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Simulation of pseudo-CT images based on deformable image registration of ultrasound images: A proof of concept for transabdominal ultrasound imaging of the prostate during radiotherapy

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Purpose: Imaging of patient anatomy during treatment is a necessity for position verification and for adaptive radiotherapy based on daily dose recalculation. Ultrasound (US) image guided radiotherapy systems are currently available to collect US images at the simulation stage (US$_{sim}$), coregistered with the simulation computed tomography (CT), and during all treatment fractions. The authors hypothesize that a deformation field derived from US-based deformable image registration can be used to create a daily pseudo-CT (CT$_{ps}$) image that is more representative of the patients’ geometry during treatment than the CT acquired at simulation stage (CT$_{sim}$).

Methods: The three prostate patients, considered to evaluate this hypothesis, had coregistered CT and US scans on various days. In particular, two patients had two US–CT datasets each and the third one had five US–CT datasets. Deformation fields were computed between pairs of US images of the same patient and then applied to the corresponding US$_{sim}$ scan to yield a new deformed CT$_{ps}$ scan. The original treatment plans were used to recalculate dose distributions in the simulation, deformed and ground truth CT (CT$_{gt}$) images to compare dice similarity coefficients, maximum absolute distance, and mean absolute distance on CT delineations and gamma index ($\gamma$) evaluations on both the Hounsfield units (HUs) and the dose.

Results: In the majority, deformation did improve the results for all three evaluation methods. The change in gamma failure for dose ($\gamma_{Dose}$, 3%, 3 mm) ranged from an improvement of 11.2% in the prostate volume to a deterioration of 1.3% in the prostate and bladder. The change in gamma failure for the CT images ($\gamma_{CT}$, 50 HU, 3 mm) ranged from an improvement of 20.5% in the anus and rectum to a deterioration of 3.2% in the prostate.

Conclusions: This new technique may generate CT$_{ps}$ images that are more representative of the actual patient anatomy than the CT$_{sim}$ scan. © 2016 American Association of Physicists in Medicine. [http://dx.doi.org/10.1118/1.4944064]

Key words: ultrasound imaging, image guided radiotherapy, deformable image registration, adaptive radiotherapy, prostate cancer

1. INTRODUCTION

Image guidance has become an essential part of radiotherapy (RT) treatment to allow for safe delivery of radiation doses. Image guided RT (IGRT) is often performed for several or all treatment fractions to position the patient correctly. Beyond the aim of image guidance, the availability of daily imaging also allows for the possibility of adaptive RT (ART).

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The goal of ART is to improve RT treatment by systematically monitoring dose discrepancies and incorporating them to reoptimize the treatment plan. Normally only the planning computed tomography (CT) image, acquired at simulation stage, is available for the dose calculation, but both interfraction and intrafraction patient anatomy motion and changes (like tumor shrinkage, nodal volume changes, and weight loss) may alter the dose distribution.\(^3\,4\) In ART, the anatomy from the planning CT is updated by the anatomy from the daily imaging, acquired during the IGRT workflow to monitor dose distribution and if necessary adapt the treatment plan.

CT scanners are usually not available in the treatment room. Instead, cone-beam computed tomography (CBCT) can be used for dose calculations either directly\(^7\,\,8\) or indirectly with deformable image registration (DIR)\(^11,\,12\) even though they offer a lower image quality when compared to CT scanners. In some studies, using the CBCT directly for dose calculations, the inaccuracies in the Hounsfield units (HUs) are large enough to result in clinically relevant dose errors.\(^13\,\,15\)

In this paper, a workflow is introduced to produce pseudo-CT images based on deformable registration of ultrasound (US) volumes. A 3D US IGRT system can acquire volumetric, high-contrast soft-tissue images noninvasively on a daily basis without using ionizing radiation (Fig. 1). Subsequently, deformable registration of these volumes can reveal changes in tissue distribution that occurred over time.

Relatively few papers on US to US deformable registration can be found in the literature and as far as we could find, there are presently no papers involving deformable registration of pelvic or abdominal US volumes in RT. In other medical fields, however, some publications are available. For example, Shekhar et al.\(^16\) proposed a nonrigid method based on mutual information to register cardiac US images in different phases throughout the complete cardiac cycle.

A similar workflow as proposed in this study was presented for brain surgery applications by Pennec et al.\(^17\) In this study, preoperative magnetic resonance (MR) images and US images were acquired. Subsequently, intraoperative US images were used to create pseudo-MR images of the brain. This resulted in acceptable representations of the brain anatomy during surgery.

As these results were promising, we used a similar approach to create pseudo-CT (CT\(_{ps}\)) images. We hypothesize that a pseudo-CT image can be created based on CT\(_{sim}\) using a deformation field calculated between US\(_{sim}\) and US\(_{tx}\). We expect that the CT\(_{ps}\) so created gives a better representation of the patient’s anatomy during treatment delivery than the planning CT\(_{sim}\).

\section{2. MATERIALS AND METHODS}

\subsection*{2.A. The concept}

In the proposed workflow (Fig. 2) for CT\(_{ps}\) image creation, DIR has to be performed to calculate a deformation field between US\(_{sim}\) and US\(_{tx}\). Subsequently, this deformation field has to be applied to CT\(_{sim}\) which results in the creation of CT\(_{ps}\).

\subsection*{2.B. Patient scans}

Clinical examples with multiple coregistered US–CT combinations at the simulation stage (instead of the treatment stage) were used to validate the concept. In this study, three prostate cancer patients from a previous study\(^18\) were used. Due to clinical reasons, these patients underwent additional US and CT imaging next to US\(_{sim}\) and CT\(_{sim}\) acquisitions. In the normal clinical workflow, these extra CT and US images are not acquired. The extra CT scans were used as ground truth (CT\(_{gt}\)) scans to which the derived CT\(_{ps}\) scans can be compared in this proof of concept study. In Table I, the method used to calculate and evaluate the result from the deformations is described.

The coregistered CT–US images were acquired at two time points for patients 1 and 2 (three and one weeks apart, respectively). Acquisitions for patient 3 were made for five time points where the first two were two weeks apart and the following three time points were one week apart.

![Workflow of acquisition of CT\(_{sim}\), US\(_{sim}\), and US\(_{tx}\) images (Clarity US system; Elekta) (adapted from Elekta with their permission).](image-url)
All coregistered US–CT combinations were acquired in the CT-room with the patient’s external skin markers positioned along the room lasers. The 3D US scans (Clarity system; Elekta, Stockholm, Sweden, voxels: $1 \times 1 \text{mm}^2 \times 3 \text{mm}$ slice thickness; US probe type C5-2/60, center frequency 3.5 MHz; Sonix Series; Ultrasonix Medical Corporation, Richmond, BC, Canada) were performed transabdominally immediately before or after the CT scan. The number of voxels of the US images varied between $[512, 512, 90]$ and $[512, 512, 131]$. For each patient, the images were resampled to match the dimensions of the first acquired US volume (US$_{sim}$).

The CT scans were acquired using a SOMATOM Sensation Open (Syngo CT 2006A, Siemens, Germany; voxels: $1 \times 1 \text{mm}^2 \times 3 \text{mm}$ slice thickness). Both scans were performed in the same supine patient position, stabilized with knee fix and foot support (Combifix, Civco Medical Solutions, Kalona, IA, USA), resulting in a correct automatic fusion of the US and CT images.

In all US images, the prostate was delineated. All CT images had delineations of the body contour, prostate, seminal vesiculae (SV, except for patient 3), anus, rectum, and bladder (except for patient 1).

### 2.C. Deformation

For each US–CT combination (as detailed in Table I), deformation fields were calculated using a DIR algorithm (B-spline method from ElastiX; Utrecht, The Netherlands). Prior to the deformation field calculation, all volumes were resampled to the same image dimensions per patient. In addition, segmentation of the CT$_{sim}$ images resulted in a binary mask of the bones and the region of interest (ROI) was defined as the overlapping parts of the US images (ROI: $US_{sim} \cap US_{tx}$). All these preprocessing steps were performed in the MATLAB (MathWorks, Inc., Natick, MA) software.

During the acquisition of the different US–CT combinations, the patients were in the same position with the body markers aligned to the lasers. For this reason, no rigid transformation was performed prior to the deformable registration, in particular, to prevent erroneous full body shifts based on internal shifts of the prostate.

As mentioned before, the deformable registration was performed using the ElastiX software. This software package requires three inputs: fixed image (US$_{tx}$), moving image (US$_{sim}$), and a parameter file. The parameter file contains all the parameters that determine the characteristics of the registration. In Sec. A of the supplementary material, an example of such a parameter file is detailed.

In this study, the deformable registration was performed either on the overlapping parts of the US images or on binary masks of the delineated prostate volumes only. In total, five different parameter sets (parameters A–E in Table II) were defined for this purpose using the file in Sec. A of the supplementary material as a basis.

The deformation field calculations were based on the overlapping parts of the US images, but were propagated further through the image (Fig. 3). Also bones were sometimes present in these overlapping parts. As bones are in principle rigid structures, they are not expected to undergo deformations. Therefore, the binary bone mask defined during preprocessing was input in the rigidity penalty of ElastiX to prevent bones from deforming.

### 2.D. Evaluation of the deformation

The created CT$_{ps}$ and the deformed CT delineations were then compared to the ground truth, i.e., the corresponding CT$_{gt}$ and its delineations. The contours were evaluated using the dice similarity coefficient 

$$DSC = \frac{2|X \cap Y|}{|X| + |Y|},$$

A DSC ratio of 1 indicates complete overlap, while 0 indicates no overlap.
Five different parameter sets (A–E) were used during the deformable registration. This registration could be based on the whole US volume or on the binary mask of the delineated prostate volume only (reported in the columns: fixed image and moving image). In addition, both the metric and iterations were varied among the different sets.

| Parameter set | Fixed image   | Moving image | Metric        | Iterations |
|---------------|---------------|--------------|---------------|------------|
| A             | US_tx         | US_sim       | Normalized-correlation | 10         |
| B             | US_tx         | US_sim       | Normalized-correlation | 50         |
| C             | US_tx         | US_sim       | Normalized-correlation | 100        |
| D             | Prostate mask | Prostate mask | Mean-squares   | 100        |
| E             | Prostate mask | Prostate mask | Mean-squares   | 300        |

Note: US_tx, daily acquired US image at treatment stage. US_sim, reference/planning US acquired at the time of CT simulations.

In addition, the prostate contours were also evaluated using both the maximum absolute distance (MAX) and the mean absolute distance (MAD).\(^{24}\) The MAX defines the largest difference between two contours, e.g., prostate contour A and prostate contour B. For each point a on prostate contour A, the minimal distance to all points on prostate contour B was calculated. The same was repeated for each point b on prostate contour B with respect to prostate contour A. This resulted in a set of minimal distances and the maximum of this set is referred to as MAX. Calculating the mean of this set gave the MAD.

The CT_sim and CT_ps images were compared to CT_gt using a gamma ($\gamma$) index evaluation.\(^{25,26}\) The $\gamma$ index is commonly used for dose evaluations. Prior to the index calculation, two acceptance criteria need to be set: voxel-by-voxel numerical dose difference and distance-to-agreement (DTA: distance between a voxel on one volume and the nearest voxel in the other volume that has the same dose). The resulting index gives information on a voxel scale, while taking the voxels in the vicinity into account as well.

In this case, not only dose was evaluated with the $\gamma$ index but also HU ($\gamma_{CT}$). The $\gamma$ values were calculated using an in-house developed method\(^{27,28}\) using MATLAB and C++. The used method allows the sign of the $\gamma$ value to indicate whether an overdose ($\gamma > 0$) or underdose ($\gamma < 0$) is found for each voxel.\(^{28}\) In this case, because we evaluate HU, a $\gamma > 0$ means that the HU is relatively higher than the reference and $\gamma < 0$ means that the HU is relatively lower. A value $|\gamma| > 1$ in a voxel indicates that the voxel fails to meet the acceptance criteria; in this case, a 50 HU voxel intensity difference and a 3 mm distance-to-agreement. (The 50 HU is a conservative measure based on that for typical radiotherapy beams; to produce a 1% error in dosimetry would require errors of over 8% in bone electron density\(^{29}\) and hence HU. The 3 mm distance-to-agreement is a commonly used criterion in dosimetry.\(^{26}\))

The percentages of the volume with a $|\gamma_{CT}| > 1$ within the contours “intersection body contours,” “prostate,” “anus and rectum,” and “bladder” were reported. The percentages of gamma failure and DSC evaluations are reported using the contours of the CT_gt, except for the intersection body contours which is the overlapping part of the body contours of both CT_sim and CT_gt.

### 2.E. Dose calculation and evaluation

Dose distributions were obtained by recalculating the original treatment plans (five-beam IMRT plans; XiO CMS 4.51, Elekta, Stockholm, Sweden) designed on the planning CT_sim, on the CT_sim, CT_ps, and CT_gt scans. For this, an in-house developed software was used, based on Monte Carlo

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**Fig. 3.** Example of overlap between CT (gray) and US (color) (a) and between two US images (b) of patient 1. US-based DIR can only be performed on the area where both CT and US information (of both US_sim and US_tx) is available. In this example, only the prostate and its surrounding tissue, e.g., a part of the bladder, are present in both US images. In (c), only the overlapping area of both US images (yellow contour) contains information where the deformation field (2D representation with red arrows) is based on. The field propagates further beyond this border (see color version online).
Five evaluation methods were used to evaluate the delineated prostate contours. The first and second columns detail the patient and the used evaluation method. Both gamma index values show the volume percentage of gamma failure, $\gamma_{DCT(50, 3\,mm)}$ and $\gamma_{Dose(95, 3\,mm)}$, respectively. In the third column, the reference situation (comparison between CTsim and CTps) can be found. In the final five columns, the results for each of the parameter sets (A–E) are detailed. The bold numbers indicate which parameter sets resulted in the same result or in an improvement with respect to the reference.

**Table III.** Five evaluation methods were used to evaluate the delineated prostate contours. The first and second columns detail the patient and the used evaluation method. Both gamma index values show the volume percentage of gamma failure, $\gamma_{DCT(50, 3\,mm)}$ and $\gamma_{Dose(95, 3\,mm)}$, respectively. In the third column, the reference situation (comparison between CTsim and CTps) can be found. In the final five columns, the results for each of the parameter sets (A–E) are detailed. The bold numbers indicate which parameter sets resulted in the same result or in an improvement with respect to the reference.

| Patient | Metric | Ref. | A | B | C | D | E |
|---------|--------|------|---|---|---|---|---|
|         | DSC    |      | 0.4 | 0.7 | 0.7 | 0.7 | 0.7 |
| 1       | MAD (mm) |      | 7.5 | 3.3 | 3.5 | 3.7 | 2.7 |
| 2       | MAX (mm) |      | 27.9 | **15.3** | 16.3 | 16.0 | 9.8 | 12.2 |
| 3        | $\gamma_{CT}$ (%) | | 12.0 | **4.6** | 2.9 | 3.0 | 5.3 | 7.1 |
| 3        | $\gamma_{Dose}$ (%) | | 18.3 | **12.4** | 8.1 | 7.1 | **13.0** | 13.7 |
| 1       | DSC    |      | 0.5 | 0.5 | 0.5 | 0.6 | 0.6 |
| 2       | MAD (mm) |      | 5.1 | 5.5 | 5.5 | 5.7 | 3.9 |
| 3        | MAX (mm) | | 16.0 | 18.1 | 21.6 | 23.2 | **13.9** |
| 3        | $\gamma_{CT}$ (%) | | 11.5 | 14.6 | 12.8 | 12.3 | **10.2** |
| 3        | $\gamma_{Dose}$ (%) | | 1.6 | 2.2 | 2.8 | 2.9 | **1.4** |
| 3a      | DSC    |      | 0.8 | 0.6 | 0.4 | 0.4 | 0.6 |
| 3b      | MAD (mm) |      | 2.3 | 4.3 | 4.2 | 4.4 | **2.1** | 2.3 |
| 3c      | MAX (mm) |      | 8.4 | 16.4 | 18.9 | 19.1 | **5.9** | 6.1 |
| 3d      | $\gamma_{CT}$ (%) | | 6.6 | 6.6 | 7.0 | 6.8 | **5.0** | 5.1 |
| 3d      | $\gamma_{Dose}$ (%) | | 3.8 | 3.5 | 2.7 | 3.2 | **1.8** | 2.2 |
| 3        | DSC    |      | 0.6 | 0.5 | 0.5 | 0.5 | 0.7 |
| 3        | MAD (mm) |      | 4.4 | **3.8** | 4.4 | 4.9 | 2.5 | 2.2 |
| 3        | MAX (mm) |      | 12.4 | 14.0 | **12.4** | 13.0 | **7.1** | 6.2 |
| 3        | $\gamma_{CT}$ (%) | | 9.9 | 7.1 | 7.7 | 7.2 | **7.9** | 6.8 |
| 3        | $\gamma_{Dose}$ (%) | | 4.1 | 3.3 | 3.5 | 4.2 | **3.4** | 3.8 |
| 3       | DSC    |      | 0.4 | **0.5** | 0.6 | 0.7 | 0.8 |
| 3       | MAD (mm) |      | 6.6 | **5.9** | 4.5 | 4.0 | **2.1** | 1.9 |
| 3       | MAX (mm) |      | 20.1 | 22.0 | 25.7 | 27.5 | **10.4** | 9.7 |
| 3        | $\gamma_{CT}$ (%) | | 11.8 | **6.7** | 4.4 | 4.0 | **10.1** | 9.3 |
| 3        | $\gamma_{Dose}$ (%) | | 10.3 | **9.9** | 9.5 | 8.7 | 6.9 | **6.5** |

Note: DSC, dice similarity coefficient; MAD, mean absolute distance; MAX, maximum absolute distance; and $\gamma_{CT}$, $\gamma_{DCT(50, 3\,mm)}$, $\gamma_{Dose(95, 3\,mm)}$. For the changes in CT HU values, the percentage of the volume with a $|\gamma_{DCT(50, 3\,mm)}| > 1$ for prostate is shown in Table III and for the other contours, in the supplementary material [Table B and Figs. B(C,G,K,O,S,W)]23. A maximum improvement was seen of 20.5% (14.6% for contour based) and the poorest results gave an increase of 3.2% (2.2% for contour based) in the volume with $|\gamma_{DCT(50, 3\,mm)}| > 1$.

Looking at the prostate results as shown in Table III, in case an improvement was achieved, the contour parameter set (D, 100 iterations) seemed to give an improvement in most cases, yet it was not always the best one. The results for the other contours (body, anus and rectum, and bladder) that can be found in Table B in the supplementary material confirm this as well.
4. DISCUSSION

We have evaluated the impact of applying US-derived tissue deformations to approximate CT images to the real anatomical organ position of prostate patients during radiation therapy. As noted before, a similar workflow was presented by Pennec et al.\textsuperscript{17} for brain surgery applications. However, in that study, pseudo-MR images of the brain were created. To our knowledge, this is the first time a similar method is used for RT applications.

In this study, patients 1 and 3d would have benefited most from the deformations (>3% volume decrease for the volume...
with a $|\gamma_{Dose}| > 1)$. In addition, the difference in dose between 
$CT_{sim}$ and $CT_{gt}$ was there also the largest (10% volume with 
a $|\gamma_{Dose}| > 1)$. For the other patient cases, the improvements 
were not clinically relevant.

Ideally, one should be able to evaluate beforehand which 
patients would benefit from applying the deformations. The 
only metric that is available prior to DIR and could be suitable 
is the DSC of the prostate contours on US$_{sim}$ and US$_{gt}$. A statisti-
cal evaluation was performed to find a possible correlation 
between these DSCs and the effect on the dose deposition 
on the prostate ($|\gamma_{Dose}| > 1)$. Unfortunately such a correlation 
was not found, possibly due to the limited number of patients. 
However, there seems to be a trend that the patients with the 
largest geometric changes benefit most from deformations, but 
a future study with a larger image database will be necessary 
to validate the predictive power of this DSC parameter to get 
a clearer indication when it is worthwhile to perform DIR.

Besides a larger database to perform statistics, such a 
database could be used to find an optimal metric and 
parameter set for the DIR. For this proof-of-principle study, 
two deformation metrics were used and only the number of 
iterations varied. Optimization of the metrics and parameter 
set may improve the results. In the current study, the results of 
the evaluation methods were not always in agreement. Even 
between the CT and dose values, there were some differences 
due to the cumulative effect of the dose along the beam path. 
The differences between change in $\gamma_{CT}$ and $\gamma_{Dose}$ are caused 
by the fact that the dose in the organs is not only dependent on 
the local HU but also on the HU along the beam path. The best 
evaluation method is dependent on the purpose; the evaluation 
of the best parameter set should therefore always be assessed 
with the correct evaluation method. In case of ART, this could be 
$\gamma_{Dose}(3\% , 3 \text{ mm})$.

A limitation of an US-based deformation field is that the 
volume of the CT on which one can directly calculate the 
deformation field is limited to the volume of the US data 
available (Fig. 3). The deformation field propagates further, 
but this is not based on image data and is therefore maybe less 
reliable. For patient 2, a small overlap of US volumes resulted 
in a failure in parameter set E. Standardization of scanning, 
so that at least the complete prostate is visible and the US 
volume overlap is maximal, and US images with larger fields 
of view may improve the results. Transperineal scanning with 
a larger image sector or perhaps even fusion of multiple US 
scans from different directions can extend the field of view.

However the US image will never completely overlap 
the CT image, therefore part of the deformation field will 
still be based on only an extrapolated deformation field. For 
an ideal exact extrapolation, it may be crucial to take into 
account the mechanical properties of tissues and organs, such 
as skin, bones, and bladder, which are positioned outside of 
the overlapping US images. In this work, some deformation 
field propagation outside of the overlapping US volumes is 
already inherently taken into account, due to the use of the 
so-called multiresolution approach during the deformable 
registration. In this approach, the registration starts with 
images that have a lower complexity. For example, images 
that were smoothed and possibly down sampled. During the 
registration, a B-spline control point grid is overlaid on the 
fixed image. This grid is always rectangular. Control points 
that are outside of the region of interest (overlapping parts of 
the US volumes) are in principle not affected. However, due 
to the multiresolution approach, the control point spacing is 
larger at lower resolutions than at higher resolutions. For this 
reason, a larger area around the region of interest is affected 
at lower resolutions, which typically produces deformations 
outside of the region of interest.

Another reason why it is important to have standardization 
of the US scanning is that, just like with the IGRT usage 
of the US images, it is important to have reproducible US 
images. In particular, the probe pressure$^{18, 32}$ and speed-
of-sound aberration$^{33}$ along the imaging beam should be 
comparable. One cannot distinguish between the US imaging 
dependent changes caused by nonstandardized procedures 
or a real anatomy changes. Therefore it is best to prevent 
them or correct$^{35–38}$ for them before the DIR procedure. For 
our specific cases, preliminary inspection revealed that these 
corrections were not necessary.

Validation of the DIR methods in general is also still neces-
sary to reliably perform DIR for ART. Different deformation 
algorithms lead to different results, therefore more research is 
necessary.

5. CONCLUSIONS

It was possible to generate a pseudo-CT$_{us}$ with the use of 
DIR based on US imaging which was more representative of 
CT$_{gt}$ than CT$_{sim}$. For the patients with the smaller prostate 
change over time, the procedure did not improve the dose 
calculations much. The largest improvements were seen for 
patients with the largest anatomical changes. More research 
with a larger image database is necessary to find an optimal 
deformation metric and parameter set. With a larger database, 
it might be possible to find a predictive measure and criteria 
to decide whether DIR is worthwhile for individual patients.

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