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## Deformable image registration for geometrical evaluation of DIBH radiotherapy treatment of lung cancer patients

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**Abstract.** Respiration and anatomical variation during radiotherapy (RT) of lung cancer yield dosimetric uncertainties of the delivered dose, possibly affecting the clinical outcome if not corrected for. Adaptive radiotherapy (ART), based on deformable image registration (DIR) and Deep-Inspiration-Breath-Hold (DIBH) gating can potentially improve the accuracy of RT. *Purpose:* The objective was to investigate the performance of contour propagation on repeated CT and Cone Beam CT (CBCT) images in DIBH compared to images acquired in free breathing (FB), using a recently released DIR software. *Method:* Three locally advanced non-small cell lung cancer patients were included, each with a planning-, midterm- and final CT (pCT, mCT, fCT) and 7 CBCTs acquired weekly and on the same day as the mCT and fCT. All imaging were performed in both FB and DIBH, using Varian RPM system for respiratory tracking. Delineations of anatomical structures were performed on each image set. The CT images were retrospectively rigidly and deformable registered to all obtained images using the Varian Smart Adapt v. 11.0. The registered images were analysed for volume change and Dice Similarity Coefficient (DSC). *Result:* Geometrical similarities were found between propagated and manually delineated structures, with a slightly favour of FB imaging. Special notice should be taken to registrations where image artefacts or low tissue contrast are present. *Conclusion:* This study does not support the hypothesis that DIBH images perform better image registration than FB images. However DIR is a feasible tool for ART of lung cancer.

### 1. Introduction

Anatomical changes and variations due to respiration influence the accuracy of imaging, treatment planning and treatment delivery, and may affect the outcome of the planned treatment if not corrected for [1]. In ART, the treatment plan is adjusted during the course of treatment to minimize the divergence from the planned treatment, in terms of target dose coverage and sparing of dose to adjacent healthy organs at risk. Thus, ART has the potential to account for major anatomical changes not accounted for by applied margins [1]. Conventionally, lung cancer patients are treated in FB. However, breathing adapted radiotherapy (BART) by means of DIBH may suppress the geometric and

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dosimetric uncertainties related to respiration. Furthermore BART makes it possible to safely reduce the margins to the targets, yielding a reduction of irradiated volume [3,4]. The advantages of BART and ART illustrates that more individualized treatments are called for to improve the quality of RT. ART is, however, a time consuming process since anatomical structure delineations are needed on each new image set. DIR may be a promising tool in assisting with the delineation process, by deforming the reference contours from the planning CT into the anatomy of a second CT or CBCT. Our hypothesis is that image registrations performed based on DIBH images will result in improved image registrations, with enhanced correlation of volumes and higher scoring of DSC, since they often have visually better image quality compared to images in FB. The objective of this study was to investigate the performance of contour propagation on repeated CT and CBCT images of the thorax over the course of lung cancer treatment, imaged in DIBH, compared to conventional FB, using a recently released DIR software, based on a modified demons algorithm [5].

## 2. Material and methods

### 2.1. Patient data

Three locally advanced non-small cell lung cancer patients treated in 33 fractions (fx) using volumetric modulated arc therapy with a prescribed dose of 66 Gy (2 Gy/fx, 5 fx/week) at Herlev Hospital, between December 2012 and May 2013, were included in this study. They were treated on Varian Clinac iX 2300 linear accelerators [6,7] (Varian Medical Systems, Palo Alto, CA) equipped with On-Board Imagers (OBI) capable of performing FB and DIBH CBCT, using version 1.4 of the OBI software.

### 2.2. Image acquisition

Each patient was dual-CT scanned (acquiring a 4DCT in FB and a DIBH CT) before the start of, in the middle of, and after completion of the course of treatment, (pCT, mCT, fCT, respectively). All imaging were performed in treatment position [6]. They were scanned in a 16 slice Philips Brilliance CT Big Bore, version 3.5.17001 (Philips Medical Systems, Cleveland, OH) integrated with a Varian real-time position management (RPM) system, version 1.7 (Varian Medical Systems), for monitoring the patients' respiration during CT scanning. Intra venous (IV) contrast was administered to the patients during both 4DCT and DIBH imaging, for better contrast of nodal anatomy in the mediastinum. During DIBH imaging, the patients were audio-visually guided to hold their breath within a predefined amplitude level and gating window of 2-3 mm width. Additionally, all patients had 6-7 dual-CBCTs (in FB and DIBH) acquired on the treatment unit using the OBI. The CBCTs were acquired weekly and on the same day as the mCT and fCT. The Varian RPM system was once more used for monitoring the respiration to acquire DIBH gated imaging.

### 2.3. Definition of target and organs at risk

Delineations of anatomical structures for each patient were performed according to standard protocol by only one experienced oncologist (JLA or SB) on all image sets for that patient [6]. Delineations were carried out in the treatment planning system Eclipse v. 10 (Varian Medical Systems). Contouring of FB and DIBH Gross Tumor Volumes (GTVs) were performed by the oncologist in collaboration with an experienced radiologist. Residual FB and DIBH structures such as Clinical Target Volume (CTV), Planning Target Volume (PTV), medulla, heart, oesophagus, lung and body were additionally delineated by the oncologist. The heart, oesophagus, and lung were not delineated in the CBCT images, since they extended the CBCT scanning range.

### 2.4. Deformable registration and contour propagation

All CT images were retrospective pre-aligned by semi-automatic rigid registration and subsequently automatic deformed registered to all obtained images (both CBCT and secondary CT images) using Smart Adapt v. 11.0 (Varian Medical Systems). This resulted in 54 rigid and 54 deformable

registrations per patient (corresponding numbers were 48 for the one patient with only 6 CBCT scans), which in total resulted in 312 registrations for all patients. The rigid pre-alignment increased the accuracy of the subsequent DIR, and prevented large unrealistic deformations [5]. The initial rigid registrations were based on the bony anatomy of the column (50-3000 Hounsfield units), where the rest of the settings were predefined from the manufacturer. The rigid registration was done in three steps, each step with a higher image resolution, which improved the efficiency of the algorithm. The default DIR algorithm used in Smart Adapt was derived from a modified demons algorithm [5] based on a diffusion model. In the algorithm additional interaction forces (demons) are added to the original demons algorithm [8] and the voxel resolution of the images gradually increases during the optimization process. The floating image is warped to form a deformed image that match the reference image as closely as possible voxel-by-voxel [5,8]. The driving forces are based on the intensity differences between the two images, as well as the gradient of the image object. A symmetric force is also built into the solver to fulfill the consistency requirement for DIR, i.e. the transformation that maps the reference image to the floating image should be consistent with the inverse transformation that maps the floating image to the reference image. The DIR in this study was restricted to the field of view of the smallest image (typically the CBCT scan), resulting in a volume of interest (VOI) which was further analyzed. All structures extending the VOI (typically the heart, oesophagus, medulla, and body) were cropped to be comprised by the VOI, such that a common ground for comparison was created. For each DIR, the contours on the floating CT image were propagated onto the resulting deformed image (dCT) using the obtained image transformation.

### 2.5. Geometrical comparison

Rigidly and deformed registered structure volumes ( $V_{\text{RIG,DIR}}$ ) were analyzed relative to the corresponding structure volumes ( $V_{\text{REF}}$ ) on the reference image for volume change and DSC, where DSC was calculated according to equation 1 [9].

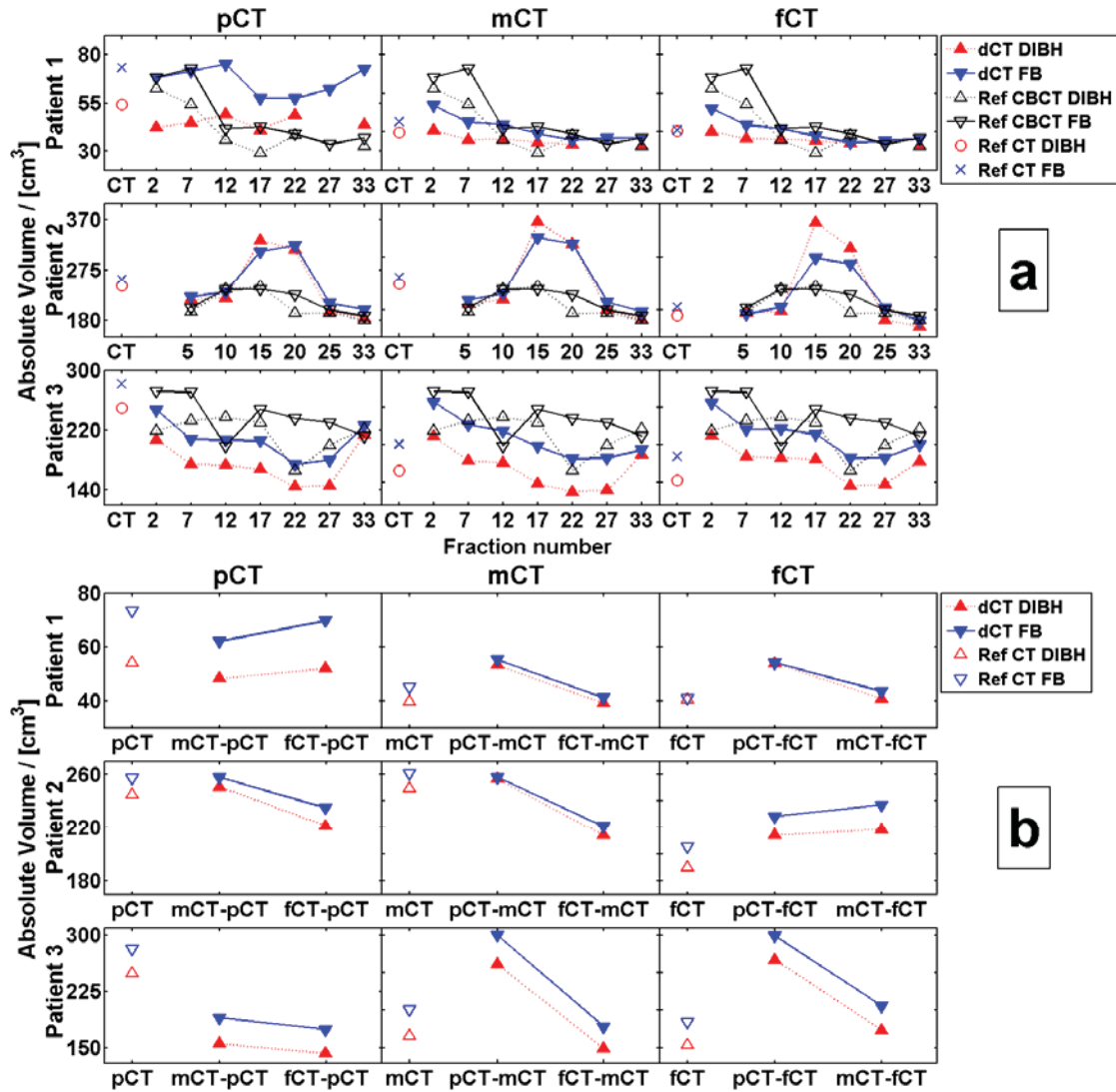
$$DSC = 2 \cdot \frac{V_{\text{RIG,DIR}} \cap V_{\text{REF}}}{V_{\text{RIG,DIR}} + V_{\text{REF}}} \quad (1)$$

For statistical analysis MATLAB Statistics Toolbox version 8.3 (R2013b) (The MathWorks, Natick, MA) was used. Paired t-tests to evaluate the median DSC measures of the various structures were performed, where differences were considered significant for  $p < 0.05$ .

## 3. Results/Discussion

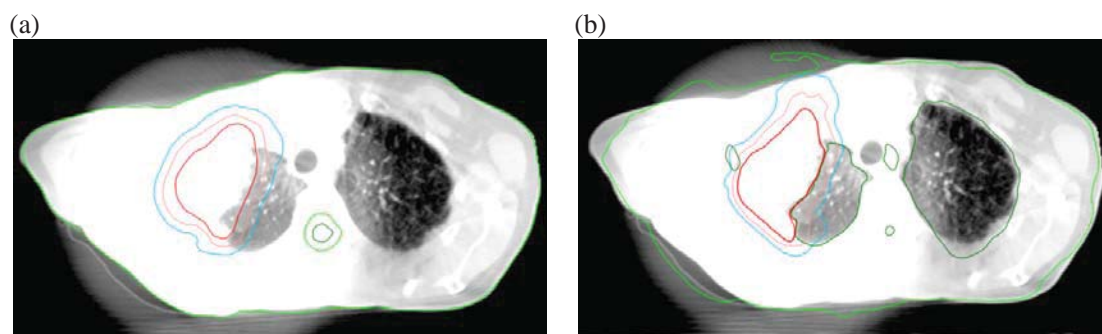
Figure 1 (open triangles) illustrates that the manually delineated reference CT and CBCT GTVs overall are decreasing over the course of treatment. The DIBH volumes (upward pointing triangles) are in general smaller compared to FB (downward pointing triangles) which may be due to the lesser image artefacts (e.g motion blurring) in the DIBH images resulting in smaller targets. The dCT GTVs do not correlate well with the manually delineated reference CBCT (figure 1 (a)) or CT (figure 1 (b)) volumes. If a perfect volume correlation was achieved between the dCT structures and the reference volumes, the filled triangles (figure 1) would follow the corresponding curves with open markers (figure 1 (a)) or be the same volume as the open markers (figure 1 (b)). The dCTs of the pCT at fx 2 and 7 of patient 1 correlate well with the reference CBCTs, but for the remaining fractions the dCT of the mCT and fCT have better correlation with the reference CBCTs. This illustrates the difficulty to perform DIR registration when the anatomy changes over time. In this case, the patient would benefit from ART. It is clearly seen in figure 1 (a), at fx 15-20 for patient 2, that appearing image ring artefacts (figure 2) in the reference CBCT image affect the DIR process, and thus the propagation of structures. The effect was equally seen for DIBH and FB images, and for all CT-CBCT registrations at fx 15-20 for patient 2. The CT-CBCT and CT-CT registrations of patient 3 (figure 1) systematically underestimate the GTVs, both for FB and DIBH images. This may be due to DIR issues in regions

with low level of tissue contrast (since the demons algorithm uses intensity values for registration) as the tumor for this patient was closely situated to the mediastinum.



**Figure 1.** (a) Absolute volume per each fraction of the dCT GTVs (filled triangles) in relation to the manually delineated reference CBCT GTVs (open triangles) along with the manually delineated GTVs of pCT, mCT and fCT (x and circles) utilized when performing CT-CBCT DIR. Upward pointing triangles correspond to DIBH, and downward pointing triangles represent FB. In the pCT column it is the pCT that is deformed to match the CBCTs and similar for the columns labelled mCT and fCT. (b) Corresponding absolute volume of dCT GTVs (filled triangles) in relation to manually delineated reference CT GTVs (open triangles) when performing CT-CT DIR between the pCT, mCT and fCT. In the pCT column it is the mCT and fCT that is deformed to match the pCT and similar for the columns labelled mCT and fCT.





**Figure 2.** (a) The reference CBCT (fx 15) of patient 2 with manually delineated CBCT structures. (b) The same CBCT (fx 15) overlaid with the dCT structures, i.e. the propagated deformed pCT structures. The red, pink, blue and the outer light green delineations represent GTV, CTV, PTV and body contour, respectively. Colors are available in the online version.

No significant difference among DSC measures of the various structures were observed between DIBH and FB CT-CBCT and CT-CT image registrations over the course of treatment (table 1). However, the FB images had slightly higher DSC median value compared to DIBH images (both for CT-CBCT registrations and CT-CT registrations). This observation conflicts with our hypothesis that DIBH imaging resulting in visually less image artefacts compared to FB imaging, yielding better image registration. The applied DIR improved the median DSC measure, compared to rigid registrations, except for some CT-CBCT registrations (indicated by bold font), though still within one standard deviation, and no significant difference was observed.

**Table 1.** Median DSC measures (one standard deviation) of the propagated deformed structures and rigidly registered structures for all patients during CT-CBCT and CT-CT registration. Bold values indicate that rigidly registered structures have a higher DSC score compared to the propagated structures of the dCT.

Structures	CT-CBCT				CT-CT			
	FB		DIBH		FB		DIBH	
	RIG <sup>a</sup>	DIR <sup>b</sup>	RIG <sup>a</sup>	DIR <sup>b</sup>	RIG <sup>a</sup>	DIR <sup>b</sup>	RIG <sup>a</sup>	DIR <sup>b</sup>
<b>GTV</b>	0.74(0.10)	0.78(0.13)	0.73(0.13)	0.74(0.15)	0.76(0.13)	0.84(0.16)	0.75(0.13)	0.83(0.20)
<b>CTV</b>	0.80(0.07)	0.81(0.09)	<b>0.79(0.10)</b>	0.78(0.11)	0.82(0.09)	0.88(0.12)	0.79(0.11)	0.86(0.17)
<b>PTV</b>	0.83(0.07)	0.84(0.07)	<b>0.82(0.08)</b>	0.81(0.08)	0.86(0.07)	0.89(0.09)	0.83(0.10)	0.87(0.14)
<b>Body</b>	0.98(0.01)	0.98(0.01)	0.97(0.01)	0.98(0.04)	0.97(0.01)	0.99(0.01)	0.97(0.01)	0.99(0.01)
<b>Medulla</b>	<b>0.75(0.10)</b>	0.72(0.13)	<b>0.77(0.05)</b>	0.74(0.14)	0.74(0.05)	0.76(0.05)	0.75(0.08)	0.78(0.07)
<b>Oesophagus</b>	NaN <sup>c</sup>	NaN <sup>c</sup>	NaN <sup>c</sup>	NaN <sup>c</sup>	0.58(0.10)	0.73(0.08)	0.59(0.09)	0.70(0.08)
<b>Heart</b>	NaN <sup>c</sup>	NaN <sup>c</sup>	NaN <sup>c</sup>	NaN <sup>c</sup>	0.85(0.05)	0.90(0.06)	0.87(0.13)	0.93(0.08)
<b>Total lung</b>	NaN <sup>c</sup>	NaN <sup>c</sup>	NaN <sup>c</sup>	NaN <sup>c</sup>	0.89(0.01)	0.95(0.01)	0.93(0.04)	0.97(0.02)

<sup>a</sup>Rigid image registration

<sup>b</sup>Deformable image registration

<sup>c</sup>Not available number

#### 4. Conclusion

This study does not support the hypothesis that DIBH images result in better image registrations (both rigid and deformed) when using a modified demons type algorithm for deformable image registration. Large variation was observed for organs without sharp contrast boundaries (including tumors close to mediastinum, atelectasis and thorax wall). Notice should also be taken to image artefacts and bad image quality that can affect the outcome of DIR (e.g. fx 15-20 for patient 2, figure 2). Our observations indicate that ART planning may be necessary during the course of treatment for optimal

lung cancer RT, since the pCT not always can be registered correctly to subsequent CBCT and CT images over the course of treatment due to large and rapid volume changes (eg. fx 12 for patient 1, figure 1 (a)). Based on this small patient dataset, it turned out that DIR sometime resulted in a worse median DSC measure compared to conventional rigid registration, though still within one standard deviation. The median DSC of the DIR for these three patients was however mostly higher compared to rigid registrations. Unrealistic deformation vector fields were also sometimes created during DIR. These unrealistic deformation vector fields should carefully be employed if used for other applications, e.g. such as dose deformation. DIR analysis provides a feasible and promising tool for indicating if adaptive re-planning is necessary based on geometrical variations throughout the course of lung cancer treatment, with slightly better correlation for FB than DIBH imaging.

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