Four-dimensional imaging in radiotherapy for lung cancer patients
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Technical realization

Fusion of respiration-correlated PET and CT scans: Correlated lung tumor motion in anatomical and functional scans

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Abstract

**Purpose** Lower lobe lung tumors in particular can move up to 2 cm in the cranio-caudal direction during the respiration cycle. This breathing motion causes image artefacts in conventional free-breathing CT and PET scanning, rendering delineation of structures for radiotherapy inaccurate. The purpose of this study was to develop a method for four-dimensional (4D) respiration-correlated (RC) acquisition of both CT and PET scans and to develop a framework to fuse these modalities.

**Methods and Materials** The breathing signal was acquired using a thermometer in the breathing airflow of the patient. Using this breathing signal, the acquired CT and PET data were grouped to the corresponding respiratory phases, thereby obtaining 4D CT and PET scans. Tumor motion curves were assessed in both image modalities. From these tumor motion curves, the deviation with respect to the mean tumor position was calculated for each phase. The absolute position of the center of the tumor, relative to the bony anatomy, in the 4D CT and 4D gated PET scans was determined. This 4D acquisition and 4D fusion methodology was performed for five patients with lower lobe tumors.

**Results** The peak-to-peak amplitude range in this sample group was 1 - 2 cm. The 3D tumor motion curve differed less than 1 mm between PET and CT for all phases. The mean difference in amplitude was less than 1 mm. The position of the center of the tumor (relative to the bony anatomy) in the 4D CT and 4D gated PET scan was similar (difference < 1 mm) when no atelectasis was present.

**Conclusions** Based on these results, we conclude that the method described in this study allows for accurate quantification of tumor motion in CT and PET scans and yields accurate respiration-correlated 4D anatomical and functional information of the tumor region.
1. Introduction

Computed Tomography (CT) has become the standard modality for three-dimensional (3D) target definition in radiotherapy. For lung tumors, which can move up to 20 mm [1], two uncertainties causes inaccurate delineation of the tumor on conventional free-breathing CTs: (i) problems in distinguishing tumor from atelectasis and pleural effusion, and (ii) uncertainty in tumor position and tumor shape due to breathing motion [2,3]. The first uncertainty can be reduced by combining CT information with fluorodeoxyglucose positron emission tomography ($^{18}$FDG-PET) [4], based on the underlying assumption that the FDG distribution reflects the increased glucose metabolism of tumor cells compared to normal tissue. However, PET is subject to similar uncertainties due to tumor motion as CT, since the long acquisition time of the PET scan results in motion-blurring of the tumor activity and consequently an uncertainty in tumor size. It is therefore necessary that both CT and PET be acquired using a four-dimensional (4D; i.e., time-resolved) acquisition protocol. For CT, several methods to acquire 4D scans have been described in literature [5-8]. For PET, a gated procedure might be used using an adapted version of the cardiac gating mode of the scanner [9].

Fused anatomical CT and functional PET scans can be acquired using hybrid PET-CT scanners but often separate imaging sessions on separate scanners are currently undertaken due to the facilities available. If CT and PET acquisition is performed on separate scanners, geometrical fusion is performed as a post-processing procedure. The advent of hybrid PET-CT scanners would in principle make geometrical fusion obsolete, since in principle these scanners lead to intrinsically geometrically fused scans (sometimes called “hardware fusion”). However, this procedure assumes that patient setup movement is negligible between the CT and PET scan. Until now this assumption has not been validated for a large group of patients [10]. If CT and PET are fused without taking into account tumor motion, large discrepancies, up to 8 mm, may occur in tumor position [11,12]. This discrepancy equally applies to both hybrid and separate PET-CT scanners. Combining the tumor information of 4D CT and PET scans is therefore meaningful only when, besides space registration, the two scans are also registered in time, i.e., there is a phase-to-phase match of the tumor motion in the two scans and the motion characteristics in both scans are similar.

In this work, we present methods to perform software fusion of 4D CT and PET, both in space and time. The details of the 4D respiration-correlated (RC) acquisition procedure on CT and PET will be described and methods will be presented to fuse these scans and analyse tumor motion characteristics in detail.
2. Patients, methods and materials

2.1. Patient group
For this study, patients with a lung tumor exhibiting respiration-induced motion larger than 1 cm were eligible. The tumor motion was initially determined visually by a clinician using fluoroscopy. For all patients, the tumor was located in the lower part of the lung region. All patients gave informed consent to participate in this study. Besides scans for conventional treatment-planning, patients received additional PET and CT scans within an interval of 1 week.

2.2. Respiration-correlated 4D CT imaging
During CT scanning, patients were positioned supine with their arms raised above the head using an arm support. A flat table-top was placed on the couch of the single-slice CT scanner (GE HiSpeed LX/i) to obtain a treatment position similar to that of the treatment couch. No contrast medium was administered. The patient was instructed to breath normally and freely.

We applied a method of RC 4D CT scanning and post-processing similar to Ford et al. [5], Vedam et al. [8] and van Herk et al. [13]. An oversampled helical CT scan was acquired with a slice thickness of 3 mm, a low pitch (0.3), reconstructed slice distance (0.9 mm), and a tube rotation time of 0.8 s. These settings were chosen as they are feasible for the scanner, useful for treatment-planning purposes and compatible with the range of respiratory periods generally observed (4 – 6 s/cycle), but may not work satisfactory for particularly fast and slow respiration patterns. The typical number of slices, necessary to cover the complete lung volume (30 cm in cranio-caudal (CC) direction), was between 300 and 350. Scans were made at 120 kV beam voltage and 60 mA beam current. The scan acquisition took approximately 5 minutes.

During scanning, respiration was recorded using a thermocouple (Type T, copper-constantan, Volenec S-CC-U-O-7/1) inserted into the entry of an “oxygen mask”, covering mouth and nose. The thermocouple registered the flow of warm (expiration) and cold (inspiration) air. The temperature range of the air was between 25º and 35º C. The respiration signal was sampled at 50 samples/s. The raw respiration signal was processed to remove noise (small kernel median and averaging filter) and trends e.g., due to warming up of the mask (large kernel averaging filter). The average respiration cycle length was determined, and the signal was converted into magnitude and phase using a Hilbert transformation [14-16]. Applying signal processing and Hilbert transformation to the respiratory thermometer signal provided a phase signal almost linear in time within one respiration cycle.

The CT scanner generates a signal when slices are acquired (“X-ray ON status”). From this signal, time stamps for each CT slice were derived, enabling correlation
of each slice with its respiration phase. By selecting slices acquired in the same respiration phase, a 3D reconstruction of the thorax was generated with minimum respiration artifacts. Linear (gray-value) interpolation between two surrounding slices of the raw (350 slices) CT scan was applied when no slice was available at the desired phase. This interpolation gave slices with the correct phase and arbitrary CC location between the 2 slices (Figure 2-1a and b). Repeating this process for multiple phases, a full set of CT scans of the thorax was reconstructed. As noted by Ford et al [5], the number of independent reconstructed phase CTs is very low (between 5 and 10, depending on the breathing frequency of the patient), but in this study a higher number of phase reconstructions (32) was implemented for smooth visualization. The resulting phase scans (frames) were resampled, using linear (gray-value) interpolation between 2 adjacent slices, on a 1.8x1.8x1.8 mm³ voxel grid for practical reasons (Figure 2-1c). Tumor motion within the acquisition time frame of one slice was disregarded.

2.3. Four-dimensional gated PET

During PET scanning (Siemens ECAT ACCEL) a flat polystyrene table inlay was used to obtain a similar patient position (supine positioning, arms raised above the head) as during CT scanning and treatment. Since the aperture of the PET scanner is smaller than the aperture of the CT scanner, a different arm support was used which approximates the CT arm support.
All patients were injected one hour before scanning with $^{18}$FDG at 6.1 MBq/kg body weight (30% more activity than normally used in our department). After the acquisition of a normal whole-body emission PET scan for diagnostic purposes (taking about 30 minutes), a second emission PET scan was made at a single bed position (covering 16 cm in the CC direction) centered at the tumor area. The scan was performed in 3D mode without septa. This second scan took 15 minutes and uses the cardiac gating procedure, however with a modified input signal (respiration signal) [9,17]. Respiration was measured with the same thermometer equipment as for 4D CT scanning, except with a different AD converter, which sampled at 25 samples/s (the AD converter was part of the trigger system). Since for the average lung cancer patient, the mean variation in the length of a respiration cycle is 13% (1 SD) [1], breathing cycles with a cycle length deviating more than 40% (~3 SD) from the average cycle length were rejected. The scanner was triggered halfway between inhale and exhale. The trigger system calculates a trigger line continuously by averaging the maximum and minimum envelope temperature of the respiration signal in each respiration cycle. Therefore the trigger line is not very sensitive to trends and noise, even without median or average filtering of the respiration signal. The trigger point is the point when the trigger line crosses the respiration signal at inhale. No adjustments by the technicians were needed to give a stable, regular and real-time trigger output.

The full breathing cycle, i.e., the time between two trigger pulses, was divided into 16 equivalent time bins. The acquired emission data was retrospectively binned to its corresponding phase bin after every cycle. All data acquired in a specific bin were reconstructed to yield a 3D scan for each of the 16 phases in the respiratory cycle (0°-360°). The gated emission data were reconstructed using an Ordered-Subset Expectation Maximization (OSEM [18]) algorithm with two iterations and eight subsets.

Figure 2-2 Procedure for the registration of the 4D gated PET scans to 4D CT scans. The average 4D CT is a derivative from the 4D CT scan and has the same bony coordinate system as the 4D CT. The transmission PET scan is inherently matched to the emission PET scan. Matching transmission PET to average 4D CT yields the same bony coordinate system for the 4D gated emission PET and the 4D CT scan.
A Gaussian filter of 6 mm FWHM was used in 3 directions. The reconstructed voxel size was 5.2 mm in left-right (LR) and anterior-posterior (AP) direction and 3.5 mm in CC direction.

A non-gated transmission PET scan of 6 minutes, covering the scan area, was made immediately after the gated emission scan for image registration purposes. For patients 2 and 3, the transmission scan was reconstructed with the same OSEM algorithm as the emission scans. To get a more detailed scan, the transmission scan of the other patients was reconstructed with OSEM to 2.6x2.6x3.5 mm³ with Gaussian filtering of 2 mm FWHM. Patient motion between emission and transmission scans was assumed to be negligible.

2.4. Respiration characteristics

The 4D CT and 4D gated PET scans were acquired at different locations and on different days (although within 1 week of each other). Consequently, the respiration pattern, i.e., the amplitude and shape of the motion, could be different in both modalities [1]. Since fusion of 4D images is only meaningful if the tumor motion characteristics are similar, the respiration pattern in 4D CT and 4D gated PET scans was determined.

a. Tumor motion determination and amplitudes

Tumor motion in each individual scan was determined using an image registration procedure. Prior to the determination, in both 4D CT and 4D gated PET scans the tumor was visually inspected in all phase reconstructions to select a reference frame, in which the tumor was detached from the thorax wall and diaphragm or abdomen (if possible). The abdomen could give apparent tumor shape variations in PET due to a considerable background activity. When there was no phase available where the tumor was detached, the maximum exhale phase was chosen as reference phase. A region-of-interest (ROI) was defined around the tumor in the reference frame using a drawn mask. This mask was large enough to encompass the tumor using different level-and-window settings. The ROI was subsequently registered to the scans of the other phases based on gray-value using the correlation ratio [19] of all voxels in the ROI. The correlation ratio measures the functional dependence between two images (a ROI template and a floating image). It takes values between 0 (no correlation) to 1 (full correlation). An extensive explanation about correlation ratio can be found in Roche et al. [19] and Dekker et al. [20].

Rotations of the tumor between phases were assumed to be small and not taken into account in the registration procedure. The results of the registration procedure were visually checked by feeding the transformations back into the 4D scan, i.e., shifting all single frames to the mean position of the tumor resulting in tumor images fitting each other in all frames. Movie loops of orthogonal reconstructions through the tumor at successive phases were displayed, which must result in a stationary tumor
if the registration between the different phases was correct. From the translations, tumor motion was reconstructed along the three principal axes (i.e., displacement versus phase). The peak-to-peak amplitude ($A_{4DCT}$ and $A_{gPET}$) was calculated from the tumor motion.

b. Scan phase shift

Scan acquisition of both modalities is different; the first frame of the 4D gated PET represents a different respiration phase (halfway inhale and exhale) than the first frame of the 4D CT (maximum inhale). The trigger point of the 4D gated PET may vary slightly since the asymmetry of the respiratory motion between exhale and inhale [21] is patient dependent. This patient dependent phase shift between the tumor motion in 4D gated PET and 4D CT scans needs to be determined in order to correctly fuse the images in time.

To determine this phase shift, from both tumor motion curves the magnitude $m$ and angle $\phi$ were calculated using a Hilbert transformation as mentioned in Section 2-2.2. Subsequently, the phase shift $\Phi_{\text{shift}}(j)$ was calculated for all three directions $j$ ($j = x,y,z$) as the mean of the phase difference between the 4D CT and the 4D gated PET over one full respiration cycle (Equation 1).

$$\Phi_{\text{shift}}(j) = \frac{1}{P} \sum_{i=1}^{P} (\varphi_{4DCT}(i,j) - \varphi_{gPET}(i,j))$$

Here, $\varphi_{4DCT}$ and $\varphi_{gPET}$ denote the phase of the 4D CT and 4D gated PET, respectively. $P$ denotes the total number of phase bins in the respiration cycle and $i$ the phase of the respiration. The overall phase shift $\Phi_{\text{overall shift}}$ was the weighted sum of the three phase shifts (weighted by the magnitudes of the 4D CT and 4D gated PET tumor motion to reduce the contributions of noise in small motion amplitudes). The 4D gated PET motion curve data was spline-interpolated from 16 phases to 32 phases to match the number of phases of the 4D CT.

In the actual image fusion of PET and CT, the phase shift between the two modalities could only be corrected with the smallest increment of phases of 11.3°, which was the size of the CT phase bin. A smaller number of CT phase reconstructions yield larger phase increments for corrections.

1.1.1.1.a Motion curve shape difference

Difference in the shape of the tumor motion curves of 4D CT and 4D gated PET was quantified using the quantity $D(j)$ (Eq. 2):

$$D(j) = \sqrt{\frac{1}{P} \sum_{i=1}^{P} \left( \frac{T_{4DCT}(i,j) - \langle T_{4DCT}(i,j) \rangle}{T_{gPET}(i + \Phi_{\text{overall shift}},j) - \langle T_{gPET}(i,j) \rangle} \right)^2}$$

$D(j)$ is the Root-Mean-Square (RMS) of the differences between the tumor translations ($T_{4DCT}$ and $T_{gPET}$) in 4D CT and 4D gated PET after applying the overall phase shift.
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\[ \Phi_{\text{overall shift}} \] i.e., a distance measure between the 4D CT and 4D gated PET tumor motion curve. \(<x>\) symbolizes the mean operator.

2.5. Four-dimensions CT and 4D gated PET fusion

a. Match method

The fusion procedure of the 4D gated PET scan with the 4D CT scan is depicted schematically in Figure 2-2. An average 4D CT was created by averaging the Hounsfield units of all respiratory phases to make the 4D CT more like the transmission PET. This average scan was matched to the transmission PET scan using a volume match. The first two and the last two slices of the transmission PET scan were not used because an accurate match was hampered by the noise in those slices. The matching was performed in two steps. In the first step the whole transmission PET scan was matched (gray-value, correlation ratio) to the average 4D CT scan to obtain a rough estimate of the transformation. In the second step, a refinement was done by matching (gray-value, correlation ratio) the vertebrae in the transmission PET scan, which were segmented using a manually drawn mask, to the 4D CT. The match result was verified by visually inspecting the alignment of the structures present in the two scans. Since the PET transmission scan was inherently matched to the PET emission scan, the “transmission PET – 4D CT”-match yields the bony transformation from the coordinate system of the PET emission scan to the 4D CT scan.

b. Absolute tumor position

To verify the tumor registration between the different phases in CT and PET, the absolute position of the tumor was determined in both 4D CT and 4D gated PET scan. These tumor registrations (i.e., translations in the LR, CC and AP directions) were fed back to the 4D scan, as mentioned in Section 2-2.4, obtaining a (stationary) tumor-registered image sequence of the 4D scan. The bony anatomy of the original non-transformed 4D CT scan defined the Cartesian bony-space, which will be fixed during the image sequence.

The absolute position of the tumor, in bony-space coordinates (i.e., the bony anatomy of the non-transformed scan), was assessed by determining the center-of-gravity (CoG) of the tumor. For each phase the CoG of the tumor, in both 4D CT and 4D gated PET, was calculated by gray-value weighted averaging of the coordinates of all pixels within the ROI around the tumor. The CoG should be approximately the same for all phases. The variation in CoG, expressed in the standard deviation, depends on the tumor match accuracy and possible CoG variation between phases. Finally, the mean CoG of the tumor was calculated in 4D gated PET and 4D CT and subtracted from each other obtaining the difference in absolute position of the center of the tumor.
Five patients with lower lobe lung tumors (4 male, 1 female) were included in this study. The tumors were located in the right sinus pleurae (patient 1, tumor volume: ~4 cm\(^3\), stage T\(_3\)N\(_2\)M\(_1\)), right thorax wall (patient 2, tumor volume: ~4 cm\(^3\), stage T\(_1\)N\(_0\)M\(_0\)), right hilum (patient 3, tumor volume: ~100 cm\(^3\), stage T\(_2\)N\(_2\)M\(_0\)), right hilum (patient 4, tumor volume: ~100 cm\(^3\), stage: cT\(_1\)N\(_0\)M\(_0\)) and right lung in close proximity to the diaphragm and mediastinum (patient 5, tumor volume: ~100 cm\(^3\), stage T\(_2\)N\(_2\)M\(_0\)). Due to hardware problems of the PET scanner, image data of patient 4 consisted of half a respiration cycle only, which made shape difference impossible to evaluate and phase shift determinations less accurate.

The average respiration cycle length of 4D gated PET (3.5 – 5 s) was shorter than in 4D CT (5 – 6 s) for four out of five patients (Table 2-1). The standard deviation of the respiratory cycle length was smaller than 25% of the average respiration cycle. As a result, less than 10% of the cycles where rejected because those cycles deviated more than 40% from the average cycle length.

In Figure 2-3a, tumor motion of patient 1 in the 4D CT and the 4D gated PET is plotted as a function of the respiration phase in the LR, AP, CC directions (for clarity, the respiration cycle is shown twice). All translations are given with respect to the mean tumor position and are corrected for scan phase shift. Figure 2-3b shows the same motion curves in a 3D representation. Tumor motion is comparable in 4D gated PET and 4D CT scans. The largest tumor motion (2 cm) was found in the CC direction. For all patients, the amplitudes of the motion (\(A_{4DCT}\) and \(A_{gPET}\)) were similar for both modalities (Table 2-2). The amplitudes over all directions and patients were systematically (0.4 mm) smaller in 4D gated PET than in 4D CT. The shape difference (\(D\)) of the motion of the 4D gated PET with respect to the 4D CT was very small and primarily caused by small amplitude differences. Except for patient 4, the mean shape difference was 0.3 mm, 1.1 mm and 0.5 mm for the LR, CC and AP directions, respectively.

### Table 2-1

The mean and standard deviation (SD) of the respiration cycle length of the 5 patients during 4D CT and 4D gated PET scanning using the raw thermocouple signal. The last column shows the percentage of the respiration cycles that deviate more than 40% of the average respiration length during PET scanning.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Respiration cycle length (s)</th>
<th>Deviation of cycle length &gt; 40% of average length (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4D CT</td>
<td>4D gated PET</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>1</td>
<td>5.5</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>4.9</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>4.5</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>3.7</td>
<td>0.7</td>
</tr>
<tr>
<td>5</td>
<td>4.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>
The overall phase shifts were about 120° (range 112° - 125°). For most of the patients (four out of five), the separate phase shifts differed in three directions from the overall phase shift but the difference was less than one 4D gated PET phase bin (23°).

The results of the fusion of 4D gated PET and 4D CT of patient 1 are illustrated in Figure 2-4. The tumor region is shown in eight frames from halfway inhale (phase 0°) to exhale (phase 135°) and back to inhale (phase 270°) in a coronal and sagittal view. The image sequence shows the motion of the tumor as well as the accurate fusion of features of the image data. The small (white) spot in the gated PET data refers to the most active part of the tumor. The dim and swell of the spot shows that the tumor also moves out-of-plane, following a 3D motion.

The mean value of the center-of-gravity (CoG), representing the absolute position, depends on the definition of the origin of the scan, and is therefore not shown. The origin of the scan (0,0,0) is set in the center of the tumor at the mean position in the 4D CT scan. The standard deviations in the CoG determinations of the tumor in the 4D CT and 4D gated PET scans, representing the variation in CoG over the phases, were small (Table 2-3). The mean standard deviation was 0.3 mm and 0.2 mm for 4D CT and 4D gated PET, respectively. The mean difference between both modalities of the CoG of all phases was smaller than 4 mm and the accompanying variation of the difference was less than 0.6 mm (1 SD).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Amplitude (Peak-to-Peak) (mm)</th>
<th>Shape difference (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4D CT</td>
<td>4D gated PET</td>
</tr>
<tr>
<td></td>
<td>LR</td>
<td>CC</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

For patient 4, the D could not be calculated (nc*) from the data, because of missing data due to hardware problems.
4. Discussion

4.1. Scan acquisition and quantification of tumor motion

A stable and regular respiration in terms of cycle length and amplitude results in higher image quality and more accurate tumor motion tracking in PET and CT scans than unstable and irregular respiration. The breathing cycle length of the patients differed significantly ($p < 0.001$) during CT and PET scanning but the mean difference between both modalities was small (about 0.5 s). The small number of cycles with lengths deviating more than 40% of the average length indicates that the patients had a reproducible quiet breathing pattern, making 4D image fusion more reliable.

Due to the undersampling in the cranio-caudal direction of the reconstructed CT, spatial gaps between 2 successive slices exist [5] where a particular phase reconstruction is not available. The authors showed that this gap is equal to $Z(p^*\tau_{\text{resp}}/\tau_{\text{gantryrot}} - 1)$, where $Z$ denotes slice thickness, $p$ the pitch, $\tau_{\text{resp}}$ the respiration cycle length and $\tau_{\text{gantryrot}}$ the full gantry rotation time. For the five patients in this chapter the average gap size was 2.1 mm. However, gaps do not automatically imply a decrease in tumor match accuracy. The influence of a gap on the match accuracy can be neglected when the ratio between tumor size and gap size is large. If a gap doesn’t occur at the bottom or top of the tumor, the gap will be interpolated without significantly changing the shape of the tumor. Moreover, using a high number (32) of CT reconstructions, the gap will never be exactly at the same position in successive reconstructions and therefore not obscure the same information in each respiratory phase. To get an estimate of the tumor match accuracy, we performed tumor matches for patient 2 with other phases as reference phase. Since this patient’s tumor is small (4 cm$^3$) and the gap relatively large, this can be regarded as a worst-case
scenario. In principle, for N reconstructed phases, N-1 independent matches can be performed. For simplicity, the depended match is neglected. However, as described by Ford et al. [5], overlap and interpolation of CT slices resulted in a limited number of independent reconstructed CT frames (between 5 and 10), depending on the breathing frequency of the patient. Given the parameters from Section 2-2.2 for 4D CT scanning and the breathing frequency of patient 2, five independent frames of the 4D CT can be reconstructed. Therefore tumor matches were performed for 1 out of 5 frames. The standard deviations of these tumor matches were 0.3 mm, 0.8 mm and 0.2 mm in LR, CC and AP direction, respectively. For the PET data, tumor matches were performed for all frames obtaining 16 tumor motion curves. In this case, the standard deviations of the tumor matches were 0.2 mm, 0.3 mm and 0.2 mm in LR, CC and AP direction, respectively. These small standard deviations imply that tumor matching is accurate. The sub-pixel accuracy can be explained by the inherent use of in-slice gray-value information (perpendicular to the slice direction) in gray-value match algorithms. The influence of the gaps is visible in terms of an increased standard deviation of 4D CT compared to 4D gated PET of 0.5 mm in the CC direction. However this is considerably smaller than the calculated gap of more than 3 mm for this patient.

Figure 2-3 (a) Tumor movement of patient 1 in the left-right, cranio-caudal and anterior-posterior direction determined from the 4D gated PET and 4D CT scans. The (red) line with circles refers to tumor motion in 4D CT scan and the (black) line with asterisks to the tumor motion in the 4D gated PET. The motion curves are shown twice (720°) for clarity. (b) Data from Figure 2-3a plotted in 3D space.
For four out of five patients the amplitude in the PET scans is slightly smaller than in the 4D CT scans (Table 2-2). The breathing cycle length during PET acquisition was also shorter than during 4D CT acquisition (Table 2-1). This is probably due to the fact that PET scanning was less comfortable and patients became stressed due to a longer acquisition time resulting in faster and shallower respiration.

The shape differences \( D \) (Table 2-2) were small compared to the amplitudes of motion and are probably mainly caused by the differences in amplitude between 4D CT and 4D gated PET using the RMS equation 2. Since the amplitude difference was largest in the CC direction, the shape differences in the CC direction was larger than in the AP or LR direction. However, considering the tumor motion curves with respect to their amplitudes, the shape difference was relatively smaller in the direction of large tumor motion (CC) than in the direction of the small motions (AP and LR). Note here that since the motion was plotted as a function of respiration phase, the shape difference was not caused by difference in tumor motion due to a shorter respiration cycle length during PET scanning. The shape differences were always less than the voxel size of the scans. Therefore, when the breathing level during PET and CT was similar (same absolute mean tumor position) and a valid registration of PET and CT scans was possible, the misalignment of the tumors was smaller than half of the voxel size for each phase of the respiratory cycle. Moreover, it shows that even without respiratory training or audio instructions, and with one week between both acquisitions, the tumor motion was comparable.

The overall phase shift (about 120°) between 4D CT and 4D gated PET is dependent on the equipment (starting trigger point in PET, time response of the thermocouple, etc (responsible for 90°-100°)) and slightly on the patient (different respiration cycle asymmetry during CT and PET scanning (responsible for 20°-30°)). The phase determination was only inaccurate for directions with small motion, resulting in a significant difference in phase between the other directions.

The tumor motion curve of the 4D CT and the 4D gated PET (Figure 2-3b) shows that for patient 1 hysteresis was present. The presence of hysteresis in one plane (here the coronal plane) could be determined by calculating the phase difference between the LR and the CC tumor motion. Hysteresis can be different during PET or CT scanning e.g., the tumor follows a slightly different trajectory [1]. For this patient, the phase difference of the tumor motion between LR and CC direction was 65° for gated PET and 24° for 4D CT. The phase difference gives a contribution to the tumor misregistration of PET and CT in LR direction. The misregistration, reflected in a difference in translation between PET and CT, was approximately half of the peak-to-peak amplitude in LR direction (Figure 2-3a), which is less than 0.5 mm. This contribution, which was also present for other patients, can be neglected in image fusion.
4.2. *Image fusion and center-of-gravity*

Errors in tumor alignment in 4D CT and 4D gated PET scans were influenced by the respiration pattern (shape and amplitude) and the matching procedure for the alignment of the bony anatomy. A reproducibility study of matching PET transmission scans to average 4D CT scans has not yet been performed due to the small number of patients. For the patients with transmissions scans of a finer voxel grid, the matching of the transmission scan and the average 4D CT scan becomes easier (verification) and faster (less iterations) probably due to the four times larger amount of voxels taken into account. Slomka *et al.* [22], using a mutual information criterion [23], found a reproducibility of registration of 0.3 pixels, 1.1% and 0.2° in translations, scaling and rotations, respectively, using transmission scans and conventional CT scans. We performed gray-value matches of both scans using mutual information and correlation ratio criteria without taking scaling into account. We noticed that correlation ratio gave visually better alignment of structures. Possibly the number of voxels of a single bed position is too small for mutual information to result in a good match result. This comparison, in combination with the results of Slomka *et al.*, yields an estimate of the accuracy less than 1 mm for translations and 0.2° for rotations using the voxel sizes of our scans.

The small standard deviation of center-of-gravity (CoG) of the tumor (< 1 mm in each direction) suggests that the shape of the tumor does not change significantly during respiration for this study population. Because the CoG determination was influenced by motion tracking, a small standard deviation implies that the tumor matching, needed for motion tracking, was accurate and the absolute position of the tumor can be determined accurately. For patient 1, there was a contribution of the diaphragm that entered the ROI in some phases, this resulted in a larger standard deviation in the CoG (1 mm). Background activity of the abdomen can sometimes give shape differences in PET scans in certain frames but this effect was not very clear for this patient. The differences in tumor CoG between 4D gated PET and 4D CT were smaller than the voxel size except for patient 3 (the CoG-difference of 3.1 mm in the lateral direction of patient 1 was also due to the diaphragm contribution). The difference in CoG of patients 3 and 5 were probably due to the presence of atelectasis. For tumors with large amount of atelectasis, the tumor CoG in PET and CT cannot be compared to each other. For small tumors the amount of atelectasis could not be distinguished from tumor tissue due to the partial volume effect in PET scans. Patients 1 and 2 in particular, show that the registration of the PET and CT scan was accurate and the breathing level of the patients was similar during acquisition of both scans. The variation of the difference in CoG over the breathing cycle was small (< 0.6 mm, 1SD), indicating that the tumor motion was comparable, as also concluded from Table 2-2. The small standard deviations and small differences of the CoG indicated the high correlation between the tumor motion in 4D gated PET and 4D
Figure 2-4 Results of the fusion of 4D gated PET and 4D CT for patient 1. The tumor region is shown in 8 phases from halfway inhale (phase 0°) to exhale (phase 135°) and back to inhale (phase 270°) for a coronal and a sagittal view. The three rows depict the 4D CT, 4D gated PET and the fused 4D CT with PET scans. The fused images show the 4D CT scan as background (gray scale) overlaid with iso-activity contours of the 4D gated PET. Note that the tumor also moves out-of-plane, following a 3D motion.
CT and is in accordance with the match accuracy of about 1 mm as estimated by Slomka et al. [22].

As stated in the Section 2-2.2, motion within a time frame of a bin was disregarded. This blurring can be seen in phases at mid-ventilation where motion is at maximum (Figure 2-4), but at maximum inhale and exhale (where the tumor stands still) images contain a good representation of tumor and internal structures. Since the gantry rotation time was smaller than half a breathing cycle, not all tumor motion will be blurred in-slice. Therefore, although that this motion-blurring appears for some phases were motion is largest, the results shows that tumor motion tracking was less influenced by the inner slice motion-blurring.

Several articles were recently published concerning hybrid PET-CT systems [11,24,25]. Supposedly, the advantage of these systems is that post-registration is not necessary since patients are aligned inherently. This inherent registration is also known as “hardware fusion” referring to the design of the machine. However, no data about the registration accuracy of bony anatomy in hybrid PET-CT scanners has been published yet. Using hybrid PET-CT scans, the acquired image sets are calibrated to be overlaid correctly within a certain error but are not routinely corrected for breathing artefacts or accidental positioning changes [10]. These accidental changes can be caused by hardware deflections of the scanner and also by patient movement invoked when transporting the patient (60 - 80 cm) from the PET part to the CT part of the hybrid scanner. In these cases post-registration is still needed.

When making 4D multi-modality scans on a hybrid scanner, tumor motion tracking and verification techniques as proposed in this chapter are still required since those scans were acquired sequentially instead of simultaneously using different acquisition and reconstruction methods. Moreover, tumor motion information is used is radiotherapy for dose planning purposes.

Recently, Nehmeh et al. [26] published a study regarding quantification of respiratory motion during 4D PET-CT acquisition. The major differences between their method and the method proposed in this chapter is the use of external markers for motion verification instead of the tumor itself, which reduces the reliability of PET-CT image fusion. Moreover, Nehmeh et al used a cine CT reconstruction and a prospective PET gating scanning method, both using non-linear phase-sorting (no linear phase-time relationship). These physical properties of their hybrid PET-CT scanner limited the possibility of image fusion of PET and CT scans of all phases.
5. **Conclusions**

A method has been developed to fuse respiration-correlated 4D CT scans with 4D gated PET scans. This procedure makes it possible to accurately combine functional PET information with anatomical CT information, without the usual distortions due to respiration.

Although the number of patients is still small, the results show that the method is clinically feasible and provides data to verify respiration motion on different days. This chapter concerns stand-alone PET and CT scanners, however, the 3D motion determination and verification methods still can still be applied using hybrid PET-CT scanners. The 4D acquisition and fusion of PET and CT scans can be contributed to the improvement of diagnostic and (radio) therapeutic outcomes.

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