Published in final edited form as:

Phys Med Biol. 2012 September 7; 57(17): . doi:10.1088/0031-9155/57/17/5361.

Evaluation of the deformation and corresponding dosimetric implications in prostate cancer treatment

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Abstract

The cone-beam computed tomography (CBCT) imaging modality is an integral component of image-guided adaptive radiation therapy (IGART), which uses patient-specific dynamic/temporal information for potential treatment plan modification. In this study, an offline process for the integral component IGART framework has been implemented that consists of deformable image registration (DIR) and its validation, dose reconstruction, dose accumulation and dose verification. This study compares the differences between planned and estimated delivered doses under an IGART framework of five patients undergoing prostate cancer radiation therapy. The dose calculation accuracy on CBCT was verified by measurements made in a Rando pelvic phantom. The accuracy of DIR on patient image sets was evaluated in three ways: landmark matching with fiducial markers, visual image evaluation and unbalanced energy (UE); UE has been previously demonstrated to be a feasible method for the validation of DIR accuracy at a voxel level. The dose calculated on each CBCT image set was reconstructed and accumulated over all fractions to reflect the 'actual dose' delivered to the patient. The deformably accumulated (delivered) plans were then compared to the original (static) plans to evaluate tumor and normal tissue dose discrepancies. The results support the utility of adaptive planning, which can be used to fully elucidate the dosimetric impact based on the simulated delivered dose to achieve the desired tumor control and normal tissue sparing, which may be of particular importance in the context of hypofractionated radiotherapy regimens.

1. Introduction

The advent of cone-beam computed tomography (CBCT) has increased target localization accuracy in prostate cancer radiotherapy by providing daily positional information used for online correction. More precise localization of the target volume allows for improved patient positioning, and hence, overall margin reduction. By reducing margins, dose escalation is more plausible, which has been shown to improve overall prostate cancer radiotherapy outcomes (Peeters *et al* 2006, Song *et al* 2006, Kuban *et al* 2008). With reduced margins, however, caution must be exercised because intra- and inter-fraction prostate motions can more easily result in a geographic miss.

While the benefits of online repositioning for prostate cancer have been observed (Ghilezan *et al* 2004, Wu *et al* 2006), daily deformations in the target and critical organs cannot be fully accounted for using image-guided radiotherapy (IGRT) alone. It has been demonstrated that changes in the target and organ at risk (OAR) location, volume and deformation between the initial simulation and subsequent treatments complicate online registration, and may negatively impact tumor control and normal tissue complication probability (Dawson *et al* 1998, Zelefsky *et al* 1999, Pollack *et al* 2002). Daily patient anatomy and positioning information obtained from CBCT allow access to the daily volumetric deformation and dosimetric implications, while creating an opportunity to make corrections during the course of treatment.

With 3D volume information, CBCT offers the opportunity to perform radiotherapy to the next level: image-guided adaptive radiation therapy (IGART). IGART offers a systematic evaluation of uncertainties related to organ deformation, inter-fraction setup errors and a solution to previous deviations in dosimetric deliveries (Nuver *et al* 2007, Ghilezan *et al* 2010, Wu *et al* 2011). However, challenges remain for widespread clinical acceptance of IGART, including deformable image registration (DIR) accuracy and validation, database maintenance and quality assurance. This work presents a comprehensive description of an IGART framework, including dose calculation on CBCT data sets, validation of DIR accuracy, dose reconstruction and evaluation using dose volume histograms (DVHs) and isodose lines, and finally, incorporation of radiobiological modeling. The IGART framework is first validated in phantom experiments, and then applied to five prostate cancer patient cases, with the overarching goal of integrating IGART for prostate cancer radiotherapy in a clinical setting.

2. Materials and methods

2.1. IGART framework

In this study, an offline process for the IGART framework has been implemented that consists of DIR and validation of the DIR algorithm, dose reconstruction, dose accumulation and dose verification as shown in figure 1. The IGART framework consists of a closed-loop system that incorporates feedback from the updated patient geometry and anatomical information in order to recompute dose and determine the actual dose delivered to the target and surrounding healthy tissues. While similar concepts have been proposed previously (Yan *et al* 1997, de la Zerda *et al* 2007), our approach includes a systematic validation of the DIR algorithm and dose accumulation techniques, as well as a novel method, based on unbalanced energy (UE), for the verification of the DIR accuracy. Moreover, we have applied our IGART framework to a patient planning study and have performed thorough evaluation of the delivered dose distributions using standard dose metrics as well as radiobiological dose indices.

2.1.1. DIR description and phantom validation—DIR was implemented in Elastix (University Medical Center Utrecht, Utrecht, Netherlands) using a multi-resolution grayscale-based approach applied to minimize the cost function using the gradient descent method and B-spline transformation. This process generated displacement vector fields (DVF) that defined the voxel-to-voxel mapping between the fixed (i.e. SIM-CT) and moving images (i.e. CBCT). From there, the dose was calculated on the CBCT using a copy of the SIM-CT treatment plan, and the dose matrix was warped back to SIM-CT for feedback into the IGART framework.

A digital pelvic phantom was developed to optimize the parameter sets used in the DIR algorithm, including the number of spatial samples at each resolution level, iterations, B-Spline grid spacing, etc. The generated phantom images contained structures that

represented the bladder, rectum, prostate and femoral heads (figure 2(a)). The moving phantom images were derived based on the existing DVF created from DIR on a patient (figure 2(b)) (Zhong *et al* 2010). The phantom was deformed using B-Spline transformation and a deformed image was generated as shown in figure 2(c). Voxel-to-voxel DIR results were quantitatively evaluated by comparing the DVF created from B-Spline registration and the known DVF. The offset between the two DVFs in the central axis region (anterior–posterior direction) was calculated (figure 2(d)). The parameters were considered optimized when the difference between the two DVFs was within 1 mm.

2.1.2. DIR performance evaluation—Because the integrity of the IGART framework relies heavily on the performance of DIR and the resultant DVFs, their accuracy was evaluated in three ways: landmark matching with fiducial markers, visual image evaluation and validating the registration with a voxel-based algorithm, as described below.

- *Visual image evaluation (qualitative)*. With a perfect registration, the deformed image should be exactly the same as the fixed image. The congruence of these two images can be assessed through an overlay and checked by split view, checkerboard view, blending view or spyglass available in the Registration Workspace of the Eclipse Treatment Planning System (v8.6, Varian Medical Systems, Palo Alto, CA).
- *Fiducial marker based validation (quantitative)*. Three Acculoc fiducial markers (1 mm diameter, 3 mm length, Northwest Medical Physics Equipment, MEDTEC Company, Orange City, IA) were implanted in each patient's prostate gland, with the first seed placed at the base of the prostate on the left or right side, the second placed toward the mid-prostate gland and the third implanted toward the apex. Seed location was tracked to evaluate the accuracy of the registration, under the assumption that no seed migration occurred. The relative position of the markers between the SIM-CT and deformed CBCTs was calculated to evaluate the registration error. The registration error in the 3D rigid registration was also calculated as a baseline to evaluate the improvement of the registration accuracy in DIR. Each seed's mean offset and standard deviation over 42 treatment fractions were calculated in three dimensions after rigid registration and DIR. The three markers were used to infer the registration accuracy of the entire prostate volume.
- *Unbalanced energy (qualitative)*. DVF accuracy is vital to achieve accurate dose reconstruction for the deformed organ. For areas with relatively low image intensity contrast like the prostate, displacement variations are relatively insensitive to the similarity metrics that may result in DIR error. Furthermore, DIR performance can be complicated by CBCTs that are noisy and have compromised image quality. As a technique to quantify DVF error, Zhong *et al* proposed an automatic method using UE (Zhong *et al* 2007). UE characterizes organ deformation similar to the displacement and elastic force based on solid continuum mechanics. Briefly, the DVF derived from DIR is substituted into a finite-element-based elastic framework to calculate the UE for each element. Three-dimensional UE images were reconstructed by assigning UE to the vertices of each element, thus providing a qualitative means to evaluate the DIR and DVF quality. UE images were reconstructed for the sampling voxels and overall UE was computed by averaging the number in three directions. In regions of high UE values (higher image intensity), registration errors likely exist. To reduce calculation time, UE analysis was focused on truncated images consisting of prostate and nearby OARs.

Once the DIR between SIM-CT and CBCT for all fractions was validated using the above three techniques, the DVF generated from DIR was then used to reconstruct dose as described in the following section.

2.2. Dose reconstruction and accumulation

Clinically used treatment plans originally calculated on the SIM-CT were copied to each CBCT and the dose was calculated with the same treatment plan parameters (beam angle, MU, fluence, dose calculation algorithm etc) and a dose grid size of 2.5 mm. However, since this dose grid resolution was not equivalent to the B-Spline DIR grid, direct transformation could not be applied. As a solution, the CBCT dose was first warped back to the SIM-CT image grid using direct approximation via the transformation matrix. The closest neighboring points on the SIM-CT image grid were estimated by B-Spline interpolation. Then the warped dose on the SIM-CT was resampled to match the location on the planning dose grid with B-Spline interpolation. The raw data of each CBCT dose were converted into DICOM format and imported into the Eclipse Treatment Planning System. Dose accumulation was performed by directly summing the dose at each fraction.

2.2.1. Simulated treatment adaptation—Accumulated dose was used to simulate the actual dose delivered to the patient over the treatment course. This delivered dose was compared to the static dose to evaluate the dose discrepancy for the PTV and OARs.

2.2.2. Phantom study—CBCT offers great potential to be used for IGART by providing volumetric information, while demonstrating a daily representation of patient positioning and anatomy. However, CBCT can be prone to scatter and image artifacts (Siewerdsen and Jaffray 2001) which may limit applicability for both target delineation and dose calculation, which are essential for an effective IGART framework. While the feasibility of using CBCT for dose calculation has been demonstrated previously (Yoo and Yin 2006, Ding *et al* 2007), a series of phantom experiments were conducted to evaluate our approach. All CBCT images were acquired on a Trilogy linear accelerator equipped with CBCT (On-Board Imager, OBI, Varian Medical Systems).

2.2.3. Validation: CBCT dose calculation—The Catphan 500 phantom (The Phantom Laboratory, Salem, NY) was used to evaluate the Hounsfield unit (HU) to electron density relationship using the CTP404 module. This module consists seven high contrast sensitometric targets, including Teflon[®], Delrin[®], acrylic, Polystyrene and low-density polyethylene (LDPE), polymethylpentene (PMP) and air. The CT numbers for these targets range from -1000 to 1000 HU. A CBCT of the Catphan was performed in the half-fan pelvic mode, using settings of 125 kV, 80 mA, 13 ms with the half bow-tie filter in place. The blade size (i.e. collimation) was set to 12 cm. The Catphan was also scanned using multi-slice helical CT (SIM-CT) (Brilliance Big Bore; Philips Health Care, Cleveland, OH). Acquisition parameters were set to 120 kV and 80 mA. Both CBCT and SIM-CT were exported to the Eclipse TPS and the HU for each sensitometric target was measured by averaging the value of ten points surrounding the center of the target.

To evaluate the accuracy of dose calculation on CBCT, the Rando pelvic phantom was used. Using the same imaging acquisition parameters described for the Catphan, the Rando phantom was scanned with both SIM-CT and CBCT. The two image sets were manually registered in the Eclipse Registration Workspace. Prostate, bladder and rectum structures were delineated on the SIM-CT and copied to the CBCT and the contour volume discrepancy was assessed. Two treatment plans were derived: four-field box technique with and without inhomogeneity correction, and nine-field intensity modulated radiation therapy (IMRT). The former consisted of a 3D pelvis plan providing a relative high dose box at the

intersection of the beams, while the latter was consistent with our clinical protocol for prostate cancer radiotherapy consisting of nine IMRT fields at gantry angles of 200°, 240°, 280°, 320°, 0°, 40°, 80°, 120°, and 160°. First, the IMRT treatment plan was optimized and dose was calculated on the SIM-CT using 6MV, pencil beam algorithm and a modified Batho method for inhomogeneity correction. The plan, keeping the MU and fluences fixed, was then copied to the CBCT and dose was recalculated. Per cent dose discrepancies between the SIM-CT and CBCT were calculated for the mean dose (D_{mean}), minimum dose (D_{min}) and maximum dose (D_{max}) using the following equation:

$$\% \text{Diff} = \frac{D_{\text{CBCT}} - D_{\text{SIM-CT}}}{D_{\text{SIM-CT}}} \times 100\% \quad (1)$$

2.2.4. Patient study—Once dose calculation accuracy on CBCT was confirmed in the phantom study, our approach was applied to five patient plans through a retrospective protocol approved by the Henry Ford Health System Institutional Review Board. The mean patient age was 69.2 years (range 61–78), with prostate cancer staging of T1c or T2, prescription doses of 75.6 (42 fractions) or 80 Gy (40 fractions), respectively. The clinical target volumes (CTVs), defined as the prostate plus 1 cm of the proximal seminal vesicles, were, on average, 52.9 ± 14.5 cc. Planning target volumes (PTVs) were defined as the CTV plus 1 cm in all dimensions except posterior, where a margin of 4 or 6 mm was used at the prostate/rectal interface. During the simulation procedure, all patients were instructed to be present with a full bladder and empty rectum, and this was maintained throughout treatment. Daily CBCTs were acquired before radiation therapy for online image guidance, yielding 206 CBCTs (mean 41 per patient) evaluated over the patient population. Twenty-seven CBCTs were lost due to technical problems with the OBI, or patient compliance with the bladder/rectal status and physician's approval to treat using skin-mark-based alignment only for that fraction. Patients were repositioned (3D translational shift) based on the rigid registration performed between the CBCT and SIM-CT (i.e. the reference image), with an emphasis on the rectal/prostate interface.

Clinically used IMRT treatment plans originally calculated on the SIM-CT were copied to each CBCT and the dose was recalculated. As described in the IGART framework section, offline DIR was performed and DVFs were generated. The dose was reconstructed and accumulated over all fractions to reflect the 'actual dose' delivered to the patient. The delivered plans were then compared to the static plans to evaluate PTV and OAR dose discrepancies. The assessment of triggering re-optimization will be discussed in a separate paper. On the rare occasion when a CBCT was not available for the treatment fraction due to the reasons listed above, the SIM-CT dose represented the fractional dose for that treatment session.

2.3. Radiobiological model

Tumor control probability (TCP) and normal tissue complication probability (NTCP) have been well defined in the literature (Webb and Nahum 1993, Keall and Webb 2007). The TCP and NTCP were assessed to demonstrate an explicit comparison in effectiveness between the planned and actual doses. The TCP explored in this study was based on a Poisson statistics-based model that has been previously described (Liu *et al* 2009). Briefly, the model assumes that tumor dose response is sigmoidal in shape and the number of surviving clonogens follows a Poisson distribution coupled with the linear-quadratic (LQ) model. The model is expressed as

$$TCP = e^{-\sum_i N_i SF_i(D_i)}, \quad (2)$$

where N_i is the initial clonogenic cells density of the voxel i in the tumor and $SF_i(D_i)$ is the surviving fraction of the voxel i at given prescription dose. One assumption in this model is that the clonogenic cells are evenly distributed across the PTV. To evaluate simulated tumor control, the TCP was calculated for each CTV. Because there has been much discussion in the literature regarding the α/β value for the prostate, surviving fraction and clonogenic cells density, a broad range of numbers was used for TCP evaluation (Brenner *et al* 2002, Williams *et al* 2007, Proust-Lima *et al* 2011). The α/β ratio was varied from 1.5 to 9.5 in unit increments. SF_2 values of 0.5 and 0.6 were used. The cell density was $10^N/\text{cm}^3$ where N ranged from 3 to 6.

NTCP explored in this study included the classic four-parameter Lyman–Kutcher–Burman model using parameters defined by Rancati *et al* through a multi-center trial of 547 prostate cancer patients for gastrointestinal toxicity (i.e. late grade 2/3 and grade 3 rectal bleeding) (Rancati *et al* 2004). Using grade 2/3 late bleeding as the endpoint, the parameters were as follows: TD50 = 81.9 Gy, steepness m was 0.19 and seriality n was 0.23, whereas for grade 3 late bleeding as the endpoint, TD50 = 78.6 Gy, steepness m was 0.06 and seriality n was 0.06. Parameters for genitourinary (GU) (i.e. bladder) toxicity were derived by Cheung *et al* from 128 patients, using grade 1 or greater late GU toxicity as the endpoint with TD50 = 77.6 Gy, steepness m of 0.02 and seriality n was 0.01. gEUD was also calculated using Niemierko's formula (Niemierko 1999)

$$gEUD = \left(\sum_{i=1}^N v_i D_i^a \right)^{1/a}, \quad (3)$$

where (v_i, D_i) are bins of the dose volume histogram and a is equal to $1/n$.

3. Results

3.1. Computer-generated pelvis phantom

In general, image registration errors were difficult to detect by visual comparison alone. Figure 2(d) shows the offset between two DVFs along the central axis in the anterior–posterior direction. The agreement was within 1 mm for all voxels except at the anterior boundary region, where a larger discrepancy (> 1 mm) was observed. Increased error can be expected at the boundary in B-Spline registration due to the large deformation region at the boundary. The optimized parameters of DIR were applied when performing DIR between SIM-CTs and daily CBCTs for all fractions of five patients.

3.2. Deformable image registration validation

Generally speaking, visual comparison of agreement between the SIM-CT and deformed CBCT provided a qualitative means to evaluate DIR performance. Images were compared slice by slice between the SIM-CT and deformed CBCT in all 38 treatment fractions for patient 1 (CBCT images were not taken in the other four fractions due to technical problems). It showed good match in the prostate region in each registration although this method was found to be somewhat subjective as it was difficult to detect errors of the order of 1 mm with the human eye. The deformed CBCT showed large distortion in the superior/inferior borders due to large scatters in the original CBCT slices. The anterior portion of the bladder was mismatched when there was large deformation in the CBCT images. To more quantitatively evaluate the registration performance, the offsets of each implanted marker were compared after both rigid registration and DIR for one patient (figure 3). The deviation

along the superior–inferior (S/I) direction was the highest among all three directions due to the 3 mm space between slices. Table 1 demonstrates the mean and standard deviation of registration results for this patient over 42 fractions of treatment. Overall, the mean registration difference of each seed was 5.0 ± 2.1 , 5.6 ± 2.2 and 4.8 ± 2.4 mm, respectively, for the rigid registration result. After DIR, the mean marker offset was 0.0 mm in all three directions, with a standard deviation of 0.5, 0.7 and 0.7 mm, respectively.

In order to detect the registration error systematically in three dimensions, UE was employed. If a region included both correct and mis-registered nodes, the elasticity energy calculated by the FEM model would have large unbalanced values in this region. The UE values corresponded to the brightness in images. A higher magnitude of unbalanced energy suggested less accurate DIR, which were shown as brighter in the UE images. Figure 4 demonstrates the UE analysis for an imaging fraction of a patient case. The images were sampled every 9 mm in the pelvic region for illustration purpose. The value of UE was in the range of 0–120 milli-Joules. There was a brighter region in the UE image shown in the third raw image (figure 4(c)) which indicated higher UE. Compared to the SIM-CT image, the deformed CBCT image was distorted in the regions of seminal vesicles, bladder and rectum, and these regions have high UE values as shown in figure 4(c). In contrast, the UE values in the target were small, corresponding to the low registration error of the target, as illustrated by the seed positions in figures 4(a) and (b). The seed-based verifications had shown that the overall quality of DIR was acceptable in the prostate region. The low UE values (0–30 milli-Joules) also indicated that the registration result was good in the prostate region. The UE values are not correlated with the registration error exactly in the current development stage. However, it is still a valuable tool to detect the areas in the registration that require further assessment.

3.3. HU-ED calibration and dose calculation on CBCT

On average, the HU for the CBCT was 10.1% lower compared to the HU for the SIM-CT (range: 2.2% to 65.8%). The largest absolute HU discrepancy between the two scans was observed for the highest density material (i.e. Teflon).

On the Rando phantom, when contours were copied from the SIM-CT to the CBCT, a slight difference (<1%) of the volumes in the two image sets was observed due to interpolation since the pixel matrix is different between SIM-CT (512×512) and CBCT (384×384). When the four-field box technique was used with inhomogeneity correction turned off, the dose discrepancy between the SIM-CT and CBCT was 0.0%, 0.0%, and 1.3%, for the D_{mean} , D_{max} , and D_{min} , respectively.

Table 2 summarizes the dose discrepancies for the prostate, rectum and bladder using the four-field box (3D) and IMRT planning techniques with inhomogeneity correction. For the four-field box plan when inhomogeneity correction was enabled, up to 2% difference was observed for the prostate and OARs. The DVHs both with and without inhomogeneity correction are displayed in figure 5. Only slight deviations in the dose distributions can be observed in the DVH comparison between the CBCT and SIM-CT.

For the nine-field IMRT plan, the dose distribution in the prostate calculated on the CBCT was very close to the SIM-CT plan, with D_{max} and D_{min} CBCT doses 1.3% and 1.2% higher, respectively, than the SIM-CT dose. The prescription isodose coverage, as defined by D95% was also very similar between the SIM-CT and CBCT, with a 2% average difference. The dose to the rectum showed more discrepancy with about 5.4% difference in the minimum dose. However, the absolute dose difference of 0.3 Gy was very small.

3.4. Plan evaluation

3.4.1. Target coverage—The static and delivered planar dose distributions were compared on a slice-by-slice basis for all the five cases studied. Clearly, the isodose distributions in the two cases were very similar. Both CTV and PTV were well covered by the prescription dose in this case. DVH comparisons of PTV, CTV, rectum and bladder for all five patients are shown in figure 6 and dose statistics comparisons are shown in table 3. The maximum and minimum doses were slightly different for the CTV in the two plans. With a 10 mm margin expansion, planned dose statistics for the CTV were very close to the deformed values for all five patients. Differences of mean, minimum and maximum doses of CTV were all within 2%, although the minimum PTV doses showed a larger discrepancy (from -1.9% to 17.9%) between the static and delivered plans. However, for patients 1 and 3, the deformed PTV minimum doses matched the planned doses within 2%. Patient 5 showed the highest discrepancy in the PTV minimum dose coverage, where the difference was up to 17.9%. For all five patients, the maximum and mean PTV doses were still within 2%.

To evaluate simulated tumor control, the TCP was calculated for each CTV with varied parameters of α/β ratio, SF_2 , and cell density as described in section 2. When SF_2 was 0.5, TCP for all plans for these five patients was within 99% for the static and delivered plans, revealing undetectable differences between the plans (not shown). TCP was almost independent of cell density, with only a slight (0.1%) variation from 10^3 to $10^6/\text{cm}^3$. When SF_2 was 0.6, the TCP value depended on N_0 and the patient-specific dose distribution. If tumor cell density was less than $10^5/\text{cm}^3$, then the TCP was close to 1. As cell density increased from 10^5 to 10^6 , the reduction in TCP for each patient varied. TCP ranged from 0.81 to 0.9 depending on the patient dose distribution as shown in figure 7.

3.4.2. Normal tissue complications—Rectum and bladder doses were also compared for each patient. As noted in figure 6, the deformed bladder and rectum doses were higher than originally planned for all five patients studied. Table 4 shows the gEUD found to evaluate grade 2/3 and grade 3 late rectal bleeding between the delivered and static dose distribution for five patients. gEUD of grade 2/3 rectal bleeding ranged from 53 to 58 Gy based on the static plan and increased 8–15% in the delivered plan, while the gEUD (grade 3 rectal bleeding endpoint) was between 67 and 74 Gy in the static plan and increased 2–4% in the delivered plan. The corresponding NTCPs for grades 2/3 and grade 3 rectal bleeding are shown in figures 8(a) and (b), respectively, between dose distributions in the static and delivered plans. The mean change in NTCP for grades 2/3 bleeding between the static and delivered plans for five patients was 4.6%. A similar trend was shown in NTCP for grade 3 toxicity, an increase of 4.5% in average. The mean change in NCTP for grade 1 or greater late GU toxicity between the static and delivered plans for five patients was -7.3%.

4. Discussion

This paper sought to compare the differences between static and delivered doses following the implementation of an IGART framework for prostate cancer radiation therapy. Each aspect of the IGART framework was described and validated.

The evaluation of seed positions provided more quantitative analysis of DIR accuracy. The seed position correlated very well between SIM-CT and deformed CBCT after DIR, although the magnitude of displacement in the S/I direction was of higher magnitude (~3–4 mm) for the rigid registration when compared to the deformable image registration. This was due to the larger voxel dimension (3 mm CT slice thickness) in the z-direction as compared to the voxel size of 1.07 mm in both x- and y-directions. One limitation of this analysis was that the three seeds represented the target volume (Kupelian *et al* 2007). To

compliment these results, UE was calculated by a finite-element-based framework to evaluate DIR performance. UE values were low in the whole prostate, indicating less distortion and high accuracy for the DIR in the target region. The UE screening process helps ensure the quality of the performed DIR in the target region.

Patient 5 demonstrated the largest dose discrepancy in PTV minimum dose coverage. Because of poor bladder or bowel preparation, this patient had instances where the dose gradient at the edge of PTV was very sharp, and target deformation or displacement pushed a portion of PTV out of prescription isodose line, thereby significantly reducing the minimum PTV dose. During simulation and subsequent treatment, all five patients were given specific bowel and bladder preparation instructions (empty and full, respectively). Upon review of the physiological statuses on the daily CBCT, our clinical practice is to stop treatment until the initial simulation conditions have been met. Even with this intervention, some patients are non-compliant with the bladder and rectal filling status requirements and this was found to influence the delivered plan of patient 5.

Overall, rectum and bladder doses were shown to increase in this IGART framework, likely due to both daily tissue deformation and the lack of adherence to the full bladder/empty rectum initial conditions in the SIM-CT. The level of the patient compliance of bladder/rectal status was patient dependent, although it was found that the variation of NTCP was sensitive to the patient factor and rectal volume size using late rectal bleeding as the end point. Late GU toxicity was not sensitive because the maximum bladder doses did not increase in the delivered dose estimations. Limited data are available on GU toxicity, largely due to delayed onset and limitations introduced by unstable daily bladder volumes. Cheung and colleagues used NTCP calculation to evaluate late GU toxicity of grade ≥ 1 , although in this study, n was very small and the bladder was considered to be a serial organ (Cheung *et al* 2007). Their findings suggested that GU complications were directly correlated with maximum dose to the bladder. In our study, the bladder NTCPs between the delivered and static dose distributions were very similar, which was expected because the magnitude of $D_{\max}$ did not vary appreciably despite daily deformations in the target and OARs. Patient 3 had almost no predicted likelihood of complication ($D_{\max} = 74$ Gy), while patient 2 had 100% predicted likelihood of GU toxicity since $D_{\max}$ was about 80 Gy (figure 8).

Despite being historically thought of as a serial organ (Burman *et al* 1991), more recent literature supports the rectum as a parallel organ based on the Italian multi-centric study (Rancati *et al* 2004) particularly when grade ≥ 2 late rectal bleeding is considered as an end point. The presence of bleeding primarily largely depends on the rectal volume at 40–50 Gy regions. When considering grade 3 late bleeding, the rectum has been shown to behave more like a serial organ. For all five patients studied, increased rectal dose in the intermediate dose regions (i.e. 40–50 Gy) was observed in the delivered plan. This suggests that a higher complication probability of grade ≥ 2 late rectal bleeding may be expected. In the case of patient 2, this complication doubled since the patient had difficulty maintaining an empty rectum, causing the rectum to fall into a higher dose region, thereby increasing the probability of late rectal bleeding.

The patient population is limited to 42 fractions in five early stage (i.e. low risk) prostate cancer patients. Patients with advanced disease (i.e. lymph node involvement or other pelvic treatment) were not included in the study due to limitations in the CBCT longitudinal scan range (~ 20 cm), with slightly less data available in the 3D reconstruction due to the loss of information at the peripheral region. However, the impact of scatter in CBCT is known to be proportional to scan volume, so increasing scan range may also be detrimental to CBCT image quality, thus impacting DIR performance. Guan and Dong (2009) have suggested that HU-ED calibration should be done for each CBCT acquisition mode, although only one

acquisition mode (i.e. pelvis) was explored in this study. An alternative solution to increase the longitudinal scan range is to use the multiple orbit acquisition or helical scan method (Yang *et al* 2012). Such techniques will fully extend the application range of CBCT to many cancer sites.

Another known limitation in this study is that the Catphan was used to generate the HU-ED calibration curve for CBCT. It has been demonstrated that Catphan materials such as high density Teflon are not representative of cortical bone due to the difference in the effective atomic number between the materials (8.5 and 13.8, respectively) (Craig *et al* 1999). Even with this limitation, it has been reported that an 8% difference in electron density yields ~1% difference in dose calculation for bony material (Thomas 1999). Furthermore, Yang and colleagues also revealed that CBCT could be applied for the dose calculation on the prostate site (Yang *et al* 2007).

The IGART framework and associated tools described in this work will be used to determine the actual doses delivered to patients during daily treatment, ultimately assessing the benefit of daily CBCT imaging in the context of planning margins/normal tissue doses, dose escalation to the target for equivalent normal tissue doses or adapting the plans to make the delivered dose distribution match the prescribed dose distribution. Future work will involve evaluating plan re-optimization strategies including balancing the complexity of data management and labor hours with re-optimization frequency, and assessment of triggering re-optimization. Associations with clinical outcomes (toxicities, survival, and other endpoints) were not explored in this study. The cost–benefit analysis should also be conducted to evaluate improvement of dosimetric outcome and complexity created from frequent re-optimization. The clinical assessment of these criteria has been undergoing development and is beyond the scope of this feasibility study.

5. Conclusions

We have developed an IGART planning framework for prostate cancer radiotherapy and have demonstrated initial results. All aspects of the IGART framework were validated using phantom tests. The framework was applied to a population of five patients with early-stage prostate cancers. The results support the utility of adaptive planning, which can be used to fully elucidate the dosimetric impact based on the simulated delivered dose to achieve desired tumor control and normal tissue sparing, which may be of particular importance in the context of hypofractionated radiotherapy regimens.

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Figure 1.
Image-guided adaptive radiotherapy (IGART) framework used in the patient studies.

Figure 2. (a) Fixed images generated by computer to represent pelvis which included bladder, rectum, prostate and femoral head. The phantom image grid consists of $160 \times 160 \times 160$ voxels with voxel size of 1 mm in all three dimensions, (b) the moving images deformed from the fixed images based on the DVF derived from an actual patient, (c) the deformed images derived from the moving images using B-Spline registration and (d) the offset between the two DVFs in the central axis region (anterior–posterior direction).

Figure 3.

Scatter plot demonstrating seed displacement, calculated as the difference in seed position in the prostate at each fraction after DIR and rigid registration. Blue point represents the L–R direction. Red point represents the A–P direction. Yellow point represents the S–I direction. The upper row shows the offset of seeds 1, 2, 3 between SIM-CT and deformed CBCT in the L–R, A–P, S–I directions, while as the lower row shows the offset of seeds 1, 2, 3 after the rigid registration in all three directions.

Figure 4. DIR validation calculated with unbalanced energy. (a) SIM-CT images sampled with 9 mm spacing, (b) corresponding deformed CBCT images and (c) the UE images corresponding to the ROI highlighted in CT images. The higher intensity of the UE, the poor quality of DIR was achieved.

Figure 5. DVH comparison of prostate (red), rectum (blue) and bladder (pink) between the plans calculated on SIM-CT (solid line) and CBCT (dashed line) images with and without the inhomogeneity correction.

Figure 6.

DVH comparisons between the static and delivered plans for patients 1–5. CTV coverage was similar between the static and delivered doses, whereas dose degradation was apparent in the delivered PTV doses. Doses to the rectum and bladder tended to be higher in the delivered plans, likely due to changed geometry from the initial CT simulation.

Figure 7. TCP versus N_0 between the static and delivered doses of patients 1–5. The α/β ratio is 4.5 and SF_2 is 0.6. Solid lines indicate a static plan and dashed lines indicate a delivered plan. The TCP value only showed small difference when N_0 was up to 10^6 .

Figure 8.

NTCP comparison for five patients between the static and delivered plans over the treatment course for (a) grade 2/3 late rectal bleeding, (b) grade 3 late rectal bleeding and (c) late GU toxicity with grade ≥ 1 . Metrics used in the NTCP calculation (i.e. TD_{50} , n and m) can be found in the text.

Table 1

Comparison of seed offsets between rigid registration and deformable image registration (DIR). Mean and standard deviation over 42 fractions are calculated for three seeds at each direction (lateral, anterior-posterior, and superior-inferior) and overall vector length.

		Lateral (mm)	A/P (mm)	S/I (mm)	Vector (mm)
Rigid	Seed 1 (rt base)	0 ± 1.16	3 ± 2.06	3 ± 2.48	4.97 ± 2.12
	Seed 2 (lt base)	0 ± 1.21	3 ± 1.87	4 ± 2.6	5.55 ± 2.22
	Seed 3 (apex)	0 ± 1.50	-2 ± 2.14	4 ± 2.47	4.78 ± 2.44
DIR	Seed 1 (rt Base)	0 ± 0.40	0 ± 0.47	0 ± 0	0.37 ± 0.53
	Seed 2 (lt base)	0 ± 0.51	0 ± 0.54	0 ± 0.5	0.53 ± 0.72
	Seed 3 (apex)	0 ± 0.50	0 ± 0.52	0 ± 0.50	0.55 ± 0.71

Table 2

Minimum, maximum and mean per cent doses for prostate, rectum and bladder using the four-field box (3D) and IMRT planning techniques with inhomogeneity correction in a Rando phantom.

		3D			IMRT		
		SIM-CT (% dose)	CBCCT (% dose)	Difference (%)	SIM-CT (% dose)	CBCCT (% dose)	Difference (%)
Prostate	$D_{\min}$	94.9	93.6	-1.37%	94.5	93.4	-1.16%
	$D_{\max}$	102.2	101.5	-0.68%	105.7	104.3	-1.32%
	D_{mean}	99.4	98	-1.41%	100	98.2	-1.80%
	$D_{95\%}$	97.2	95.3	-1.95%	97.8	96	-1.84%
Rectum	$D_{\min}$	47.4	46.8	-1.27%	5.6	5.9	5.35%
	$D_{\max}$	101.7	101.1	-0.59%	100.6	98.3	-2.29%
	D_{mean}	63.0	62.5	-0.79%	22.8	22.1	-3.07%
	$D_{95\%}$	49.3	48.8	-1.01%	5.9	5.9	0.00%
Bladder	$D_{\min}$	99.8	98.7	-1.10%	101.6	102.9	1.28%
	$D_{\max}$	58.7	58.3	-0.68%	22.4	23	2.68%
	D_{mean}						

Table 3

Dose statistics comparison of CTV, PTV, rectum and bladder between static and delivered dose distributions for five patients.

Pt	Dose (Gy)	CTV			PTV			Rectum			Bladder		
		Static	Deliver	% Diff	Static	Deliver	% Diff	Static	Deliver	% Diff	Static	Deliver	% Diff
1	Min	76.56	77.49	1.21	59.21	60.44	2.08	3.55	3.14	-11.55	0.79	0.53	-32.91
	Mean	78.71	78.91	0.25	79.07	79.13	0.08	33.55	38.92	16.01	24.89	27.53	10.61
	Max	82.34	82.83	0.60	83.48	83.23	-0.30	81.04	81.61	0.70	83	82.1	-1.08
2	Min	79.03	79.97	1.19	50.78	55.29	8.88	2.43	2.81	15.64	2.52	2.74	8.73
	Mean	83.57	82.77	-0.96	83.41	81.8	-1.93	36.97	45.46	22.96	38.03	36.75	-3.37
	Max	87.66	86.25	-1.61	88.01	87.13	-1.00	87.17	85.79	-1.58	86.75	84.77	-2.28
3	Min	76.29	76.22	-0.09	67.06	67.84	1.16	2.46	5.44	121.14	2.36	2.42	2.54
	Mean	77.61	77.61	0.00	77.51	77.37	-0.18	35.63	50.74	42.41	34.78	36.28	4.31
	Max	79.33	79.32	-0.01	79.61	79.41	-0.25	78.28	78.11	-0.22	78.04	77.85	-0.24
4	Min	80.83	80.18	-0.80	67.58	71.02	5.09	2.55	2.57	0.78	1.16	1.76	51.72
	Mean	82.05	81.03	-1.24	82.2	81.14	-1.29	40.89	45.34	10.88	30.3	39.6	30.69
	Max	83.59	82.29	-1.56	84.47	83.14	-1.57	83.37	82.04	-1.60	83.28	81.44	-2.21
5	Min	75.89	76.9	1.33	58.4	68.85	17.89	3.01	4.43	47.18	8.84	11.81	33.60
	Mean	78.52	78.08	-0.56	78.54	78.14	-0.51	41.52	49.83	20.01	42.89	48.39	12.82
	Max	81.02	79.74	-1.58	81.17	80.28	-1.10	79.39	78.48	-1.15	79.58	78.41	-1.47

Table 4

gEUD calculated in the delivered and static dose distributions to evaluate grade 2/3 and grade 3 late rectal bleeding. Per cent difference was calculated as $(\text{Deformed gEUD} - \text{Planned gEUD}) \times 100\% / \text{Planned gEUD}$.

	Patient	Deformed gEUD (Gy)	Planned gEUD (Gy)	%Diff
Grade 2/3	1	57	53	7.55
	2	64	58	10.34
	3	61	53	15.09
	4	61	56	8.93
	5	61	55	10.91
Grade 3	1	71	69	2.90
	2	75	74	1.35
	3	69	67	2.99
	4	73	70	4.29
	5	70	67	4.48