Utilization of 4D-CT and contrast enhanced expiration breath-hold CT for 3D treatment planning of lung tumors.

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Abstract

Proper RT of lung tumors with involved lymph nodes in the mediastinum is very much dependent on an artifact-free representation of the tumor and proper contrast enhancement in the mediastinal region. Therefore we have implemented a deformable registration procedure in which all phases of a 4D-CT are registered to a contrast enhanced expiration breath-hold(BH)-CT. With this procedure the time-weighted average 3D-CT scan of the patients' anatomy can be created by deforming the BH-CT. Subsequently the tumor amplitude is derived from the deformable registration, which can be used to calculate PTV margins. Using the BH-CT as reference scan resulted in virtually the same representation of the tumor compared to the previous method, where a 4D-CT frame was used as reference, but contrast in the mediastinal vessels at the level of the tumor increased with 120 Hounsfield. More accurate and reproducible delineation of the tumor and involved lymph nodes can be expected.

Keywords

4D- CT, deformable registration, treatment planning, contrast enhancement, lung cancer

Introduction

Four-dimensional (4D) respiration correlated imaging techniques can be used to obtain respiration artefact-free computed tomography (CT) images of the thorax. Most radiotherapy treatment planning systems, however, do not support 4D-CT data. One way to deal with 4D-CT in treatment planning is to take the frame that is closest to the time weighted average position of the tumor (MidV-CT [1]). This mid-ventilation approach, however, suffers from the following (possible) problems, artifacts due to motion and breathing irregularities, lower signal to noise ratio compared to standard 3D-CT scans, and for tumors moving on an elliptical trajectory, hysteresis results in a small systematic error.

In order to deal with these problems Wolthaus et al. [2] proposed to use deformable registration to deform all information of the 4D-CT to a time weighted average 3D-CT scan (MidP-CT). Using this approach, signal to noise ratio increases, hysteresis errors disappear, and small artifacts from single frames are averaged out.

For lung cancer treatment with involved mediastinal lymph nodes, the use of contrast enhancement is very important for target delineation. Optimal contrast enhancement is very dependent on timing. Due to the relatively long scan time of 4D-CT scans (about 60 s) contrast enhancement during 4D-CT acquisition is generally sub-optimal.

The aim of this study was to combine the concept of MidP-CT with contrast enhanced expiration breath-hold (BH) scans to increase the image quality of the 3D planning CT.

Material and methods

Patients and scans

For this study 10 lung cancer patients were selected with a clearly visible tumor in the periphery of the lungs. For all patients a 4D-CT and expiration BH-CT were acquired. For 5 patients contrast enhancement was given during acquisition of the BH-CT, for the others no contrast enhancement was used. For 4D-CT acquisition, thermocouple sensor based respiration-correlated CT scanning and post-processing [1] was used. The 4D-CT scans were reconstructed in 10 equidistant time-percentage bins, starting from end inhale (frame 0) to end exhale (± frame 5) and back to inhale. All scans were reconstructed in 3 mm slices and 512 x 512 pixels, yielding ~130 slices per bin/scan.

Deformable registration

To determine the motion from frame to frame in the 4D-CT a slightly modified workflow of the proposed iterative multi-scale phase-based optical flow motion

estimation procedure of Wolthaus et al. [2] was used. Each deformable registration was performed in an iterative course-to-fine image scale approach, where first large differences between scans were estimated, followed by more and more details. The finest grid used during deformable registration was 256 x 256 pixels per slice, with 0.6 cm spacing between the control points.
For each patient 2 different 4D deformable registration methods were performed.
During the first deformable registration (Ref_5) the maximum expiration frame (frame 5) of the 4D-CT was used as reference scan to which all other frames were registered, yielding 9 deformation vector fields (DVF) plus a reference DVF with motion 0. Subsequently the average DVF over all frames was subtracted from each DVF yielding all deformations with respect to the time weighted average positions. This DVF was used to deform all frames to the time weighted average position. This application was done on the full 512 x 512 resolution using b-spline interpolation of the gray values. Subsequently the MidP-CT_{Ref_5} was calculated by taking the median of the grey values in the 10 frames for each pixel.
In the second registration procedure, the expiration BH-CT was taken as reference scan (Ref_BH) instead of frame 5. All registration and calculation steps were repeated, and besides the MidP-CT_{Ref_BH}, also a DVF from the BH-CT to the time-weighted average position was calculated. With the latter, also a representation of the BH-CT in the time-weighted average position of the 4D-CT can be calculated (MidP-BH-CT) by deforming the BH-CT.
In order to deal with sliding-tissue in the thorax a mask was used which was automatically created by segmenting the lungs and bony anatomy on the reference scan. The regions where the distance between lung tissue and bony tissue was less than 1 cm were separated in the tri-linear interpolation between control points during deformable registration.
To determine the deformations from frame to frame the whole registration was performed in a 2-way parallel process, using two computers or two cores of the same computer. First the 2 frames closest to the reference frame were registered. Subsequently the 2nd closest 2 frames were registered, using the DVF of the previous registrations as start point. For Ref_5, the order was frame 4 and 6, followed by 3 and 7, etc. For Ref_BH, the procedure was similar, but the frame closest to the expiration-BH-CT was used as start point, and this was determined by calculating the correlation ratio of the BH-CT and each frame.
Loading of the scans, preparation of the sliding tissue mask, storage of the separate frames, calculation of the final DVF and deformation of the scans were performed on a 64-bit Windows vista machine with a core2 duo 2.8 Ghz processor and 4 GB of RAM. For the deformable registration of the frames itself a 64-bit Linux based Pelican cluster of 2 core2 duo 2.13 Ghz computers was used with each 2 GB of RAM. Total computation time was calculated over the whole procedure, excluding the load time of the scans. Only in-house developed software was used.

Quantification of the results

In order to validate the deformable registration a comparison between rigid grey-value registration of the tumor over the 10 frames and tumor movement in the DVF's was made. Rigid registration was performed by segmentation of the tumor plus approximately 1 cm of surrounding tissue, edited to remove stationary structures (e.g., ribs), on phase 0 [3]. This segmented volume was subsequently registered on grey-value for translations only to all other phases to find the tumor trajectory. The volume that was used to segment phase 0 was subsequently translated to the time-weighted average position derived from the rigid registrations. With this volume the tumor trajectory from the 4D DVF of the Ref_5 and Ref_BH registration was segmented. Results were quantified by a phase by phase comparison as well as a tumor amplitude comparison.
The effect of the different deformable registrations on the MidP-CT was also quantified by comparing grey-value segmented tumor shapes (grey-value 662, halfway between the pixel values of lung and water) from the MidP-CT_{Ref_5}, MidP-CT_{Ref_BH} and the MidP-BH-CT. Results were compared by means of volume, overlap and edge distance.
The influence of contrast enhancement in the mediastinal region was quantified by comparing the average signal and noise in the MidV-CT, MidP-CT_{Ref_5}, MidP-CT_{Ref_BH} and the MidP-BH-CT in a large vessel at the level of the tumor.

Results and discussion

Deformable registration

On average the Ref_5 registration procedure took 12.6±1.1 minutes. The Ref_BH procedure took on average only 50 seconds extra, which was mainly needed because besides a MidP-CT from the 4D-CT also a MidP-CT from the BH-CT was calculated. Computation of the DVF's was the same because of the paralell proces. The BH-CT scans were on average closest to frame 4 of the 4D-CT (range: frame 2 to 6), illustrating the poor reproducibility of the expiration BH compared to end exhale.

Tumor amplitude

The measured tumor amplitudes from the 2 deformable registration methods were on average slightly smaller than with the rigid registration method (Table 1). This was especially the case for moving tumors which were close to the thoracic wall, e.g. sliding tissue. Between

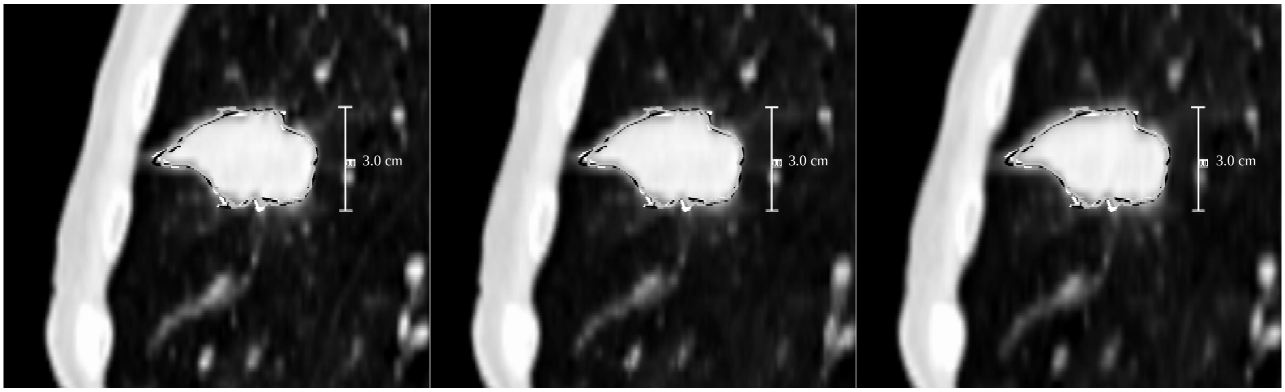

Figure 1: Sagittal view of a segmented tumor on the MidP-CT $_{Ref\_5}$ (left, white delineation), the MidP-CT$_{Ref_BH}$ (middle, black delineation) and a MidP-BH-CT (Right, grey delineation).

the Ref_5 and Ref_BH method no differences in amplitude were present.

For the phase by phase comparison, the differences in trajectory between the registration methods was calculated per patient. For each phase the standard deviation (SD) of the differences were calculated, and the root-mean-square (RMS) over all 10 phases was calculated. The RMS of the SD's of the differences between Ref_5 and Rigid and between Ref_BH and rigid were both 0.03, 0.05 and 0.04 cm for LR, CC and AP, respectively. Differences between Ref_5 and Ref_BH were negligible (0.01, 0.02 and 0.01 cm for LR, CC and AP). The largest differences between the deformable methods and rigid were found at end inhale with a SD of the differences of 0.05, 0.08 and 0.06 for LR, CC and AP. In 5 of the 10 patients it was clearly visible that in one or more phases small imaging artifacts were present at the level of the tumor in the 4D-CT. Differences between the rigid and the deformable registrations might be caused by these artefacts. The use of contrast enhancement in the BH-CT did not lead to registration differences compared to non-enhanced BH-CT scans.

	Left-Right	Cranio-Caudal	Anterior-Posterior
Rigid	0.14 (0.02-0.30)	0.56 (0.07-1.50)	0.34 (0.10-0.83)
Ref_5	0.13 (0.04-0.23)	0.53 (0.07-1.25)	0.26 (0.10-0.54)
Ref_BH	0.12 (0.04-0.23)	0.53 (0.07-1.23)	0.26 (0.09-0.52)

Table 1: Average tumor amplitude in cm (range)

Tumor segmentation

The tumor volumes that were segmented on the MidP-CT$_{Ref_5}$, MidP-CT$_{Ref_BH}$ and MidP-BH-CT were almost identical (Table 2). With on average 88% overlap ranging from 72 to 96% and in general small tumor volumes, no clinically significant differences between the segmentations were present. Maximum edge differences between the segmentations were in the order of 2 - 3 mm, while for the majority of the edges no differences were visible (average SD < 1 mm) (Figure 1).

	Volume cc (range)	Avg % overlap with others (range)	Avg % overlap by others (range)
MidP-CT$_{Ref_5}$	4.4 (0.5–21.8)	89 (78–95)	87 (72–96)
MidP-CT$_{Ref_BH}$	4.5 (0.5–22.2)	87 (72-95)	88 (76–96)
MidP-BH-CT	4.4 (0.4–21.2)	87 (73–95)	87 (75–94)

Table 2: Segmented tumor statistics

Mediastinal signal to noise

The signal in the vessels at the level of the tumor significantly increased with approximately 120 when a MidP-BH-CT with contrast enhancement was used (Figure 2). The noise in these scans was also lower compared to the conventional use of a MidV-CT, but compared to MidP-CT$_{Ref_5}$ and MidP$_{Ref_BH}$ noise was slightly higher. This is due to the fact that, in our clinic, more imaging dose is used to acquire a 4D-CT compared to a BH-CT. As a reference, we also looked at contrast enhanced 4D-CT scans of 5 other patients, for which we do not have expiration BH-CT scans. In these patients the signal in the vessels at the level of the tumor was on average 1150, which was significantly lower (p 0.03, 1-sided t-test). The contrast in the 4D-CT was however, very much dependent on the level of the tumor. Since all 4D-CT's are scanned from caudal to cranial, signal in the more caudal regions is much higher than in the cranial regions (Figure 3). The 5 patients with contrast in the 4D-CT had middle or lower lobe tumors. In more cranial tumor 4D-CT scans, lower signal in the vessels will be measured.

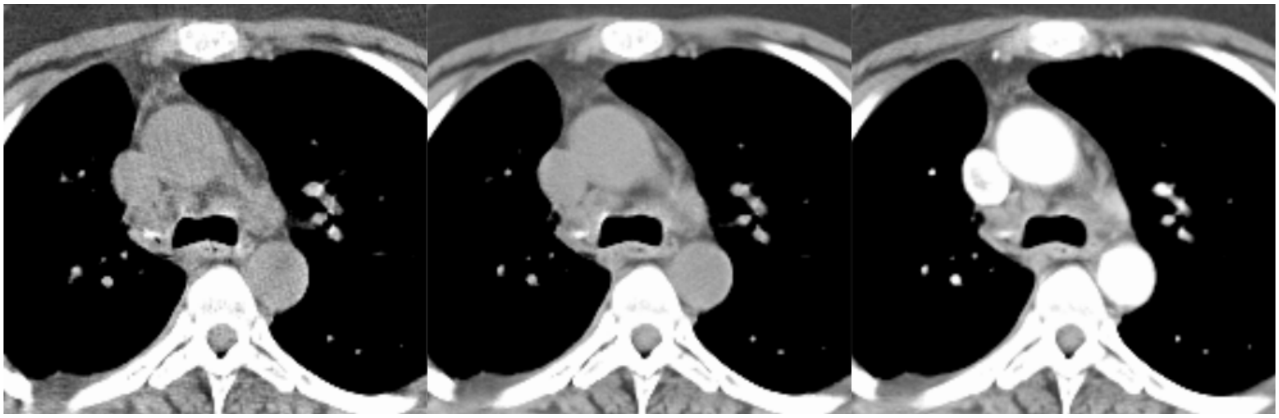

Figure 2: Overview of the image quality in the mediastinal region when using a MidV-CT (left), a MidP-CT_{Ref_5} (middle) and a MidP-BH-CT (Right) of the same patient at exactly the same level and window settings

Clinical implementation of MidP-BH-CT

All in all, the results acquired using the BH-CT as reference during deformable registration are comparable to the results of Wolthaus et al. [2]. Contrast enhancement in the BH-CT clearly increased the signal in the vessels while tumor segmentations where virtually identical in the MidP-BH-CT compared to the other methods. We will therefore implement the contrast enhanced MidP-BH-CT scan for patients with expected nodal involvement, while for patients without involved lymph nodes we will use the MidP-CT_{Ref_5}. Since the MidP-CT_{Ref_BH} does not need to be calculated when the MidP-BH-CT is used, the total calculation time will remain approximately 10 minutes, which is clinically acceptable. Further improvement in calculation time by using a larger cluster did not seem to be feasible, since registration accuracy got worse when inhale and exhale were registered without an initial DVF. Improvements are still needed to decrease registration problems due to sliding tissues, ie., for tumors that are located close to the chest wall.

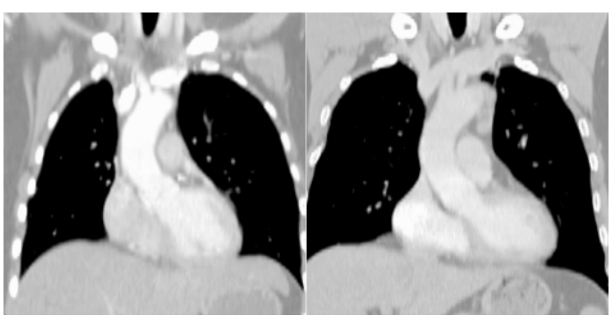

Figure 3: Example of a contrast enhanced BH-CT (left) and a contrast enhanced 4D-CT (right), both deformed to a time-weighted average 3D Mid-position CT. Both scans, from different patients, are at the same level and window setting.

	Average signal (HU)	Noise (HU)
MidV-CT	1079	22.8
MidP-CT_{Ref_5}	1078	8.6
MidP-CT_{Ref_BH}	1078	8.0
MidP-BH-CT no contrast	1085	11.6
MidP-BH-CT with contrast	1197	13.0

Table 3: *Signal in mediastinal vessels at the tumor level*

Conclusion

The use of a contrast enhanced expiration BH-CT as reference scan for deformable registration of a 4D-CT to determine the mid-position scan is feasible: the procedure does not lead to different results compared to the use of one of the 4D-CT phases as reference, and allows optimal contrast enhancement. With this procedure more accurate and reproducible delineation of the tumor and involved lymph nodes can be expected.

References

[1] Wolthaus JW, Schneider C, Sonke JJ, *et al.* Mid-ventilation CT scan construction from four-dimensional respiration-correlated CT scans for radiotherapy planning of lung cancer patients. *Int J Radiat Oncol Biol Phys* 2006; 65:1560-1571

[2] Wolthaus JW, Sonke JJ, van Herk M, *et al.* Reconstruction of a time-averaged midposition CT scan for radiotherapy planning of lung cancer patients using deformable registration. *Med. Phys.* 2008; 35:3998-4011

[3] Nijkamp J, Wolthaus JW, Sonke JJ, *et al.* Mid-ventilation determination with automatic four-dimensional rigid grey-value registration on respiration-correlated computed tomography scans with moving lung tumours. *ICCR 2007*; 258-262