td>
<td>5.9</td>
</tr>
</tbody>
</table>
The estimated parameters found by Cheung et al. (2007) and used for the LKB model with endpoint grade 1 or greater late genitourinary toxicity are given in table 8. The parameter $n$ is very close to zero, which indicates that the volume effect is small and the maximal doses (hotspots) to the bladder are crucial for the toxicity outcome. In table 9 the results of the NTCP calculations are shown. In all cases the risk of developing grade 1 or greater late genitourinary toxicity is exceeding 90%. Figure 17 shows the dose distribution and the organs of interest of one transversal CT slice. The PTV (prostate and SV plus margin) overlaps the bladder, which results in hotspots to the bladder and high risk of late toxicity. Figures 18 a) and b) show the bladder enclosing the top of the prostate and SV.

**Table 8**: Estimated parameter values for the LKB model for late genitourinary toxicity (grade $\geq 1$) (Cheung et al. 2007).

<table>
<thead>
<tr>
<th>Model</th>
<th>$D_{50}$ [Gy]</th>
<th>$m$</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>LKB</td>
<td>77.6</td>
<td>0.022</td>
<td>0.00995</td>
</tr>
</tbody>
</table>

**Table 9**: Calculated NTCP values for the reference bladder and for the bladder at 6 treatment fractions using the LKB model with the endpoint late genitourinary toxicity (grade $\geq 1$).

<table>
<thead>
<tr>
<th>3D-image</th>
<th>NTCP LKB [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference bladder</td>
<td>94.4</td>
</tr>
<tr>
<td>Fraction 1</td>
<td>97.2</td>
</tr>
<tr>
<td>Fraction 2</td>
<td>92.6</td>
</tr>
<tr>
<td>Fraction 3</td>
<td>94.4</td>
</tr>
<tr>
<td>Fraction 4</td>
<td>97.4</td>
</tr>
<tr>
<td>Fraction 5</td>
<td>96.8</td>
</tr>
<tr>
<td>Fraction 6</td>
<td>98.8</td>
</tr>
</tbody>
</table>
Figure 17: Dose distribution of a transversal slice of the reference CT with bladder (blue structure), PTV (green structure) and rectum (brown structure).

Figure 18 a): 3D view of bladder (blue structure), PTV (green structure) and rectum (brown structure) on reference CT.
At the Karolinska University Hospital more cases of late bladder complications have been reported than of late rectal complications. The long time follow-up of the patients after finished treatment course is crucial for late toxicity evaluations of the OAR and for potential adjustments of the dose constraints. However, few investigations on bladder NTCP have been performed until today and the accuracy of the parameters used for the NTCP calculations of the bladder is questionable.

3.3.3 Reoptimization of the dose plan

The bladder DVH in fraction 1 (see figure 15, section 3.3.1) largely exceeds the dose-volume constraints (see table 4). For this case a reoptimization was performed. Figures 19 a) and b), 20 and 21 show the reoptimized, recalculated and the reference CT DVH of the contoured organs. To make the small dose-volume deviations in the high dose region of the prostate and SV in figure 19 a) visible, figure 19 b) shows the dose between 90% and 115% on the x-axis. In table 10 some relevant relative volume and dose values of the prostate and SV DVHs are listed. The maximum dose to the prostate and SV (dose to 0% of the volume) is about 109% in all three cases. However, the upper limit of the dose to 100% of the volume, i.e. the dose just before the beginning of the slope of the DVH, shows variations. The planned dose to this
volume is 101.2%. The actual dose however (the dose after recalculation of the plan) given to
100% of the volume at this fraction is reduced to 94.4%. After reoptimization of the plan
102.3% can be reached, which means that the dose to the prostate and SV can be slightly
improved after reoptimization. The mean doses to the prostate and SV after reoptimization
and recalculation listed in table 11 are in good agreement with the planned mean dose.

**Table 10:** Relative doses to 0 resp. 100% of the prostate and SV volume.

<table>
<thead>
<tr>
<th>Volume [%]</th>
<th>Dose [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference CT DVH</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Recalculated DVH</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Reoptimized DVH</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 11:** Relative dose deviations to the prostate and SV, rectum and bladder compared to the relative dose to the reference prostate and SV, rectum and bladder.

<table>
<thead>
<tr>
<th>Organ</th>
<th>After reoptimization</th>
<th>After recalculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate+ves</td>
<td>$\Delta D_{\text{mean}} = +1.2 %$</td>
<td>$\Delta D_{\text{mean}} = +0.6 %$</td>
</tr>
<tr>
<td>Rectum</td>
<td>$\Delta D_{\text{max}} = +0.8 %$</td>
<td>$\Delta D_{\text{max}} = +0.1 %$</td>
</tr>
<tr>
<td>Bladder</td>
<td>$\Delta D_{\text{max}} = -1.6 %$</td>
<td>$\Delta D_{\text{max}} = 0.0 %$</td>
</tr>
</tbody>
</table>
Figure 19 a): Relative cumulative DVHs of prostate and SV for fraction 1 with reoptimized dose plan (red line) and recalculated dose distribution (green line). Blue line represents the reference CT DVH.

Figure 19 b): High dose region of the DVHs in figure 19 a).
For this special treatment fraction for this single patient, the delivered dose to the prostate and SV can possibly be slightly improved after reoptimization but there is no large benefit of reoptimizing the treatment plan to improve the accuracy of dose delivery to the target.

In figure 20 both the rectal DVHs after recalculation and after reoptimization are shifted to lower doses in the high dose region compared to the reference DVH. The dose to the rectum can also be reduced in the low dose region after reoptimization. The dose maxima remain about the same as the planned dose maximum, table 11. Since in this study the rectum showed to be quite stable during the period in which CBCT images were acquired, the effect of the reoptimization process on the rectal dose was small. However, the DVHs of Kupelian et al. (2006) (figure 14, section 3.3.1) illustrate a patient with large variability in daily delivered doses due to rectal distention. In this case reoptimization processes would result in essential dose sparing to the rectum which on the other hand would enable dose escalations to the tumor.

![Figure 20](image.png)

**Figure 20:** Relative cumulative DVHs of rectum for fraction 1 with reoptimized dose plan (red line) and recalculated dose distribution (green line). Blue line represents the reference CT DVH.
Figure 21 shows that the bladder DVH, after reoptimization of the plan (red DVH), is shifted to lower doses with a remarkable amount relative the actual DVH (green line). The dose maximum listed in table 11 can be reduced by 1.6% of the delivered dose maximum. Hence, for this patient a significant dose reduction to the bladder can be achieved by a reoptimization process.

Figure 21: Relative cumulative DVHs of bladder for fraction 1 with reoptimized dose plan (red line) and recalculated dose distribution (green line). Blue line represents the reference CT DVH.
4 IMPLEMENTATION OF ART FOR PROSTATE CANCER PATIENTS

The opportunity of acquiring 3D CBCT images at the Karolinska University Hospital offers great possibilities for future ART techniques. Some problems though still remain. In the phantom study, dose deviations between the CT and the CBCT images were observed due to differences in HU. For a patient the deviations may increase due to more photon scattering in different tissues. Therefore, to assure accurate dose calculations and reoptimization processes needed for ART, a suitable HU correction strategy should be found and a limited FOV should be used. Still, the most important remaining contribution to the ART process is developing a fast and fully automatic deformable image registration technique.

4.1 DEFORMABLE IMAGE REGISTRATION TECHNIQUES

Deformable image registration tries to match the corresponding structures properly by taking into account the deformation of the organs. It offers the opportunity both of calculating deformable dose accumulations and of automatic organ recontouring. Deformable dose accumulation shows the properly accumulated delivered dose to a deformable organ based on daily images. Automatic recontouring is an important contribution to the on-line reoptimization ART technique. Several techniques have been developed, but most of them can be categorized as either point-based or intensity-based. Point based techniques minimize the distance between points, curves or surfaces of corresponding anatomical structures. These techniques though require a certain amount of human interaction. Intensity-based methods use similarity measures such as the mutual information between images, but they usually require demanding computations. In 2004 Lu et al. (2004) developed a fast and fully automatic deformable image registration technique for same modality images based on free-form deformation. In 2006 the group of Lu reported their investigations on deformable image registration between the planning kVCT and the daily MVCT image sets (Lu et al. 2006b). They used the same free-form deformation method but an ‘edge-preserving smoothing’ was applied to the MVCT image prior to the deformable image registration process to reduce noise and contrast resolution differences between the kVCT and the MVCT. The deformable image registration method produces deformation maps, which are the voxel-to-voxel displacements between the reference image and the daily images. The deformable dose accumulation can then be calculated for each voxel. Lu et al. (2006a) also developed a
technique for automatic re-contouring that is based on the deformable image registration and surface construction. For prostate treatment though this method can show large errors for the rectum contours, since the rectal contents can vary between the planning image and the repeat images and the intensity values become inconsistent. Most of the deformable image registration methods assume that, if two images are being registered, every point of one image corresponds to a point in the other. In most cases however, this is not valid for pelvic images, since the amount of bowel gas present may vary between treatment fractions. Foskey et al. (2005) described a fully automatic intensity-based deformable image registration method, which permits large deformations and is able to eliminate bowel gas, so that accurate image registration of the rectum can be performed.

4.2 SUITABLE ART TECHNIQUE

From our patient CBCT studies we can establish that image guided IMRT has showed acceptable dose delivery to the target. When concerning the OAR though, inter-fractional dose variations may occur. The implementation of a dose plan modification technique according to inter-fractional OAR movements and deformations could improve the dose accuracy to these organs and lower the risk for late rectal and bladder toxicity.

In section 1.1 an overview of possible ART methods was given. However, the developed methods are based on different treatment techniques. Most of the described ART methods are not combined with IGRT, i.e. isocenter corrections, and the authors have developed an ART method not only to correct for inter-fractional organ motions and deformations but also for set-up errors. With IGRT though, the set-up errors and rigid tumor motion can be eliminated directly on-line by shifting the couch to the correct treatment position. Therefore, a combination of IGRT and a suitable ART technique could be an alternative treatment opportunity for specific prostate cancer patients at the Karolinska University Hospital.

Hoogeman et al. (2005) developed an off-line ART method which used an average prostate and rectum shape calculated from 3D-images of the first treatment days. The treatment plan could then be modified to adapt the dose distribution to the average structures. Since the bone structures of the repeat CT scans and the planning CT scan were matched, the deviations between the prostates on the different CT images were primarily due to organ motion. The deformation of the prostate and seminal SV was found to be small compared to
the organ motion and the prostate was treated as a rigid body. At the Karolinska University Hospital, the prostate motion can be eliminated by couch shift. Since the deformation of the prostate has showed to be small, an average prostate shape would not bring any essential benefits to the treatment. The rectum though is a deformable organ and its volume depends on rectal filling. The shape and size of the rectum at the time of planning CT may not be representative for the whole treatment course. An average rectum based on CBCT images acquired in the first treatment week could show to be more representative for the overall rectum shape. The dose plan could then be reoptimized based on the original prostate and SV and an average rectum. To evaluate this ART method, pelvic CBCT images acquired over the whole treatment course are required. Additionally a way of creating an average rectum must be found. Hoogeman et al. (2004) mapped the rectal structure in each repeat CT scan and the coordinates of corresponding points were averaged to obtain the average rectum shape. This may be a possible way of finding an average rectum, but would be very time consuming. With an accurate deformable image registration technique, the mapping of the rectal volumes can be performed faster, but still a way of calculating the average coordinates and plotting the corresponding structure must be developed. Deformable image registration is also needed for calculating accumulated doses to the organs. When having created an average rectum based on the CBCT images of the first treatment week, the reoptimization is performed. Based on the reoptimized plan the dose to the rectum on the CBCT images of the remaining weeks is accumulated, i.e. the accumulated dose to the rectum when applying the ART method is calculated. Additionally for each remaining CBCT image the fractional dose distribution is calculated based on the original plan and with a deformable image registration program the actual accumulated dose to the rectum during the remaining weeks can be determined. The accumulated dose of the rectum after reoptimization and the actual accumulated dose of the rectum are compared with the planned accumulated dose to the original rectum of the remaining weeks for example by comparing the DVHs. For this proposed ART method to being beneficial, the deviation of the rectal DVH after reoptimization and the original rectal DVH should be smaller than the deviation of the actual rectal DVH and the original rectal DVH. The off-line ART method should then be applied for those prostate cancer patients who show large inter-fractional rectal variations during the first week of treatment.

On-line reoptimization is probably the most accurate dose delivery method, but there is a long way to go before this on-line ART technique can be implemented as a clinical routine.
New faster 3D imaging equipments should be developed and installed and as mentioned before a fast fully automatic deformable image registration technique should be found.

Another possible method that would not require on-line reoptimization but recalculation of the dose would be the so called dose guided radiotherapy suggested by Kupelian et al. (2006). This method includes patient position shift not only based on the target position, but also on-line evaluation of rectum and bladder doses. The patient would be moved to different positions and dose recalculation would be performed for each position. The most optimal position considering prostate, bladder and rectum would then be applied. However, as for the other methods, a fast and accurate automatic method of contouring the organs at every fraction would be required for dose recalculations.
5 CONCLUSIONS

In the first part of this work the 2D-2D and the 3D-3D match applications were compared. The results showed statistically significant systematic deviations between the two methods in lateral and longitudinal direction when considering the measurements of all the patients without relating them to corresponding patients. However, when testing the hypothesis that there is a common systematic deviation for all patients, the measurement data lead to a rejection of this hypothesis. Hence, there seems to be a statistically significant observed difference between the two methods, which differs among the patients. However, the method includes the uncertainty in the applied couch correction.

In the second part of the thesis dose verifications, dose plan reoptimization and NTCP calculations and measurements on an Alderson phantom were performed. The phantom measurements showed small dose deviations between the CT and CBCT image, particularly towards the center of the image and at the location of small bladder doses. The dose deviations can primarily be related to disagreements between CT and CBCT HU. Applying a CBCT HU correction program would improve the HU accuracy of the CBCT images. Dose verification measurements on the prostate cancer patient showed doses to the prostate and SV treated as one organ being acceptable. The deformation of the prostate was small, while the deformation and movement of the SV relative the prostate were considerable larger. The accuracy of the dose to the SV alone should be further investigated by treating them as a separate organ. In this work rotation of the prostate and SV was not considered due to time aspects, but further investigations on this topic would be interesting. The rectum showed no significant deformations, volume changes or movements relatively to the prostate. However, CBCT images acquired over the whole treatment course would be required to become a more appropriate overview of the overall rectal changes. The largest inter-fractional variations in volume and shape were observed for the bladder which resulted in large dose deviations. It should be mentioned that the effect of intra-fractional organ motion on the delivered dose has not been investigated in this thesis, but would also be an interesting study. In the NTCP feasibility study, the NTCP calculations of rectum and bladder were restricted to 6 CBCT images and performed on every single CBCT DVH normalized to 78 Gy. More accurate NTCP calculations based on the actual accumulated DVH at the end of the treatment course would require CBCT images from all treatment fractions and accumulated doses based on deformable image registration. The first trial of a reoptimization process in this study showed
that for this patient at this specific treatment fraction, the dose to the bladder could be reduced while the dose to the target could be slightly improved after reoptimization. However, the question remains if the treatment benefits of an on-line reoptimization ART are worth the additional costs, treatment time, education and work for the employees.

All the results obtained in the patient CBCT study of the second part are based on the analysis of one single patient and not representative for a larger population. This work has therefore to be interpreted as a first approach to using volumetric images acquired with the OBI for dose verification and dose optimization. To draw reliable conclusions whether the image guided IMRT technique is being sufficient for accurate prostate cancer treatment or if a suitable ART method should be applied, more patient CBCT studies with daily CBCT images have to be performed.
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Lu W., Olivera G. H., Chen Q., et al. Deformable registration of the planning image (kVCT) and the daily images (MVCT) for adaptive radiation therapy. *Phys Med Biol* 2006;51:4357-4374.


APPENDIX

A1. STATISTICAL TESTS

The Sign test

First of all the probability of having a systematic deviation between the two matching methods should be tested with a rough method. In this study the so called Sign test has been used, which does not include any differentiation of the patients. This test appears in many text books on basic statistics, for example in Blom et al. (2005). With the Sign test for example the difference of two measurements is studied and replaced by + or – depending on whether the difference is > 0 or < 0.

In each of the directions there are \( N \) measurements \( X_1, \ldots, X_N \) in total, which already represent the deviation of the two matching methods. Let \( z \) be the number of measurements < 0. If the methods are equivalent, the number of + should be about the same as the number of -.

Let \( H_0 \) be the null hypothesis that the two methods are equivalent:
\[ H_0: P(X_i < 0) = P(X_i > 0) = \frac{1}{2} \]
If the null hypothesis \( H_0 \) is true, then \( z \) is an outcome of the random variable \( Z \) that is Bin\((N, 1/2)\) distributed.

For a two-sided test let \( H_1 \) be the following alternative hypothesis:
\[ H_1: P(X_i < 0) \neq P(X_i > 0). \]
If we suspect that the – will be in majority, then we may choose to make a one-sided test and let the alternative hypothesis \( H_1 \) be given by:
\[ H_1: P(X_i < 0) > P(X_i > 0). \]
If we suspect that the + will be in majority, then we may choose to make a one-sided test and let the alternative hypothesis \( H_1 \) be given by:
\[ H_1: P(X_i < 0) < P(X_i > 0). \]

Let us test \( H_0 \) against \( H_1 \) with the \( P \)-value method. The \( P \)-value is the probability under \( H_0 \) of observing a deviation from what is expected under \( H_0 \) that is larger or equal to our actual outcome.
For the two-sided test:
\[ P = P(Z \geq z) + P(Z \leq N - z) \] if \( z > N/2 \)
\[ P = P(Z \leq z) + P(Z \geq N - z) \] if \( z < N/2 \)

\[ P = 2 \cdot \sum_{i=z}^{N} \binom{N}{i} \left( \frac{1}{2} \right)^i \left( 1 - \frac{1}{2} \right)^{N-i} = 2 \cdot \sum_{i=z}^{N} \binom{N}{i} \left( \frac{1}{2} \right)^N. \]

For the one-sided test:
\[ P = P(Z \geq z) \] if \( z > N/2 \)
\[ P = P(Z \leq z) \] if \( z < N/2 \)

\[ P = \sum_{i=z}^{N} \binom{N}{i} \left( \frac{1}{2} \right)^i \left( 1 - \frac{1}{2} \right)^{N-i} = \sum_{i=z}^{N} \binom{N}{i} \left( \frac{1}{2} \right)^N. \]

If \( P < 0.05 \) then \( H_0 \) is rejected at significance level 0.05, i.e. there is a probability of less than 0.05 that we reject \( H_0 \) when \( H_0 \) is true. If \( P \) is small, a further analysis of the measurement data with a more sensitive test like the Wald test can be performed.

The measured values are \( N = 46 \) and \( z_{\text{vert}} = 18, z_{\text{lat}} = 32 \) and \( z_{\text{long}} = 11 \) with \( z = \# \) measurements < 0. Since for the lateral direction, the number of measurements < 0 is large, a one-sided test is performed. For the longitudinal direction \( z \) is small and a one-sided test for \( Z \) being the number of measurements > 0 is performed. For the lateral direction a two-sided test is executed.

Lateral direction:
\( Z = \# \) measurements < 0 and \( Z \sim \text{Bin}(46,1/2) \) under \( H_0 \). The \( P \)-value is \( P = P(Z \geq z_{\text{lat}}) = P(Z \geq 32) \approx 0.0057. \)

Longitudinal direction:
\( Z = \# \) measurements > 0 and \( Z \sim \text{Bin}(46,1/2) \) under \( H_0 \). The \( P \)-value is \( P = P(Z \geq n- z_{\text{long}} ) = P(Z \geq 46-11) = P(Z \geq 35) \approx 0.00027. \)

Vertical direction:
\( P = P(Z \leq 18) + P(Z \geq 46-18) = 2 P(Z \geq 28) \approx 0.182 \)
In both the lateral and longitudinal direction the null hypothesis $H_0$ can be rejected at significance level less than 0.01. This means that the result for the lateral direction shows a significant systematic deviation in the negative direction and a significant systematic deviation in the positive direction for the longitudinal direction. However, in the vertical direction there is a risk of about 18% to falsely reject $H_0$. Since two directions show systematic deviations, an additional refined test is performed which is referred to as the Wald test. It is a classical test in the literature on linear models and in econometrics. It appears in most text books on econometrics, for example in Johnston and Dinardo (1997).

**The Wald test**

With the Wald test we want to investigate if there are similar patient specific systematic deviations. There are $P$ patients and $n_p$ measurements, out of $N$ measurements in total, have been made on patient number $p$ in each of the three directions.

We assume the following model:

\[ X_{pj} = \mu_p + \sigma \varepsilon_{pj}, \quad p = 1, \ldots, P, \ j = 1, \ldots, n_p \text{ and } n_1 + \ldots + n_P = N \]

where $X_{pj}$ is the measured deviation between the two matching methods in a given direction. $\mu_p$ is the mean deviation for patient $p$, i.e. the systematic deviation of the two matching methods in a given direction. $\sigma$ is the standard deviation of the distribution of the measurement error and is unknown. $\varepsilon_{pj}$ is a random value for patient $p$ and measurement $j$ and all $\varepsilon_{pj}$ are independent with $E(\varepsilon_{pj}) = 0$ and $E(\varepsilon_{pj}^2) = 1$.

We want to test the hypotheses (A) and (B) given by

(A) $\mu_1 = \ldots = \mu_p$, \hspace{1cm} (B) $\mu_1 = \ldots = \mu_p = 0$.

The testing of hypothesis (B) is only of interest if hypothesis (A) can be accepted.

The following quantities will appear in the test:

\[ m_p = \frac{1}{n_p} \sum_{j=1}^{n_p} X_{pj}, \quad m_{\text{overall}} = \frac{1}{N} \sum_{p=1}^{P} \sum_{j=1}^{n_p} X_{pj}, \]

\[ S_p^2 = \frac{1}{n_p - 1} \sum_{j=1}^{n_p} (X_{pj} - m_p)^2, \quad S^2 = \frac{1}{N - P} \sum_{p=1}^{P} (n_p - 1)S_p^2. \]
Here $m_p$ is the estimate of the mean $\mu_p$ for patient $p$, $m_{overall}$ is the estimate of the overall mean, $S_p^2$ is the estimate of $\sigma^2$ based on the measurements on patient $p$ and $S^2$ is the estimate of $\sigma^2$ based on all measurements.

The hypotheses are tested with the so called Wald test.

Testing hypothesis (A):

One can find in the literature that the expression
\[ \frac{1}{S^2} \sum_{p=1}^{P} n_p (m_p - m_{overall})^2 \]

is approximately $\chi^2(P-1)$-distributed under hypothesis (A). The hypothesis is rejected at significance level $\alpha$ if
\[ \frac{1}{S^2} \sum_{p=1}^{P} n_p (m_p - m_{overall})^2 > \chi^2_{1-\alpha}(P-1) \]

Here $\chi^2_{1-\alpha}(P-1)$ is the $(1-\alpha)$-quantile of the $\chi^2(P-1)$-distribution. Typical values for $\alpha$ are $\alpha = 0.01$ and $\alpha = 0.05$. If we reject the hypothesis at significance level $\alpha$, then with probability $\alpha$ we have falsely rejected the hypothesis.

For $P = 10$ and $N = 46$ we have the following relevant quantile values for the $\chi^2$ distribution with $P-1 = 9$ degrees of freedom:

<table>
<thead>
<tr>
<th></th>
<th>$\chi^2_{0.95}(9)$</th>
<th>$\chi^2_{0.99}(9)$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16.91898</td>
<td>21.66599</td>
</tr>
</tbody>
</table>

We compare the values above with the following calculated values based on our measurements:
Table A2: Calculated values for the approximately $\chi^2(P-1)$-distributed expression

$$\frac{1}{S^2} \sum_{p=1}^{P} n_p (m_p - m_{overall})^2$$

under hypothesis (A).

<table>
<thead>
<tr>
<th>Vert</th>
<th>Lat</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>21.97049</td>
<td>23.78145</td>
<td>24.844573</td>
</tr>
</tbody>
</table>

In all three directions the calculated values are larger than the quantile values. This means that, at significance level 0.01, for all three directions we have to reject the hypothesis that the mean values $\mu_p$ are the same and the hypothesis (B) is therefore not tested.
A2. GRADING SYSTEMS

Table A3: Modified RTOG protocol used as a grading system for late rectal bleeding (Boersma et al. 1998, table 1).

<table>
<thead>
<tr>
<th>RTOG/EORTC grade</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macosal loss</td>
<td>slight/moderate</td>
<td>moderate/excessive intermittent/frequent</td>
<td>minor surgery or multiple laser treatments or transfusions</td>
<td>severe → major surgery</td>
</tr>
<tr>
<td>Bleeding</td>
<td>incidental/intermittent, no treatment required</td>
<td>intermittent/single laser treatment or transfusion</td>
<td>intestinal or colon obstruction</td>
<td>generalized fibrosis, perforation</td>
</tr>
<tr>
<td>Pain</td>
<td>mild cramping</td>
<td>intermittent/severe cramping</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table A4: The grading system used for late genitourinary toxicity (Cheung et al. 2007, table 1)

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia twice baseline</td>
<td>Moderate frequency</td>
<td>Severe frequency and dysuria</td>
<td>Severe hemorrhagic cystitis</td>
<td>Fatal toxicity</td>
</tr>
<tr>
<td>Microscopic hematuria</td>
<td>Nocturia more than twice baseline</td>
<td>Nocturia more frequent than once every hour</td>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>Light macosal atrophy and minor telangiectasia</td>
<td>Generalized telangiectasia</td>
<td>Reduction in bladder capacity (150 cc)</td>
<td>Requirement for urinary diversion and/or cystectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermittent macroscopic hematuria</td>
<td>Frequent hematuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two or fewer blood transfusions</td>
<td>More than two transfusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two or fewer coagulations</td>
<td>More than one coagulation for hematuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regular non-narcotic or occasional narcotic for pain</td>
<td>Regular narcotic for pain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>