Impact of internal variations on the dose distribution during the course of radiotherapy of prostatectomy patients

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Abstract

Purpose: The purpose of this study was to identify the best performing algorithm option for deformable registrations between planning computed tomography (pCT and cone-beam CT (CBCT) in Velocity using image sets from prostate cancer patients receiving radiation therapy after prostatectomy. Different parameters were studied in an attempt to find parameters related to the success of a deformable registration. Differences between planned dose distributions and new estimations of delivered dose distributions based on weekly CBCTs were investigated.

Method: The pCT was registered and deformed into the CBCT geometry, and a calculation of the absorbed dose was performed for each treatment occasion using Velocity Advanced Imaging (AI) which is a deformable image registration (DIR) software. Velocity AI offers several different options for the deformable registration e.g. grid size. 28 patients were included in the study and had weekly CBCTs taken. Deformable registrations were made between the CBCTs and the pCT for each patient. To evaluate the different algorithm options in Velocity three patients with a total of 35 deformed CBCT image sets were analysed using Dice Similarity Coefficient, Hausdorff distance and Mean distance to agreement between structure contours. The delivered dose distribution of the whole treatment course, was estimated using two different methods; Dose recalculation method (dose calculated on each deformed pCT), and Dose deformation method (planned dose distribution deformed based on deformable registration between the pCT and the CBCT). Differences between the pCT and the CBCTs in rectum size, separation of the ventral rectum wall and bladder volume were grouped based on their registration status; successful or unsuccessful, in an attempt to identify parameters related to the success of a deformable registration.

Result: The algorithm option that performed best was the “CBCT corrected deformable multi-pass”. For the performed estimation of delivered dose distribution (17 out of 28), both methods estimated that CTV had an adequate dose coverage. For the dose recalculation method, all CTV mean doses part from one were larger compared to the mean doses in the original treatment plans. For the dose deformation method, the CTV mean dose results were similar to the mean doses in the original treatment plans. Concerning the rectum, the V90 volumes were generally larger for both methods compared to the doses in the original treatment plans with a few exceptions. In three cases, the dose exceeded the dose restriction value for the rectum while the corresponding values of the original treatment plan were below. The bladder V70 Gy volumes for the dose recalculation method were generally larger than the corresponding original plan volumes while the dose deformation V70 Gy volumes were smaller. The V65 Gy volumes were smaller or similar to the original treatment plan for both methods.

Conclusion: The “CBCT corrected deformable multi-pass” was the algorithm option in Velocity that performed the best deformable registrations between CBCT and pCT for the images studied. A separation greater than 20-25 mm between the ventral rectum walls in the CBCT and the pCT at the level of the cranial part of the CTV or a
difference in rectum area greater than 200% at the level of the cranial part of the CTV increases the risk of a less accurate registration. The ability to deformably register successfully was not affected by differences in the bladder. The estimation of delivered doses based on CBCT images showed an adequate CTV dose coverage and an increased rectum dose.
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Introduction

For the last 100 years radiation has been used to treat various cancers. Today about 50% of all cancer patients receive radiotherapy (RT) alone or in combination with other treatments, such as chemotherapy, surgery, immunotherapy and hormonal therapy. In external beam radiotherapy the treatment preparation process begins with a computed tomography (CT). The CT image-set is then used to calculate the absorbed dose in the treatment planned. This CT is referred to as the planning CT (pCT). The ability to deliver the planned dose in radiotherapy relies on that the patient geometry and position during the acquisition of the pCT can be reproduced on the treatment couch. Several uncertainties are associated with this requirement, such as uncertainties in the positioning of the patient and uncertainties due to inter- and intra-treatment movements e.g. respiration, organ movements or bowel filling. To minimize these uncertainties different techniques are used. Some examples of techniques are internal and/or external markers, x-ray images and fixation devices. Wall or frame mounted lasers and external markers can be used to reproduce the patients positioning on the treatment table. X-ray images acquired using an on-board imaging system allows for comparison of internal fiducial markers or anatomical landmarks e.g. bony structures, this procedure is often referred to as online matching. This ensures that the patient’s internal geometry and position have a good agreement with the position and geometry the patient had during the acquisition of the pCT.

In the case of post prostatectomy radiotherapy treatments at Sahlgrenska University Hospital, knee support, external markers and online matching (bone structures) are used on a daily basis to help reproduce the patient pCT position and geometry. Variations of the target location for post prostatectomy patients are not reflected by the position of bony structures, which currently are the structures used as anatomical landmarks in the online matching process. For prostatectomy patients the target is often located closely to the ventral part of the rectum and the bottom of the bladder. Therefore, the target location is varying due to differences in volume and position of the rectum and bladder. To account for the inter- and intra-treatment variations and to ensure dose coverage of the clinical treatment volume (CTV) a margin around the CTV is applied, this margin delineates a new volume called planning treatment volume (PTV). At Sahlgrenska University Hospital, a PTV margin of 10 mm in all direction is used for post prostatectomy radiotherapy treatments. The choice of used treatment techniques, e.g. volumetric modulated arc therapy (VMAT) or 3-dimensional conformal radiation therapy (3DCRT), will affect the delivered dose to both target and organs at risk (OAR).

Both bladder and rectum are radiation sensitive organs and considered OAR’s. This poses a challenge when planning the treatment since a high dose to the CTV is desired while neighbouring regions may have a dose restriction. Other studies have investigated the dose to OAR’s in the prostate region. Akino et al. (2013) investigated the generalized equivalent uniform dose (gEUD), a mean dose which accounts for volumetric dependence of the dose-response relationship for the organ, for bladder and rectum of prostate cancer patients and found a mean difference in gEUD between the planned dose and the estimated delivered dose of 6.3 % and 14.3 % for the rectum and bladder, respectively. Wen et al. (2012) reported mean dose differences of 22.45 % and 12.36 % to rectum and bladder, respectively. In the report of Wen et al. (2012) all delivered rectum doses were higher than the planned while in the report of Akino et al. (2013) the reported doses also contained cases of lower delivered dose. Gill et al. (2014) investigated the PTV margins for 50 post prostatectomy patients using two different margins, 10 mm in all directions (PTV10) and 5 mm posterior and 10 mm in all other directions (PTV5). They reported a geographical miss in 5.4 % and 9.6 % of the cases for PTV10 and PTV5, respectively.

It would be desirable to know the actual delivered dose during an ongoing treatment in order to be able to adapt the treatment if needed. This could optimize the dose to the target volume
and spare surrounding healthy tissue. Modern radiotherapy treatment machines have the ability to use the on-board imager (OBI) to acquire a 3D image (cone-beam CT (CBCT)), hence imaging the actual position and geometry of the patient during the treatment session. The information from the CBCT can be used to estimate the dose delivery in the actual patient geometry at that treatment occasion.

A necessity to be able to perform a dose calculation is that it exists a CT calibration curve to correlate the Hounsfield units (HU) in the CT-images to the relative electron density. The electron density is used in the treatment planning system (TPS) when calculating how the dose distributes in the patient. In a CBCT the HU is not as consistent as in a CT, which makes a calibration curve less accurate. A study that investigated the dosimetric impact of dose calculation based on a Varian on-board CBCT reported a dose difference of 2-5 % compared to the pCT (Dong et al. 2006). Furthermore, it is common that the CBCT images do not include the whole region of interest but rather focus on a certain region within the patient. One possible method of estimating the delivered dose from the treatment session is to use image registration.

**Image registration**

Image registration is a process where two points in two separate images are linked together, basically identifying them as being the same point in the object. The simplest registration is rigid registration which means that two images are overlaid and rigidly moved in relation to each other to achieve as good agreement between the images as possible. Despite the use of positioning techniques, such as e.g. external markers, fixation devices or orthogonal x-ray images, it is not unusual that there are differences in the patient position and geometry between the pCT and the CBCT. This could be due to e.g. varying bladder or intestinal filling. In rigid registration, the relations within the image do not change, the proportions are retained. This however, is not the case for non-rigid registrations. Non-rigid registrations are able to change the proportions in the image to account for e.g. differences in volume or organ location. This type of registration is also referred to as deformable image registration (DIR) due to the possible deformation of one image to agree with another. Development and research regarding DIR has been growing lately and it is a fundamental part of image guided adaptive radiotherapy (IGART). IGART is a technique that uses images to track the target’s deformation during the treatment and adjust the treatment delivery to better suit the new geometry. This ensures dose coverage of the target volume and spare surrounding healthy tissue. A lot of different DIR-algorithms are available today, both commercially as well as freeware and open source.

**Velocity Advanced Imaging**

Velocity AI is a commercially available DIR software distributed via Varian Medical Systems, Palo Alto, California, USA. It uses a b-spline based algorithm in combination with Mattes formulation of mutual information to identify and deform structures in the image (Nie et al. 2016). Mattes formulation of mutual information evaluates the joint histogram of bins of voxels, which adds a resistance to pixel noise (Lawson et al. 2007). Only parts of the images are used for the evaluation, which makes the algorithm faster (Thevenaz et al. 1997). B-spline is a piecewise polynomial function and the place where two pieces meet are called knots. The algorithm adds a mesh to the image where the junctions are the b-spline knots. A property of b-spline is that although each piece is its own separate polynomial function they are all continuous over the knots. Due to the properties of b-spline the deformation is locally controlled which means that displacement of a knot is only influenced by the displacement of the knots in the close vicinity. The algorithm does not add or remove voxels it only resizes them if needed. Crossing of knots is not allowed by the algorithm, which prevents unnatural results and makes the deformation conform to physical movements.
Velocity offers a registration option called “CBCT corrected deformable registration”, which adds a filter to compensate for attenuation effects in the CBCT, this is only used during the deformable registration and not visual to the user. Both deformable registration and CBCT corrected deformable registration have further options, single-pass and multi-pass. These options refer to the grid size where single-pass only use a single grid size, this size can be set by the user and range from coarse to fine. Multi-pass means that the deformation is performed in three steps using three different grid sizes, coarse, medium and fine. Furthermore, all deformations in Velocity have an inversion.

When performing a registration in Velocity a link is set between the voxels in the two image sets. Once a deformation field is acquired all the associated values are linked, i.e. a deformable registration done using HU values will also deform the dose distribution if one is available. A dose distribution acquired on a pCT can be transferred to the CBCT (or the other way around) if a registration has been performed between the pCT and the CBCT.

A study regarding the accuracy of Velocity has reported a mean 3D registration error of $2.7 \pm 0.8$ mm using a landmark approach on 5 patients from DIR-lab’s (dir-lab.com) thoracic dataset (Kadoya et al., 2014). Varadhan et al. (2016) used a deformable phantom to study the DIR accuracy by applying forces ranging from 10 to 70 N along one axis, resulting in deformations along that axis ranging from 3 to 28 mm. The phantom had internal landmarks that were synthetically masked by setting the landmark HU to be equal to the surrounding. They found the DIR accuracy to range between 0.8 and 4.0 mm with a mean of 2.5 mm. Lawson et al. (2007) evaluated another DIR algorithm based on b-splines and Mattes formulation of mutual information and found its accuracy for phantom images to be 2 mm. They used a Quasar Body phantom with five inserts of different materials, HU’s ranging from -1000 to 735. They also noticed that high HU homogeneity decreases the performance of the algorithm.

Hausdorff distance can be used to evaluate the agreement of two volumes. The Hausdorff distance is the longest distance from any point on the surface of one of the volumes to the nearest point on the surface of the other volume. Depending on which surface you start from you can get two different distances, the Hausdorff distance is the largest of those two.

Dice similarity coefficient (DSC) is another commonly used parameter for evaluation of registration result. DSC is a measure of the agreement between two volumes and is defined as twice the intersection divided by the sum of the volumes, see figure 1. Akino et al. (2013) reviewed 231 series of CBCT images along with their corresponding pCTs from 8 patients with prostate cancer. On both the pCT and the CBCT the HU values within the rectum contour were replaced by the mean surrounding HU value +100. They reported that the DIR improved the rectum DSC value between the pCT and CBCT with DSC values going from 0.75 ±0.04 pre DIR to 0.9 ±0.02 post DIR. In a study by Nie et al. (2016) the bladder was digitally deformed, up to 19.5 mm difference, and then registered to the original non-deformed CT using DIR. DSC values of 0.79 ±0.18 and 0.87 ±0.05 were reported for prostate target and prostate related OAR’s, respectively.

At Sahlgrenska University Hospital a disagreement of up to 3mm between the x-ray image and the digitally reconstructed radiograph from the TPS is allowed for post prostatectomy cancer patients, a larger disagreement will be corrected by moving the treatment couch. This threshold is comparable to the DIRs above mentioned reported spatial accuracy of 2.5 – 2.7 mm.

![Figure 1: Definition of Dice similarity coefficient (DSC).](image)
Aim

This study concern prostate cancer patients receiving radiotherapy after prostatectomy and aimed to:

- Evaluate the optimal algorithm option in Velocity AI for deformable registration of CBCT and pCT.
- Study parameters to predict the success of a deformable registration between CBCT and pCT.
- Investigate the difference between planned and estimated delivered dose distributions using weekly CBCT images and DIR.
Material and Method

The patient material consisted of treatment plans, pCTs and CBCTs (kV) (5 to 9 per patient). The CBCTs were taken weekly over the course of treatment for 29 patients who received RT during the period 2013-2014 at Sahlgrenska University Hospital in Gothenburg, Sweden, after their prostatectomy. One patient was excluded in this study because of double hip prosthesis that caused image artifacts. Structures in the pCT were delineated by different oncologists. The structures delineated in the CBCTs were made by one oncologist. Delineated structures were bladder, rectum, PTV and CTV on the pCT. The CBCTs had bladder and rectum delineated. The patient material came from an earlier study which had an approval from the Regional Ethical Review Board in Gothenburg, Sweden (Diary number 346-13,2013), and included bladder volume differences between the pCT and the CBCTs of up to 500% and differences in rectum location of up to 4.5 cm. All patients were prescribed 70 Gy delivered in 2 Gy fractions for a total of 35 treatment occasions. The dose restrictions used for treatment planning of prostate cancer patients with gold fiducial markers are at Sahlgrenska used also for prostatectomy patients. These dose restrictions for rectum are, less than 50% of the rectum volume can receive 50% of the prescribed dose ($V_{50\%}<50\%$), less than 35% of the rectum volume can receive 80% of the prescribed dose ($V_{80\%}<35\%$) and less than 15% of the rectum volume can receive 90% of the prescribed dose ($V_{90\%}<15\%$). The rectum restriction ($V_{90\%}<15\%$) is sought but is much more difficult to meet for this group of patients due to the target volume often being located closer to the rectum compared to target volumes of non-prostatectomy prostate cancer patients. The bladder does not have any restrictions but the dose should be kept as low as reasonably possible.

The treatment techniques used were 3D conformal radiation therapy (3DCRT) (3-field 0°, 90° and 270°, 15MV) or volumetric modulated arc therapy (6MV VMAT). The treatment planning system used was Eclipse (Varian Medical Systems, Palo Alto, California, USA).

Comparisons of different algorithm options in Velocity

Three patients with the whole bladder included in each CBCT were selected. The selected three patients had 7 CBCT images each for a total of 21 CBCT image sets. The CBCT and the pCT were rigidly registered, with rotation, to increase the performance of the following deformable registration, as recommended by the Velocity manual. Six different deformable registrations were performed between the pCT and the CBCT, deforming the CBCT into the pCT using different algorithm options:

1. Deformable single-pass. Grid size coarse.
3. Deformable multi-pass
4. CBCT corrected deformable single-pass. Grid size coarse.
5. CBCT corrected deformable single-pass. Grid size medium.
6. CBCT corrected deformable multi-pass

Rectum and bladder structures from the deformed CBCT and the pCT were compared and parameters collected. Collected parameters for rectum and bladder were:

- Dice Similarity Coefficient (DSC).
- Hausdorff distance (maximal length).
- Mean distance to agreement between the structure contours.

Additional collected parameter for the bladder was volume and for the rectum the length between the most cranial and the most caudal slices of the rectum structure. Furthermore, the
percentage difference of the bladder volume between the deformed CBCT and the pCT was calculated.

**Prediction of DIR success**

The CBCTs were rigidly registered, with rotation, and then deformably registered to their corresponding pCT for all 28 patients, to a total of 206 registrations, according to the optimal choice of algorithm option found in this study (see earlier section). The results were analysed and the unsuccessful registrations were identified. A registration was considered unsuccessful if the difference of location of the ventral rectum wall between the rectum in the pCT and the deformed CBCT was greater than 3 mm at either of three cranio-caudal positions; in the level of the cranial, middle and caudal part of the CTV. A maximum disagreement of 3 mm is allowed when verifying the patient position on the treatment couch using orthogonal x-ray images at Sahlgrenska University Hospital. A visual general assessment was done to assure that there were no cases with small differences of ventral rectum wall positions but large differences in other regions. The visual assessment focused on surrounding bony structures, body contour and muscles.

To identify parameters related to the success of a deformable registration the area of the delineated rectum in transversal planes at the level of the most cranial and caudal parts of the CTV was measured in both the CBCTs and pCT for 15 patients, all patients with at least one unsuccessful deformable registration were included. This is considered as a measure of the difference in rectum size in the different images to be registered. For the same images, the bladder volume was registered as well to study the influence of differences in bladder size on the success of a deformable registration. The bladder volume in the CBCTs relative to the bladder volume in the pCT was registered.

The CBCTs and the pCT had earlier been rigidly registered (with rotation) for each patient in Eclipse treatment planning system and the separation of the ventral rectum wall position between the registered image sets was measured at the cranial level of the CTV. This was made in a study using the same patient material. The measurements were coupled with the success of their corresponding deformable registration.

**Deformable registration and dose estimation**

Two different methods were used to obtain an estimated dose distribution based on the patient position and geometry in the CBCTs. Both methods resulted in an estimated dose distribution based on the CBCT geometry but presented in the pCT geometry. Presenting the CBCT dose distribution in the pCT geometry makes summation of different CBCT dose distributions easy. One of the methods (Dose recalculation) was suggested by the Velocity manual and the other method was based on dose deformation.

Both methods used the same rigid and deformable registrations, the rigid registration was without rotation to better mimic the treatment situation. A schematic representation of the involving registrations can be seen in figure 2. As all registrations in Velocity has an inverse the registrations can be used in either way, i.e. pCT to CBCT or CBCT to pCT. However, all registrations were made as the pCT as primary, meaning that the CBCTs were deformably registered into pCT geometry.
Figur 2. Schematic figure of the registrations made between the CBCT and the pCT, these are reversible as all registrations in Velocity have an inverse. The rigid registration (A) is without rotation. These are the registrations used in the dose recalculation method and the dose deformation method.

Dose recalculation method

This method deforms the pCT into the CBCT geometry using Velocity and then a new dose distribution is calculated on the deformed pCT. The calculated dose distribution is then deformed back into pCT original geometry for dose summation.

The pCT was deformed into the geometry of the CBCT (B) using Velocity and a synthetic CT (sCT) was created (2). A sCT is basically a pCT image set that is deformed over the corresponding volume expansion of the CBCT and a copy of the original pCT outside that volume (reshaped option in Velocity). The sCT has the geometry of the CBCT but the frame of reference (FOR) of the pCT. The pCT FOR is needed to apply the original treatment plan to the sCT image set. The sCT is exported to a TPS and a dose distribution based on the CBCT geometry is calculated (3). The dose distribution calculated on the sCT image set is then imported back to Velocity (4). The sCT based dose distribution is in CBCT geometry but in the FOR of the pCT. The previously created rigid registration (figure 2 (A)) between the CBCT and the pCT is used to move the dose distribution back to the CBCT FOR (5). The inverse of the previously created deformable registration (figure 2 (B)) made between the CBCT and the pCT is applied to the sCT dose distribution (6) in order to present the sCT dose distribution in pCT geometry. The endpoint is an estimated CBCT dose distribution presented in the geometry of the pCT, see figure 3 for a schematic representation of the method.
Figure 3. Schematic figure showing the workflow for the dose recalculation method. A and B refer to registrations schematically presented in figure 2. The pCT (1) is deformably registered to the CBCT and a sCT (2) is created. The sCT is exported to a TPS for dose calculation (3) and the resulting dose distribution is imported back to Velocity (4). The sCT dose distribution is rigidly registered using the rigid registration (A) made between the pCT and the CBCT (figure 2). The sCT dose distribution is then deformable registered using the deformable registration (B) made between the CBCT and pCT in order to get the CBCT dose distribution in the pCT geometry.

Dose deformation method

This method assumes that changes in patient geometry and position does not alter the shape of the dose distribution but rather the location of the dose distribution within the patient. It also assumes a good agreement of bony structures, which is the structure used for online matching.

The planned pCT dose distribution (7) is moved into the FOR of the CBCT (8) using the rigid registration (figure 2 (A)) created between the pCT and the CBCT. This is assumed to represent the dose distribution in the CBCT geometry. With the dose distribution in the FOR of the CBCT the deformable registration (figure 2 (B)) created between the pCT and the CBCT is applied to present the CBCT dose distribution in the pCT geometry (9). See figure 4 for a schematic representation of the method.
Figure 4. Schematic figure showing the workflow of the dose deformation method. A and B refer to registrations schematically presented in figure 2. The pCT dose distribution (7) is registered using the rigid registration (A) between the CBCT and the pCT (figure 2) to set the FOR to that of the CBCT. The pCT dose distribution in the CBCT FOR (8) is deformable registered using the deformable registration (B) between the CBCT and the pCT (figure 2) to get the CBCT dose in the pCT geometry (9).

Dose summation

For each patient the CBCT dose distributions were summed together with the pCT dose and scaled according to 1/number of CBCT’s + 1. This gives each CBCT dose distribution the same weight as the pCT dose distribution.

Dose evaluation

From the dose-volume histograms (DVH) the following values were collected:

- **CTV**
  - Mean dose
  - Volume% that received 98% (68.6 Gy) of the prescribed dose or more. ($V_{98\%}$)
  - Volume% that received 95% (66.5 Gy) of the prescribed dose or more. ($V_{95\%}$)

- **Rectum**
  - Volume% that received 70 Gy or more. ($V_{100\%}$)
  - Volume% that received 63 Gy or more. ($V_{90\%}$)
  - Volume% that received 56 Gy or more. ($V_{80\%}$)
  - Volume% that received 35 Gy or more. ($V_{50\%}$)

- **Bladder**
  - Volume% that received 70 Gy or more. ($V_{70\text{ Gy}}$)
  - Volume% that received 65 Gy or more. ($V_{65\text{ Gy}}$)
Results

Comparisons of different algorithm options in Velocity

The selected three patients had 7 CBCT images each. The 21 CBCT images were deformably registered 6 times each using the selected six deformable registration options. The mean DSC value for the different options are presented in table 2. The DCS values ranged from 0.8 to 0.84 and 0.67 to 0.7 for the bladder and the rectum, respectively. For the bladder, the options 3 and 6, “deformable multi-pass” and “CBCT corrected deformable multi-pass” respectively, yielded the highest scores. For the rectum, the best performing options were the “CBCT corrected” options (options 4-6). A perfect agreement would yield a DSC of 1 and a total separation of the structures would yield a DSC value of 0. Option 6 (“CBCT corrected deformable multi-pass”) had the highest score considering both bladder and rectum.

Table 2. Mean Dice similarity coefficient values for the comparison of the deformed CBCT and the pCT structures for different registration algorithm options. The option numbers are according to the numbers listed in the section Method – Comparisons of different algorithm options in Velocity.

<table>
<thead>
<tr>
<th>Option</th>
<th>Mean DSC</th>
<th>Bladder</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.80</td>
<td>0.68</td>
<td></td>
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<tr>
<td>2</td>
<td>0.83</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.84</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.80</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.82</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.84</td>
<td>0.70</td>
<td></td>
</tr>
</tbody>
</table>

The mean Hausdorff distances ranged from 14.0 to 15.0 mm and 20.0 to 21.1 mm for the bladder and rectum, respectively. For the bladder, the option 3 (“deformable multi-pass”) achieved the lowest distances while option 6 (“CBCT corrected deformable multi-pass”) achieved the lowest distances considering the rectum. The mean distance to agreement result ranged from 2.9 to 3.8 and 3.9 to 4.4 for the bladder and rectum, respectively. Options 3 and 6 (“deformable multi-pass” and “CBCT corrected deformable multi-pass”, respectively) achieved the lowest mean distances for the bladder and option 6 also achieved the lowest distance considering the rectum. Each algorithm options mean distances can be seen in table 3.

Table 3. Mean Hausdorff distances and mean distance to agreement results for the bladder and rectum. Comparison between deformed CBCT and pCT structures. The option numbers are according to the listing in Method – Comparisons of different algorithm options in Velocity.

<table>
<thead>
<tr>
<th>Option</th>
<th>Bladder</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Hausdorff distance [mm]</td>
<td>Mean distance to agreement [mm]</td>
</tr>
<tr>
<td>1</td>
<td>15.0</td>
<td>3.7</td>
</tr>
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<td>2</td>
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<td>3.1</td>
</tr>
<tr>
<td>3</td>
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<td>2.9</td>
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<tr>
<td>4</td>
<td>15.0</td>
<td>3.8</td>
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<tr>
<td>5</td>
<td>15.0</td>
<td>3.3</td>
</tr>
<tr>
<td>6</td>
<td>14.9</td>
<td>2.9</td>
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</table>
The mean difference between the deformed CBCT and the pCT bladder volumes ranged from 17.6 % to 32.2 % for the different registration options. Differences in cranial-caudal rectum length ranged from 9.1 mm to 13.3 mm. In table 4 it can be seen that the CBCT corrected deformable multi-pass (option 6) performed best in both cases.

Table 4. Deformably registered CBCT bladder volumes relative their corresponding pCT volume for comparison of the different algorithm options. Post deformable registration differences in cranial-caudal rectum length between the deformably registered CBCT and the corresponding pCT rectum structure. The option numbers are according to the numbers listed in the section Method – Comparisons of different algorithm options in Velocity.

<table>
<thead>
<tr>
<th>Option</th>
<th>Bladder volume differences [%]</th>
<th>Rectum differences [mm]</th>
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<tbody>
<tr>
<td>1</td>
<td>32.2</td>
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<td>9.3</td>
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<td>17.6</td>
<td>9.1</td>
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</table>

Predictive DiR success

The 28 patients included in the study resulted in 206 deformable registrations. Out of the 206 deformable registrations, 21 had a separation greater than 3 mm between the ventral part of the rectum wall in the deformed pCT compared to the rectum wall in the CBCT and were therefore considered as unsuccessful registrations. Out of the 21 unsuccessful registrations the separation between the CBCT and deformed pCT rectum structures greater than 3 mm occurred at the level of the cranial part of CTV in all but 3 cases where a separation greater than 3 mm also occurred in the middle level of CTV. The visual general assessment concluded that all registrations with < 3 mm separation between the CBCT and the deformed pCT ventral rectum walls also had a visually good agreement considering pelvic diaphragm, body contour and surrounding bony structures. In six cases the separation between the CBCT and the deformed pCT rectum structures at the level of the caudal part of CTV was greater than 3 mm while the separation was < 3 mm at the level of the middle and cranial part of CTV. In these cases, due to high HU homogeneity and low image quality, the agreement assessment was based on surrounding structures such as surgical clips or the pelvic diaphragm instead of the separation of delineated rectum structures and they were considered successful.

The results from plotting the non-deformed CBCT rectum area (at the level of the cranial part of CTV) versus its corresponding bladder volume, both relative to their corresponding pCT value, can be seen in figure 5. The plot contains the values from all patients who had at least one registration that was considered unsuccessful i.e. had a separation greater than 3 mm between the deformed pCT and the CBCT rectum wall at the most cranial part of CTV. In figure 5 blue marks correspond to successful registrations and red marks correspond to unsuccessful registrations. The bladder volume does not seem to affect the algorithms ability to successfully deformably register the images using the “CBCT corrected deformable multi-pass” option. However, area differences of 200% or more in rectum area at the level of the cranial part of CTV between the CBCT and the pCT seem to lower the algorithm’s ability to successfully deformably register the images.
Figure 5. Rectum area (measured at the cranial part of CTV) plotted against bladder volume, both relative their corresponding pCT structure. Unsuccessful deformable registrations are marked in red and successful deformable registrations are marked in blue. The figure contains a total of 206 registrations, 21 unsuccessful and 185 successful.

The measured separations after rigid registration, with rotation, between the ventral rectum wall at the cranial part of the CTV between CBCTs and the pCT are shown in figure 6. A successful deformable registration seems less likely if the separation is greater than 20-25 mm, though not impossible.

Figure 6. The separation between the rectum ventral wall in the most cranial part of the CTV in the CBCT and its corresponding pCT. Red marks correspond to unsuccessful registrations and blue marks correspond to successful registrations.

Deformable registration and dose summation

Out of the 28 patients, 17 dose summations were achieved. Eleven patients were excluded from the dose summation due to one or more unsuccessful deformable registrations. An
unsuccessful registration was defined as a separation greater than 3 mm between the ventral rectum wall in the deformed pCT and the ventral rectum wall in the CBCT at the cranial level of the CTV.

The resulting summed doses from the dose recalculation method and the dose deformation method can be seen in figures 7 to 9 along with their corresponding planned dose. The patients are grouped according to technique used to deliver the dose, i.e. VMAT or 3DCRT.

Compared to the planned dose all estimated dose summations resulted in a larger or equal CTV volume that received 68.6 Gy, i.e. 98% of the prescribed 70 Gy dose. For the 3DCRT group both the planned CTV V_{98%} volumes as well as the estimated CTV V_{98%} volumes were at 99.7% or more. In the patient group that received RT delivered by VMAT technique there were larger variations in CTV volumes receiving 68.9 Gy. In the VMAT group, all the dose distributions estimated with the dose recalculation method were at or close to 100% but the distributions estimated with the dose deformation method could be as low as 92% however always larger than the planned dose distribution (see figure 7A). The CTV mean dose estimated with the dose deformation method did not differ much from the planned CTV mean dose. However, the CTV mean doses estimated with the dose recalculation method were all larger than their corresponding planned CTV mean dose. The differences in CTV mean dose between the planned CTV mean dose and the CTV mean doses estimated with the dose deformation method ranged from -0.1 to 0.09 Gy. All CTV mean doses estimated with the dose recalculation method were larger than their corresponding planned CTV mean dose and the differences ranged from 0.04 to 1.69 Gy, as can be seen in figure 7B.

![Figure 7](image.png)

**Figure 7.** In 7A the estimated V_{98%} volumes from both methods and the planned V_{98%} volume are shown for each patient. In 7B the estimated CTV mean dose from both methods as well as the planned CTV mean dose are
shown for each patient. The patients are separated into two groups according to technique used to deliver the dose. The left-hand group were treated using VMAT technique and the right-hand group using 3DCRT.

In figure 8A it can be seen that, compared to the corresponding planned volume, a larger rectum volume received 70 Gy in all cases but one for the dose recalculation method. For the dose deformation method, the 70 Gy volumes were smaller or the same as the planned, in all cases but one. The largest differences in estimated $V_{100\%}$ volume compared to the planned $V_{100\%}$ volume were found in the volumes belonging in the VMAT group and estimated by the dose recalculation method. Looking at the volume receiving 63 Gy in figure 8B it can be seen that in most cases the differences in volume between the estimated $V_{90\%}$ volumes and the planned $V_{90\%}$ volumes are smaller compared to the corresponding $V_{100\%}$ volume differences in figure 8A. It is worth noting that in the cases when larger volume differences occurred between the planned volume and either of the estimated volumes, the estimated volume was always larger than the planned volume. Apart from the $V_{100\%}$ volumes no obvious bias toward either treatment technique could be seen in figure 8B-D. In Figure 8A (rectum $V_{100\%}$) it can be seen that the $V_{100\%}$ volumes in the VMAT group estimated with the dose recalculation method deviated more from their corresponding planned $V_{100\%}$ volume than the volumes estimated with the dose recalculation method in the 3DCRT group.

Looking at the dose criterion $V_{90\%} < 15\%$ it can be seen in figure 8B that only one $V_{90\%}$ volume estimated with the dose recalculation method fulfilled that criterion, while 4 of the $V_{90\%}$ volumes estimated with the dose deformation method and 3 of the planned $V_{90\%}$ volumes fulfilled the criterion. The dose criterion $V_{80\%} < 35\%$ was fulfilled by all estimated $V_{80\%}$ volumes and planned $V_{80\%}$ volumes except for one patient where all three volumes were larger than 35% of the rectum. 14 of the planned $V_{50\%}$ volumes fulfilled the $V_{50\%} < 50\%$ criterion while only 12 of the $V_{50\%}$ volumes estimated with the dose calculation method or the deformation method met that criterion.
Figure 8. Percental rectum volume receiving at least (A) 100% (70 Gy), (B) 90% (63 Gy), (C) 80% (56 Gy) and (D) 50% (35 Gy) of the prescribed dose. Resulting volumes from both the dose recalculation and the dose deformation methods as well as the volumes from the original treatment plan. Note that the scales on y-axis of the figures A-D do not cover the same range but their ranges are equally large so the differences are visually comparable. On the patient axes the patients are grouped according to treatment technique used, VMAT to the right and 3DCRT on the left.

Bladder V_{70 Gy} volumes estimated with the dose deformation method were all smaller than their corresponding planned V_{70 Gy} volume. All but one V_{70 Gy} volumes estimated with the dose recalculation method were larger than their corresponding planned V_{70 Gy} volume. The difference in volume between the V_{70 Gy} volumes estimated with the dose recalculation
method and their corresponding planned $V_{70\text{ Gy}}$ volume were larger in the VMAT group than those in the 3DCRT group, as can be seen in figure 9A. The estimated $V_{65\text{ Gy}}$ volumes were mostly similar to their corresponding planned $V_{70\text{ Gy}}$ volume. In 5 cases (patient number 7, 8, 10, 15 and 17) the estimated $V_{70\text{ Gy}}$ volumes differed from their corresponding planned $V_{70\text{ Gy}}$ volume, in all these cases the estimated $V_{70\text{ Gy}}$ volumes were smaller than their corresponding planned $V_{70\text{ Gy}}$ volume as can be seen in figure 9B.

**Figure 9.** The figure shows the percental bladder volume that received at least (A) 70 Gy or (B) 65 Gy. Resulting volumes estimated with the dose recalculation or the dose deformation methods as well as their corresponding planned volume. Note that the scales on the y-axis of the figures A and B do not cover the same range but their ranges are equally large so the separations are visually comparable. On the patient axes the patients are grouped according to treatment technique used, VMAT to the right and 3DCRT on the left.
Discussion

The algorithm option that overall performed the best was the CBCT corrected deformable multi-pass (option 6), which also is the option suggested in the Velocity manual when registering CBCT images. In those cases that option 6 did not yield the best result it was still close to the option that did perform best in that case, usually deformable multipass (option 3). The DSC results for the bladder are in line with earlier reported bladder mean DSC values (0.87 ±0.05 and 0.81) (Nie et al., 2016; Saleh et al., 2016). For the rectum the mean DSC results are slightly lower than reported rectum DSC values (0.9 ±0.02 and 0.72 ±0.1) (Akino et al., 2013; Saleh et al., 2016). This could be due to statistical variations as the rectum DSC values in this study are within the lower range (0.62) of the reported rectum mean DSC values. DSC can be a good measure of the success of a registration, however it is dependent on that the same structures are delineated in both images. In the case of comparing volumes between a CT and a CBCT, it can be hard to delineate the structure exactly the same in both images due to image quality differences which can cause a structure to not be fully visible in either of the images. Also, segmentation of soft tissue performed by a human is inaccurate. In a report by Fiorino et al. (1998) the variability of delineated structures was found to be 5% intra-observer and 10-18% inter-observer. DSC does not give any information about the magnitude of the displacements and smaller volumes score lower for equal spatial displacements. This means that DSC values for different objects cannot be compared. The volume and the fact that the rectum is only partly delineated are both reasons for the lower DSC scores achieved for rectum compared to the bladder. When selecting patients for this part of the study 3 patients had to be excluded due to the cranial part of their bladders not being included in the CBCT, this would add more uncertainties to the bladder DSC since the entirety of the bladder was not available. While there are some rather large Hausdorff distances in the results (see table 3), the mean distances are close to previously reported values (2-4 mm) (Hoffmann et al., 2014) and the medians are all lower than their corresponding means. The largest Hausdorff distances seemed to be located at the cranial part of the structures, far away from the CTV region. This in combination with the low medians points to a good overall fit in the lower regions of the structure.

Looking at figure 5 it seems that a 200% rectum area difference could be an indication that the algorithm, using option 6, will be less likely to successfully deformably register the images. Differences in bladder volume does not seem to affect the ability to perform successful deformable registrations in the region of the prostate. The bladder is fairly stable in size in the CTV region, which is the region in which the structures are assessed in this study. However, there are a few exceptions in figure 5 namely; two successful deformable registrations with CBCT rectum area differences greater than 200% and 4 unsuccessful deformable registrations with CBCT rectum area differences less than 200%. It was noted in some unsuccessful deformations that rectum gases were introduced in the CBCT while no gas was present in the corresponding pCT, see figure 10 for an example. Added or removed tissues or air in the CBCTs compared to pCT could be a problem as Velocity does not change the number of voxels in the deformation process, it only resizes the voxels. This could affect both the bladder and the rectum and the implications it may have on the deformable registrations need to be investigated further. However, there were at least 3 successful deformable registrations where gases had been introduced in the CBCT. No real differentiation for the two successful deformable registrations with greater than 200% rectum area differences were found, though their CBCT images were of good quality and no air was introduced in the CBCT images. It has been noted and mentioned by others that the algorithm is less effective in regions with high HU homogeneity. High contrasts in the image will be very influential on the deformable registration. Bony structures are more likely to achieve a good agreement between the image sets, compared to soft tissue structures embedded in other soft tissue without prominent boarders. The quality of the CBCT will of course influence the end result so one should strive for as good CBCT quality as reasonably possible.
Figure 10. The figure shows a transversal slice of the CBCT and pCT (both non-deformed) from two patients where the following deformations were unsuccessful (A) and successful (B). The corresponding points in figure 5 for these two registrations are (A) 298/25 and (B) 294/41 bladder/rectum.

Ideally the dose deformation and the dose recalculation methods should produce similar results, which was not the case. For the VMAT group, the dose recalculation method produced noticeably higher CTV mean doses compared to the planned CTV mean doses and the CTV mean doses estimated with the dose deformation method. It was noticed that in the VMAT treatment plans, the CTV was often surrounded by regions of higher dose than within the CTV, see figure 11. One theory was that small positional errors could lead to high dose regions entering the CTV and hence cause an increase in CTV mean dose. A robustness evaluation was performed in Eclipse as this would show the impact on the dose distribution due to positional errors. Patient 3 was selected for the robustness evaluation due to the large CTV mean dose difference between the planned CTV mean dose and the CTV mean dose estimated with the dose recalculation method. Furthermore, the measured difference in location of the rectum ventral walls in the CBCT and the pCT was within 1 cm. The robustness evaluation isocenter offset was set to 1 cm and 0.5 cm. Due to the rectum location differences, in patient number 3’s CBCTs, being within the limits of the offset the CTV mean dose estimated with the dose recalculation method was expected to be somewhere in between the minimum and maximum CTV mean doses estimated by the robustness evaluation. The CTV V98% volumes estimated by the robustness evaluation ranged from 63.4 % to 97 % for the 1 cm offset and 62.2 % to 89.9 % for the 0.5 cm offset. The estimated CTV mean doses using the 1 cm offset ranged from 68.91 Gy to 69.61 Gy while the CTV mean doses estimated with the 0.5 cm offset ranged between 68.95 Gy and 69.36 Gy.
The CTV $V_{98\%}$ volumes estimated by the robustness evaluation showed that, in that particular case, the CTV $V_{98\%}$ volumes estimated with the dose deformation method were between the minimum and maximum CTV $V_{98\%}$ volumes estimated by the 1 cm offset robustness evaluation performed in Eclipse. The CTV mean doses estimated with the dose deformation method were within the range of CTV mean doses estimated by the robustness evaluation. However, CTV mean doses and CTV $V_{98\%}$ volumes estimated with the dose recalculation method were all larger than the maximum CTV mean dose and CTV $V_{98\%}$ volume estimated by the robustness evaluation. This could indicate that the dose recalculation method erroneously overestimates doses in this region. However, this needs to be further investigated especially as the dose recalculation method is the method suggested by the Velocity manual. The robustness evaluation showed that the high CTV mean doses estimated by the dose recalculation method could not be explained by small positional errors. Also, this would not explain the increased CTV mean dose seen in some patients treated with 3DCRT technique. Estimated dose distributions from the two methods can be seen in figure 12 next to the dose distribution from the corresponding pCT. In figure 12 it can be seen that the dose recalculation method (left image) estimated a dose distribution with higher doses compared to the planned dose distribution and the dose distribution estimated by the dose deformation method. It can also be seen that the dose distributions from the dose recalculation and the dose deformation methods are similar in shape. Some differences are seen as expected since the dose deformation method does not account for changes in dose distribution due to soft tissue displacement.

The dose deformation method is based on the assumption that soft tissue displacements between the pCT and the CBCT do not affect the dose distribution in any major way. Therefore, the original dose distribution can be applied to the CBCT and an estimated dose distribution for that CBCT geometry will be received. The deformable registration is needed in order to deform the CBCT dose distribution back to the pCT geometry, this makes dose summation of other CBCT dose distributions easier.
The largest rectum area difference successfully deformed had a 294.9% larger rectum area in the CBCT relative to the rectum area in the pCT (point (294.9, 41.4) in figure 5). This CBCT was chosen to represent a “worst case”, i.e. it was the patient geometry during the whole course of treatment, to give further insight of the impact on the dose distribution due to large rectum differences, see figure 13. This resulted in estimated mean CTV doses of 72.1 Gy and 69.2 Gy for the dose recalculation method and dose deformation method, respectively, which could be compared to the corresponding mean dose in the original treatment plan which was 69.3 Gy.

For the rectum and bladder, the largest dose volume differences in the study were seen in the V$^{70\text{ Gy}}$ results (see figure 8 and 9). This is probably due to high dose-gradients near the edges.
of the PTV. It is desired to have a high dose coverage of the PTV while sparing surrounding healthy tissue. In order to achieve this, steep dose gradients are needed close to the boarders of the PTV. This means that small movements can cause large differences in dose in those regions.

Looking at CTV V98% it can be seen that the dose deformation method resulted in a better CTV coverage for all patients except for one which had 0.3 % smaller CTV V98% compared to the planned CTV V98% volume. The CTV mean doses from both the methods were very similar to the original plan with an overall CTV mean dose deviation of 0.08%. The CTV seems to get the prescribed dose even with differences in rectum area of up to 200% in the level of the cranial part of the CTV between the pCT and CBCT. These results are not the actual final dose distribution received from the treatment but rather an estimation. The original treatment plan is also an estimation since it is based on a stationary image while in reality it is a highly variable environment. The presented results are an approximation of the distribution based on multiple stationary images spread out over time rather than one stationary image. The results should therefore not be viewed as an answer key of the treatment but rather as an indicator. Daily CBCT would be needed to get a more accurate estimation of the delivered dose distribution, though it still would not capture inter fraction movements.
Conclusion

The algorithm option in Velocity that performed the best deformable registration between CBCT and pCT for the prostate cancer prostatectomy patients studied was the “CBCT corrected deformable multi-pass”.

The success of a deformable registration seems harder to fulfil if the separation between the CBCT and pCT position of the ventral rectum wall at the level of the cranial part of the CTV is greater than 20 - 25 mm or if the difference in the CBCT rectum area at the level of the cranial part of CTV is larger than 200% of the pCT rectum area. The ability to perform a successful deformable registration was not affected by differences in bladder volume between the pCT and the CBCT.

The estimated CTV mean doses and CTV $V_{98\%}$ volumes were similar to or larger than their corresponding planned counterparts. Larger variations were found for the rectum and bladder volumes, e.g. the rectum $V_{90\%}$ could be as large as 10 percentage units larger than the corresponding planned $V_{90\%}$ volume and the bladder $V_{65\, Gy}$ volume could be as small as -13.8 percentage units smaller than its corresponding planned volume.
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Reference list


