Four-dimensional imaging in radiotherapy for lung cancer patients

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Although 'average' sounds very boring.
It's still not worth ignoring.
I know advanced stuff sounds more fun
But it's difficult and restrictingly dumb!
Then using a method that's simple and rough
Has never been successful enough
(it is just bluff).
Therefore
Treating patients with radiation at Mid-ventilation
Will certainly give rise to better treatment and elation!

Lung cancer is the most common cause of cancer related death. Overall survival is often poor after treatment with conventional radiotherapy. Improvements may be obtained by increasing the radiation dose; however, this can lead to unacceptable complications of healthy organs in or near the irradiation field. The size of the irradiation field is defined by the size of the tumor plus a treatment margin, to allow for geometrical uncertainties during treatment.

The aim of this thesis is to reduce respiration-related geometrical uncertainties by improved imaging, creating patient-specific treatment plans. As a result treatment dose can be increased and/or the risk of complications reduced. For this purpose, four-dimensional imaging acquisition and post-processing techniques were developed and implemented in the clinic.

Jochem Wolthaus
Four-dimensional imaging in radiotherapy for lung cancer patients
Four-dimensional imaging in radiotherapy for lung cancer patients

Jochem Willem Heiko Wolthaus
“Your time is limited, so don’t waste it living someone else’s life. Don’t be trapped by dogma - which is living with the results of other people’s thinking. Don’t let the noise of other’s opinions drown out your own inner voice. And most important, have the courage to follow your heart and intuition. They somehow already know what you truly want to become. Everything else is secondary.”

-Steve Jobs-
Four-dimensional imaging in radiotherapy for lung cancer patients

ACADEMISCH PROEFSCHRIFT

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Introduction
1. **Epidemiology of lung cancer**

Lung cancer is a leading and increasing cause of cancer related deaths [1]. Worldwide some 1.4 million new cases of this disease are diagnosed each year (in 2002), accounting for 12% of all cancer cases [2]. Currently, smoking is still the major cause of lung cancer, 90% of male and 70% of female lung cancer patients being (former) smokers [3]. Due to the repressive smoking policy by the government, this number is likely to decline in Europe and America. However, in industrialized countries air pollution is reported to cause an increase in the number of lung cancer cases [4,5,6]. Clinical advances in the treatment of lung cancer therefore continue to be of essential importance.

2. **Treatment modalities**

Curative treatment options for lung cancer patients are surgery and radiotherapy, possibly in combination with adjuvant chemotherapy. Surgery is the treatment of choice for otherwise fit patients with small tumors and no nodal involvement or distant metastasis. Depending on the tumor stage, the 5-year survival rate after surgery is between 30 and 65%. Due to loco-regional tumor extension, extra-thoracic spread or poor physical condition at the time of diagnosis about 80% of the lung cancer patients are (medically or technically) inoperable [1]. For the vast majority of these patients radiotherapy is then the main treatment option. Radiotherapy uses electromagnetic ionizing radiation to kill cancer cells by causing irreversible damage to their DNA. DNA of unaffected healthy tissue may also be damaged in the process; however, healthy tissue is better capable to recover. The current prognosis for non-small-cell lung cancer (NSCLC) using conventional radiotherapy doses is poor, with a 5-year survival of only 15%, partly due to a high local recurrence rate [7].

3. **Local tumor control and complications**

The aim of curative radiotherapy is to reach local tumor control (killing all primary tumor cells) resulting in a better failure-free and overall survival. Strategies to improve the local control include escalation of the (biological equivalent) radiation dose to the tumor (Figure 1-1a) [e.g., 8-15], altering fractionation schemes i.e., accelerated treatment and hypo-fractionation [16,17], and/or adding (radio-sensitizing) chemotherapy [18,19]. Dose escalation, however, is associated with an increased risk of complications. The surrounding healthy lung tissue, the heart, blood vessels, spinal cord and the oesophagus are sensitive to radiation and therefore these organs limit the prescription dose [20,21]. These risks can be reduced by making the treatment volumes smaller, i.e., excluding sensitive surrounding tissues from the irradiated volume. However, due to the geometrical uncertainties, associated with the limited precision of the radiation treatment preparation and delivery (see Section
1-6), substantial irradiated volumes are required since additional margins need to be taken into account to cover these uncertainties and prevent geometrical misses. For example the incidence of radiation pneumonitis, the most common complication of lung radiotherapy, is related to the mean lung dose (MLD; integral radiation dose to the lung divided by the total lung volume) [22]. Increasing the dose without reducing the irradiated volume results in an increase of the MLD, thereby increasing the incidence of complication (Figure 1-1b). A detailed description of the relation between the dose distribution and the radiation induced lung damage is given elsewhere [23-27].

4. Imaging modalities

Computed Tomography (CT; Figure 1-2a) has become the standard imaging modality for three-dimensional (3D) target definition in radiotherapy. A CT scan consists of a stack of two-dimensional (2D) slices representing the anatomy of a patient in three dimensions. CT is used to identify and localize the tumor and the organs-at-risk, and to calculate and optimize the dose delivered to the patient. The gray-values in the CT image represent the local tissue density of the patient, which is necessary for accurate dose calculation. Other imaging modalities like 18-Fluoro-2-Deoxy-Glucose positron emission tomography (18FDG-PET; Figure 1-2b) and single photon emission computed tomography (SPECT; Figure 1-2c) represent functional information of the tumor and normal tissues, respectively. FDG-PET imaging is used for diagnosis and to specify the target. PET imaging can help to distinguish tumor from atelectasis and pleural effusion [28-30]. To take full advantage of the PET data in radiotherapy planning, the PET scan has to be co-registered to the CT scan [this thesis and 31], resulting in improved accuracy of tumor determination and segmentation [32-34].

Figure 1-1. A schematic representation of (a) the dose effect relation reported in the literature [8-10] and (b) the relation between complications (radiation pneumonitis >= grade 2) and the mean lung dose (MLD) reported in the literature [8,10].
SPECT imaging with 99mTc labeled microspheres can be used to determine the perfusion of the lung (“lung function”), which may be used in the optimization of the treatment beam directions [35]. SPECT is, however, not considered in this thesis.

To determine and correct patient setup errors, 2D (Mega Volt –MV–) portal imaging prior to treatment delivery is used to measure the position of bony structures, as a surrogate for tumor position. However, the small bony structures in thoracic region and the low contrast of MV portal images often result in poor registration to the planning scan of the target and anatomy. In addition, bony structures and tumor can move differentially [36]. Cone beam computed tomography (CBCT; Figure 1-2d) is
therefore used widely nowadays. CBCT is an adapted CT technique for use on a linear accelerator to visualize the 3D anatomy of the patient just before treatment. CBCT allows image-guided radiotherapy (IGRT), i.e., using in-room acquired images, prior to delivery, to determine and correct geometrical errors in the position of the tumor and other concerned organs.

Conventionally in lung cancer imaging for radiotherapy planning, 2D CT slices of the thoracic region are acquired while the patient breathes freely and these are therefore not related to the respiration phase of the patient (for diagnostic imaging these scans are generally acquired during breath-hold). Since each slice corresponds to an arbitrary breathing phase, imaging artifacts and distortions are caused in the resulting 3D volume (Figure 1-2a). Together with this 3D CT scan, fluoroscopic imaging is then used to obtain tumor motion information. Note that conventional PET, SPECT and CBCT imaging are also affected by the respiration of the patient resulting in blurred image structures (Figure 1-2b,c,d).

5. Target volume description

Usually, a CT scan is used to delineate the (visual) tumor volume (gross tumor volume –GTV–; Figure 1-3). According to the ICRU 62 report [37], the GTV should first be expanded into the clinical target volume (CTV) to account for microscopic tumor extensions (i.e., a small number of malignant cells in a small region around the visual tumor volume; Figure 1-3). For lung tumors, this margin is generally taken to be 0 or 5 mm [38,39]. Subsequently, geometrical uncertainties associated with radiotherapy may lead to a geographical miss and underdosage. In order to prevent...
such geographical misses, a margin, added to the CTV, is needed, thereby defining
the planning target volume (PTV; Figure 1-3). In our clinic, this margin ranges between
7 and 16 mm, depending on the patient’s movements and treatment technique.

6. **Geometrical uncertainties**

The position and shape of the tumor during treatment delivery can deviate from
the position and shape during treatment-planning. These geometrical uncertainties
can be attributed to treatment preparation, the treatment delivery, or anatomical
changes as a result of treatment. The uncertainties are divided into systematic
errors (a component of the deviation that is constant during the complete course
of treatment) and random errors (daily variation in patient setup or organ position).
There are four main error sources: (1) uncertainty in tumor definition/delineation
(prior to irradiation); (2) tumor motion due to respiration; (3) tumor baseline variation;
and (4) setup uncertainty. The latter three uncertainties are depicted in Figure 1-4.

6.1. **Uncertainty in tumor delineation**

The uncertainty in tumor delineation is caused by the inability of CT imaging to
distinguish tumor from atelectasis or inflammation, imaging artifacts due to respiration
[40,41] and uncertainty in the observer’s interpretation of the images [42,43].
However, the last mentioned uncertainty is influenced by the first two uncertainties.
Although the contribution of the delineation uncertainty is relatively large compared
to the other uncertainties [44], it is not the topic of this thesis.

6.2. **Tumor motion due to respiration**

Lung tumors can move up to 40 mm due to breathing [45,46]. However, on most
cases the motion is less than 20 mm. Respiratory motion causes an uncertainty in the
tumor position and tumor shape in conventional imaging modalities. In conventional
3D CT, artifacts are generated since the CT slices are arbitrary snapshots acquired
without any time-information of the moving tumor [40,43,this thesis]. Due to the long
acquisition time, conventional 3D PET is also subject to uncertainties with respect
to respiratory tumor motion, resulting in (motion-) blurring of the tumor activity and
uncertainty in tumor size, position and measured tracer uptake.

During treatment delivery, the tumor can move into and out of the irradiation beam
due to respiration as well as the surrounding organs (tissue density variation),
causing a blur of the delivered dose to the target.

6.3. **Baseline, amplitude and phase variation**

Besides the variation in tumor position over the respiratory cycle (respiratory tumor
motion), there is also variation in the *mean* tumor position [46]. The mean tumor
position (baseline) is defined as the time-weighted average position of the tumor
Introduction

Planning Fraction 1 Fraction 2 Fraction n
Maximum exhale
Maximum inhale

Tumor trajectory (different amplitudes)
Tumor position in the 4D CT
Mid-ventilation
Mean tumor position (baseline) during treatment
Mean tumor position (baseline) relative to bone according to planning
Baseline shift
Set-up based on bony anatomy
Error due to hysteresis

Figure 1-4. Schematic overview of the different uncertainties related to external beam radiotherapy of lung tumors. From a 4D CT scan (10 frames from 0% (inhale) to 90%) the time-weighted mean position of the tumor is computed and the corresponding CT representation is used to plan the treatment. However, during treatment, the patient’s position, mean tumor position and amplitude can vary, which introduces geometrical uncertainties. In addition, the mean-position tumor state is physically not available when the tumor moves in an ellipsoid (hysteresis). Therefore, a simplification is currently clinically applied by using the 4D CT frame where the tumor is closest to that mean position. However, this only introduces a small additional error (smaller than suggested in this figure).
over the observed respiratory cycle(s) with respect to the bony anatomy (the center of this trajectory; depicted in Figure 1-4 as the red-dotted plus-sign). Differences in baseline position over the course of treatment are referred to as baseline variation (Figure 1-4, black arrow).

The amplitude of the respiration (respiration depth) can also vary during and between fractions or CT scanning (Figure 1-4, varying ellipsoid size) [45,47]. Finally, a phase shift can occur between different internal lung structures or internal structures and external body features (respiratory signals that are used to drive the gated imaging or treatment) [48,49]. These phase shifts can differ from day-to-day.

The (physiologic) processes causing these variations are not well understood. Baseline variation has a weak correlation with motion amplitude, which implies some diaphragm position interference that may be caused by differences in stomach filling. Phase shifts can occur when the tumor grows into the thoracic wall or the mediastinum or due to change from abdominal to thoracic breathing and vice versa. Change in atelectasis, pleural effusion, stress or cardiac status might also play a role [46].

6.4. Setup uncertainty

Setup uncertainties are the variation in patients’ position during the course of treatment compared to the position of the patient during treatment preparation (planning CT

Figure 1-5. (Top row) Example of a 4D CT scan, showing the moving anatomy of the thorax in 10 different phases. (Middle row) Example of a 4D PET scan, showing functional information in the moving anatomy. (Bottom row) Example of fused 4D PET and CT images. The red dashed lines are guides.
scan in combination with a defined iso-center; Figure 1-4, black-dotted arrow). These setup errors can also be described by systematic and random components. Generally, this displacement is determined using alignment of the bony anatomy by portal imaging or CBCT. Current CBCT image quality is good enough to register soft tissues (especially the tumor) to the corresponding tissue in the planning CT scan (which is not well possible with MV portal images). Using CBCT an accurate value of the tumor position displacement compared to the planning position [36] can be determined, correcting both setup uncertainties and baseline shift.

7. Uncertainty margins
To cover the above-mentioned geometrical uncertainties, additional margins need to be applied to the CTV. For each patient individually, the margin necessary to deliver a dose of at least 95% of the prescribed dose to the CTV (to statistically cover 90% of the population) can be computed by the (statistic) margin recipe of van Herk et al. [50-52] in its simplified form: $M_{CTV-PTV} = 2.5\Sigma+0.7\sigma$, where $\Sigma$ and $\sigma$ denote the standard deviations (SDs) of the systematic errors and random errors, respectively. It is clear that the influence of systematic errors is much larger than those of the random errors. The various systematic and random uncertainties are summed in quadrature to generate the margin.
To determine correct uncertainty margins, information about the (residual) error distributions of geometrical uncertainties, such as organ (target) movement, setup error, and delineation uncertainty must be available. These uncertainties differ from institution to institution and on the image guidance procedures in use, and it is therefore essential that they are quantified accurately for each institute.

8. **Reduction of respiration-induced geometrical uncertainties**

To enable safe dose escalation (for improved treatment outcome), uncertainty margins (CTV-to-PTV) and the associated target volumes should be minimized. To do so, the systematic and random geometrical errors need to be reduced. The first step is reduction of the influence of respiration on imaging (i.e., reducing imaging artifacts), which reduces the systematic geometrical errors. By correlating the imaging techniques to the respiration, these respiration imaging artifacts are reduced [53,54].

The resulting respiration-correlated scan is a set of 3D scans each corresponding to a different breathing phase, therefore often referred to a 4D scan. This 4D scan contains the motion information of all structures, including the tumor (Figure 1-5). Respiration-correlated scanning techniques have been developed for all imaging modalities (PET and CT are considered in this thesis). For PET images there is, due to the reduction of image blurring, also an improvement in the quantification of the tracer uptake. The $^{18}$FDG tracer uptake (standardized uptake value –SUV–) is a strong predictor for the treatment outcome and therefore it is important to determine this value accurately [55].

To deal with tumor motion during treatment delivery several authors have investigated voluntary breath-hold [56,57], active breathing control (ABC) [58] and respiratory gating [59-61]. These methods aim to irradiate only during a portion of the respiratory cycle (usually maximum exhale phase for gating, or maximum inhale phase for breath-hold), thereby reducing some geometrical uncertainties. Other studies suggest to...
use a single suitable CT scan in combination with a margin to account for the effects of respiratory motion based on analytical determinations and simulations [51,62,63]. These last mentioned approaches only affect the acquisition process of the planning CT and not the actual radiation delivery. Three methods are reported in literature and will be discussed in this thesis: Use of a slow CT (a respiratory-blurred scan; Figure 1-6) [64,65] in which the target is defined by a certain gray-value threshold applied to the image; a maximum intensity projection (MIP) CT scan [66,67] (Figure 1-6) in which the target is defined as a tumor volume encompassing the complete motion extent as visible in the 4D scan; and the mid-ventilation (or mid-position) CT scan, which represents the tumor in the time-weighted average position over the respiratory cycle [68, this thesis] (Figure 1-4, red circle; Figure 1-6).

9. **Background of this thesis at the institution**

Each year the department of radiation oncology at the Netherlands Cancer Institute (NKI) treats approximately 200 new lung cancer patients using nine accelerators, five of which have an integrated CBCT. Research of the department is focused on the interaction between clinical research and radiation physics and radiobiology, with much expertise in introducing new techniques and applications into daily practice with extensive quality control. The department has a long history in lung research on various topics: Radiation-induced toxicity [69], local dose-effect relations for radiation-induced perfusion and ventilation loss [23,24,70], overall response parameters for optimization of the 3D dose [25], dose-escalation trials [12] and, currently, hypo-fractionated stereotactic body radiotherapy [71]. An important research line is the development of image-guided radiotherapy using electronic portal imaging devices (EPIDs) and CBCT scanners. In-house developed software is running clinically to assess bony movements (with EPIDs) or soft-tissue variation in position and shape (with CBCTs). Strategies to deal with correction and guidance in the presence of these anatomical changes are also developed. Specifically, for lung treatment, 4D imaging tools and techniques have been developed to handle and analyze respiration-correlated 4D data, of which this thesis is a result.

10. **Objective of this thesis**

The main objective of the work described in this thesis is to reduce the geometrical uncertainties related to patient respiration by improved imaging for radiotherapy planning (anatomical CT and functional/biological PET). The study involves the technical realization of 4D imaging (Chapter 2) and clinical implementation (Chapter 3). The methodology and workflow to obtain high image quality treatment-planning
scans of lung cancer patients are developed and evaluated in terms of image quality (Chapter 5), uncertainty (PTV) margin reduction (Chapter 6) and planned dose delivery (Chapter 7). As a result of the work described in this thesis, an individualized optimization of the treatment plan and more accurate delineation of the tumor is made possible. The methodology must be easy to implement in the clinic in advanced radiotherapy centers (in combination with IGRT protocols based on soft-tissue alignment) as well in less utilized radiotherapy centers (in combination with IGRT protocols based on bony anatomy alignment).
References

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 cause 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 breathe 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.](image-url)
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 $\varphi$ 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):

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

$D(j)$ 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.
\Phi_{\text{overallshift}}, i.e., a distance measure between the 4D CT and 4D gated PET tumor motion curve. \langle x \rangle 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: \( \sim 4 \text{ cm}^3 \), stage \( T_3N_2M_1 \)), right thorax wall (patient 2, tumor volume: \( \sim 4 \text{ cm}^3 \), stage \( T_1N_0M_0 \)), right hilum (patient 3, tumor volume: \( \sim 100 \text{ cm}^3 \), stage \( T_2N_2M_0 \)), right hilum (patient 4, tumor volume: \( \sim 100 \text{ cm}^3 \), stage: \( cT_1N_0M_0 \) and right lung in close proximity to the diaphragm and mediastinum (patient 5, tumor volume: \( \sim 100 \text{ cm}^3 \), stage \( T_2N_2M_0 \)). 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 were 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.
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>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>
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<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.
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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 $Z(p^*\tau_{resp}/\tau_{gantryrot} - 1)$, where $Z$ denotes slice thickness, $p$ the pitch, $\tau_{resp}$ the respiration cycle length and $\tau_{gantryrot}$ 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

<table>
<thead>
<tr>
<th>Patient</th>
<th>4D CT Variation (SD)</th>
<th>4D gated PET Variation (SD)</th>
<th>4D CT, 4D gPET Difference</th>
<th>4D CT, 4D gPET Variation (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
<td>CC</td>
<td>AP</td>
<td>LR</td>
</tr>
<tr>
<td>1</td>
<td>0.5</td>
<td>0.8</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>0.2</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.1</td>
<td>0.6</td>
<td>0.1</td>
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<tr>
<td>5</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

For patient 4, the difference and variation in CoG could not be calculated (nc*) from the data, because of missing data due to hardware problems.
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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Clinical implementation

Mid-ventilation CT scan construction from 4D respiration-correlated CT scans for radiotherapy treatment-planning of lung cancer patients

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International Journal in Radiation Oncology, Biology and Physics 65 - 2006
Abstract

Purpose Four-dimensional (4D) respiration-correlated imaging techniques can be used to obtain (respiration) artifact-free computed tomography (CT) images of the thorax. Current radiotherapy planning systems, however, do not accommodate 4D CT data. The purpose of this study was to develop a simple, new concept to incorporate patient-specific motion information, using 4D CT scans, in the radiotherapy planning process of lung cancer patients to enable smaller error margins.

Methods and Materials A single CT scan was selected from the 4D CT data set. This scan represented the tumor in its time-averaged position over the respiratory cycle (the mid-ventilation CT scan). To select the appropriate CT scan, two methods were used. First, the three-dimensional (3D) tumor motion was analyzed semi-automatically to calculate the mean tumor position and the corresponding respiration phase. An alternative automated method was developed to select the correct CT scan using the diaphragm motion.

Results Owing to hysteresis, mid-ventilation selection using the 3D tumor motion had a tumor position accuracy (with respect to the mean tumor position) better than 1.1±1.1 mm for all three directions (inhalation and exhalation). The accuracy in the diaphragm motion method was better than 1.1±1.1 mm. Conventional free-breathing CT scanning had an accuracy better than 0±3.9 mm. The mid-ventilation concept can result in an average irradiated volume reduction of 20% for tumors with a diameter of 40 mm.

Conclusions Tumor motion and diaphragm motion method can be used to select the (artifact-free) mid-ventilation CT scan, enabling a significant reduction of the irradiated volume.
1. INTRODUCTION

Treatment outcome for non-small-cell lung cancer (NSCLC) using conventional radiation doses are poor, and the local recurrence rate is high. Tumor control can probably be improved by increasing the dose (e.g., [1]). However, the surrounding healthy lung tissue and the oesophagus are dose limiting [e.g., 2,3]. To enable dose escalation, the irradiated surrounding normal tissue volume should be minimized. One possible approach is to reconsider the margins for the conventional planning target volume (PTV). The PTV is generally defined as the clinical target volume (CTV = visible tumor plus margin for microscopic extensions) plus a margin to account for geometrical uncertainties [4]. The most important inter-fractional geometrical uncertainties are patient setup errors, tumor shrinkage or growth, and respiratory baseline shifts (i.e., shifts in respiration levels). Intra-fractional geometrical uncertainties are due to respiratory and cardiac motion. Eliminating geometrical uncertainties allows for a reduction of the CTV to PTV margins, reducing the volume of irradiated normal tissue and normal tissue complication probability and enabling dose escalation. A single free-breathing computed tomography (CT) scan is often used for radiotherapy planning for lung tumors. However, respiration-induced tumor motion (TM) during acquisition causes artifacts in tumor shape and position (e.g., [5,6]). The cause of these artifacts is that the CT scanner acquires a stack of images without time information from the moving tumor, thus obtaining a set of arbitrary snapshots of moving structures. To overcome this problem, time-resolved four-dimensional (4D) scanning techniques were developed [7-12]. Basically, all these methods are similar i.e., the acquired oversampled three-dimensional (3D) data are sorted by the patient’s respiratory phase using an external breathing signal, yielding a set of 3D reconstructions at different breathing phases. This set (i.e., 4D image data) provides temporal and spatial motion information that can be used to optimize treatment-planning. Currently, however, available commercial treatment-planning systems cannot handle a 4D CT data set as input for treatment-planning. Several strategies for the implementation of 4D data sets in the treatment-planning process have been published:

- **Slow CT scan** Van Sørensen de Koste *et al.* [13] used a slow CT scan (which can be considered as the time average of the 4D data set) to delineate the target volume encompassing the tumor at any position during the breathing cycle (internal target volume –ITV–). A 5 mm expansion was added to the ITV to cover the CTV and a 5 mm expansion was added from the CTV to the PTV.

- **Maximum inhale and exhale composite delineation** Allen *et al.* [14] studied the delineation of the gross tumor volume (GTV) in a maximum inhale scan and a maximum exhale scan and created a composite of the two delineation sets for planning (GTV to CTV margin recipe was not given).
• **All-phase composite segmented tumor** Rietzel *et al.* [15] and Underberg *et al.* [16] proposed a method (based on maximum intensity projection - MIP) that automatically creates a composite segmented CT scan of all respiratory phase scans (frames; the full 4D set). From this composite CT scan, the composite GTV was delineated (GTV to CTV margin recipe was not given).

• **Breath-hold CT scan (with active breathing control)** Wong *et al.* [17] and Rosenzweig *et al.* [18] studied breath-hold CT acquisition using the active breathing control (ABC) device and voluntary breath-hold, respectively, to obtain a single 3D scan without motion artifacts for treatment-planning purposes (GTV to CTV margin recipe was not given).

---

**Figure 3-1.** Considerations presented in this chapter can be summarized in the following clinical protocol currently in use in our institution. The protocol is divided into 2 parts: During and after scanning. **4D** = four-dimensional; **MidV** = mid-ventilation.
Deformation dose mapping Keall et al. [19] proposed a 4D dose calculation method based on 4D deformation maps from the 4D CT scan. The deformation maps were applied to the peak-inhale delineations of the tumor and other structures. For each respiratory phase of the 4D set, an optimized treatment plan was calculated.

The first three methods can be summarized as composite target volume concepts, in which the target volumes are often enlarged. Moreover, delineation of moving structures in the slow CT method is difficult because of motion-blurring. The second and third method need multiple reconstructions for tumor delineation and dose calculation. The breath-hold method is not applicable to all lung cancer patients because of their physical condition. Moreover, breathing control also needs to be maintained during treatment. The effectiveness of the last method, by Keall et al. [19], was demonstrated in a feasibility study, but its clinical implementation is not yet possible because of hardware limitations.

In this chapter, we have proposed the selection of a single well-chosen CT scan from a 4D set. The choice of the single CT scan was based on studies by Engelsman et al. [20] and Witte et al. [21]. These studies showed that if the tumor is irradiated at its average position during the respiration cycle, because of the presence of the wide-beam penumbra in the lung, good dose coverage would still be obtained even if the tumor was not fully within the high-dose region for a small part of the breathing cycle (0.6% and 6% tumor control probability loss for 5 mm and 15 mm motion amplitude with zero margin, respectively, no setup errors). Such an approach makes margin reduction possible.

The aim of this study was to eliminate the systematic errors in the imaging process induced by respiratory motion and to obtain a more representative scan for delineation of the target area, normal structures, and dose calculation. In the presented approach, motion was not taken into account when delineating the tumor (thus no ITV) but will be incorporated in the margin expansion from CTV to PTV. This margin included the dose blurring caused by respiratory motion during treatment. See Figure 3-1 for the clinical protocol for 4D analysis and scan selection currently used in our hospital.

2. METHODS AND MATERIALS

2.1. Patient group

Patients with a lung tumor who were scheduled for radiotherapy underwent fluoroscopy to estimate tumor motion (TM) due to respiration. If the tumor was estimated to move ≥ 0.5 cm owing to respiration, the patients were eligible for this study. All patients (12 male, 3 female) included in the study gave written informed consent to participate. The local medical ethics committee approved the study.
Figure 3-2 (a) Schematic overview of the trajectory of the tumor with its mean position (M) and the multiple mid-ventilation positions in exhalation (t%midv-exhale) and inhalation (t%midv-inhale) due to hysteresis (multiple closest distances between tumor and mean tumor position). Geometrical error with respect to the mean position is denoted by εh. (b) Simplification of concept by considering cranio-caudal (CC) movements only. Error in the determination of the time-percentage (εmidv%), due to simplification of only using the CC motion direction; and (c) shows the CC projection of the tumor trajectory, which is used to estimate the mid-ventilation time-percentages. Because of hysteresis, a phase shift exists between the motion curves of the different directions (c, lower panel), resulting in a geometrical error εh for the other directions.
2.2. Respiration-correlated 4D CT imaging

a. 4D CT Scanning

During 4D CT scanning, the patient was instructed to breathe freely and normally. Patient respiration was registered using a thermocouple (Type T, copper-constantan, S-CC-U-O-7/1, Volenec, Hradec Králové, Czech Republic) inserted into the entry of a regular oxygen mask, which measures temperature changes in the airflow during inhalation (cold) and exhalation (warm).

During CT scanning, patients were positioned supine with their arms raised above their head using an in-house developed forearm support. To obtain a position similar to that on the treatment couch, a flat tabletop (Sinmed, Reeuwijk, the Netherlands) was placed on the couch of the CT scanner (20 slice Somatom Sensation Open, Siemens, Forchheim, Germany). The helical cardiac scanning mode of the CT scanner was used for the respiration-correlated imaging. However, the thermocouple respiratory signal was used for data sorting, instead of the cardiac input signal.

The scans were made at 120 kV, 1000 eff.mAs. The complete thorax was scanned (30-35 cm) from 5 cm above the top of the lung down to 5 cm below the diaphragm in inhale position. The scan time was 60 - 70 s.

b. Scan reconstruction

The beam-on signal of the CT scanner was used to synchronize the respiration signal with the CT data. The time delay (response time) between the movement of the internal structures of the lung and the external (thermocouple) breathing signal (0.4 s, see Appendix), was corrected by back shifting the respiratory signal with respect to the beam-on signal. After this time delay correction, the respiratory signal should, in principle, be in phase with the CT data of the internal structures. The respiration-correlated protocol on the scanner, an adaptation of the cardiac protocol, uses the peaks (maximum inhalation) of the respiration signal to sort the raw CT data. Between the peaks, the respiratory cycle is divided into 10 equidistant time-percentage bins (0% at maximum inhalation to 90%). Within one cycle, the time bins are equidistant, but from cycle to cycle, the exact length of a certain bin may vary owing to variations in the breathing period. Using equidistant time bins, which is equal to linear data sampling, the asymmetry between inhalation and exhalation length is incorporated in the fourth dimension of the resulting 4D scan by having a different number (generally more) 3D CT frames in the exhalation phase than in the inhalation phase.

For each table position (every 3 mm) and time-percentage within the breathing cycle, the corresponding location in the CT sinogram (as a function of table position and gantry angle) was determined. A slice was reconstructed using data from -110° to +110° (180° plus fan angle) from the determined gantry angle. The number of slices within one time bin was approximately 100 for the chosen slice thickness of 3 mm.
c. **Choice of CT acquisition parameters**

The quality of 4D scanning in the helical mode depends critically on the interplay between the breathing characteristics of the patient and the acquisition parameters used for scanning. According to Ford et al. [7], complete coverage of moving structures over a full breathing cycle is obtained when:

\[
CL_{\text{Gantry-rotation}} = pitch \times CL_{\text{Respiration}}
\]

where \( CL_{\text{Respiration}} \) is the breathing cycle length of the patient and \( CL_{\text{Gantry-rotation}} \) the gantry rotation time. If the \( CL_{\text{Gantry-rotation}} \) is shorter than \( pitch \times CL_{\text{Respiration}} \) undersampling of the data will occur, leading to gaps in the 4D data for particular phases. If the \( CL_{\text{Gantry-rotation}} \) is longer, oversampling will occur and motion is blurred in the slice. The Somatom 20-slice scanner allows gantry rotation times of 0.5 and 1.0 second.

We therefore used two different sets of acquisition parameters: When the average \( CL_{\text{Respiration}} \) + 1 standard deviation was less than 5 seconds, a \( CL_{\text{Gantry-rotation}} \) of 0.5 s and \( pitch = 0.1 \) was used, otherwise a \( CL_{\text{Gantry-rotation}} \) of 1.0 s and \( pitch = 0.15 \) was used. This procedure prevented undersampling of a breathing period up to 6.7 seconds. The degree of oversampling may vary in a single 4D scan, depending on the variability of the breathing cycle length of a patient during scan acquisition.

2.3. **Concept and definition of mid-ventilation scans**

To plan the radiation of the tumor in the mean tumor position, we reconstructed a single 3D CT scan from the 4D data set that represents the mobile structures close to their (time-weighted) mean position. This scan was called the mid-ventilation (MidV) CT scan and was used for delineation of the tumor and normal tissue, as well as for treatment-planning dose calculation. First, we defined the mean position and the mid-ventilation time-percentage (\( t_{\text{midv}}^{\%} \)) (Figure 3-2).

**Definition** The mean position (\( \overline{M} \)) of a moving tumor or structure is the time-weighted mean position of the center-of-gravity of that tumor or structure in all three dimensions (left-right (LR), cranio-caudal (CC) and anterior-posterior (AP)). If hysteresis occurs in the tumor motion [22], this mean position is not necessarily on the trajectory of the object (Figure 3-2a).

**Definition** Mid-ventilation time-percentage is that time-percentage in the respiration cycle at which the tumor is closest to the time-weighted mean position. In general two solutions are possible: The mid-ventilation time-percentage can be defined during exhalation and inhalation (Figure 3-2a).

When the tumor moves in more than one direction (hysteresis), it might be possible that there is more than one closest distance between tumor and mean position (\( \overline{M} \)) (Figure 3-2a). To overcome this ambiguity in the determination of the \( t_{\text{midv}}^{\%} \), only the CC motion curve was considered (Figure 3-2b and c). The CC respiratory movements were usually dominant compared to the LR and AP movements. The CC motion curve does not give the real minimum distance between the tumor and mean
position, but provides an unambiguous single $t_{\%midv}$ for exhalation and inhalation. As a consequence of this approach, two types of errors are introduced: First, a geometrical error with respect to the mean position ($\varepsilon_h$), due to the hysteresis in the TM; and second, an error in the determination of the time-percentage ($\varepsilon_{midv\%}$), owing to simplification from using the CC motion direction only. Because of hysteresis, phase shifts exist between the motion curves of the different directions (Figure 3-2c, lower panel), resulting in a geometrical error $\varepsilon_h$ for the other directions. To calculate the $t_{\%midv}$, the $\bar{M}$ was calculated using the normalized (scaled between 0 and 1) CC motion curve (as inferred from Section 3-2.4a), indicated by the horizontal solid line in Figure 3-2. Subsequently, the motion curve was interpolated using cubic spline interpolation. The $t_{\%midv}$ in the exhalation phase ($t_{\%midv-exhale}$) and in the inhalation phase ($t_{\%midv-inhale}$) were determined. Finally, the corresponding MidV CT scan was reconstructed (at $t_{\%midv-exhale}$ or $t_{\%midv-inhale}$).

a. Verification of the MidV CT scan selection

To check whether this reconstructed MidV CT was acceptable, the scan was verified by visually inspecting the position of the structures of the MidV CT with respect to the corresponding moving structures in the 4D CT scan using an in-house developed composite viewer (Figure 3-3). In this composite viewer [23], the MidV CT is represented by the color purple (magenta) and the 4D CT scan represented by the color green. When overlapping, regions of corresponding density are then represented in gray-scale, unmatched regions will preserve their color. Verifying the geometrical average with the human eye is a good first estimate of the time-weighted mean-position.

2.4. Determination of motion

a. Determination of tumor motion by tumor-tracking

The TM in the 4D CT scan was determined using an image registration procedure [12]. A region-of-interest (ROI) was defined around the tumor in a reference CT.
frame (0%) using a manually drawn mask, encompassing the tumor. The ROI was subsequently registered to the scans of the other time-percentages based on gray-value using the correlation ratio [24] of all voxels in the ROI. This procedure was repeated three times for three different reference CT frames (0%, 30% and 70%). From each TM curve the mean tumor position was subtracted to obtain the relative motion curves. The three curves were averaged to reduce spurious results due to random drawing or matching errors, resulting in one (relative) motion curve that was used for further analysis (Figure 3-4). The TM curves were considered to be the reference standard.

b. Automated determination of diaphragm motion
Automated determination of the tumor trajectory can be complex, especially if segmentation of the tumor is not available. Moreover, if the tumor is not solitary but is attached to the mediastinum or thoracic wall, tumor segmentation becomes difficult. We therefore investigated whether the diaphragm motion (DM) derived from the image information in the 4D CT scan could be used as a surrogate for CC tumor motion. This method is fully automated after the tumor has been located in the right or left lung. First, the first frame (0% time-percentage) from the 4D scan is selected. This scan is projected on an axial plane (Figure 3-5a) and subsequently projected on the LR axis obtaining a one-dimensional profile of the pixel intensities (Figure 3-5b). The position of the maximum is used to distinguish the left from right lung (Figure 3-5c). Because the patient in the example of Figure 3-5 had a tumor in the left lung, we considered the lower left part of the 4D CT scan (Figure 3-5d). This selection was cropped to the lung region, subsequently cropped to the lower half of the lung and taken as the ROI. An average CT ROI was obtained by averaging the 10 time-percentages of the 4D ROI. The first (single) CT frame ROI (0%) was then subtracted from the average ROI (Figure 3-5e and f). Finally, all voxels of the subtracted ROIs were averaged over space (Figure 3-5g and h). The steps “e” through “g” were repeated for all 10 CT frames, and the 10 averaged values resulted in the motion...
The steps through the process are described in the text. Initially, a single CT frame was chosen as the reference frame (0% time percentage). Then, the pixel intensities were averaged over space to create a one-dimensional profile of the pixel intensities, which was used to distinguish the left and right lungs (Figure 3-5). Since the patient had a tumor in the left lung, we considered the left part of the 4D CT scan.

The selection was cropped to the lower half of the lung region, and the average gradient values were calculated over all voxels. The steps through the process were repeated for all 10 CT frames, and the average image of each phase scan was calculated. The maximum inspiration (Max) and expiration (Min) time percentages were determined from the scans.

The resulting curve was used to determine the diaphragm motion (DM) over all voxels. The motion curves were averaged over space to obtain the final curve. The steps through the process were repeated for all 10 CT frames, resulting in the motion curves for each phase scan.
curve of the diaphragm (Figure 3-5h). The DM curve was scaled between 1 and 0 for comparison with tumor motion. The $t_{\%_{\text{midv}}}$ and the corresponding mid-ventilation tumor position derived from the DM were compared with the mean tumor position as inferred from analysis of the tumor motion (resulting in error $\epsilon_{\text{DM}}$).

### 2.5. Validation of the external respiration signal

Previous studies [25,26] have reported that breathing measurements using an external device correlate well with movements of the internal structures, but phase shifts and time delays may exist between the two signals. Therefore, this phase shift and time delay was determined for the equipment used in our study. The verification of the thermocouple system, post-processing of the thermocouple signal and correlation to the diaphragm motion is described in the Appendix. The post-processed thermocouple signal, which is in phase with the diaphragm motion, was used during 4D CT reconstructions.

### 3. Results

3.1. *Respiration cycle length and amplitude*

15 patients were included in this study (6 upper lobe, 1 middle lobe, and 8 lower lobe tumors). The average breathing cycle length was 4.4 seconds over all patients and over all cycles during scanning (Table 3-1), however, the cycle length varied between 1.8 s and 10.1 s. Seven patients had a mean cycle length + 1 standard deviation larger than 5 s, and 10 out of 15 patients had at least one cycle that was longer than 5 s. 10 patients underwent scanning with the 0.5 s gantry rotation protocol and 5 with the 1.0 s gantry rotation protocol. Three patients were breathing with a shorter cycle before the scanning than during scanning; therefore, the choice of scanning parameters was not optimal. For two patients, a too short gantry-rotation time was accidentally chosen (0.5 instead of 1.0 s). Although this affected the scan quality, it did not seriously hamper the quantitative measurements (e.g., artifacts were not present in all 4D CT frames and the resulting motion curves were smooth). Cranio-caudal amplitudes (Table 3-1) of the tumor motion, as inferred from analysis of tumor motion (Section 3-2.4) ranged from 2 to 26 mm (mean±1SD is 12.3±7.1 mm).
3.2. Thermocouple time delay

The mean thermocouple time delay (see Appendix), measured over approximately 6x80 breathing cycles, was (mean±1SD) 0.40±0.18 s. Note that this delay was equipment dependent and must be determined for the equipment used. In addition, it appeared that a very weak correlation was present between the cycle length and time delay (correlation coefficient = 0.22).

3.3. Mid-ventilation

Figure 3-6 shows a typical example of the diaphragm motion curve with the corresponding CC tumor motion curve. The diaphragm motion correlated highly with tumor motion.

The average $t%_{midv}$ according to the CC tumor motion (reference standard) was 17.4±5.5% for exhalation and 75.0±6.5% for inhalation (Table 2). Note that the difference in $t%_{midv}$ between exhalation and inhalation did not appear to correspond to the scheme presented in Figure 3-2c, which was because of an unexpected phase shift (see Section 3-4.2). To make the geometrical results of the MidV CT concept comparable with other geometrical error contributions in radiotherapy, $\varepsilon_h$ and $\varepsilon_{DM}$ were calculated as the mean (group mean) and the standard deviation (Σ).

<table>
<thead>
<tr>
<th>$t%_{midv}$ (%)</th>
<th>(\varepsilon_h) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exhale</td>
</tr>
<tr>
<td>Mean LR</td>
<td>17.4</td>
</tr>
<tr>
<td>Mean CC</td>
<td>0.0</td>
</tr>
<tr>
<td>Mean AP</td>
<td>-0.7</td>
</tr>
<tr>
<td>SD LR</td>
<td>5.5</td>
</tr>
<tr>
<td>SD CC</td>
<td>0.0</td>
</tr>
<tr>
<td>SD AP</td>
<td>0.0</td>
</tr>
</tbody>
</table>

LR = left-right, CC = cranio-caudal, AP = anterior-posterior.

Figure 3-6. An example of the high correlation between cranio-caudal tumor motion (solid curve) and diaphragm motion computed by the image gradient of the four-dimensional scan (dashed curve). Both motion curves were scaled between maximum inspiration (1) and maximum exhalation (0). Note that time scale runs from 0% to 200% to emphasize periodicity.
The geometrical error, $\varepsilon_h$, with respect to the mean position (Table 2) was for exhalation $0.2\pm0.3$ mm in the LR direction and $-0.7\pm0.8$ mm in the AP direction. For inhalation, $\varepsilon_h$ is $0.0\pm0.4$ mm in the LR direction and $1.1\pm1.1$ mm in the AP direction. By definition, $\varepsilon_h$ in the CC direction was 0 because of the one-dimensional CC determination of $t_{\%\text{midv}}$.

Using the diaphragm motion method, the average $t_{\%\text{midv}}$ for exhalation was $19.9\pm4.1\%$ and for inhalation, $76.7\pm5.3\%$ (Table 3-3). The difference between the DM and TM methods were significant (exhale and inhale $p=0.01$, pair-wise T-test), but very small relative to the bin size of 10\% (exhalation, $2.5\pm3.5\%$). The maximum geometrical error, $\varepsilon_{DM}$, with respect to the mean position (Table 3-3) in the CC direction, is $-0.2\pm0.8$ mm for exhalation and $0.6\pm1.5$ mm for inhalation. The corresponding values in the AP and LR direction for exhalation and inhalation were smaller than $1.1\pm1.1$ mm, which was not significantly different from the reference standard tumor motion ($p>0.1$). Correcting for the systematic time-percentage difference between diaphragm motion and tumor motion did not result in a smaller geometrical error with respect to the mean tumor position ($\varepsilon_{DM}$).

### 4. Discussion

The results of this work have shown that the mid-ventilation concept is a useful solution to incorporate motion information from 4D CT scans in the treatment-planning process. Determination of the mid-ventilation time-percentage using tumor motion and diaphragm motion is accurate; therefore, the appropriate planning CT scan can be selected from the 4D data set. The use of a single CT scan (with the tumor in the mean position) allows margin reduction, resulting in a smaller irradiated volume (see Section 3-4.4).

#### 4.1. Thermocouple time delay

The comparison of the thermocouple signal versus diaphragm motion showed that the delay time of the thermocouple is stable and equipment dependent (see Appendix). If this time delay is not corrected, a time-percentage difference $\Delta t\%$
will exist between the first frame of the 4D CT scan (0%) and the actual maximum inhalation. $\Delta t\%$ can be estimated (after reconstruction of the 4D CT) using diaphragm motion determination, as described in this chapter. However, correction for this time delay before CT reconstruction is important, because wrong synchronization of the thermocouple signal to the raw CT data will result in incorrect sorting of data into respiratory phases. This can be clarified in a worst-case scenario example: When a patient would be scanned during two subsequent breathing cycles, with a cycle length of 3 and 6 seconds, respectively; and if a thermocouple time delay of 3 s exists, that has not been corrected for, the first half of the CT data of the second breathing cycle would be sorted over a full cycle. This type of error in sorting can result in serious imaging artifacts (e.g., when using external thorax movement respiration signal, Section 3-4.2a). However, the delay time of our thermocouple equipment (0.4 s) and the standard deviation of the cycle length were small (Table 3-1) compared to the breathing cycle length, which results in negligibly small artifacts in the 4D image reconstruction, even if the delay was not corrected.

4.2. Mid-ventilation determination

a. Phase shifts due to imperfections of the 4D CT

Because the 4D CT data were sorted between the two maximum inhalation peaks after correcting for thermocouple time delay as described in the Section 3-2.2b, the first CT frame (0%) of the 4D set was expected to represent maximum inhalation phase. However, in general, a small time-percentage difference ($\Delta t\%$) was still found between the first frame of the 4D CT scan (0%) and the actual maximum inhalation phase. The $\Delta t\%$ was 3.3±5.1% based on tumor motion and 1.0±4.1% based on the diaphragm motion method.

A possible cause for $\Delta t\%$ could be the quantization or binning error, which was 5% for the low number of bins (10) used during reconstruction. A second possible cause could be the existence of a (small) phase variation between internal structures and the external respiration system (see Section 3-4.1). Finally, the use of a one-dimensional (CC) simplification could be a third cause of the determined phase shift, because it does not have to represent the maximum inhale position in three dimensions.

Rietzel et al. [15] reported a significant phase difference between external thorax movements (from the Varian RPM respiratory measurement system) and internal structures. If this phase difference is stable during the entire 4D scan acquisition, the phase difference can be found retrospectively by methods described in this chapter. However, when patients switch from lower body (abdomen) to upper body (chest) respiration during scanning, a significant phase change may occur, which may result in severe artifacts in 4D images.
b. Mid-ventilation time-percentage
The $t_{\text{midv}}$ derived from the tumor motion (TM) curve and the diaphragm motion (DM) curve appeared to be significantly different (Table 3-2 and 3-3). However, relative to the bin size (10%) the difference was small; therefore, the automated DM method can be used as a surrogate for the MidV estimation with the TM method. Moreover, after correcting the $t_{\text{midv}}$ for the patients’ individual time-percentage difference $\Delta t\%$ (thus setting maximum inhalation to 0%, see previous section), the $t_{\text{midv}}$ was no longer very different. The $t_{\text{midv}}$ was 20.7±2.6% and 20.7±2.2% and 78.7±2.9% and 78.8±2.9% in exhalation and inhalation for TM and DM-method respectively. The standard deviation in $t_{\text{midv}}$ was reduced, supporting the use of the DM method as a surrogate for TM. These results of the $t_{\text{midv}}$ were in agreement with the asymmetric properties of respiration ($t_{\text{midv}}$ is not 25 % or 75 %) as described by Seppenwoolde et al. [22]. It appeared that TM and DM curves were in phase except for patients with the tumor attached to the mediastinum or chest wall. In those cases, the curves were also slightly different in shape, resulting in a different $t_{\text{midv}}$ for TM and DM. Tumor motion will be used to select the MidV CT scan.

c. Uncertainties of mid-ventilation with respect to mean tumor position
From the standard deviation in $\varepsilon_h$ and $\varepsilon_{DM}$ (Table 3-2 and 3-3), it can be concluded that a MidV reconstruction in exhalation is more accurate than that with inhalation. Because the exhalation phase is longer than the inhalation phase, the excursion per time-percentage is greater during inhalation than during exhalation. A small uncertainty in $t_{\text{midv}}$ will thus result in a larger geometrical error at inhalation than at exhalation.

For clinical practice, a cut-off value in the tumor motion amplitude, below which the automated DM method can be safely used, might be beneficial. First, over all patients, the mean and standard deviation of the geometrical error relative to the amplitude was computed in the three directions for all patients. This relative error ($\varepsilon_{rel}$) was 0.14±0.04 [mm/mm], 0.07±0.04 [mm/mm], 0.31±0.10 [mm/mm] for LR, CC and AP direction respectively. Limiting the mean geometrical error plus 1 standard deviation to 2 mm for all directions can be described as a constraint:

$$\max\{\varepsilon_{rel,LR} \times A_{LR}; \varepsilon_{rel,CC} \times A_{CC}; \varepsilon_{rel,AP} \times A_{AP}\} < 2 \text{ mm}$$

Using the statistics of the amplitude for this patient group (Table 3-1), the proportions of the mean amplitudes in the LR and AP direction relative to the CC amplitude were: $A_{LR} = 0.18 A_{CC}$ and $A_{AP} = 0.29 A_{CC}$.

Applying these amplitude relations in the constraint equation above showed that the use of the automated DM method is limited to a maximum CC tumor excursion of 2 cm.
To evaluate the methods for the construction of a treatment-planning CT scan, we compared the results with those of conventional CT scanning (no respiration-correlated imaging). Because we had determined the tumor motion for all directions and all patients, we can easily estimate the errors in conventional imaging ($\epsilon_{\text{conv}}$), which is the standard deviation of the motion over the respiratory cycle [27]. The mean is zero per definition. The standard deviations over all patients were 0.8 mm (LR), 3.9 mm (CC) and 1.5 mm (AP) (Table 3-4). This is in agreement with the conclusions of van Herk et al. [27], that the geometrical error with respect to mean tumor position ($\epsilon_{\text{conv}}$) was 1/3 of the peak-to-peak amplitude. Comparing the diaphragm motion method to conventional scanning, the geometrical variation $\epsilon_{\text{DM}}$ is 4 times smaller in the CC direction than $\epsilon_{\text{conv}}$ (Table 3-3).

Dose verification of the new MidV concept is beyond the scope of this chapter, however, we refer to Cho et al. [28] who showed that, with constant error margins, small geometrical variations have a negligible influence on the dose distribution (see also Chapter 7). Application of the result of Cho et al. to the relatively small geometrical differences between conventional and MidV CT scans, show that MidV CT scans can safely replace conventional CT scans. Note, that the improvement gained by the use of MidV CT will primarily be the reduction in error margins.

A clinical protocol (based on the presented results) concerning 4D scanning and mid-ventilation CT reconstruction is given in Figure 3-1.

d. **Comparison of MidV CT with conventional CT**

To evaluate the methods for the construction of a treatment-planning CT scan, we compared the results with those of conventional CT scanning (no respiration-correlated imaging). Because we had determined the tumor motion for all directions and all patients, we can easily estimate the errors in conventional imaging ($\epsilon_{\text{conv}}$), which is the standard deviation of the motion over the respiratory cycle [27]. The mean is zero per definition. The standard deviations over all patients were 0.8 mm (LR), 3.9 mm (CC) and 1.5 mm (AP) (Table 3-4). This is in agreement with the conclusions of van Herk et al. [27], that the geometrical error with respect to mean tumor position ($\epsilon_{\text{conv}}$) was 1/3 of the peak-to-peak amplitude. Comparing the diaphragm motion method to conventional scanning, the geometrical variation $\epsilon_{\text{DM}}$ is 4 times smaller in the CC direction than $\epsilon_{\text{conv}}$ (Table 3-3).

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A clinical protocol (based on the presented results) concerning 4D scanning and mid-ventilation CT reconstruction is given in Figure 3-1.

e. **Reproducibility of respiratory patterns**

Reproducibility in respiratory patterns during 4D imaging and treatment delivery is an important issue. Currently we have begun a study on the possible changes in breathing pattern and mean tumor position when using an oxygen mask. Additional 3D scans are made prior to treatment with a cone-beam system mounted on a linear accelerator [29]. These scans can be reconstructed into 4D scans [30] and mean tumor position and amplitude are determined. Although the preliminary results show no significant difference in breathing pattern with or without a mask, the final conclusions cannot yet be made.
4.3. Influence of breathing cycle length on 4D CT reconstructions

The small standard deviation in the average cycle length (Table 3-1) suggests that the patients were breathing regularly during scanning, resulting in stable and practically artifact-free 4D CT reconstructions. This makes a choice for one of the two protocols (0.5 s or 1.0 s gantry rotation) justified. However, a lower pitch or more choices of gantry rotation speed would be desirable to overcome the remaining artifacts. Interpolation artifacts in the 4D image appeared at locations where undersampling occurred. If the number of these artifacts were small, tumor match and diaphragm movement measurements are not seriously hampered. In some cases, the patient was breathing faster during setup than during the actual 4D scanning. Consequently, the gantry rotation was too fast compared to the patients’ cycle length, causing multiple imaging artifacts, which make delineation of structures or tumor more difficult. However, quantitative measurements were not noticeably influenced. For patients that showed irregular breathing, one solution was to wait a couple of minutes until the respiration stabilized, before measuring the cycle length, which was included in the 4D scanning protocol. In addition, audio/visual breathing coaching can stabilize the breathing signal amplitude and period [31], which will improve the image quality of the MidV CT scans. However, coaching is often not applicable to this patient group because of physical limitations. Moreover, the influence of coaching on the baseline (mean respiration level) variation is still unknown. Amplitude based CT data binning [32] during regular breathing would not result in better image quality, and has the drawback that time information is lost, which is necessary to calculate the time-weighted mean position. Furthermore, with irregular breathing some amplitude bins can be sparsely filled resulting in serious artifacts (gaps). See also Section 8-1.

A principle disadvantage of our proposed method is that the tumor has the highest speed at mid-ventilation, and can result in more residual imaging artifacts than at maximum inhalation or maximum exhalation. However, according to Rietzel et al. [26], these artifacts are smaller than the artifacts due to irregular breathing. Moreover, compared with conventional scanning, these speed-induced artifacts are negligible.

4.4. Potential of reduced margins due to improved imaging

Treatment margins (from GTV to PTV), can be calculated using the margin recipe of van Herk et al. [33,34]: Margin = 2.5 \(\Sigma\) + 0.7 \(\sigma\), where \(\Sigma\) and \(\sigma\) denote the standard deviations of the systematic and random errors, respectively. These errors consist of contributions from respiration (periodic motion and mean tumor position) and setup errors (errors due to cardiac motion were not considered). Delineation uncertainties also contribute to additional margins [21,35] and are expected to become smaller using 4D treatment-planning, because of an improved visualization of the tumor shape. However, we did not consider detailed knowledge on delineation uncertainty using free-breathing scan [36,37].
Margins due to systematic and random errors were estimated for a patient with a spherical tumor of 20 mm diameter and a 20 mm CC tumor movement in two cases (Table 3-5): Without using 4D imaging (column 1 and 2) and with using of 4D imaging (column 3 and 4). The displaced tumor in the conventional planning CT (a random snapshot of the tumor) with respect to the mean position of the moving tumor is referred to as the systematic contribution of the periodic motion. The probability distribution of the tumor in a certain position during treatment, which has a standard deviation of 1/3 of the peak-to-peak amplitude [27], is referred to as the random contribution of the periodic motion. The systematic and random setup errors were set at 1.5 mm and 3.1 mm, respectively, in both the conventional and the 4D MidV situation using portal images [38].

Using 4D imaging will theoretically reduce the systematic contribution due to breathing motion to zero. The random error distribution due to respiration will not change because respiration is still present during treatment. However, the margin for random errors might possibly be reduced, such as was shown in simulations due to the shallow penumbra in lung tissue [20,21]. The additional margins needed to compensate for the breathing motion are small if the irradiated volume is centered at the average position of the tumor using 4D imaging techniques. Variation in the average position of the tumor (baseline) gives a contribution that still remains in 4D treatment-planning. This contribution can only be reduced when using an off-line 4D verification protocol (using multiple 4D CT scans), reducing the systematic average position variation, or an on-line 4D verification protocol (using multiple 4D CT scans on the treatment machine [21,30,39]), reducing the systematic and random average position variation. Using multiple 4D CBCT scans from 10 patients [40], this average position error was estimated to be 2 mm for both systematic and random errors. For the patient data in Table 3-5 with a CC tumor motion of 20 mm, the use of 4D imaging will result in a reduction of the required margin in CC direction with a factor of 2.

### Table 3-5 Estimated magnitude of existing uncertainties in the cranio-caudal direction for two cases: Using a conventional 3D CT scan or a 4D CT scan for treatment-planning.

<table>
<thead>
<tr>
<th></th>
<th>Conventional 3D CT</th>
<th>4D CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Σ (mm)</td>
<td>σ (mm)</td>
</tr>
<tr>
<td>Respiration (A_{cc} = 20 mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periodic motion</td>
<td>6.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Baseline variation</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Set-up error</td>
<td>1.5</td>
<td>3.1</td>
</tr>
<tr>
<td>Total</td>
<td>7.2</td>
<td>7.6</td>
</tr>
<tr>
<td>Margin (CTV to PTV)</td>
<td>23.2</td>
<td></td>
</tr>
</tbody>
</table>

The required margin from CTV (clinical target volume) to PTV (planning target volume) has been calculated using the recipe of van Herk et al.: Margin = 2.5 Σ + 0.7 σ, where Σ and σ denote the standard deviations of the distribution of systematic and random errors, respectively. A_{cc} denotes the peak-to-peak amplitude of the tumor motion in cranio-caudal direction.
With an amplitude in LR direction of 4 mm, and 6 mm in AP direction (see Section 3-4.2c), the margins in these directions will be 10 mm and 11 mm for conventional free-breathing CT scan and 9 mm and 9 mm for MidV CT scans, respectively. In this example (spherical tumor of 20 mm diameter), this margin reduction decreases the PTV volume from 14.4 cm$^3$ to 8.3 cm$^3$ (43% reduction). In addition, using the mean motion amplitude values of Table 3-1, the average PTV reductions for tumors with diameters between 10 and 80 mm are between 33% and 12%, respectively. Finally, for the patient group used in this study, the composite target volumes methods described in the introduction (Slow CT and MIP) would result in an increased irradiated volume of 11±3% (setup error and baseline variation as above). Our proposed MidV CT method results in a significant reduction of 12±11% irradiated volume reductions.

5. Conclusions

We have developed a new concept for using 4D CT scans to incorporate patient-specific motion information in radiotherapy for lung cancer. On the basis of the tumor motion, a single 3D CT scan is chosen from the 4D CT data set, which represents all lung structures in the time-average position. An alternative automated method was also developed to select the single 3D CT scan using the diaphragm motion. Using MidV CT scans for treatment-planning instead of the conventional free-breathing CT scans, margin reduction is possible, which can reduce the treatment volume up to 50%.

Acknowledgements:
The authors would like to thank Jasper Nijkamp for his clinical software development and Harry Bartelink, Ben Mijnheer and Leah McDermott for critical reading of the manuscript.

![Figure 3-7. An example of the thermocouple respiration signal (dashed curve) and the diaphragm motion (solid curve) determined from cone-beam CT projection images. Both signals were scaled between maximum inspiration (1) and maximum exhalation (0). τ denotes the time delay between the two signals.](image)
Appendix – Thermocouple response time

To verify the functioning of the thermocouple system and to determine the correlation with diaphragm motion, we measured the diaphragm movements using projection images from a cone-beam CT scanner mounted on a linear accelerator [29] concurrent with the thermocouple respiration signal system for six patients during 7 minutes. The respiration signal was acquired using an Analog-to-Digital-converter simultaneously with the X-ray exposure pulses that were generated by the cone-beam imager. The exposure peaks provided a time stamp for each projection image. These time stamps of the acquired projection images were synchronized to the thermocouple signal. Subsequently, diaphragm height was determined automatically in each projection image [30,39]. These measurements do not require a cone-beam CT system, but can be performed with conventional fluoroscopy.

Because the thermocouple (temperature) and diaphragm position (distance) have different units, both signals were scaled between 0 (maximum exhalation) and 1 (maximum inhalation) as follows. An upper and lower envelope was created by drawing one line intersecting all peaks in the signal and a second line intersecting all valleys, respectively. The original signals were scaled between their upper and lower envelopes. The advantage of this method is that it is easy to calculate, preserves the asymmetric shape of the curve (different length of exhalation and inhalation) and removes a possible global trend. In Figure 3-7 an example of the two signals is plotted, where the solid curve represents the thermocouple signal and red dashed black curve represents the diaphragm signal.

There is a time delay in the thermocouple signal with respect to the diaphragm (Figure 3-7). The thermocouple time delay is due to the warming up and cooling down of the thermocouple, the presence of stationary air (end of expiration, end of inspiration), and the response time of the signal amplifier equipment. The mean thermocouple time delay, measured over approximately 6x80 breathing cycles, was 0.40±0.18 s (Note that this delay is equipment dependent and should be determined for the equipment used). Considering the quantization error in the acquisition of a cone-beam projection image (standard deviation of a uniform distribution = acquisition time / √12 = 0.371/√12 = 0.107 s) and additional noise, the standard deviation is quite acceptable. From this data it appeared that there was a very weak correlation between cycle length and time delay (correlation coefficient = 0.22), suggesting that little phase delay exists and therefore the response time is mainly equipment dependent. This delay (determined with the cone-beam CT system) will be corrected during 4D CT reconstructions on a standard CT scanner.
References


Deformable registration

Appendix of the article “Reconstruction of a time-averaged mid-position CT scan for radiotherapy planning of lung cancer patients using deformable registration”

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J.J. Sonke
M. van Herk
E.M.F. Damen

Medical Physics 35 - 2008
1. Introduction

This chapter, as intermezzo, describes the motion estimation algorithm used to deform the four-dimensional (4D) CT scans to the mid-position. Conventional optical flow methods based on the gradient of the image assume intensity conservation between frames. However, this assumption can be violated in real applications (e.g., registration of cone-beam CT to conventional CT). A remedy is to compute constraints on local motion based on the image-phase (image transitions from bright to dark and vice versa). Therefore, the motion (or displacement) estimation method is divided into two parts (Figure 4-2): An image-processing operation to compute the phase of the image; and the actual motion estimation procedure based on optical flow.

Figure 4-1. Motion estimating scheme used in this article. First, an image-processing operation is applied to the reference \( I_R \) and floating \( I_F \) scan for 9 directional filters, resulting the image phase \( \theta_R \) and \( \theta_F \) and magnitude \( M_R \) and \( M_F \) of the scan. Subsequently, an optical flow approach is used to compute the local motion vectors. CM denotes the confidence measure; \( c \) is the constraint vector (equation 3).
2. Quadrature image-processing filter

The optical flow motion estimation method (Section 4-2) uses the image-phase instead of the “original” image data. The phase of an image is related to transitions from bright to dark regions in the input image and vice versa (Figure 4-2) and is computed using a quadrature filter [1]. A quadrature filter is a complex band-pass filter that simultaneously computes the local magnitude ($M$) and phase ($\theta$) of the image. The phase is wrapped between 0 and $2\pi$. The magnitude is used in the motion estimation step to compute a confidence measure, which helps to detect false motion estimates (Section 4-3). The filters are tuned in a particular direction, analogous to gradient filters. Each filter is defined as zero over one half of the Fourier domain and non-zero over the other half. The complex output is computed in the spatial domain as the convolution of the quadrature filter and the input image. The band-pass part of the filter enhances (e.g., vessels) and suppresses (noise) features of the input image. Nine quadrature filters are used in different directions in three-dimensional (3D) space (using one-dimensional –1D– filters along the 3 axes and two-dimensional –2D– filters along the 6 diagonals) [2] to split features oriented in different directions into different filter outputs to reduce interference and duplication of features, resulting in 9 different filter outputs.

3. Optical flow motion estimation

In the optical flow method, a motion constraint is derived from the image-phase and is defined as an equation that the local motion vector ($\mathbf{v}$) must satisfy; in other words, a change in position is only enforced by the change in phase (in time and space), i.e., conservation of image-phase density. Using the phase $\theta$ of the image, this (linear) flow equation is:

![Figure 4-2. Quadrature filtering of 3D images. (a) Coronal slice of an original 3D scan, input image for the quadrature filter. Phase (b) and magnitude (c) output after filtering image with the quadrature filter tuned in the 45 degree direction from the cranio-caudal and left-right axes. Note that phase is wrapped between 0 and 2π.](image-url)
\[
\frac{\partial \theta}{\partial x} \frac{\partial x}{\partial t} + \frac{\partial \theta}{\partial y} \frac{\partial y}{\partial t} + \frac{\partial \theta}{\partial z} \frac{\partial z}{\partial t} = 0 \Rightarrow \frac{\partial \theta}{\partial x} \Delta x + \frac{\partial \theta}{\partial y} \Delta y + \frac{\partial \theta}{\partial z} \Delta z + \Delta \theta = 0 \quad (1)
\]

where \( \Delta x, \Delta y, \Delta z \) are the translations of the features in the image from frame to frame. In Figure 4-3, a graphical representation of equation (1) in one direction is shown. If the local change of phase is a 1st order derivative (i.e., phase is locally linear), the translation between the reference image and floating image (\( \Delta x \)) can be estimated by the gradient of the phase in the image (\( c_x = \frac{\partial \theta}{\partial x} \)) and the difference in phase between the reference and floating image (\( \partial \theta \)). Equation 1 can be rewritten (in matrix notation) as:

\[
c^T \begin{pmatrix} v_x \\ v_y \\ v_z \\ 1 \end{pmatrix} = 0, \text{ where } c = \begin{pmatrix} c_x & c_y & c_z & c_t \end{pmatrix}^T \text{ and } v = \begin{pmatrix} v_x & v_y & v_z \end{pmatrix}^T \quad (2)
\]

where \( c_x, c_y, c_z \) define the change in phase over space; and \( c_t \) defines the change in phase over time.

For each voxel \( (x) \) and for each quadrature filter output, the parameters of the motion constraint equation are computed:

\[
c_k(x) = \begin{pmatrix} c_{k,x} \\ c_{k,y} \\ c_{k,z} \\ c_{k,t} \end{pmatrix} = \begin{pmatrix} \frac{1}{2} \frac{\partial}{\partial x} \left( \theta_{\text{Floating},k}(x) + \theta_{\text{Ref},k}(x) \right) \\ \frac{1}{2} \frac{\partial}{\partial y} \left( \theta_{\text{Floating},k}(x) + \theta_{\text{Ref},k}(x) \right) \\ \frac{1}{2} \frac{\partial}{\partial z} \left( \theta_{\text{Floating},k}(x) + \theta_{\text{Ref},k}(x) \right) \\ \theta_{\text{Floating},k}(x) - \theta_{\text{Ref},k}(x) \end{pmatrix} \quad (3)
\]

where \( \theta_{\text{Floating}} \) and \( \theta_{\text{Ref}} \) are the phase of the floating image and reference image, respectively. The index \( k \) denotes the different voxels or quadrature filter outputs.

Note that in the first three elements, the phase is the average of the phase of the two frames to suppress variation in phase, which improves estimation accuracy; this averaging of the phases is allowed since the conservation of the image data (phase density) after translation implies equal phase). To find a (stable) solution for this equation, different quadrature filters \( (f_k) \) as well as multiple voxels in a local region can be combined into a single constraint equation at the center of the local region (control-point).

To clarify the method, in Figure 4-4a, a single motion constraint equation for a 2D case is plotted in motion vector space \( (v_x, v_y) \), \( v_y = -(c_y/c_x)v_x + (-c_t/c_z) \). It is clear that there are multiple relationships between \( v_x \) and \( v_y \) that satisfy the (single) constraint line.
A single constraint line represents the motion of a plane that can only be detected perpendicular to the plane. Therefore, multiple constraints (i.e., from different quadrature filters and/or voxels) are necessary. For a local translation, these constraints (all representing the same motion) must intersect at a common point in the motion vector space (Figure 4-4b), giving the motion of the considered voxel or ROI. In theory, only three constraints are necessary; however, a total of only three directional quadrature filters \((x, y, z)\) can be insufficient. Estimation of motion of large (larger than the quadrature filter kernel size) one-direction-oriented structures (for example vessels) suffer from the aperture problem, i.e., when determining

\[
\theta_{\text{Ref}} \quad \Delta \theta \quad \theta_{\text{Floating}}
\]

\[
\frac{\partial \theta}{\partial x}
\]

\[
\Delta x = \frac{\Delta \theta}{\frac{\partial \theta}{\partial x}}
\]

A one-dimensional graphical representation of the optical flow method using the phase of the image. “Ref” and “Floating” denote the phase \((\theta)\) in the reference and floating image, respectively. The translation between the reference image and floating image \((\Delta x)\) can be determined by the gradient of the phase \((c_x = \partial \theta / \partial x)\) and difference in phase between the two images \((\Delta \theta)\).

![Figure 4-3](image.png)

Figure 4-4. (a) A constraint line for a 2D case is plotted in a motion vector space \((v_x, v_y)\). There are multiple relations between \(v_x\) and \(v_y\) that satisfy the constraint line. Time \(t\) is oriented perpendicular to this line. (b) Multiple motion constraints \(c\) (for example from multiple quadrature filters or pixels in the neighborhood) in an image with a pure shift motion. In this case all corresponding constraints must intersect at a single common point in the motion vector space.
motion in a kernel size (small window or aperture), only motion perpendicular to the structure can be estimated. For this reason, extra filters in the diagonal directions are used to connect the three directions.

Subsequently, these local constraint-equations \( \mathbf{c} \) are converted to translations. Using the least-squares method (also known as minimum-norm constraint solution method) the local motion vector \( \mathbf{v} \) is estimated that matches the local constraint-equation \( \mathbf{c}^T \mathbf{v} = 0; \) i.e., finding the intersecting point of the constraints in the motion vector space. This operation has an analytical solution (involving a matrix inversion), and does not require an optimization process [3].

4. Confidence measure

Some motion constraints \( \mathbf{c}_k(\mathbf{x}) \) are unreliable, e.g., these constraints correspond to small or low-intensity (weak) features (or features that exist only in one of the two images) and noise. To distinguish these constraints, a confidence measure (CM) is used as a weight factor for the constraints: \( \mathbf{c}_k'(\mathbf{x}) = \text{CM}_k \cdot \mathbf{c}_k(\mathbf{x}) \). The CM is a combination of several factors, which will be discussed briefly in this section. A more extensive and quantitative explanation is given by Hemmendorff et al. [3,4]. First, the magnitude of the quadrature filter output is used as a measure of the strength of the features in the images. Second, the method expects that a change of phase in space must be linearly compensated by a change of phase in time (equation (1)). A first order (linear) approximation of the changes of phase in the image is, therefore, required (spatial linearity). For most voxels, the quadrature filter (which also smooths the image data) results in locally linear phase data (depending on the size of the relevant features [3,4]). Furthermore, the tissue motion (from frame to reference frame) is assumed to be small (time linearity). However, phase may not be completely linear everywhere. The error of the linear approximation can be computed and is integrated over the neighborhood to give a confidence measure for the local linearity. The third factor is based on the similarity of the gradient of the phase in the two images (phase conservation, i.e., to check if the gradient of the phase can be averaged; equation 3). Finally, phase singularities must be avoided. These singularities can be found by comparing the direction of the phase from the quadrature filter output to the direction of the filter (which must be similar for non-singular voxels).

5. System properties

To estimate large motions with high accuracy, a multi-scale (coarse-to-fine) approach was used (Figure 4-1). Motion resulting from a coarse scale can be used to transform the phase and magnitude images and improve the motion results in a finer scale. Scale is defined as the resolution of the original input image divided by 2 to the power of a certain level \( (2^2, 2^1, 2^0) \) for each direction, resulting in images of \( 64^3 \).
then $128^3$ and finally $256^3$ voxel resolution for cubic images. The entire image is divided into a number of sub-volumes, with the center of each sub-volume as control-point. Each sub-volume is chosen to be $3^3$ voxels large for each scale. Within each sub-volume, the constraints are averaged (Section 4-2). After each iteration, the resulting motion at the control-points is used as input for the next iteration. Between the control-points, the motion is (tri-linear) interpolated to obtain a motion vector for each voxel. In the next iteration, the phase and magnitude data of the floating image (the reference image is fixed) are first deformed using the motion output from the previous iteration, then new constraints are derived (at a finer scale) and the remaining motion is computed. This remaining motion is (vector-based) added to the estimated motion of the previous iteration. To improve accuracy, more than one iteration is done within each scale. The number of iterations depends on the distances to measure between the frames and the image quality. Generally 3 iterations and 3 scales were used.

6. **Data filtering and lung-tissue border issue**

To convert the motion-model to translations using the least-squares method, a matrix inversion is used (for each control-point). However, matrix inversion is sensitive to singularities of the input data (here the constraint motion-model). To prevent singularities, smoothing was applied to the constraints over the control-points before using the least-squares method (Figure 4-1). A second smoothing filter operation was performed after solving the motion-model to suppress singular results as well as to regularize the motion vectors (preventing folding of the motion vectors; Figure 4-1). In addition, this second filter was used to suppress the registration of artifacts (which is related to non-physical motion). All filters were adjusted to the scale and iteration step.

![CT image](image1)

**Figure 4-5.** Example of filtering the motion field (in the cranio-caudal direction) using a uniform blurring filter and using the adaptive filter (section 4.5).
A main issue in deformable registration of thorax images is the fact that the motion direction of lung tissue is different from the thoracic wall and/or mediastinum (sliding tissue; Section 5-2.4 and 5-4.2). Due to this discontinuity many registration algorithms often fail (i.e., do not register correctly) in the transition regions. To overcome this problem, we used an adaptive filter besides a standard Gaussian smoothing filter. The adaptive filter smoothes only those control-points within the kernel, which have similar density value in CT (Hounsfield units), conserving the motion direction of the center control-point in the kernel.

The adaptive filter uses the minimum-projection image of the 4D CT as a weight-factor image (for each voxel, the minimum value over the frames is selected). Within the kernel of the filter, only those voxels or control-points \( p_i \) are averaged that have weight-values \( w_i \) (voxel values of the minimum-projection image, \( w_0 \) is center voxel of the kernel) in the same range, i.e., the difference between weight-values must be small to be taken into account. The resulting output value \( p'_0 \) for each voxel or control-points is computed by:

\[
p'_0 = \frac{\sum_{i \text{in kernel}} WF_i p_i}{\sum_{i \text{in kernel}} WF_i}, \quad \text{with } WF_i = \exp\left(-\alpha \|v_i - w_0\|\right)
\]  

(4)

The coefficient \( \alpha \) is a “stiffness” factor, which specifies the range of weight-value differences that is taken into account (\( \alpha = 0.01 \) was used). This adaptive filter preserves sharp edges (lung-thoracic wall) and smoothes small variation of the input signal (here, the motion-model or motion). In Figure 4-5, an example of the adaptive filter output is shown.

The adaptive filter with larger kernel is applied first, and finally, to remove remaining small irregularities at edge structures in the image, a Gaussian filter with very small kernel is applied.

7. **Computation time**

Computation time depends on the size of the image (since it is voxel based) and the number of iterations in different image scales, but less on the number of control-points. The computation time of the image-processing part and optical flow part (using 3 iterations and 3 scales) were almost equal. Total computation time is typically 10 minutes for a set of two 256x256x100 images on a Pentium 4 – 3.0 Ghz processor. However, computation time can be decreased by applying parallel computing (the method can easily be split into segments to be used in parallel computing) and avoiding computation of the background region, which is the case in our current implementation.
References

Image quality optimization

Reconstruction of a time-averaged mid-position CT scan for radiotherapy planning of lung cancer patients using deformable registration

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Abstract

Purpose Lower lobe lung tumors move with amplitudes of up to 2 cm due to respiration. To reduce respiration imaging artifacts in planning CT scans, four-dimensional (4D) imaging techniques are used. Currently, we use a single (mid-ventilation) frame of the 4D data set for clinical delineation of structures and radiotherapy planning. A single frame, however, often contains artifacts due to breathing irregularities, and is noisier than a conventional CT scan since the exposure per frame is lower. Moreover, the tumor may be displaced from the mean tumor position due to hysteresis. The aim of this work is to develop a framework for the acquisition of a good quality scan representing all scanned anatomy in the mean position by averaging transformed (deformed) CT frames, i.e., canceling out motion. A non-rigid registration method is necessary since motion varies over the lung.

Methods and Materials Four-dimensional and inspiration breath-hold (BH) CT scans were acquired for 13 patients. An iterative multi-scale motion estimation technique was applied to the 4D CT scan, similar to optical flow but using image phase (gray-value transitions from bright to dark and vice versa) instead. From the (4D) deformation vector field (DVF) derived, the local mean position in the respiratory cycle was computed and the 4D DVF was modified to deform all structures of the original 4D CT scan to this mean position. A 3D mid-position (MidP) CT scan was then obtained by (arithmetic or median) averaging of the deformed 4D CT scan. Image registration accuracy, tumor shape deviation with respect to the BH CT scan, and noise were determined to evaluate the image fidelity of the MidP CT scan and the performance of the technique.

Results Accuracy of the used deformable image registration method was comparable to established automated locally rigid registration and to manual landmark registration (average difference to both methods < 0.5 mm for all directions) for the tumor region. From visual assessment, the registration was good for the clearly visible features (e.g., tumor and diaphragm). The shape of the tumor, with respect to that of in the BH CT scan, was better represented by the MidP reconstructions than any of the 4D CT frames (including MidV; reduction of “shape differences” was 66%). The MidP scans contained about one-third the noise of individual 4D CT scan frames.

Conclusions We implemented an accurate method to estimate the motion of structures in a 4D CT scan. Subsequently, a novel method to create a mid-position CT scan (time-weighted average of the anatomy) for treatment-planning with reduced noise and artifacts was introduced. Tumor shape and position in the MidP CT scan represents that of the BH CT scan better than MidV CT scan and, therefore, found to be appropriate for treatment-planning.
1. INTRODUCTION
Breathing motion in the thoracic and abdominal region (more than 2 cm close to the diaphragm) causes image artifacts in conventional free-breathing CT scans. Four-dimensional (4D) respiration-correlated [1,2] imaging techniques are used to obtain (respiration) artifact-free CT images of the thorax. For treatment-planning, several CT reconstructions from this 4D data set have been proposed in the literature, e.g., maximum intensity projection (MIP) [3] and exhale mid-ventilation images (MidV) [4]. These scans are used for delineation of the internal structures (target and organs) and possibly for dose calculation. The target delineation of the MIP CT results in the internal planning target volume, which has been shown to be larger than the planning target volume necessary for appropriate radiotherapy treatment [5] (Chapter 6). In addition, the computed target and (mean) lung dose may not be correct since the target and lung volume are not correctly determined. Considering MidV CT scans, delineation of the tumor and other structures using a single frame is sometimes problematic since small artifacts occur due to remaining motion and breathing irregularities. Moreover, a 4D scan is noisier than a conventional CT scan because the exposure per frame is lower. Finally, a (small) systematic geometrical error with respect to the mean position is introduced in the MidV CT scan when there is hysteresis in the tumor motion (i.e., tumor trajectory from inhale to exhale is not equal to that of exhale to inhale, resulting in a three-dimensional (3D) elliptical tumor trajectory instead of retracing a line [6]). An error is incurred because none of the frames of the 4D CT scan represents the mean position accurately.

The aim of this study is to address the problems associated with the MidV CT scan, and introduce the mid-position (MidP) CT concept. MidP is a refinement of the MidV concept, whereby a new CT scan is reconstructed from the entire 4D CT data set, where all anatomy, including the tumor, is represented in the time-weighted mean position over the respiratory cycle. Since the MidP approach uses information of all frames of the 4D CT scan instead of a single frame, this approach is more efficient compared to MidV CT in terms of dose and CT information and, therefore, results in an increased image quality compared to the 4D and MidV CT scans [7].

2. METHODS AND MATERIALS
In the framework to create a 3D MidP CT scan (Figure 5-1), the physical motion in the 4D CT scan is estimated from each frame and subsequently compensated to the time-weighted mean position, thereby eliminating motion. Averaging these frames of the motion-compensated 4D CT scan (over time) results in a 3D CT scan with reduced artifacts and noise: The MidP CT scan.

Since motion varies over the lung, a non-rigid registration method is necessary to determine the local motion for each voxel. Motion estimation is a large field of
research and there are several algorithms, often using a similarity measure to drive the registration [8,9]. In this chapter, motion between two frames of the 4D CT scan was determined using a phase-based optical flow motion estimation procedure based on the work of Hemmendorff [10,11]. To obtain the full motion during a respiratory cycle, this procedure was applied to all frames of the 4D scan, registering each of them to a reference frame.

This chapter is structured as follows: First a short description of the 4D CT scan and MidV reconstructions is given. Second, the reconstruction of the mid-position CT scan is described. Subsequently, the deformable registration is explained shortly (a more extensive description was given in the Chapter 4) and finally, quantification of the image registration performance and image fidelity improvements is described.

2.1. Patient group

All patients received a contrast enhanced 4D CT scan (Section 5-2.2) and an inhale breath-hold (BH) CT scan, according to routine clinical protocols. Four-dimensional CT data sets of 13 patients (10 male and 3 female) with various stages of lung cancer and substantial tumor motion were used in this retrospective study: 30% upper thorax tumors and 70% lower thorax tumors. Tumor motion ranged from 9 to 34 mm in the cranio-caudal (CC) direction. The tumor volume in the BH CT scan ranged from 2.5 to 53 cm³. The 4D scans differed in image quality and number of imaging artifacts (mainly due to difference in patient size and breathing irregularities). The BH CT scan was used as a reference for tumor shape and volume, and verification of the various CT reconstructions (Section 5-2.6b). Tumor deformation was assumed to be negligible.

2.2. Respiration-correlated 4D CT imaging

During 4D CT scanning, the patient was instructed to breathe normally. The respiration of the patient was registered using a thermocouple inserted into the entry of a regular
oxygen mask, which measures temperature changes in airflow during inhalation (cold) and exhalation (warm) [12]. The helical cardiac scanning mode of the CT scanner (24 slice Somatom Sensation Open, Siemens, Forchheim, Germany) was used for respiratory-correlated imaging. A 4D CT scan with 10 respiratory phases (or frames) was reconstructed using phase-sorting. Frame 0% represented maximum inhale [12]. Each frame represents 1/10th of the breathing period and contains ~ 100 slices; scan slice resolution was 512x512 voxels. In this study, the scan slice resolution was reduced to 256x256 voxels to save memory and computation time (voxel size of 2 mm in the left-right (LR) and anterior-posterior (AP) directions and 3 mm in the cranio-caudal (CC) direction).

2.3. Mid-ventilation CT scans using rigid registration

The mid-ventilation (MidV) CT scan is a single 3D CT frame of a 4D data set, with the tumor closest to its mean position [4]. To obtain this scan, first the tumor motion in the 4D CT scan was determined [4,13]. To that end, a shaped region-of-interest (ROI) was manually defined in a reference CT frame, roughly encompassing the visual tumor. This ROI was subsequently registered to each frame of the 4D scan based on the correlation ratio of all voxels within the ROI to obtain a motion curve [13]. The tumor motion curve was used to determine the time-percentage (0-100% is a full cycle) in which the tumor is closest to its time-weighted mean position (clinically, the MidV is in exhalation). Subsequently, a new CT scan at the MidV time-percentage was reconstructed from the 4D CT (raw) sinogram data set. Using this 3D MidV CT scan, the systematic error due to breathing motion in the planning scan is reduced to nearly zero.

2.4. Deformable registration

For this part of the study, the maximum expiration frame from the 4D CT data set was chosen as the reference scan, since this frame is expected to have the least number of imaging artifacts (due to minimal tumor motion and higher reproducibility of the tumor position compared to the other frames). A second scan was then registered to the reference scan (floating scan; Figure 5-1).

First, an image-processing operation (Section 4-1) was applied to the reference and floating scans, to convert the image into image-phase data (gray-value transitions from bright to dark and vice versa). The second part contains the actual motion estimation procedure based on optical flow using the image-phase data instead of the original image data. From the phase data, motion constraint equations were derived (for every voxel), representing a relationship of the phase change in space (x,y,z) and time (t), i.e., from floating scan to reference scan. Subsequently, the local translations (motion vectors) were found that matched the local constraint equations. This motion vector was then used to deform the floating scan to the reference scan.
Registration accuracy and speed were improved using an iterative coarse-to-fine image scale approach with multiple registration steps.

An important issue in deformable registration of thorax images is the fact that the motion direction of the lung tissue is opposite to the motion direction of the thoracic wall and the mediastinum (sliding tissue). Therefore, an adaptive filter was used in this method to regularize the motion constraints and the motion field (smoothing small errors) to separately filter the motion of the lung and surrounding tissues (Section 4-5).

2.5. **Reconstruction of the mid-position CT scan**

For each frame of the 4D data set a deformation vector field (DVF) was computed to a reference scan (Figure 5-1) using the method described in Section 5-2.4 and Chapter 4. Since the same reference scan (maximum expiration frame) was used in each DVF, the mean motion of all voxels can be computed by averaging the 10 DVFs (9 computed + 1 reference –motion = 0–); Figure 5-2). Subsequently, for each DVF the mean DVF was subtracted, resulting in a set of DVFs with respect to the mean position (instead of with respect to the reference (exhale) frame).

Registration accuracy and speed were improved using an iterative coarse-to-fine image scale approach with multiple registration steps.

An important issue in deformable registration of thorax images is the fact that the motion direction of the lung tissue is opposite to the motion direction of the thoracic wall and the mediastinum (sliding tissue). Therefore, an adaptive filter was used in this method to regularize the motion constraints and the motion field (smoothing small errors) to separately filter the motion of the lung and surrounding tissues (Section 4-5).
to obtain the MidP CT scan, where all the internal structures, including the tumor, were in their exact time-weighted mean position of the respiratory motion. Arithmetic averaging ($\text{MidP}_{\text{mean}}$) as well as median averaging ($\text{MidP}_{\text{median}}$) were investigated.

2.6. **Image fidelity and performance measurements**

Image registration accuracy and shape changes (with respect to the BH CT representation) were investigated to determine artifact reduction in the MidP reconstruction compared to the original 4D and MidV CT scans.

a. **Image registration accuracy**

Besides visual inspection of the different structures in the transformed frames of the 4D CT scan, two quantitative tests were performed to estimate the accuracy of the registration algorithm. The first test determined the differences in estimated tumor motion between an established locally rigid registration method (which is locally very accurate [13]; Section 5-2.3), and our deformable registration method. In the case of the deformable registration method, the deformation vectors within a manually defined ROI (encompassing the tumor) were combined (averaged) to derive a single motion curve.

The second test used the publicly available POPI-model data set [14], containing a 4D CT scan and a list of 40 landmarks identified manually by a medical expert in each of the 3D frames. The difference between the corresponding position of the landmarks in a certain frame and the reference frame represented the motion and was considered as “truth”. The accuracy of the motion estimate was determined by comparing the estimated motion at the positions of the landmarks to those manually determined.

b. **Quantification of tumor size and shape changes**

The tumor shape in CT reconstructions were compared to the tumor shape in the BH CT scan, assuming that the tumor does not deform noticeably over the respiratory cycle. For each patient, a ROI (mask) over the tumor was defined manually. The tumor in the different scans were locally registered to the tumor in the BH CT scan (similar as described in Section 5-2.3), resulting in 14 matched tumor regions (BH, 10 frames 4D, MidV, MidP$_{\text{mean}}$, MidP$_{\text{median}}$). Subsequently, the tumor within the ROI was segmented by a patient-specific threshold of halfway the foreground and background voxel value (approximately 650 HU), in each of the 14 tumor-registered scans. The tumor volume was determined by counting the number of segmented voxels in all reconstructions. Shape changes were determined by counting segmented voxels that differed from their corresponding voxel in the BH CT scan. An example of the ROI, the segmentation, and the difference with respect to the BH CT scan is given in the results section.
c. **Quantification of noise**
For all 14 scans, the noise (standard deviation of pixel intensity within a ROI) was measured for tissue (mediastinum) and air (outside the patient) regions. These regions were manually drawn in homogeneous areas.

3. **Results**

3.1. **Image registration accuracy**
The tumor in each CT frame was matched using locally rigid registration and deformable registration to the maximum expiration phase (Section 5-2.3 and 5-2.4), resulting in nearly identical tumor motion curves. For the 13 patients in this study, the mean differences between the rigid registration and the deformable registration method applied to the tumor were (mean±1SD) 0.0±0.8 mm (LR), 0.0±1.0 mm (CC) and 0.0±0.6 mm (AP) over all respiratory phases. The maximum difference was found in the maximum inhale phase (1.1±1.4 mm –CC–) and the maximum exhale phase (-0.7±1.1 mm –CC–).

Comparison of the motion of 40 landmarks in the POPI-model, using deformable registration and manual identification resulted in a difference (mean±1SD) of 0.1±0.5 mm, -0.3±0.7 mm, -0.1±0.5 mm for the LR, CC and AP directions, retrospectively. To participate in the study of Vandemeulebroucke [14], for this POPI-model test only, the maximum inhalation frame (0%) was used as reference scan. There was no correlation between the difference (between automated and manual registration) and the respiratory phase. In Figure 5-3, the 4D CT images of the POPI model as well as the subtraction images of the original and transformed CT frames were compared to maximum inhalation frame, showing a strong reduction of the image difference after deformable registration. The right-most column shows the median average of the CT frames transformed to maximum inhalation frame and the median average scan subtracted from the phase 0% CT frame.

![Figure 5-3. Sagittal slices of the 4D CT scan of the POPI model (top row) as well as the subtraction images of the original CT frames and phase 0% (middle row) and the subtraction images of the transformed CT frames and phase 0% (bottom row). The right-most column shows the median average of the transformed CT frames (to phase 0%) and the median average scan subtracted from the phase 0% CT frame.](image-url)
scan subtracted from the maximum inhalation frame. The result shows smaller differences compared to the maximum inhalation frame with respect to the other 4D CT frames.

3.2. **Quantification of tumor size and shape changes**

For one patient (CC tumor motion was 18 mm peak-to-peak; tumor volume was 16 cm³), the ROI of the tumor (matched to the BH CT), the segmentation and the difference of the segmentations between the different CT reconstructions and the BH CT scan are shown in Figure 5-4a. The tumor volume was compared with the tumor volume of the BH scan (ratio). This tumor volume ratio of the 4D CT scan varied over the respiratory phases (Figure 5-4b). The tumor volume ratio of the MidP reconstruc-

![Figure 5-4. An example of the shape differences and volume determination of one patient. (a) A sagittal slice of the ROI of the tumor (top row), matched to the BH CT, as well as the segmentation (middle row). The bottom row shows the difference of the BH CT segmentation with the different CT segmentations: 4D CT, Mid-ventilation (MidV), Mid-position with mean (MidP mean) and median (MidP median). (b) The tumor volume relative to the tumor in the BH CT scan for the different CT reconstruction (ratio). (c) The relative number of voxels (relative to the total number of voxels of the BH tumor representation; fraction) for which the shape of the tumor in the particular CT reconstructions differ from the shape in the BH CT scan (the relative number for BH representation is zero).](image-url)
Figure 5-5. (a) The mean (red line with circles) and mean±standard deviation (black thin lines) of the relative tumor volume (relative to the tumor volume of the BH tumor representation; ratio) in the particular CT reconstructions. (b) Similar plot of the relative number of voxels (relative to the total number of voxels of the BH tumor representation; fraction) for which the shape of the tumor in the particular CT reconstructions differ from the shape in the BH CT scan (the relative number for BH representation is zero).
tions are almost identical to the mean tumor volume ratio of the 4D CT (1.03, 1.10 and 1.05 for the MidP mean, MidP median and the 4D CT, respectively). On average, the volume of the tumor (ratio>1) in the 4D CT (including MidV and MidP reconstructions) was larger than the tumor volume of the BH CT scan (between 0 and 20%, except for the first two 4D CT frames; Figure 5-5a). The tumor volume of the MidP reconstructions (especially the MidP mean) is close to the average of the volumes in the separate frames of the 4D CT. The systematic overestimation of the tumor volume in the 4D CT scans and their derivates results in an offset to shape differences. The differences in shape were expressed as the fraction of the total number of voxels in the segmentation of the tumor in BH representation. The example in Figure 5-4 shows smaller differences in shape in the MidP CT reconstructions (14% and 4% for MidP mean and MidP median, respectively) than in the 4D CT frames (especially in the exhale (frame 20%) and inhale (frame 60%) MidV CT frames) compared to the BH CT. This pattern is also visible in the overall results for all the patients (Figure 5-5b). Note that the difference between the shape of the tumor in the different reconstructions compared to the shape of the tumor in the BH CT scan were analyzed in terms of absolute difference; therefore, these results were always positive. The mean relative difference (offset) over all patients was 0.3±0.1.

By splitting the patient group based on the tumor size in the BH CT reconstruction (> mean tumor size (17±17 cm³ over all patients) = 5 patients and < mean tumor size = 8 patients), the overestimation of the volume was on average 26% for large tumors and 10% for small tumors (p<0.01, t-test). This suggests a relation between tumor size and tumor volume (and shape differences) in the 4D CT scan.

3.3. **Quantification of noise**

The noise in the air region as well as the tissue region was comparable for all 4D CT frames and MidV CT scan (Figure 5-6). The noise in the BH scan was lower than that of the 4D reconstructions (26%). The MidP mean and MidP median reconstruction showed a significantly lower noise compared to the 4D scan (reduction was 66%) since all 10 CT frames of the 4D CT scan were used for the construction of the MidP scans. The noise of the MidP median scan was slightly higher than for the MidP mean scan (8%).

4. **Discussion**

4.1. **Image registration accuracy**

The accuracy of the deformable registration algorithm is comparable to established locally rigid registration methods (differences in tumor position are in the order of 0.5 mm). This implies that, at least for the tumor region, our deformable registration method is accurate enough for estimating and compensating tumor motion, i.e., with the MidP method an increase in image quality for delineation and treatment-
planning can be obtained. The maximum error was found at maximum inhale (phase 0%) and maximum exhale (phase 50-60%). This was caused by a small difference in the measured magnitude of the motion, which has its maximum influence in the maximum exhale and inhale phases. This difference (underestimation) of the motion using deformable registration was probably due to smoothing of motion vectors in the registration procedure and due to the merging of the motion vectors within the tumor ROI of the deformable registration results. For these patients where underestimation of motion occurs, the tumor was close to a structure with opposite motion (e.g., chest wall). Small portions of the motion field of these structures with opposite motion directions were entering the ROI in which the motion was measured; therefore, the average within the ROI was slightly reduced.

Considering the 4D CT POPI-model (Figure 5-3), it is clearly visible that the image differences with respect to maximum inhale frame (0%) are reduced after deformable registration. Residual differences in the transformed 4D CT scan of the POPI-model are probably due to small imaging artifacts in the 4D CT scan and the low resolution of the control-points grid. The last column shows the median averaged CT scan of the deformed CT frames to frame 0% (i.e., to maximum inhalation instead

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Figure 5-6. The mean (red line with circles) and mean±standard deviation (black thin lines) of the noise in a soft tissue region (mediastinum; top) and in an air (bottom) of the 14 different scans.
of the mean position). This median average reconstruction here is a qualitative visualization of the image improvements (reducing image artifacts; see the subtraction images) when combining multiple transformed CT scans.

Image registration accuracy was quantified by the differences between the motion from the manually identified landmarks and the automated estimation of the motion using deformable registration of the POPI-model. These differences were small (mean difference ≤ 0.3 mm for all three directions). Although the motion of the manually identified landmarks is defined as a reference value, it still has a limited accuracy mainly due to small landmark misidentifications and the slice thickness of 3 mm. Part of the registration errors found were due to this limited accuracy. Therefore, we estimate that the accuracy of our used deformable registration method was sufficient for the aim of this chapter and to be used for other applications such as dose accumulation (dose reconstruction grid ~ 5 mm) and delineation deformation. In addition, the method can also be used for registration of scans of the upper abdomen.

Figure 5-7. An example of the mixture of different motions in regions in the vicinity of the diaphragm. Using adaptive filtering, regions with different densities are filtered separately. However, in the upper abdomen, the density is similar to the abdominal/thoracic wall, therefore in this region blurring still occurs. The circle in the images focuses on a rib which was not transformed correctly. Arithmetic averaging results in blurring of the structures that were not registered correctly, however, the median average is more robust against these misregistration artifacts.
4.2. **Sliding tissue and adaptive filter in motion regularization**

The adaptive filter (Section 4.5) to smooth the results of the different density regions (lung, thoracic wall, and abdomen) worked reasonably well for the lung region and far above the diaphragm. However, near the diaphragm and in the upper abdomen, there is not a clear density difference between the abdominal wall and abdomen. In this region, there is still some mixture of different motions, which results, for example, in wrongly positioned ribs after deformable registration (Figure 5-7). It appeared that this “mixture problem” is mostly present when registering the extreme respiratory phases (maximum inhale, maximum exhale) since blurring of the control-points resulted in motion of the control-points in the thoracic wall (where motion is almost zero). This erroneous offset is too large to be corrected by the deformable registration method in a subsequent iteration. A solution to this problem could be to segment the lung and adjacent organs or structures and process them separately. While segmentation in lung is rather easy given the large contrast between lung and neighboring tissue, for the abdominal region, densities are more or less homogeneous making simple automatic segmentation of organs and abdominal regions not possible. To overcome this mixture of motion in the abdominal region, we are currently testing use of the motion of the non-filtered motion output (or motion from a previous iteration) to segment regions with different motions in the adaptive filter operation. These possible remaining misregistration artifacts are effectively suppressed by using the median average instead of the standard arithmetic mean in reconstruction of the MidP CT image (Section 5-4.4): A single outlier value can never be the median value (but will be the minimum or maximum value of the ordered value list) and is, therefore, not used in the MidP\text{median} reconstruction (Figure 5-7).

4.3. **Quantification of tumor size, shape changes, and image fidelity**

Shape verification was performed to determine whether the MidP CT scans represented the tumor region with the correct shape. If tumor position and shape are accurate, the MidP CT is suitable for use in treatment-planning. The number and position of artifacts in the 4D scans are patient-specific and depend on a variety of parameters, e.g., tumor size, tumor speed, breathing irregularities, and scanner speed causing large variation in the shape difference and volume (Figure 5-5). Shape difference is correlated with volume change but shape can also vary with a fixed volume. Since the shape differences of the segmented tumors in this chapter were expressed as absolute differences, a “doubling of the respiration frequency” appears in the curve, showing two peaks (Figure 5-4b and Figure 5-5b). The two peaks correspond approximately to the time-percentage at the largest tumor speed (exhalation 15% and inhalation 77%), which does not have to be the MidV time-percentage (21±4%).

In addition, we have computed the correlation-ratio (CR) [15] and the Dice’s coefficient (DC) [16] of the tumor region between the BH scan and the other scans. The
CR and DC showed a similar variation pattern and outcome as the segmentation difference discussed in this chapter: On average CR was 0.7 for the 4D CT scan (and MidV) and 0.8 for the MidP reconstructions; the DC was on average 0.8 for the 4D CT scan (and MidV) and 0.9 for the MidP reconstructions.

The lowest shape differences are roughly found at the part of the breathing cycle where tumor motion is low (maximum exhale (55±10%) and inhale (0% by definition)). Since the inspiration period is shorter than the expiration period, maximum inspiration is expected to have more shape differences on average. However, the short amount of time in which the tumor is in the maximum inspiration phase is probably large enough to scan small tumors, but probably too short to scan the entire volume of large tumors.

The relationship between tumor size and the tumor volume ratio (and shape differences) in the 4D CT scan is probably due to fact that scanning of large tumors takes longer than small tumors. In this longer time period, the average effect of breathing irregularities is larger. The systematic overestimation of the tumor volume might be explained by the fact that the maximum inspiration BH scan has a larger lung volume than any of the 4D respiratory phases, resulting in a lower density of the lung tissue (assuming mass conservation). The use of an equal threshold for tumor segmentation in any of the reconstructions will result in a smaller tumor volume of the BH reconstruction compared to any of the 4D reconstructions and its derivates. Beside tumor shape variation, small tumor registration errors also cause differences in the tumor shape. Since registration errors were in the same order of magnitude as the shape differences (registration errors < 0.5 mm, voxel size < 2x2x3 mm³) but do not correlate with the respiratory phases, the SD of the shape differences and volume over the patient group is large.

Since MidP reconstructions are created from 4D CT data that contain artifacts, it is logical that imperfections in the 4D CT scan result in imperfections in the MidP scans. In Figure 5-5b, however, a clear reduction of shape differences of the MidP reconstructions compared to the 4D CT reconstructions (of all phases) is shown. In other words, the tumor shape of the MidP reconstructions (on average) better represents the tumor shape of the BH scan (the reference) than any of the frames of the 4D CT scan. The fact that the shape difference of the MidP reconstruction (compared to the BH scan) is reduced and does not equal the average of the difference results of the 4D CT scan, suggest that variation in tumor shape over the respiratory cycle is not caused by true anatomical variation but artifacts, i.e., the tumor is locally rigid.

Comparing the MidP reconstruction to the separate 4D CT frames, the 4D CT frames appeared to have higher spatial resolution, suggesting that separate 4D frames are more useful for delineation (Figure 5-8). However, one has to be aware that the artifacts in the separate 4D CT frames may cause serious target definition errors, which are reduced considerably in the MidP CT scan.
The MidP$_\text{mean}$ reconstruction shows less shape difference than the MidP$_\text{median}$ reconstruction. This is because median averaging of the transformed 4D CT scan preserves higher frequencies in the signal (noise and small similar artifacts that exist in the majority of the frames of the 4D CT) better than normal averaging (which blurs/smoothes the signal). The advantage of the MidP$_\text{median}$ over the MidP$_\text{mean}$ reconstruction is the edge preserving property (higher frequencies) of the median average. Normal arithmetic averaging results in blurring of the artifacts present in the 4D reconstructions, reducing the visual sharpness of structures.

Note that the averaging of scans (normal and median), results in a tumor volume, approximating the average of the tumor volumes of the 4D CT scan. However, the variation in volume over the patients was smaller for the MidP reconstructions compared to the 4D CT scan since the tumor shape is more consistently represented by the MidP averaging.

4.4. **Improvements of image fidelity**

A large improvement in image fidelity of the planning CT scan is possible when using the MidP reconstructions compared to the original 4D CT reconstruction; however, image distortions and artifacts still remain. The most important solution of this problem may be found in better 4D CT reconstruction algorithm, which was not within the scope of this chapter (see Section 8-1.3c). However, coaching patients’ breathing (breathing control) can help reduce image artifacts due to irregular breathing [17] (see Section 8-1a).

The image fidelity of the MidP CT scan can be improved also by using the “cleaner” BH CT scan (containing correct tumor representation) as a reference scan in the deformable registration procedure. After registration, the BH CT scan then needs to be transformed to the mean position instead of the 4D CT. However, with this adaptation, an extra scan (BH) becomes compulsory, while normal application of the MidP CT scan would not need one. Moreover, deformable registration of the 4D CT scan to the maximum inspiration BH CT scan may be less robust due to the large distance between structures in the (extreme) maximum inspiration BH position and the 4D CT frames.

To further reduce the influence of the remaining artifacts, we recommend inspection of the 4D CT scan after deformable transformation for artifacts (manual or automatic) and exclude the CT frames with strong artifacts (Figure 5-9). This appeared to increase the image quality of the MidP scans.

4.5. **Quantification of noise**

The noise (SD) was considerably lower for the MidP reconstruction than for any of the other reconstructions owing to the fact that it is an average of 10 CT frames instead of one. The noise is expected to be lower by a factor of the square root of the
independent number of frames \([1] \sim \sqrt{10}\) than for a single frame of a 4D CT scan. However, large scanning artifacts limit the reduction of the SD, resulting in an overall reduction of a factor of three. Since median averaging preserves higher frequencies more than normal averaging (Section 5-4.3), the SD is a bit higher. The strong decrease of the noise implies an improvement in image quality.

4.6. **Hysteresis**

Tumor hysteresis in the 4D CT scan results in a displacement of the tumor position in the MidV planning CT scan relative to the time-weighted mean position, which finally adds to the patient setup error [18]. Hysteresis of the tumor motion was quantified by the distance from the MidV position in exhale to the time-weighted mean tumor position of the respiratory cycle and determined for all patients. The displacements due to hysteresis in the tumor motion were small over the patient group (mean±1SD) -0.3±0.4 mm (LR), 0.0±0.3 mm (CC) and 0.8±0.5 mm (AP). The deformable image registration approach we used has an accuracy of about 0.5 mm for each registration. Comparing these two uncertainties shows that, in terms of correction for hysteresis, a minority of the patients really benefit from the advanced MidP method in terms of local accurate representation of the anatomy. The main benefit is in the delineation accuracy by the improved image quality and fidelity.

Figure 5-8. An example of a mid-ventilation and corresponding mid-position CT scan. The mid-ventilation scan has a higher spatial-resolution than the mid-position CT scan; however the imaging artifacts possibly cause target definition errors. In the mid-position scan, the scanning artifacts were reduced considerably therefore possibly improving target definition. The dashed lines are a guide to the eye to appreciate the difference in apparent tumor size.
We have developed and implemented a new method to reconstruct a representative CT scan for radiotherapy planning: The mid-position CT scan. The MidP CT is a refinement of the MidV CT and better represents the tumor (and patient anatomy) for treatment-planning than any of the frames of the original 4D CT including the MidV CT scan. The deformable image registration method based on image-phase is accurate and suitable to be used for the reconstruction of this MidP CT scan. Improvements in image integrity (correct anatomy and tumor shape) and image fidelity of the MidP CT scan were quantified by reduction of the tumor shape differences of the MidP reconstruction with respect to the BH CT scan (considered as “truth”) and reduction of the image noise. The results showed a decrease (14 %) in shape difference of the tumor for the MidP\textsubscript{mean} CT reconstruction compared to the 4D CT scan. The noise was decreased by a factor of 3 for the MidP reconstructions compared to each frame of the 4D CT scan. The MidP approach can be used to correct for possible hysteresis in the tumor motion but hysteresis was small for the majority of the patients, also in this study. Finally, MidP\textsubscript{median} CT results in sharper planning images but based on the current quantative data, the tumor shape of the MidP\textsubscript{mean} CT better resemble that of the BH CT scan.

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*Figure 5-9. An example of the image improvement of the MidP CT reconstruction when excluding the deformed 4D CT frames with large artifacts. In this example, a large artifact (including misregistration) near the diaphragm was present.*
References

Treatment plan evaluation

Comparison of different strategies to use 4D CT in treatment-planning for lung cancer patients

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Abstract

**Purpose** Four-dimensional (4D) CT scanning provides information on respiratory induced tumor motion (TM), which can be utilized to construct a patient-specific planning target volume (PTV). Internal target volume (PTV$_{ITV}$), exhale gated radiotherapy (PTV$_{Gating}$) and a new proposed mid-position (PTV$_{MidP}$; time-weighted mean tumor position) PTVs will be discussed and compared with the conventional free-breathing CT scan PTV (PTV$_{Conv}$).

**Methods and Materials** Respiratory motion induces systematic and random geometrical uncertainties. Their contribution to the clinical target volume (CTV)-to-PTV margins differs for each PTV approach. The uncertainty margins were calculated using a dose-probability based margin recipe (based on patient statistics). TM in 4D CT scans was determined using a local rigid registration of the tumor. Geometrical uncertainties for inter-fractional setup errors and tumor baseline variation were included. For the PTV$_{Gating}$, the residual motion within a 30% gating(-time)-window was determined. The concepts were evaluated in terms of required CTV-to-PTV margin and PTV volume for 45 patients.

**Results** Over the patient group, the PTV$_{ITV}$ is on average larger (+6%), and the PTV$_{Gating}$ and PTV$_{MidP}$ are smaller (-10%) than the PTV$_{Conv}$ using an offline (bony anatomy) setup correction protocol. Using an online (soft tissue) protocol the difference in PTV compared to PTV$_{Conv}$ were +33%, -4% and 0%, respectively.

**Conclusions** The ITV method resulted in a significantly larger PTV than conventional CT scanning. The exhale Gating and MidP approaches were comparable in terms of PTV. However, MidP (or mid-ventilation) is easier to use in the clinic since it only affects the planning part of treatment and not the delivery.
1. INTRODUCTION

The current prognosis for non-small-cell lung cancer (NSCLC) is poor, with a 5-year survival rate of only 15%, partly owing to a high local recurrence rate [1]. For radiotherapy, several studies have shown that a higher radiation dose is associated with a better failure-free and overall survival [e.g., 2]. However, surrounding healthy lung tissue, the heart and the oesophagus are dose-limiting organs [3]. Increasing the dose without reducing the irradiated volume results in an increase of the mean lung dose (MLD). This leads to a higher probability of radiation pneumonitis [4]. Moreover, there is also an increase in the dose to other organs-at-risk. Therefore, to enable safe dose escalation, target volumes and the associated irradiated volumes of normal tissue should be minimized.

The construction of a target volume [5] begins with a manually delineated gross tumor volume (GTV), which is, in general, the visible tumor in the planning CT or PET scan. The GTV is expanded with a margin accounting for microscopic extensions, rendering the clinical target volume (CTV). An extra margin for systematic and random geometrical errors (e.g., variability in patient positioning, respiration, and other internal organ motion) is then added to minimize underdosage of the tumor in case of erroneous events, resulting in the planning target volume (PTV; Figure 6-1).

Because of breathing, tumor motion (TM) excursions up to 2 cm are common in lung. Use of a conventional free-breathing 3D CT scan leads to several geometrical distortions, (e.g., image artifacts in tumor shape and position, delineation errors, etc). To account for these geometrical uncertainties, large target volumes are needed, thereby limiting the effectiveness of the radiotherapy [6].

To reduce geometrical uncertainties in CT images, time-resolved four-dimensional (4D) CT scanning techniques have been developed [7-9]. These 4D CT scans potentially allow a reduction of margins from CTV to PTV, thus reducing the volume of irradiated normal lung tissue.

Various approaches for using 4D CT scans in treatment-planning have been reported recently. In this chapter we compare internal target volume (ITV; encompassing the entire tumor excursion in one breathing cycle) [10], gated treatment (Gating; irradiation to a restricted portion of the respiratory cycle) [11,12], and the newly proposed mid-position approach (MidP; irradiation at the geometrical time-weighted mean tumor position, a refinement of the mid-ventilation approach [13]; see Chapter 5).

On the basis of patient-specific data (motion amplitude and GTV), a simulation study was performed, using a dose-probability based margin recipe (based on patient statistics) [14], comparing margins and PTV volumes resulting from the ITV, Gating, and MidP approaches with those resulting from free-breathing conventional 3D CT scanning (i.e., non-time-resolved).
We investigate both the effect of an offline correction protocol (aligning bony anatomy, reducing the systematic component) and an online correction protocol (aligning soft tissue mean tumor position, reducing the systematic and random component) on the margins and PTVs.

2. **METHODS AND MATERIALS**

2.1. *Patient group*

Four-dimensional CT data sets of 45 subsequent patients (31 male and 14 female) with various stages of lung cancer were used in this retrospective study (56% upper thorax tumors and 44% lower thorax tumors).

2.2. *Simulation of the different planning concepts*

a. **Acquisition of respiration-correlated 4D CT**

During 4D CT scanning, the patient was instructed to breathe normally. The respiration of the patient was registered with a thermocouple inserted into the entry of a regular oxygen mask, which measures temperature changes in the airflow during inhalation (cold) and exhalation (warm). The helical cardiac scanning mode of the CT scanner (24 slice Somatom Sensation Open, Siemens, Forchheim, Germany)

![Figure 6-1. Schematic overview of different treatment-planning concepts: Conventional free-breathing, internal target volume (ITV), gating (at exhale) and mid-position. GTV = gross tumor volume, CTV = clinical target volume, PTV = planning target volume.](image)
was used for the respiration-correlated imaging. A 4D CT scan of 10 respiratory phases (10 frames, each frame being 1/10th of the breathing period and containing approximately 100 slices) was reconstructed using phase-sorting (scan slice resolution was 512x512 pixels).

b. Determination of tumor motion by local rigid registration
The tumor motion in the 4D CT scan was determined as described previously [9, 15] (Chapter 2). First, the scan slice resolution was reduced to 256x256 pixels. A region-of-interest (ROI) was then defined around the tumor in a reference CT frame using a manually drawn mask, encompassing the tumor. This ROI was subsequently registered to the scans of the other respiratory phases on the basis of the correlation ratio of all voxels within the ROI. This procedure was repeated three times for three different reference CT frames (at 0%, 30%, 70% of the breathing cycle). From each tumor motion curve the mean tumor position was subtracted to obtain relative motion curves. The three curves were averaged to reduce small registration inaccuracies, resulting in one (relative) motion curve that was used for further analysis (Figure 6-2). Interfraction variability in tumor amplitude is small and therefore ignored in this study [16].

c. Planning Target Volume, margin recipe and contributing uncertainties
The GTV, used in this simulation study for the different treatment-planning approaches, was determined from the delineation in the clinical treatment plans (from MidV

![Figure 6-2. An example of a tumor trajectory showing hysteresis of the tumor motion (in mm) due to respiration. Tumor trajectory was determined from the four-dimensional CT scan. The spheres show the positions of the tumor relative to phase 0%.](image)
CT scans). In this study, target delineation uncertainties were not included. The delineation uncertainties are expected to become smaller using 4D treatment-planning, owing to an improved visualization of the tumor shape, but specific data are at present not available. No margin for microscopic extensions was taken into account in this study (thus GTV or ITV = CTV).

The different target volume strategies discussed in this chapter were compared by evaluating the treatment margins from GTV to PTV and the resulting volumes of the PTV. For each patient individually, the margin necessary to deliver a dose of at least 95% of the prescribed dose to the CTV (for 90% of the population) can be computed by the margin recipe of van Herk et al. [14,17,18]:

$$M_{PTV} = 2.5\Sigma + 1.64\sqrt{\sigma^2 + \sigma_p^2} - 1.64\sigma_p$$ [mm],

where \(\Sigma\) and \(\sigma\) denote the standard deviations (SDs) of the systematic errors (localization errors in planning imaging) and random errors (localization errors during treatment), respectively. \(\sigma_p\) denotes the standard deviation of the dose gradient or "penumbra", for which we use a value of 6.4 mm in lung tissue [18]. The various components of the systematic and random uncertainties are summed in quadrature to generate the margin.

### Table 6-1 The systematic (\(\Sigma\)) and random (\(\sigma\)) baseline variation and setup errors of the patient group.

<table>
<thead>
<tr>
<th>LR</th>
<th>CC</th>
<th>AP</th>
<th>LR</th>
<th>CC</th>
<th>AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline variation</td>
<td>1.6</td>
<td>3.9</td>
<td>2.8</td>
<td>1.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Setup</td>
<td>1.6</td>
<td>1.7</td>
<td>1.5</td>
<td>2.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Margin (mm)</td>
<td>6.7</td>
<td>12.7</td>
<td>8.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are derived from four-dimensional cone-beam CT scans for the left-right (LR), cranio-caudal (CC), and anterior-posterior (AP) directions. The last row gives the required margin when no respiratory motion is present (for all four methods). Only setup errors and baseline variation will then contribute to this margin.

### Table 6-2 Overview of the error contributions to the different treatment-planning approaches.

<table>
<thead>
<tr>
<th>Respiration contribution</th>
<th>Conv CT</th>
<th>ITV</th>
<th>Gating</th>
<th>Mid-position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodic motion</td>
<td>SD(TM)</td>
<td>SD(TM)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Baseline variation</td>
<td>(\Sigma_{\text{Baseline}})</td>
<td>(\sigma_{\text{Baseline}})</td>
<td>(\Sigma_{\text{Baseline}})</td>
<td>(\sigma_{\text{Baseline}})</td>
</tr>
<tr>
<td>Setup contribution</td>
<td>(\Sigma_{\text{Setup}})</td>
<td>(\sigma_{\text{Setup}})</td>
<td>(\Sigma_{\text{Setup}})</td>
<td>(\sigma_{\text{Setup}})</td>
</tr>
<tr>
<td>ITV motion expansion</td>
<td>-</td>
<td>(A_{\text{peak-peak}}/2)</td>
<td>(Residual (A_{\text{peak-peak}}) /2)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(\Sigma\) and \(\sigma\) refer to the systematic and random errors, including those for baseline variation and setup. SD denotes standard deviation. TM and \(A_{\text{peak-peak}}\) denote tumor motion and peak-to-peak amplitude, respectively. Reg.err. stands for deformable image registration error.

* The variation in end-exhale tumor position is estimated to be the same as the baseline variation (See section 6-2.2f)
The patient-specific motion contributions differ for the different approaches and are discussed in the following sections. The inter-fraction baseline variation (day-to-day variation in the mean time-weighted tumor position; \( \Sigma_{\text{Baseline}} \), \( \sigma_{\text{Baseline}} \)) and treatment setup uncertainty (\( \Sigma_{\text{Setup}} \), \( \sigma_{\text{Setup}} \)) in Table 6-1 [16,19] were obtained from 4D respiration-correlated cone-beam CT (4D CBCT) [20] data from roughly the same patient group. Note that patient population statistics were used, not individual patient data, because (patient individual) baseline and setup data can only be obtained accurately after complete treatment. Baseline variation and treatment setup uncertainty were taken into account for each concept in this simulation. Patient setup uncertainty depends on the institution and setup correction protocol (here, a shrinking-action-level protocol on bony anatomy was used), but the values used in this study can be seen as a guide. An overview of the error contributions for the different approaches is given in Table 6-2 and will be explained in the following paragraphs.

d. Planning target volume for conventional time-uncorrelated CT (PTV\(_{\text{Conv}}\))

A conventional, time-uncorrelated 3D CT scan (Conv CT) consists of images without time information from the moving tumor and anatomy. Using a fast multi-slice CT scanner, the 3D CT scan is an arbitrary snapshot (freezing the anatomy in an arbitrary breathing phase). This uncertainty results in an undefined displacement of the tumor with respect to the mean tumor position, which is a systematic error because the planning CT scan is only made once. Systematic (and random) errors due to respiratory motion can be estimated using the standard deviation of the tumor motion (approximately 1/3 of the peak-to-peak amplitude; \( A_{\text{peak-peak}} \)) [17] and were computed for each patient individually. Additionally, tumor shape deformation in the image can occur because the image representation depends on tumor and scanner velocity [6,21]. McKenzie [22] derived a margin formula for shape changes (2.5\( \Sigma \)) showing that the margin necessary for shape changes is similar to the margin necessary for displacement errors. Considering the fact that a fast scan has a large displacement uncertainty with a small shape distortion and vice versa for a slow scan, a first-order approximation is that the combination of tumor displacement errors and shape changes is constant (independent of tumor size and scan speed). The “combined” systematic motion error (\( \Sigma_{\text{TM}} \)) is therefore estimated by SD of the tumor motion. Note that in this study no “real” Conv CT is used but that the uncertainty data are used to simulate its performance (a single “real” Conv CT would not represent all possible states).

During treatment, the patient is breathing freely, which also results in a tumor position uncertainty. However, in contrast to the acquisition of a planning CT, the radiation treatment is not delivered in a short time period (0-30 seconds per beam, multiple fractions) relative to a typical respiratory cycle length. The tumor motion during treatment is therefore a random uncertainty component: \( \sigma_{\text{TM}} = \text{SD(TM)} \).

The planning target volume for conventional time-uncorrelated CT (PTV\(_{\text{Conv}}\)) was the reference PTV to which the other concepts were compared.
e. **PTV for the internal target volume concept (PTV_{ITV})**
   A commonly used approach is to expand the CTV to cover the entire motion [5]. The resulting ITV (Figure 6-1) is defined by the volume encompassing the entire displacement of the CTV. Therefore, the ITV concept aims to provide 100% dose coverage to the CTV during the respiratory cycle. The ITV to PTV margin expansion therefore only contains contributions from setup error and baseline variation. The ITV can be delineated in a maximum intensity projection image [10,23] or in the 4D CT frames separately, subsequently taking the envelope [24].
   In contrast to clinical practice to obtain an ITV, in this simulation study the ITV was constructed by the GTV with an extension (linear addition to the GTV) of half of the peak-to-peak TM amplitude for each direction (positive and negative) separately. Note that asymmetry of the respiration in time was not incorporated because the asymmetry does not influence the overall margin or volume.

f. **PTV for idealized gated radiotherapy (PTV_{Gating})**
   For gated radiotherapy, the tumor is irradiated only during a part of the breathing cycle (gating window). During treatment, the respiration is measured externally by respiration sensors (e.g., skin markers or belt) [25] and/or internally by fluoroscopy [26,27] to determine when the beam should be on and off. Gated treatment is mostly performed with patients free-breathing [27]; however, breath-hold irradiation [28] is also described. Moreover, advanced techniques like tumor-tracking (irradiating the tumor dynamically with a moving beam) [11] result in similar target volumes as gating. In this simulation we assume ideal gating (i.e., with a perfect tumor tracing system –further discussed in Section 6-4.2–).
   Although gating primarily affects the treatment part of radiotherapy for lung cancer patients, correct definition of the target volume for gating is essential. Gating is generally performed during exhalation because exhalation respiration phase is more reproducible and takes longer than inspiration [28]. The corresponding planning CT is then obtained by selecting the maximum exhalation frame from a 4D CT or by acquiring a (deep) expiration breath-hold CT scan [29] to delineate the GTV. The width of the time-window that will be irradiated (the gate) is commonly chosen as 30% [28] of the respiratory cycle.
   In this simulation study, the residual motion within the 30% gating window at the maximum exhalation phase was derived from the full TM curve for each patient individually. Since the motion curves contain data from only 10 frames, motion data at time-percentages between these frames were computed using spline interpolation. Residual motion was taken into account by expanding the GTV to a “gated-ITV” covering the residual tumor motion in the 30% gating window [30] (linear addition to the GTV).
   Concerning gated radiotherapy, the variation in tumor position during exhale should be used instead of tumor baseline variation (variation of the mean of the whole...
respiratory cycle). However, several publications report exhale tumor position variation that is similar to the tumor baseline variation [16,31]. For simplicity, the baseline variation was therefore used as well for gated treatment-planning in this simulation study.

g. **PTV for the mid-position concept (PTV_{MidP}) and mid-ventilation concept (PTV_{MidV}).**

Due to the presence of the wide beam-penumbra in lung, Engelsman et al. [32] and Witte et al. [18] showed that if a treatment plan is designed for the tumor in its (time-weighted) average position during the respiration cycle, a good dose coverage is still obtained even if the tumor is not fully within the PTV during a small part of the breathing cycle. Such a treatment plan can be designed on the mid-ventilation (MidV) CT scan, a single 3D CT frame from a 4D data set representing the tumor closest to its mean tumor motion position [13] (Chapter 2). The TM curve (see Section 6-2.2b) was used to determine the time-percentage (0-100% a full cycle) with the tumor closest to its time-weighted mean position. Subsequently, from the 4D raw data set, a new CT scan at that particular time-percentage was reconstructed. Using this 3D MidV CT scan, the systematic contribution due to breathing motion can be reduced to nearly zero, permitting a reduction of the treatment margin. The expected dose-blurring effect of the respiration can be accounted for in the CTV to PTV margin [14]. However, a (small) systematic geometrical error with respect to the mean position ($\epsilon_h$) is introduced owing to hysteresis in the tumor motion (tumor moves asynchronously in more than one direction, resulting in a 3D elliptical tumor trajectory instead of a line [33]; Figure 6-2). To overcome the problem of hysteresis, we will use the mid-position (MidP) concept (Chapter 5), which reconstructs a new

![Figure 6-3](image-url)
CT scan from the 4D CT data set. The MidP CT concept is a refinement of the MidV concept and comprises all the internal structures, including the tumor, in their exact time-weighted mean position of the respiratory motion. As a result of this approach, the systematic error due to hysteresis is eliminated; therefore, the MidP is more applicable to the outcome of Engelsman et al. [32] and Witte et al. [18] than the MidV. In this study, we therefore discuss only the results of the MidP approach.

We adapted an existing motion estimation method based on optical flow [34] to determine the motion for each voxel and modified (warped) each frame of the 4D CT scan by transforming all features from their position in a certain frame to their time-weighted mean position with the estimated motion [35] (see Chapter 5). Subsequently, averaging over the frames (respiratory phases) of the transformed 4D CT scan results in a MidP CT scan. The GTV_{MidP} is defined by the volume of the tumor in the MidP CT scan, but in this simulation study the GTV of the MidV scan was used. Besides the elimination of the geometrical error due to hysteresis, a less noisy image (higher signal-to-noise ratio) can be obtained by averaging the transformed CT frames (Figure 6-3), which potentially will result in smaller delineation errors.

The used image registration technique has an uncertainty. Although the data of the uncertainty are preliminary, the average accuracy of our deformable registration methods in the tumor neighborhood is comparable to that of rigid registration [35], which has an average accuracy of approximately 0.5 mm [15]. Therefore this error was set to 0.5 mm in this simulation. A more extensive discussion is given in Section 6-4.3, comparing errors due to hysteresis and registration errors. The random error distribution due to respiration is identical to the Conv CT method (σ_{TM} = SD(TM)) because respiration is still present during treatment.

<table>
<thead>
<tr>
<th>Table 6-3</th>
<th>The average GTV volume (V_{GTV}) estimated tumor diameter for a spherical tumor, and the tumor motion in the three directions for 45 patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V_{GTV} (cm^3)</td>
</tr>
<tr>
<td>Upper thorax</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>27.1</td>
</tr>
<tr>
<td>St. Dev.</td>
<td>41.4</td>
</tr>
<tr>
<td>Lower thorax</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>56.3</td>
</tr>
<tr>
<td>St. Dev.</td>
<td>50.5</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>40.1</td>
</tr>
<tr>
<td>St. Dev.</td>
<td>47.5</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 6-1. Values are mean (SD). Data are shown for the whole patient group as well as divided according to the position of the tumor in the thorax.
3. **Results**

For the group of 45 patients, GTV volumes were between 2 and 200 cm$^3$, corresponding to tumor diameters between 15 and 72 mm (Table 6-3). Peak-to-peak motion amplitudes were between 0.3 and 5.5 mm for left-right (LR), 0.8 and 24.0 mm for cranio-caudal (CC) and 0.6 and 11.6 mm for anterior-posterior (AP). Sixty-four percent of the patients had a CC tumor motion smaller than 10 mm, 98% had a CC tumor motion smaller than 20 mm.

The mean systematic and random motion error (standard deviation of the motion Section 6-2.2d) over the whole patient group was LR 0.7, CC 2.7 and AP 1.1 mm. The large range in GTV volume and tumor motion indicated that the results were representative for a large variety of patients.

An example of the margin calculations for all four concepts for a patient of this patient group with 15 mm peak-to-peak amplitude in the CC direction, using an offline (on bony anatomy) and an online (on tumor) setup correction protocol is given in Table 6-4. Only CC motion is illustrated, not LR and AP motion. The residual tumor motion within 30% gating-window was 2.3 mm. The example showed that with an offline correction protocol the margin for the ITV is similar to the margin for the conventional

<table>
<thead>
<tr>
<th>Table 6-4 An example of the margin calculations in the cranio-caudal direction for all four concepts of a patient with 15 mm peak-to-peak amplitude in the cranio-caudal direction only, using an offline (on bony anatomy) and an online (on tumor) setup correction protocol.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conv CT</strong></td>
</tr>
<tr>
<td>Σ</td>
</tr>
<tr>
<td><strong>Offline correction protocol</strong></td>
</tr>
<tr>
<td>Respiration contribution</td>
</tr>
<tr>
<td>Periodic motion (mm)</td>
</tr>
<tr>
<td>Baseline variation (mm)</td>
</tr>
<tr>
<td>Setup contribution (mm)</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>ITV motion expansion (mm)</td>
</tr>
<tr>
<td>Total margin (mm)</td>
</tr>
<tr>
<td><strong>Perfect Online correction protocol</strong></td>
</tr>
<tr>
<td>Respiration contribution</td>
</tr>
<tr>
<td>Periodic motion (mm)</td>
</tr>
<tr>
<td>Baseline variation (mm)</td>
</tr>
<tr>
<td>Setup contribution (mm)</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>ITV motion expansion (mm)</td>
</tr>
<tr>
<td>Total margin (mm)</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 6-2. The contribution to Σ and/or σ of the periodic motion was estimated using 1/3 of the peak-to-peak amplitude [50].
Figure 6-4. Overview of the margins for the four different approaches in the three directions as a function of the tumor amplitude. The upper row contains the results using an offline setup correction protocol. The minimum margin using an offline protocol is plotted along the vertical axis. The bottom row contains the results when an online correction protocol is used and all systematic and random errors could be dealt with perfectly. Note that the horizontal tumor motion (in mm) axis is different for each direction. Conv = conventional, ITV = internal target volume, MidP = mid-position.
free-breathing CT scan concept (approximately 20 mm). The margins necessary in
the Gating and MidP methods (approximately 15 mm) were considerably smaller.
Using an online protocol, the margins for Conv CT, Gating, and MidP approaches are
similar, but the margin for ITV approach is twice as large.
For the whole group of 45 patients, without any respiratory motion, the margin nec-
essary to cover baseline and setup errors was LR 6.7 mm, CC 12.7 mm and AP 8.8
mm (Table 6-1, Figure 6-4). With motion, for all four methods, the average required
margin was largest in the CC direction (Table 6-5). The variation in margin was
largest in the Conv CT method and smallest when using gated radiotherapy, which
is explained by the reduced dependency on the patient-specific tumor motion. The
ITV approach resulted in a significant increase (>7%, Table 6-5) of the average
margin compared to Conv CT scanning in the AP and LR direction (p<0.01, pairwise
t-test) but it was not significant in the CC direction (p=0.5). The two other methods
showed a significant reduction of the margin (≥12% in the CC direction, p<0.01). The
large standard deviation is due to the large systematic respiratory contribution for the
Conv CT method, which results in a large variation in margin.
The bottom row of Figure 6-4 shows the results when a (perfect) online image-
guided radiotherapy correction (to the mean tumor position) protocol was used (i.e.,
when systematic respiratory and registration errors, baseline variation and setup
errors were zero). For all tumor motion amplitudes, the order of the size of the
margin was as follows: ITV (largest), Conv CT/MidP (are equal) and Gated treatment
concept (smallest). The average difference (over the patient group) in margin in the CC
direction compared to Conv CT concept was +800% (PTV_{ITV}, the Conv CT margins
became very small, almost singular), -29% (PTV_{Gating}) and 0% (PTV_{MidP}; consider the
slopes of Figure 6-4). Variation in margins at equal tumor motion amplitudes was due
to different asymmetry of the respiration, resulting in different standard deviations
(Section 6-2.2d) and therefore in different systematic and random contributions.
Using offline setup correction, the volume of the PTV for this group of 45 patients,
compared to the Conv CT concept, increased for the ITV concept (by 6%) and
decreased for the Gating (by 11%) and MidP (by 9%) concepts (Table 6-6). Using
an online setup correction on tumor, the change in PTV was +33% (increase), -4%
decrease) and 0% for the ITV, Gating and MidP concepts, respectively.

4. Discussion
Improve in radiotherapy of lung cancer are often focused on the reduction of
the PTV to enable dose escalation. The benefit of a new method to determine the
target volume should therefore be that the treatment margin could be significantly
reduced for a large group of patients. This work shows that the PTV can be reduced
compared to conventional free-breathing time-uncorrelated 3D CT PTVs by using
motion information from 4D CT scans in the treatment-planning process.
4.1. **PTV for internal target volume concept**

The ITV concept covers the entire tumor motion and therefore effectively treats all respiration motion as a systematic error. Therefore, the ITV method overestimates the influence of the motion on the tumor dose. This overestimation results in irradiation of too much surrounding healthy tissue (larger margins and PTVs compared with Conv CT). Therefore, concerning margin reduction, the ITV method is not suitable for dose escalation.

For the Conv CT concept, the relationship between the margin and the tumor motion has a quadratic component (Figure 6-4) due to the square summed (large) contributions of the systematic errors (2.5Σ). Because in the ITV approach the motion extent is linearly added to the CTV, a linear relationship between motion and CTV-PTV margin results. With an offline setup correction protocol, these two curves intersect for TM of approximately 13 mm (Figure 6-4). This intersection point depends on the baseline variation and setup errors and can differ between different institutes and correction protocols. The margins in the LR and AP directions were always (except for one instance) larger for the ITV than for the Conv CT concept (TM<13 mm, Table 6-5, Figure 6-4). In the CC direction, however, for some patients the motion is larger than 13 mm, rendering a smaller margin than Conv CT. Considering the PTV, it seemed that for 6 of the 45 patients there was a reduction in the PTV compared with the PTV_{Conv}. Thus, the ITV method results in a PTV reduction (compared with Conv CT) for only a small group of patients.

On average over all patients, using an online setup correction protocol (to the mean tumor position), the CC margin differed 800% compared with the Conv CT concept. Compared with the results of an offline protocol, both concepts have reduced margins; however, the Conv CT margins reduce more. This is because (using an online protocol) for the Conv CT concept the systematic respiration contribution is also corrected besides baseline and setup error corrections, giving very small margins (Figure 6-4). Note that, by canceling out the systematic errors in the Conv CT concept, the margin becomes rather insensitive to the patient-specific motion.

### Table 6-5 Margin (necessary to have a 95% prescribed dose inside the clinical target volume), and margin change (%), determined for all 45 patients individually.

<table>
<thead>
<tr>
<th></th>
<th>Conv CT</th>
<th>ITV</th>
<th>Gating</th>
<th>Mid-position</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LR</td>
<td>CC</td>
<td>AP</td>
<td>LR</td>
</tr>
<tr>
<td><strong>Margin (mm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>7.1</td>
<td>16.2</td>
<td>9.7</td>
<td>7.6</td>
</tr>
<tr>
<td>SD</td>
<td>0.5</td>
<td>4.3</td>
<td>1.3</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Relative change (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>+8</td>
<td>+3</td>
<td>+7</td>
<td>-4</td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>8</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 6.2.
Three comments have to be made. First, a perfect correction protocol will never be possible. These results must therefore be seen as the lower boundary. Second, although the tumor displacement in the Conv CT concept is corrected using an online correction protocol, small image distortions still remain. Using an online correction protocol, these distortions are combined in the systematic error contribution (Section 6-2.2d), but have to be taken into account in the margin computations for the perfect online correction protocol. Finally, in some institutes, the margin for the Conv CT approach is expanded by the estimated full range of tumor motion, rather than using the standard deviation of the periodic motion in a margin recipe. This approach resembles the ITV approach with similar results for margin and PTV, but the difference compared with $PTV_{\text{Gating}}$ and $PTV_{\text{MidP}}$ will be larger.

4.2. \textit{PTV for idealized gated radiotherapy}

The Gating approach gives the smallest PTV compared with the other three approaches (a reduction of 11\% (Table 6-6) compared to Conv CT, offline correction protocol). From Figure 6-4 it can be seen that because of the small residual motion, the linear relation ("gated-ITV") between the margin and tumor motion has a very shallow slope. The systematic errors due to breathing are significantly reduced, and the margin becomes insensitive to patient-specific motion.

With an online correction protocol, the margin will be less than 1 mm and therefore negligible. PTV reductions compared with the Conv CT concept will be (on average) 4\% depending on the size of the CTV.

In an idealized gated treatment the tumor position should be directly monitored, and the delivery of radiation is allowed only when the tumor is in the correct position. The main requirements are then precise and real-time tumor localization and prompt linear accelerator reaction to the gating signal. Direct detection of the tumor motion is difficult. Therefore external (Varian RPM-system, thermo-couple) or internal (fiducials, gold markers, diaphragm) surrogate signals are often used. Variations in the correlation between tumor movements and surrogate signals can lead to uncertainties resulting in a poor treatment outcome. Especially in gated treatment with external respiration monitoring, the lack of correct internal information on which to gate may lead to underestimation of the geometrical errors [36,37]. These types of errors were not taken into account, but would considerable increase the PTV.

4.3. \textit{PTV for the mid-position concept}

The mid-position concept is a simple method to obtain a safe PTV definition, with (on average) almost the same margin outcomes as idealized gated radiotherapy (12\% reduction instead of 16\% for the Gating concept for the CC direction averaged over all patients; Table 6-5). The MidP approach only involves the reconstruction of a new planning CT scan and leaves other treatment-planning and treatment delivery
Table 6.6 Relative volume change (%) for the internal target volume (ITV), gating at exhale and mid-position concepts compared to the conventional free-breathing method using an offline and perfect online setup correction protocol.

<table>
<thead>
<tr>
<th></th>
<th>ITV</th>
<th>Gating</th>
<th>MidP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offline correction</td>
<td>6 + +11</td>
<td>9 + 9</td>
<td></td>
</tr>
<tr>
<td>Online correction</td>
<td>33 + +4</td>
<td>6 + 0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 6.2.

aspects unchanged. No complex treatment-planning (not 4D) and additional verification is necessary, which makes the MidP approach easy to implement. This results in an average PTV volume reduction of 9%.

When applying an online correction protocol (on tumor), the results showed that there is no difference in margin compared with the Conv CT (ignoring shape deformations). Because for both methods the systematic and the inter-fraction random errors were corrected, the same random errors remain, resulting in the same margin. The absolute differences between the PTV_{Gating} and the PTV_{MidP} concept become negligible.

Whether to choose for gating treatment or the MidP concept, a threshold for the tumor motion amplitude was derived. Limiting the difference in margin between Gating and MidP methods to 2 mm (approximately two times the standard deviation in margin) results in a threshold of 13 mm peak-to-peak amplitude. With this threshold, only five patients of the cohort would have benefit from gated treatment. However, when taking other uncertainties into account, this threshold will increase considerably.

The MidP method needs a deformable image registration approach, which is currently not commercially available. In this simulation, image registration uncertainties were estimated to be 0.5 mm for the tumor region, which may be slightly underestimated. However, note that multiple registrations were used (9 frames to a reference frame), which, combined together, increases the overall registration accuracy of the tumor. The displacements due to hysteresis in the tumor motion were also small (over the patient group, mean±1SD: 0.1±0.4 mm –LR–, -0.3±0.7 mm –CC– and –0.4±1.2 mm –AP–). Comparing these uncertainties shows that a minority of the patients really benefits from the advanced MidP method. In other words, the simpler MidV CT scan is sufficient for a large group of lung patients (on average 8% volume reduction compared with Conv CT). However, the increase in image quality that can be obtained with MidP CT scans is an advantage because delineation is easier and shape artifacts can be removed, possibly resulting in smaller delineation uncertainties.
4.4. Intra-fraction tumor position variation and stereotactic treatment

During treatment, mean tumor position may vary (intra-fraction baseline variation or drift). From stereotactic treatments, whereby 4D CBCT scans were made prior and after treatment, this intra-fraction variation has been measured. The systematic and random errors were approximately 1.5 mm [38]. These numbers will be smaller for conventional fractionation because treatment time is approximately 1/3 of the stereotactic treatment time. With an offline correction protocol, the intra-fraction baseline variation can be ignored compared with the setup uncertainties, because they need to be summed in quadrature. However, the relative contribution to the margin of this small uncertainty increases when an online-correction protocol is used.

The results in this chapter consider conventional fractionated treatments with 95% of the prescribed dose to the PTV. However, in stereotactic treatment schemes the dose is generally prescribed to an iso-dose level of approximately 80%. The margin recipe in Section 6-2.2c changes to $M_{\text{PTV,80\%}} = 2.5\sigma + 0.8\sqrt{\sigma^2 + \sigma_p^2} - 0.8\sigma_p$ [14], resulting in even smaller margins. The margins for Gating and MidP methods then become almost equal. Especially with small number of fractions, inaccuracies have to be reduced. Therefore cone-beam image-guided radiotherapy systems have been developed, allowing verification and correction of the target position prior to each radiotherapy session for each patient.

5. Conclusions

Four-dimensional CT scanning in combination with gating, mid-position or mid-ventilation treatment-planning helps to reduce PTV volumes and enable dose escalation and irradiation of larger tumors. With an offline bony anatomy correction protocol, the PTVs for the Gating and MidP concepts were on average reduced with 10% compared to the PTV for conventional free-breathing CT scans based on a dose-probability-based margin recipe. However, the PTV$_{\text{ITV}}$ increased on average with 6%.

Using an online soft tissue correction protocol the margins and PTV volumes decreased for all concepts and were similar for the Gating, MidP and Conv CT approach. The margin for the ITV approach was considerably larger than the Conv CT concept, resulting in a PTV volume difference of 33% compared to Conv CT (i.e., the ITV concept overestimates the influence of respiration during treatment).

For the majority of patients the results for gating and mid-position were similar. We therefore advise consideration of gated treatment only for patients with large tumor movements. The mid-position concept can be safely applied to patients with large tumor motion when using an online correction protocol (or in stereotactic treatment).

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Dose accumulation and evaluation

Effects of respiration-induced anatomy variations on dose distributions

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Abstract

Purpose To investigate the effect of respiration-induced anatomy (geometry and density) variations on the estimated dose to moving structures, and consequently evaluating the necessity of using a full four-dimensional (4D) treatment-planning optimization.

Methods and Materials For ten patients, with large tumor motion (median = 1.9 cm, range 1.1-3.6 cm), the clinical treatment plan designed on the mid-ventilation (MidV) CT was recalculated on all 4D CT frames. The cumulative dose was determined by transforming the doses of all breathing phases using deformable registration to the MidV geometry, and then averaging the result. To study the effect of density variations, this cumulative dose was compared to the accumulated result after similarly deforming the planned (3D) MidV dose in each respiratory phase by the same transformation (i.e., “blurring the dose”). Geometry variations were evaluated by comparison to the static MidV dose distribution.

Results The accumulated tumor doses including and excluding density variations were almost identical. Relative differences in minimum GTV dose were below 2% for all patients. For the lung, the differences were even smaller; relative differences in mean lung dose and V20 were below 0.5% and 1%, respectively.

Conclusions The effect of respiration-induced density variations on the delivered dose is very small. Therefore, planning on the MidV CT with dose-blurring according to tumor motion, is an appropriate estimate of the full accumulated 4D dose. Moreover, when using a proper margin to account for geometrical uncertainties such as setup, baseline and respiration uncertainties, the effect of geometry variation to the delivered dose is also small.
1. Introduction

Substantial respiration-induced anatomy changes have been observed in the thoracic region. Breathing causes motion, deformation and density changes in the tumor and the organs-at-risk (OAR; e.g., lungs) as well as other structures (e.g., rib cage). Therefore, a four-dimensional (4D) approach, accounting for moving structures in time, is pursued by many studies for radiotherapy of lung cancer (eg. [1]). Consequently, 4D scanning, planning and treatment delivery are being investigated by several institutions [2-4].

A four-dimensional computed tomography (4D CT) scan is used to represent the changing patient anatomy over the respiratory cycle [5]. By employing an external breathing sensor the CT data (oversampled 4D data) are sorted into multiple three-dimensional (3D) CTs of the different breathing phases. The geometrical relationship between phases can be evaluated by local rigid or deformable registration [6-8].

There exist various methods which incorporate, to different extent, 4D CT information into treatment-planning for better dose prediction of moving structures [1,9]. Full 4D treatment-planning that utilizes the CTs of all breathing phases for dose optimization, is currently not included in most treatment-planning systems. Alternative more simple methods perform a 3D planning on a representative scan, e.g a mean density CT (in combination with a maximum intensity projection –MIP– CT) [9] or mid-ventilation (MidV) CT. Tumor motion is then accounted for with an internal target volume (ITV) or planning target volume (PTV).

To better understand the differences between the 3D and 4D approaches, it is important to realize that respiratory motion has two effects on the dose to moving structures. First, respiration induces structures to move in space, receiving dose at different positions and possibly with a changing shape. This represents respiration-induced geometry variations. Second, the dose itself is influenced by moving structures since the density changes over the breathing cycle affect the radiation delivery. This is associated with respiration-induced density changes.

In a full 4D dose accumulation approach (accumulated over the 4D trajectory) the two effects are taken into account, that is the tumor and lung trajectory (i.e., geometry variations) as well as the dose changes due to density variations for all phases. A 3D treatment-planning approach, on the other hand, ignores the density changes while the geometry variations are included via the ITV and/or PTV margin. As the geometry variations are then only indirectly taken into account, the effect of density variations can not be quantified by a straightforward comparison. Note that, to check if the planned dose (3D/4D) is an adequate estimate of the actually delivered dose, setup uncertainties and baseline variations have also to be taken into account when evaluating and accumulating the dose [10].

The aim of this study was to assess the effect of respiratory induced density variations by disentangling the effects of geometry and density variations on the dose...
and consequently evaluating the necessity of a full 4D dose calculation in treatment-planning rather than only using geometry information. To do so, the static 3D planned dose was accumulated over the 4D trajectory. In this way only geometry variations were included while density variations were explicitly excluded, as depicted in Figure 7-1. Comparing the result with the full accumulated 4D dose singles out the effect of density variations on the dose distribution.

2. Methods and materials

2.1. Patient group

Ten patients who received radiotherapy for inoperable non-small-cell lung cancer were selected in this retrospective study, based on a clearly definable primary tumor exhibiting a large peak-to-peak respiration-induced motion (amplitudes ranged from 1.1 to 3.6 cm in cranio-caudal (CC) direction). In addition, a variety of tumor locations and sizes were chosen, while patients with nodal involvement were excluded (Table

![Figure 7-1. Schematic illustration of study setup to determine the influence of geometry and density variations on the delivered dose. (Top) Measuring the combined influence of geometry and density variations within the gross target volume (GTV) or lung structure. (Bottom) Measuring the influence of geometry variations within the GTV or lung structure. The difference between these two measurements represents the influence of the density variations.](image-url)
7-1). The group, representing the top 30% of the motion generally observed in lung cancer patients [11], was selected to find an upper limit of the effect of respiratory motion. There are two treatment groups: Patients treated with conventional radiotherapy (CRT; patient 1-5) and stereotactic body radiotherapy (SBRT; patient 6-10). In each group, the patients are numbered according to increasing tumor motion.

2.2. Four-dimensional CT and mid-ventilation CT

For each patient a 4D CT scan in normal free breathing was acquired using a multislice CT scanner (24-slice Somatom Sensation Open, Siemens) in helical cardiac scanning mode. Patient respiration was registered using a thermocouple inserted into the entry of a regular oxygen mask. The thermocouple respiratory signal was then used for data sorting. By dividing the respiratory cycle into ten equidistant time-percentage bins (0% at maximum-inhalation), ten time-sorted data sets, corresponding to the ten breathing phases, were reconstructed from the sinogram data. Subsequently a single 3D mid-ventilation CT scan (MidV CT) was constructed for treatment-planning. For this purpose, first the tumor motion curve was obtained by rigid registration of a region encompassing the tumor in all ten CT frames to a reference CT frame [12]. From this motion curve the time-percentage in the exhalation part of the respiratory cycle was determined at which the tumor is closest to its time-weighted mean position. At this time-percentage (which does not need to be a multiple of 10%) the MidV CT was reconstructed from the 4D CT data [12].

| Table 7-1 Tumor location (R=right-lung, L=left-lung, U=upper-lobe, L=lower-lobe), peak-to-peak tumor motion amplitude in CC (predominant motion direction), GTV (gross tumor volume) volume, treatment and clinically used margins for all ten patients. |
|---|---|---|---|---|---|
| Patient | Tumor location | Amplitude CC (cm) | Volume (cc) | Treatment | Clinically used margins (cm) |
| | | | | | AP | CC | LR |
| 1 | LU | 1.5 | 10 | CRT | 1.3 | 1.5 | 1.3 |
| 2 | LU | 1.9 | 60 | CRT | 1.3 | 1.7 | 1.2 |
| 3 | LL | 2.1 | 70 | CRT | 1.3 | 1.7 | 1.3 |
| 4 | RL | 2.4 | 10 | CRT | 1.3 | 1.8 | 1.3 |
| 5 | RL | 3.0 | 32 | CRT | 1.3 | 1.9 | 1.3 |
| 6 | RU | 1.1 | 6 | SBRT | 0.8 | 0.9 | 0.9 |
| 7 | RU | 1.4 | 9 | SBRT | 0.9 | 1.0 | 0.8 |
| 8 | RU | 1.7 | 14 | SBRT | 0.9 | 1.1 | 0.8 |
| 9 | RL | 2.0 | 30 | SBRT | 0.5 | 1.0 | 0.5 |
| 10 | RL | 3.6 | 13 | SBRT | 0.7 | 1.3 | 0.8 |
2.3. **Treatment-planning**

The MidV CT was used to delineate the GTV (no GTV-to-CTV margin) and OARs with in-house software, consecutively a treatment plan was created with the Pinnacle treatment-planning system (version 7.6, collapsed cone convolution superposition dose calculation algorithm). Patient-specific GTV-to-PTV margins were determined according to van Herk *et al.* (e.g., [205]) including setup and baseline uncertainties. These margins (Table 7-1) only moderately depend on the patient-specific peak-to-peak tumor amplitudes because the effect of this motion is the same as a random error (and low dose gradients in lung).

The conventional treatment plans for patients 1-5 (24 fractions of 2.75 Gy) consisted of six to seven coplanar beams. They were optimized such that 99% of the PTV received at least 90% of the prescribed dose of 66 Gy. The maximum PTV dose was required to be not more than 107% of the prescribed dose, while fulfilling usual dose limit constraints for the lung, spinal cord, oesophagus and heart. The GTV-to-PTV margins for this patient group ranged from 15 to 19 mm in the CC direction, which is the predominant motion direction.

In the SBRT plans for patients 6-10, also non-coplanar angles were utilized for the 16 to 18 beams. A dose of 54 Gy (3 fractions of 18 Gy) was prescribed to the isodose line encompassing 95% of the PTV. Additionally, 99% of the PTV was required to receive minimally 90% of the prescribed dose. In this case the dose distribution in the PTV was allowed to be less homogenous than in a conventional plan, with a maximum PTV dose of 165% of the prescribed dose. The GTV-to-PTV margin ranged from 9 to 13 mm in CC direction. Differences in margin between CRT and SBRT are mainly due to differences in the image-guided radiotherapy protocols and different dose constraints [13].

2.4. **Deformable registration**

A deformable registration method was applied, registering all ten frames of the 4D CT to a reference scan, thereby accounting for non-rigid changes in the lung due to breathing. The image registration was done using a phase-based optical flow motion estimation procedure [8,14] resulting in a 4D deformation vector field (4D DVF) which defines the motion of each voxel of all ten frames with respect to the reference frame/scan (Chapter 4). The MidV CT scan was chosen as the reference scan.

2.5. **Accumulated dose over respiratory cycle**

The treatment plans designed on the MidV CT were applied to all 10 frames of the 4D CT and the dose distributions were recalculated (the result is referred to as the 4D dose distribution).

To single out the effect of respiration-induced density variations, the accumulated dose over the respiratory cycle was calculated in two different ways. First, the 4D
dose distribution was warped to the MidV position by applying the 4D DVF described above, resulting in a deformed 4D dose, which was then accumulated over the respiratory cycle to yield the accumulated 4D dose. This result includes the influence of both geometry and density variation and is illustrated in the upper panel of Figure 7-2. The accumulation was performed by a time-weighted summation, with all ten phases equally weighted in time with a factor of 0.1 corresponding to the time-sorted nature of the data.

Second, the same procedure was repeated but now the 4D DVF was applied to the MidV dose, which was copied to each phase (i.e., the same dose for all breathing phases). The resulting deformed MidV dose was accumulated, giving the

Figure 7-2. Example of a 4D, deformed 4D, and accumulated 4D dose (upper panel), and a MidV, deformed MidV, and accumulated MidV dose (lower panel). The white line indicates how the GTV moves within the dose, forming a 4D GTV trajectory over the respiratory cycle, while on the contrary the deformed dose moves around a static (MidV) GTV.
accumulated MidV dose (displayed in the lower panel of Figure 7-2). In this way, the geometry variations due to respiration are accounted for, while excluding any influence from the density variations.

In contrast, the planned dose as calculated on the MidV CT does not explicitly include information from neither density nor geometry variations (geometry variations in form of tumor motion are only indirectly taken into account in the PTV margin).

Figure 7-3 summarizes how the planned MidV dose 1, the accumulated MidV dose 2, and the accumulated 4D dose 3 are calculated. Note that the comparison between planned MidV dose 1 and accumulated 4D dose 3 does not explicitly tell you if the used GTV-to-PTV margin is adequate to cover the influence of respiration. To do so, not only the dose distributions corresponding to ten different respiratory phases have to be accumulated but also the dose distributions for different treatment plans.
ent values of setup errors, baseline shifts, etc. Since this is not the aim of this study, only geometry and density variations due to respiratory motion were investigated.

2.6. **Dose evaluation**

To qualitatively investigate the effect of geometry and density variations on the dose, differences in dose per breathing phase and in cumulative dose were evaluated using isodose lines and DVHs. Furthermore, a quantitative analysis was performed for several clinically relevant treatment parameters: Generalized equivalent uniform dose (gEUD) of the GTV, mean lung dose (MLD), and the volume of the lung that gets at least 20 Gy (V20). To calculate the MLD and V20, a contour comprising the volume of both lungs minus the GTV volume was constructed (named Lungs).

3. **Results**

The patients were chosen such that they exhibited a variety of tumor amplitudes, locations and sizes (Table 1). However, since results (like isodoseline displays, DVHs, etc.) are comparable for all patients, they are only shown for one representative patient (patient 4 who exhibited a CC tumor motion of 2.4 cm –tumor was close to the diaphragm–). Summary results in terms of clinically relevant treatment parameters are given for all patients.

3.1. **Dose distributions vs. breathing phase**

Figure 7-4a–c shows isodose lines of the 4D dose in maximum-inhale and maximum-exhale and the MidV dose. The isodose lines hardly differ between breathing phases, and the most pronounced differences occur near the diaphragm. The deformed 4D and the deformed MidV dose (inhale and exhale for both cases) are shown in Figure 7-4d–g. The differences in dose distributions are noticeable between the different breathing phases of the deformed 4D dose (Figure 7-4d,e) or the deformed MidV dose (Figure 7-4f,g). However, the difference between the two deformed dose distributions are small (Figure 7-4d–g), which indicates that geometry variations over the respiratory cycle has a larger effect on the dose than density variations.

In Figure 7-5a,b the DVHs for the tumor (a) and the lungs (b) of the 10 phases of the deformed 4D dose are displayed. Some spread between the DVHs can be observed over the respiratory cycle. This spread ranges systematically for all patients from lower lung doses in inhale to higher lung doses in exhale. This systematic difference can be explained by the fact that in inhale the lung is maximally inflated therefore covering more lower dose regions, while in exhale the opposite effect takes place. No systematic pattern over the respiratory cycle can be found for the tumor DHVs.

In Figure 7-5c the DVHs for the tumor of the deformed MidV dose and of the deformed 4D dose are compared for maximum-inhale and maximum-exhale. The deformed 4D dose is slightly higher than the deformed MidV dose in these phases.
This was seen for all breathing phases, and all patients, demonstrating that the moving tumor density has a very small (but systematic) effect on the dose. In addition for the lung, the density variations have negligible impact on the overall lung dose (data not shown).

3.2. Accumulated dose over respiratory cycle

The tumor DVHs of the accumulated 4D dose and the accumulated MidV dose together with the planned MidV dose are shown in Figure 7-5d. These plots demonstrate that the small differences between deformed MidV dose and deformed 4D dose observed for the tumor in certain breathing phases become even smaller in the accumulated dose over the respiratory cycle. But still the accumulated 4D dose is slightly higher than the accumulated MidV dose. For the lung the two different cumulative doses are virtually identical (data not shown). This is also seen in Figure 7-5e,f where the mean tumor and the mean lung dose determined from the

Figure 7-4. Isodose lines overlaid on CT for patient 4: (a,b) 4D dose – maximum-inhale phase/maximum-exhale phase, (c) MidV dose, (d,e) Deformed 4D dose – maximum-inhale phase/maximum-exhale phase, (f,g) Deformed MidV dose – maximum-inhale phase/maximum-exhale phase.
deformed MidV and from the deformed 4D dose are plotted against the breathing phase. The mean doses determined from the accumulated MidV dose, the accumulated 4D dose and the planned MidV dose are also shown. These findings were very similar for all patients (Figure 7-6). On average over all patients, the difference in mean GTV dose between planning, accumulated MidV and accumulated 4D is less than 1%. For the lung dose, this difference is even less than 0.5%.

Figure 7-7a shows the relative difference in the gEUD of the tumor between the accumulated MidV and the accumulated 4D dose for all ten patients, \( \Delta gEUD = (gEUD_{MidV} - gEUD_{4D}) / gEUD_{4D} \). The gEUD is calculated with \( a = -\infty \) (equivalent to minimum dose) and \( a = 1 \) (equivalent to mean dose) as extremes in the possible gEUD values. For \( a = -10 \) often used for tumors, the gEUD is close to the minimum dose. The observed differences are mostly below 1%, both for the conventionally treated group (patients 1-5) and for the group with stereotactic treatment (patients 6-10). Even the largest relative difference for minimum tumor dose which is calculated for patient 10 who exhibited a tumor motion of 3.6cm CC is not more than 2%. Results of the gEUD of the tumor between planned and accumulated 4D dose are not extensively given (see Section 7-4.5) since the differences depend on the margin used, while setup uncertainties and baseline shifts were not considered in the accumulation.

An equivalent plot of the MLD and the V20, Figure 7-7b, shows even smaller relative differences for all patients, which are well below 0.5% for MLD, and not more than about 1% for V20.

4. Discussion

This study shows that the effect of respiration-induced density variations on the GTV dose accumulated over the respiratory cycle is very small for all patients analyzed, even in the presence of extreme lung tumor motion. This is concluded from the fact that accumulating on the planned MidV dose results in dose distributions very close to those accumulated on the 4D dose (Figure 7-4, Figure 7-5d). For clinically relevant treatment parameters, such as minimum tumor and mean lung dose, this effect can be neglected (Figure 7-7). For other OARs not described in this study, i.e., heart or oesophagus, comparable small effects as for lung are expected since they exhibit smaller respiration-induced motion and deformation and lie in regions of more homogeneous density. Since the influence of the density variations on the (4D) dose distributions is very small, it is expected that incorporating the density variations into the optimization of the treatment plan has very limited impact and is therefore not very useful.

The accuracy of the results in this study depends on the dose calculation algorithm and the deformable registration method. The collapsed cone dose calculation algorithms used in this analysis has proven in multiple studies to be better suited
Figure 7-5. All plots from patient 4 (2.4cm cranio-caudal tumor motion). (a) DVH of the deformed 4D dose in all phases within the GTV. (b) DVH of the deformed 4D dose in all phases of the lung volume minus GTV. The deformed 4D and MidV dose in exhale and inhale (c) and accumulated over the respiratory phases (d). (e) The mean dose to the GTV from the deformed 4D and MidV dose as well as the planned dose over the respiratory cycle. (f) Same as (e) but for lung volume minus GTV.
for inhomogeneous tissues than the pencil beam algorithm, and nearly as good as Monte Carlo calculations (e.g., [15]). The accuracy of the deformable image registration was determined to be of the order of 1 mm (1SD) in all directions [8], thus demonstrating an excellent performance. The results of this study can therefore be considered to not be influenced by an insufficient dose calculation algorithm or registration procedure.

4.1. Dose tracks tumor

The accumulated 4D dose for the tumor was slightly higher than the accumulated MidV dose. This higher dose can be explained by the higher density in tumor than in lung tissue. The accumulated 4D dose (representing the actually received dose in the presence of just breathing and no other uncertainties) was determined within the tumor contour enclosing tumor tissue (Figure 7-1, upper part) in contrast to the tumor contour enclosing (partly) lung tissue in the accumulated MidV dose (Figure 7-1, lower part), resulting in a higher absorbed dose. In other words, the dose, to a some degree, “tracks” the tumor (this is also seen in e.g., [9]).

4.2. Conventional RT vs. SBRT

The small influence of density variations applies to both conventionally treated and SBRT patients. The differences in tumor dose between the accumulated MidV and accumulated 4D dose were slightly more pronounced for the SBRT group (patients 6-10 in Figure 7-7). This can be associated with the more inhomogeneous PTV doses and the smaller GTV-PTV margins in this group which in the region of steeper dose gradients make it more predisposed to a possible effect of density changes on the dose. The effect of density variations on the lung dose was negligible in both groups.

4.3. Patient selection

The patients were selected by reason of large tumor motion since these are the cases for which one expects the largest possible effect of respiration-induced density variations. However, the vast majority of the patients (about 70% [11]) exhibits tumor motions smaller than those in this study. Therefore the very small and in general negligible effect seen in this study can be considered an absolute upper limit for the entirety of all lung cancer patients.

4.4. Recalculation of the data using simplified methods

To investigate how the results behave if the analysis is further simplified, the determination of the cumulative tumor doses was repeated with a local rigid registration [16] of the region encompassing the tumor, justified by the observation that lung tumors in general are rather rigid compared to the surrounding lung. The tumor in each CT
of the 10 breathing phases was matched to its position in the MidV CT, allowing only translations. The cumulative tumor dose was calculated by shifting the MidV and the 4D dose respectively for each phase according to this tumor trajectory, and accumulating over all phases. The resulting cumulative dose distributions were nearly identical to those obtained when using deformable registration (differences < 0.5%).

As an alternative to the MLD of the accumulated dose obtained with deformable registration, the lungs were automatically segmented on all breathing phases, the MLDs within these contours were determined, and then the mean of the MLDs over all breathing phases was calculated, neither giving any significant deviations (< 0.5%).

4.5. Comparison with other literature

The studies of Guckenberger et al. [17] and Rosu et al. [18] compare the 4D dose accumulated over the respiratory cycle to the planned dose. This is, however, not a completely correct comparison because the used PTV accounts for other geometrical uncertainties as well. The comparison will show the influence of the combined effect of respiration-induced geometry and density variations but it does not tell explicitly if the used GTV-to-PTV margin is adequate to cover setup errors and baseline shifts in the presence of breathing motion. On the contrary, focusing on the influence of breathing motion by setting the GTV/ITV-to-PTV margin to zero (i.e., ignoring other uncertainties) [9], will overestimate the influence of breathing [13] since error contributions (as being a probability) are summed quadratically [20]. In addition, dose planning without an uncertainty margin is clinically irrelevant.

The above-mentioned studies used a considerably large PTV (including ITV approach covering the complete tumor motion and thereby overestimating the effect of breathing [19]). As a result the tumor (or GTV) moves within a homoge-
neous dose region and therefore only small differences between planned and accumulated GTV dose due to the geometry [20] and density variations (this chapter) is expected. Using smaller PTVs (as described in Section 7-2.3 and Chapter 3 [12]) the impact of geometry variation increases (see below) while the impact of density variations remains limited. Still performing the comparison of planned MidV to the accumulated 4D dose for the present study results in relative differences of the planned dose versus the accumulated 4D dose between -0.1% and -1.7% for the mean GTV dose, and between +0.6% and -7.9% % for the minimum GTV dose for patients 1-9. For patient 10 with a very large tumor motion (3.6 cm peak-to-peak) the highest difference in minimum GTV dose of +19.5% is seen while the difference in mean GTV dose is only +0.1%. This large dose difference was anticipated as in this case respiratory motion by far exceeded other uncertainties (i.e., planned minimum dose to the PTV equals minimum accumulated dose to the GTV).

Guckenberger et al. [17] reported larger differences in GTV dose between 4D and static dose in the exhale phase (similar findings were reported by Rosu et al. [18]). However, in that study, the dose comparison was done between calculations with tumor tissue in the exhale position and in the inhale position respectively. This represents larger density differences than in our study, which compares tumor tissue in exhale vs. in MidV position. Planning on the MidV CT ensures an appropriate representation of the mean geometry and density of the patient, especially an accurate estimate of the mean position and shape of the tumor and the lungs. When planning on the exhale CT this is not the case. For example, it was seen (Figure 7-5b,f) that the lung dose is nearly always largest in exhale, which introduces a (generally overestimating) bias in the estimate of the lung dose using an exhale CT.
5. **Conclusions**

This study has shown that although density variations due to respiration-induced tumor motion lead to some variations in the dose distribution over the respiratory cycle, the influence on the accumulated dose is very small. A full 4D dose calculation in treatment-planning does therefore not seem to be required. Planning on a MidV CT derived from a 4D CT and taking motion and deformation into account by deforming the MidV dose (or even using rigid registration) is a very good estimate of the overall effect of respiration on the cumulative dose received by the tumor and the lungs.

As a result, using a single (static) MidV CT scan with an appropriate margin (including margins for setup errors, baseline variations and breathing), the influence of geometry and density variations is small and therefore, it implies that this MidV approach is safe to use.
References


Discussion and future directions
In this thesis, a method and workflow was developed to improve the treatment of lung cancer patients based on improved treatment-planning imaging. Firstly, technical aspects of respiration-correlated four-dimensional (4D) CT and PET imaging were addressed and solutions were given to obtain and fuse these 4D images (Chapter 2). Secondly, a simple but effective approach was developed for clinical use of these 4D images (Chapter 3). This approach concerns the selection of a suitable frame from the 4D data set representing the mean geometry of the patient (mid-ventilation scan), thereby reducing systematic errors. Chapter 4 was a short intermezzo discussing a powerful deformable registration technique. The method applied enables local registration (non-rigidly) of two corresponding 3D images (e.g., scans from different respiratory phases) showing anatomical changes. As a result, displacement vectors were derived for every voxel or position in the image (deformation/displacement vector field – DVF). These DVFs can subsequently be used to map scans or corresponding dose distributions (Chapter 5 and 7). Subsequently, an image enhancement procedure was described in Chapter 5 in order to improve poor quality scans of patients with irregular breathing (causing artifacts) or overweight (which results in noisy images). The artifacts and noise in these images hamper the use the delineation of targets and structures. The described method uses the complete 4D scan (instead of a single mid-ventilation frame) and deforms each separate frame to a common state, after which they can be combined. The resulting “mid-position” scan also corrects for the tumor motion hysteresis, thereby removing the corresponding geometrical error.

To validate our newly proposed method with respect to the present standard method (i.e., free-breathing CT scan, not correlated to respiration) and other newly proposed methods reported in the literature a comparison study was performed: Chapter 6 compares our method with free-breathing CT scan (which is not correlated to respiration), with the use of an internal target volume, and with gated treatment. In this study the necessary safety margins for geometrical uncertainties and the corresponding planning target volumes (PTV) were determined for the different approaches. This study showed that PTV-volumes could be reduced considerably by using the mid-ventilation concept. The power and the simplicity of this approach resulted in a fast implementation of this technique into our clinic. Finally, a dose accumulation study (Chapter 7) was performed to verify if the mid-ventilation scan is adequate for dose calculation. This study showed that the influence of density variation on the dose accumulated over the respiratory cycle was small when using the mid-ventilation scan with an appropriate (small) margin to cover respiratory motion, tumor baseline variation and setup errors. Thus, a full 4D planning would not result in significant different dose distributions.

The work described in this thesis results in a higher geometrical accuracy of the preparation and delivery of radiotherapy for lung cancer. This results in smaller
treatment margins facilitating dose escalation and/or reduction of complications. Furthermore, the described methodology is easy to implement in the clinic in advanced radiotherapy centers (in combination with IGRT protocols based on soft-tissue alignment) as well in less utilized radiotherapy centers (in combination with IGRT protocols based on bony anatomy alignment). Note that the methods developed have shown their merits with respect to applicability and safety in clinical practice. However, there are a number of remaining problems and possible improvements, which will be discussed in the next sections.

1. Improvements in CT and PET imaging

Physics research in radiotherapy focuses for a large part on the reduction of geometrical errors. For example, in order to reduce setup uncertainties, portal imaging and cone beam (CB) CT are used to determine the shifts and rotations of the bony anatomy. Respiration-correlated 4D imaging led to significant reductions in respiration-induced image artifacts for patients with cancer in the thoracic region (lung and liver). Current 4D imaging techniques aim to represent the patients’ anatomy and motion in a single (composite) respiratory cycle. However, since scanning involves multiple respiratory cycles, 4D imaging in which data from multiple respiratory cycles are combined (as used in this thesis), intrinsically fails in case of irregular breathing, resulting in "second order" artifacts (i.e., subsequent slices of non-consecutive adjacent cycles in case of CT scanning). Several studies aiming at reduction of the corresponding geometrical uncertainties have been performed.

1.1. Four-dimensional imaging improvements

In Chapter 5 we merged multiple CT frames after transformation of each frame to a common reference state (mid-position). This post-processing step results in a single scan of considerably improved quality compared to the individual frames. Other groups have studied potential improvements in image reconstruction. Ehrhardt et al. [1] describes a two step method: An initial 4D CT is reconstructed based on an external respiratory signal, potentially missing slices at certain table positions and respiratory phases. Subsequently, the (4D) DVF is determined and a new 4D CT scan is reconstructed by interpolating the missing (raw) sinogram data using this DVF.

McClelland et al. [2] describe a method where a high quality breath-hold CT scan is registered to the frames of a free-breathing 4D CT scan of the same patient. The resulting DVF is then used to reconstruct a new 4D CT scan consisting of transformed version of the breath-hold scan. A similar approach was also suggested in Chapter 5. Motion-compensation during reconstruction has also been developed for 4D CBCT imaging techniques. In this case imaging artifacts and noise occur due to a deficiency of projection data for each phase of the respiration cycle. Although 4D CBCT is
not the subject of this thesis, the recent advances in 4D CBCT are noteworthy to mention. Rit et al. [3-5] described an motion-compensated reconstruction method to obtain a single 3D CBCT image at a reference position from all the CB projections, using an a-priori estimate of the respiratory motion in the reconstruction algorithm. They showed that their method may provide good quality CBCT scans within a few seconds after acquisition time with most motion artifacts removed.

1.2. Amplitude-, phase- and time-based sorting

Some authors claim amplitude-sorting results in fewer reconstruction artifacts than phase-based sorting [6-9]. Amplitude based sorting uses the momentary respiration depth and would therefore cope better with irregular breathing. Phase-based sorting,

![Figure 8-1. Example of the output of amplitude and phase/time-based data sorting on the respiration signal of an irregular breathing patient. The top row shows the irregular input signal. The left rows represents the output using phase/time-based sorting in six bins. Irregularities in cycle length mainly influence the sorted output. The right rows represents the output using amplitude-based sorting in six bins. Irregularities in amplitude mainly influence the sorted output.](image-url)
as well as time-based sorting (see Chapter 2 and 3), uses the moment (phase or time-percentage) within the respiratory cycle. Differences between both sorting methods are illustrated in Figure 8-1. Abdelnour et al. [9] state that in case of varying respiration depth (varying amplitude), phase-based (and time-based) binning tends to distribute the slices uniformly over the respiration bins, regardless of the time instant at which the image was taken, where amplitude binning should result in correctly grouped slices. On the other hand, in case of amplitude-based sorting, varying respiration depth results in missing slices when the actual respiration level does not (completely) cover the (pre-defined) amplitude bins, which reduces the image integrity (Figure 8-1, right column, bin 1 and 6). Missing slices are often filled with an interpolated estimate. For both sorting algorithms, strong cycle length difference between cycles can result in in-slice blurring of the structures or slice gaps due to missing image data when the bin-size is too short to reconstruct a slice (Chapter 2 and 3, [10]). Probably, the image registration procedure will be less hampered by the interpolated slices in amplitude-sorted CT scans compared to the incorrect-sorted or distorted slices in phase/time-sorted CT scans. However, a comparison study has not yet been performed.

In case of regular breathing, both amplitude and phase based sorting methods may result in a “proper” 4D CT scan but irregular breathing (in terms of varying cycle length or amplitude) results in multiple CT frames with considerable image artifacts (Figure 8-1). At maximum exhalation, however, both sorting algorithms will result in few artifacts since this phase is the most reproducible and of longer duration than the inhale phase.

While amplitude-sorting might have a potential advantage in image quality compared to phase/time based sorting, a disadvantage is the absence of the amplitude distribution over the respiratory cycle (i.e., the relative time spend in each bin) within the 4D image data. This information is necessary to compute the time-weighted mean for mid-ventilation or mid-position scans, and to dose accumulation. It is intrinsically available in time-sorted 4D CT scans (see Chapter 2 and 3) but requires separate management in amplitude (or phase) sorted scans.

1.3. **Improvements during acquisition**

Despite all kinds of image-processing or reconstruction techniques, heavily distorted images (due to a lack of raw image data) will never become perfect by post-acquisition algorithms: “Garbage in means garbage out”. Therefore, imaging improvements are preferably done at the source, i.e., the scanner. Some suggestions will be given below.

a. **Audio-visual coaching**

Several authors have investigated the use of audio-visual coaching during 4D data acquisition [e.g., 11,12]. Reproducible amplitude and cycle length result in less artifacts in the 4D image reconstruction, as described above. It has been shown,
that either audio or visual coaching alone does not improve the reproducibility of the respiration (amplitude, cycle length), but combination of the two does [11]. Comparing the coached breathing signal to the uncoached free-breathing signal shows a higher reproducibility of cycle length and amplitude in the coached signal [12]. However, also a significant systematic difference is visible in amplitude and cycle length between the two signals. Therefore, to prevent systematic errors, it is necessary to perform audio-visual coaching also during treatment delivery if the planning images were acquired using audio-visual coaching. The use of audio-visual coaching equipment might be inconvenient for clinical implementation. Note that an increased reproducibility during treatment delivery (in terms of amplitude) should reduce the treatment margin, but this reduction is (very) small since the related geometrical errors are random (i.e., resulting in a ~ 0.7σ contribution in the margin recipe, Chapter 6 and [13-15]).

b. Internal respiratory signal
Another improvement can be obtained by using a respiratory signal extracted from internal movements. Most commonly used external respiratory signals for the use in 4D image reconstruction are extracted from thoracic movements or changes in the thoracic circumference (Anzai respi-belt, Varian RPM, Philips air pressure tube). It has been shown that these signals do correlate with internal movements but that the correlation sometimes breaks down [16-18, Section 4-4.2]. Moreover, (variable) phase shifts between these external signals and internal movements are not uncommon [19,20]. These imperfections result in image distortions due to incorrect sorting of the CT data. Therefore, it is clear that a signal extracted from internal motion would be more reliable. Possible approaches are the use of online fluoroscopy (as in CBCT [21]), use of respiration extraction from the sinogram space [22] in conventional CT) or diaphragm muscle activity measure by adapted ECG equipment (a.k.a. Electro Muscle Activity) [23]. In absence of such an internal signal, a signal directly related to internal movements (e.g., absolute air-flow), synchronized to the diaphragm, can also be used.

c. Four-dimensional CT scan reconstruction
Improvement in image quality can also be obtained by adapting the current 4D reconstruction method (used in the Siemens Sensation Open applied in this thesis). This method reconstructs a single slice at a certain table position and respiratory phase using one continuous arc of 180°+fan-angle which is centered around the position in sinogram space of that certain table position and respiratory phase (Figure 8-2, upper part, see Section 3-2.2b). However, this reconstruction arc contains data from different respiratory phases, therefore, the reconstructed images may contain in-slice blurring or spiral-artifacts (Figure 8-3). Since the pitch of the scanner is very low (0.1), multiple detectors acquire the same part of the body in the same respiratory phase but originating from different respiratory cycles and table positions.
No use is currently made of the redundant (overlapping) data.
For short respiratory cycles (with respect to the gantry rotation cycle), slices of subsequent phases will contain the same data [10]. Therefore, image quality can be improved using the redundant CT data collected by the multiple detectors. Multiple small sub-arcs corresponding to the same breathing phase but different gantry angles can be selected in the sinogram space. Combining these “sub-arcs” can result in improved reconstructed images.

**d. Respiration-CT scanner feedback**

The CT image quality can also potentially be improved by applying a respiratory scanner feedback system [24,25]. Current CT scanners do not have any interaction with the patients’ respiration. In a respiratory scanner feedback system, the speed of the scanner table will be reduced or increased when the cycle length changes (pitch = respiration cycle-length divided by tube rotation cycle-length, see Chapter 3 or [10]). The scanner might even stop in case of irregular breathing and resume when the breathing becomes regular again.

**e. Multi-slice CT scanners**

A final improvement concerns the application of large detector array multi-slice CT scanners. Most CT vendors recently presented a 256- (or more) slice scanners able to scan 13 cm or more in a single gantry rotation. Using these scanners in cine mode (fixed table bed position but continuously acquiring CT data), a 4D scan of the entire thorax can be acquired within a few breathing cycles (depending on the detector size up to three bed-positions are necessary to cover the entire lung region) [26]. It is expected that the amount of imaging artifacts due to irregular breathing is considerably reduced or even absent with such a scanner.

Figure 8-2. Schematic view of a possible improvement of 4D reconstruction. (upper part) The current method reconstructs a single slice at a certain table position and respiratory phase using one continuous arc of 180°+fan-angle which is centered around the position in sinogram space of that certain table position and respiratory phase. No use is made of the redundant (overlapping) data. (lower part) For short respiratory cycles (with respect to the gantry rotation cycle), slices of subsequent phases will contain the same data. Therefore, image quality can be improved using the redundant CT data collected by the multiple detectors. Multiple small sub-arcs corresponding to the same breathing phase but different gantry angles can be selected in the sinogram space. Combining these “sub-arcs” can result in improved reconstructed images.

Figure 8-3. Example of images containing in-slice blurring or spiral artifacts, due to motion of the object during scanning. We expect that the improved method of Figure 8-2 may result in reduced artifacts since the reconstruction arcs can contain data from different respiratory cycles.
1.4. Improvements in PET imaging

Positron emission tomography (PET) has become a valuable tool for staging of cancer, predicting [27-29] and evaluating [30,31] therapy response in lung cancer. The most commonly used PET tracer is $^{18}$FDG, which reflects the glucose uptake of the tumor, that is correlated to metabolism. Unfortunately, glucose uptake (defined by the standardized uptake value –SUV–) does not correspond to the tumor cell density due to many confounding factors [32] as well as the low image resolution of PET, limiting quantitative use (and detection of early distant metastasis). Even though, Borst et al. [27] and Van Baardwijk et al. [33] showed that a high maximum SUV was highly correlated to poor radiotherapy response. This information might help to determine the most appropriate treatment strategy, improving treatment efficiency.

As a consequence, the increasing importance of (quantitative) PET images for therapeutic purposes also requires improvements in image quality. One general improvement has been the introduction of the time-of-flight image reconstruction technique, considerably improving the signal-to-noise ratio of PET images [34,35]. However, the quantitative accuracy of 3D PET in the thoracic region is still affected by image blurring (reducing the measured SUV) and respiration-induced errors in the attenuation correction (artifact related hotspots). Therefore, the determined PET threshold values and tumor volumes in the above mentioned treatment-response study [27] may have been influenced by these effects. Moreover, for individual patients, these artifacts influence the measured SUV, which for instance could lead to inappropriately decide for a less-radical treatment scheme and larger treatment volume.

It is evident that it is necessary to resolve the respiration artifacts in PET scans for treatment-planning (i.e., to obtain a correct tumor position and shape) and for correct diagnosis (i.e., to obtain a correct SUV). The development of 4D PET imaging techniques to resolve the respiration artifacts has been described in Chapter 2. However, since the photon attenuation of the body depends on the varying geometry during respiration, the attenuation correction must be respiration phase depended as well. Therefore, 4D respiratory phase-by-phase attenuation correction has been investigated and developed by several groups [36-39], all showing significant improvements in image integrity (reduction of artifacts) and SUV accuracy. To enable 4D attenuation correction, both PET and CT scans need to be acquired respiration-correlated. This imaging combination can be best performed using a hybrid PET-CT scanner (although this is not explicitly necessary), providing great advantages in the time and work-flow efficiency. Additional image registration has to be performed if the two scans have been acquired on different scanners (Chapter 2). However, even when using combined scanners, additional registration of the two image modalities is sometimes necessary since both scans are acquired sequentially (with a couple of minutes in between) and patients might move between the two scans [40]. Moreover,
the phase of the external respiration signal used for sorting may have changed in relation to the tumor motion (Chapter 2 and 3).

Image registration of PET and CT images in space is not sufficient for correct fusion of the two modalities (as discussed in Chapter 2). Depending on the used respiratory signal acquisition equipment and sorting method for the 4D CT or PET scan a phase shift is possible between two corresponding frames. Therefore, registration in phase (the 4th dimension) is also necessary, which can be performed using tumor motion information (Chapter 2). However, the respiration cycle is divided into a limited number of bins (each resulting in a single frame of the 4D scan), which may introduces a registration error up to half the smallest bin width. This phase error will result in a small geometrical error between the tumor or structure in the CT and PET scan. Using the DVF, derived from the 4D scan by deformable registration (Chapter 4), an interpolated scan can be reconstructed from the two adjacent frames (or possibly in retrospective reconstruction, see Section 8-1.1), resolving the present phase shift, resulting in a more “perfect match”.

In order to obtain a 3D PET with reasonable image quality, relative long acquisition times are now necessary (~ 4 min per bed position of typically 16 cm). Obtaining the same quality for each frame of a 4D PET scan is impractical since acquisition times will become too long for clinical practice (patient discomfort and increased patient position and geometry variation). For this reason, we limited 4D acquisition to one bed position. By applying motion-compensating strategies using deformable registration (described in Chapter 5 for CT) to PET, the image quality and the signal-to-noise ratio of PET scans can be improved considerably. Using our approach would result in a 3D MidP PET-CT scan that is convenient for clinical use (Figure 8-4). Furthermore, it is expected that reduced noise and image blurring will also increase the delineation accuracy of malignant structures [41,42].

2. Motion estimation and deformable registration

Radiotherapy applies images to plan and guide the delivery of treatment as well as for assessing treatment response. Using multiple imaging modalities is helpful to define tumor and healthy tissues accurately but most information from these
different modalities can be obtained when these images are completely co-registered (e.g., bone and soft tissues) using rigid and/or deformable registration algorithms. Improvements and limitations of these registration algorithms are discussed in this section.

2.1. Improving tumor motion determination by redundant rigid registration

The automated tumor motion determination method as described in Chapter 2 and 3 sometimes failed due to image distortions. A solution to the problem was included in the software of the final clinical implementation at the NKI and is described in this section.

To make the tumor motion determination more robust, the locally-rigid registration process was extended to a redundant registration approach of the tumor [43]. In this improved method, a rough mask is drawn manually in the first frame of the 4D CT encompassing the visible tumor, defining the ROI. This ROI is subsequently registered to the other frames of the 4D CT, resulting in a set of 9 (+1) translations representing together a complete 3D tumor motion curve. Subsequently, the manual drawn mask is shifted automatically according to the translation between the first and the second frame. In the second frame this shifted mask defines a new ROI, which will be registered to the other frames of the 4D CT scan. This process is repeated for all other frames, yielding a total of 90 registrations (10 motion curves). Averaging these redundant registrations (and removing outliers) diminishes the influence of outliers and results in a very accurate, robust and reproducible motion curve [43] which is used for amplitude determination and for determination of the mid-ventilation percentage (Figure 8-6). Due to the combination of the redundant registrations, the method does not depend very critically on the exact form of the manually delineated mask and is also less sensitive for image artifacts.

2.2. Deformable registration algorithms

Rigid registration is generally used for (large) global transformations (e.g., aligning vertebra), or for measuring displacements of small regions. To provide a detailed description of the motion of the entire anatomy deformable registration is required. Several deformable registration methods have been developed, each of them having their own strength and weakness. In general, the approaches can be divided into four different types.

Surface based algorithms perform (automated) segmentation and contouring of the organs and tumor in the two scans to be registered [44-46]. Subsequently, vectors (perpendicular to the surface) describing the transformation of the contours between the two scans are computed. Finally, these “contour”-vectors are (linearly) interpolated into a regular grid, allowing transformation of the image data set. Such contour based techniques are well suited for matching images of different modalities.
Optimization based algorithms use a control point grid in combination with a deformation function e.g., thin-plate splines or b-splines [2,47]. These functions regularize the control point grid preventing ill-conditioning and instability of solutions and local optima issues. The optimization algorithm minimizes a cost-function, describing the similarity between the image intensities of two scans (such as mutual information [48,49] or correlation ratio [50]).

Physics based algorithms compute motion vectors based on physical constraints like tissue elasticity (biomechanical models) [51,52]. It can be said that the mathematical part of these algorithms is often very similar to the one used in optimization and optical-flow algorithms.

Finally, optical flow algorithms use the image intensity variations between the two scans (assuming conservation of image intensity or density, e.g., Chapter 4 and [53,54]), resulting in a linear relation between displacement of image structures and time (between the two scans). Note that the optical flow based algorithms are not suitable for (direct) matching of multi modality images due to the intensity conservation property. However, target and organs don’t have to be (manually) delineated and data of elastic properties of the different tissues in the image are not required.

2.3. **Pitfalls and problems of deformable registration**

a. **Different modalities**

Rigid image registration within the same modality as well as between different modalities is well established and results in highly robust and reproducible image alignments, as long as the considered structures are indeed rigid. Although deformable registration methods for same modality applications were shown to be robust and accurate, multi-modality registration is more difficult since corresponding features do not show up similarly in different modalities. Due to the (small) deformation, the similarity measure needs to be sensitive to change in small image volumes. As a consequence, multi-modal similarity measures (e.g., mutual information or correlation-ratio) that work well for global rigid registration (using the complete scan) often perform poorly for local deformable registrations [55]. It has been demonstrated that contour-based deformable registration [45,48] is able to register images from different modalities. Other single-modality deformable registration algorithms could be adapted to enable multi-modality registration by adding a modality-dependent pre-processing step before registration. This step should enhance anatomical structures that can be found in both images, thereby reducing the difference between the modalities. For example, on registration of a CT and MRI scan of the lung, vessels could be extracted in both modalities by edge and/or ridge detectors (e.g., watershed or skeleton filters [56]). This results in a binary image representing the vessels. Subsequently, these converted images serve as
input for the existing registration algorithm. The clinical feasibility of these methods, however, needs further evaluation, especially in case of MRI, since there can be a shift in geometry due to inhomogeneity of the magnetic field, aliasing artifacts and/or susceptibility artifacts due to tissue-air transitions [57].

b. Structural changes

Successful (deformable/local) registration of corresponding tissues is only possible if there are no structural changes from one image to another (a structure must exist in both corresponding images). In case of lung cancer radiotherapy, big structural changes due to disappearance of the tumor, or changes in the presence of atelectasis may occur, however, in such cases deformable registration algorithms are likely to fail. One solution to cope with changing structures would be to replace the deformation vectors in the regions exhibiting structural changes by new vectors interpolated from the ones nearby. This, however, requires a manual processing step, resulting in local deformation fields depending on the neighborhood. The procedure of applying a similar structure enhancement operation before registration described above (Section 8-2.3a) may be suitable as an automated approach (assuming no “extreme” structural changes). The pre-processing step should extract corresponding ridge structures in both images (e.g., vessels). Since the ridge detector pre-processing step will not convert “homogeneous” regions such as the tumor or atelectasis into ridge structures (depending on the image pre-processing kernel size), these regions will not be represented in both processed images. Registration of the processed images will therefore be less affected by the structural changes. Subsequently, the resulting DVF can be applied to the original images.

Figure 8-5. An example of a tumor in a 4D CT scan, containing (a) a frame without imaging distortions and (b) a frame where the tumor is split in two parts due to an imaging distortion.
c. **Artifacts**

A potential problem in deformable image registration algorithms is the possibility of “accurately” registering artifacts. For radiotherapy purposes, however, the goal of deformable registration is to create a patient-specific respiratory motion model or tissue-to-tissue correspondence model (e.g., for dose accumulation), rather than a “mapping tool” for similar pixel intensities. Although in exceptional cases, registration of artifacts is desired (e.g., detection of artifacts by discontinuities in the motion field), in general, a physically possible motion model is required.

As example, a tumor represented into two parts due to irregular breathing is considered (Figure 8-5). If this frame is (deformable) registered to an undistorted reference frame, a physically realistic motion would be found. To prevent registration of artifacts, a larger blurring/smoothing kernel can be chosen to regularize the DVF. However, as lung tissue and thoracic wall have different motion directions this will also result in a mixture of motion in the vicinity of the thoracic wall. The use of an adaptive filter kernel, as described in Chapter 4, or segmentation of the regions with different motion directions and processing each region separately, may improve the situation.

3. **Selecting a representative planning CT scan**

3.1. **Improvement of the automated selection**

In Chapter 3, the MidV time-percentage was determined based on either the CC tumor motion (dominant motion direction) or using the diaphragm motion as alternative surrogate. However, if the tumor moves in a different direction, the calculated MidV time-percentage based on the CC tumor motion direction, does not necessarily represent the time-percentage with the tumor closest to the mean tumor position (Figure 8-6b; [43]). In addition, the correlation between tumor motion

![Figure 8-6. Three examples of tumor motion curves and computed mid-ventilation time-percentages in exhale and inhale using the diaphragm (□), CC-motion only (○) and minimum systematic error (Δ) method. Anterior-posterior (x) and cranio-caudal (y) axes are in cm. Examples extracted from a study by Nijkamp et al. [43].](image-url)
and diaphragm motion is sometimes weak (Chapter 3 and [43]), which reduces the applicability of the diaphragm method (Figure 8-6c). Nijkamp et al. [43] showed the feasibility of MidV time-percentage determination in three dimensions based on accurately determined tumor motion curves (Section 8-2.1) leading to reduction of the geometrical errors related to errors in the MidV time-percentage. The reduction in the distance (geometrical error) between the time-weighted average tumor position and MidV tumor position using the new technique compared to the “CC tumor motion only” or “diaphragm motion” technique was 8% and 28%, respectively. Clinical implementation of this improved MidV scan selection is discussed in Section 8-4.

3.2. Simplifying the mid-ventilation approach

The determination of the MidV time-percentage is performed using in-house developed tumor registration and analysis tools as described in this thesis. However, such tools are not yet commercially available. Therefore, we investigated the possibility to simplify the MidV CT selection, i.e., by selecting the MidV CT scan by a human observer.

A small group of lung cancer patients (n=10) with considerable tumor motion (21±7 mm in CC direction) was selected. Three untrained observers were asked to manually select the MidV CT scan (i.e., the frame from the 4D CT scan in which the tumor is closest to its time-weighted mean position) during exhalation (clinical situation) and inhalation. Subsequently, tumor motion for each patient was computed as described in Section 8-2.1 and the true (“real”) time-weighted mean tumor position was determined. Finally, the distance between the tumor position in the manual selected MidV CT and the true time-weighted mean position was computed for all patients and the three observers.

The average distance between the automated 3D determined MidV tumor position and the true time-weighted mean tumor position for these 10 patients was 1.1±0.7 mm, which is in accordance with Nijkamp et al. [43]. This residual error is due to hysteresis in the tumor motion curve. For the observer group, the average difference over the patients in manually determined and automated 3D determined MidV time-percentage was 12%±4% for exhale, corresponding to 5.0±2.5 mm (this includes the geometrical error due to hysteresis). For inhalation, these values were -0.6%±6% and 4.4±1.7 mm, respectively. This implies that it is difficult to visually determine the time-weighted MidV CT frame as the observers tend to define the MidV frame more towards maximum exhalation. Note that the error due to discretization (into 10 frames) can be estimated by the standard deviation of a uniform distribution, which is $10/\sqrt{12} \approx 3\%$, which is smaller than the observed error.

Due to the asymmetry in the respiratory cycle (i.e., duration of exhalation > duration of inhalation) more frames can be selected in exhale (~7 frames) compared to inhalation (~3 frames). This causes the difference in time-percentage variation between
exhale and inhale (12 % vs. -0.6%). Moreover, tumor displacement per frame is less in exhale than inhale, making exhale frames less distinguishable. Consequently, the corresponding geometrical error is approximately equal for exhale and inhale.

Because human observers tend to overcompensate for the longer time spend in exhale, as a first alternative, it was investigated if manual selection of the frame closest to the geometrical mean in CC direction only (half-way peak-to-peak) would be sufficient to be used as MidV scan, as also discussed by Bosman et al. [58]. In this approach, the selection would not be affected by the attempt to estimate the MidV time-weighted. The difference in MidV time-percentage between manual selection and actual value was -3%±3% for exhalation, corresponding to a distance to 2.4±0.9 mm, which is a significantly reduced geometrical error compared to the time-weighted manual selection. The geometrical error for inhale is slightly larger. As a second alternative, the use of a fixed time-percentage or fixed amplitude height (21% - corresponding to the minimum geometrical error over the used patients) was investigated. This resulted in a geometrical error of 2.5±1.7 mm. However, due to potential phase shifts between external respiration signal and internal motion (as mentioned in Chapter 2 and 3, and [16,20,59,60]), a patient depended phase shift of the CT frames would occur (thus frame 0% will not be maximum exhale for all patients). Using a fixed MidV time-percentage for all patients without correcting for this phase shift will causes an increase in the geometrical error with respect to the true mean tumor position (3.5±2.4 mm).

It should be noted that the above described "poor man's" selection of an appropriate scan is always better than using a conventional free-breathing CT scan for treatment-planning, resulting in an average error in tumor position of 6.7±2.4 mm for the 10 patients described in this paragraph. A more advanced automated time-weighted MidV approach as discussed in this thesis can reduce the systematic geometrical error induced by respiration with an extra 1 mm. The mid-position CT approach described in Chapter 5 would completely eliminate the systematic geometrical error related to respiratory motion, while at the same time improving image quality.

Note that tumor motion was considerable in this limited study. Therefore, smaller geometrical errors may be expected for the average population of lung cancer patients. Moreover, training for manual determination will possibly help to increase accuracy.

4. Clinical four-dimensional imaging and mid-ventilation protocol

In our department, the MidV approach was clinically implemented in 2005 for lung patients with a substantial tumor motion as determined by fluoroscopy. However, in general the tumor motion in fluoroscopy is overestimated [61]. From 2006 the MidV approach is therefore applied to all lung cancer patients (about 200 patients/year) selected for radiotherapy with curative intent, and fluoroscopy is omitted.
Figure 8-7: An overview of the clinical workflow to obtain 4D scans and its derivatives (Mid-ventilation -MidV- and mid-position -MidP-). DVF refers to the deformation vector field. DVFmean refers to the DVF recomputed to the time-weighted average position in the respiratory cycle.

**Current clinical workflow (4D scanning)**

1. **At the CT scanner**
   - Load 4D scan from server (PACS)
2. **Pre-acquisition of respiration signal started**
3. **Patient is setup for scanning and intravenous contrast drip system is prepared**
4. **Acquisition of respiration signal restarted**
   - Set CT gantry rotation to 0.5 s pitch = 0.10
   - Set CT gantry rotation to 1.0 s pitch = 0.15
5. **Administer contrast**
6. **Start scan delay 15 sec**
   - Acquire deep inspiration breath hold (BH) scan
   - Acquire 4D scan
7. **Reconstruct 4D scan**
8. **Send 4D scan to server (PACS)**
9. **Reconstruct BH scan**
10. **Send BH scan to server (PACS)**

**Backup procedure**

1. **Calculate and reconstruct MidP CT scan**
2. **Load BH scan from server (PACS)**
3. **Perform rigid registration of tumor volume between MidP and BH scans**
4. **Send registered BH CT scan and MidP-BH scan to treatment planning system**

**Current clinical workflow (Mid-Ventilation CT)**

1. **After scanning**
2. **Load 4D scan from server (PACS)**
3. **Determine tumor motion in 3D by automated rigid registration method**
4. **Compute mid-ventilation time-percentage during exhale (minimum syst. error)**
5. **Recompute DVF to DVFmean**
6. **Send MidV/P-BH scan to treatment planning system**
   - The transformed BH scan is used for delineation of the tumor. The MidP scan is still used for dose calculation and delineation of the nodes.

**New/future clinical workflow (Mid-Position CT)**

1. **After scanning**
2. **Load 4D scan from server (PACS)**
3. **Determine 4D-DVF by automated deformable registration method**
4. **Recompute DVF to DVFmean**
5. **Send registered BH scan and MidP-BH scan to treatment planning system**
6. **Visual verify MidP scan**
   - False
    - **Backup procedure**
    - Calculate and reconstruct MidP CT scan
   - True
    - **Send MidP CT scan to treatment planning system**

**Current clinical workflow (Mid-Ventilation CT)**

1. **After scanning**
2. **Load 4D scan from server (PACS)**
3. **Determine tumor motion in 3D by automated rigid registration method**
4. **Compute mid-ventilation time-percentage during exhale (minimum syst. error)**
5. **Recompute DVF to DVFmean**
6. **Send MidV/P-BH scan to treatment planning system**
   - The transformed BH scan is used for delineation of the tumor. The MidP scan is still used for dose calculation and delineation of the nodes.
4.1. **Description of the clinical protocol**

The clinical protocol as described in Chapter 3 (Figure 3-1) has been updated and completed based on new results. In particular, contrast administration, breath-hold scanning has been added, and MidV determination based on diaphragm motion has been replaced by using the tumor motion. Mid-position scan reconstruction will be added soon.

The current clinical protocol to acquire 4D-MidV CT scans as well as the future workflow for the use of MidP images are shown in Figure 8-7. Currently, all lung cancer patients receive contrast during 4D CT scanning if the mediastinal nodes are involved. The preparations for contrast agent application are done during patient setup. In order to ensure sufficient concentration in the mediastinum region contrast inflow starts 15 seconds before scanning. A 4D scan is performed using one of the two scan-protocols (adapting gantry and table speed) depending on the respiration frequency of the patient (see Chapter 3), taking approximately 70 seconds. After acquisition of the 4D scan, an additional deep-inspiration breath-hold (BH) scan is made.

After scan acquisition, the tumor motion is determined from the 4D CT scan as described in Section 8-2.1. The MidV time-percentage in exhale is computed (Section 8-2.1, Chapter 3). A new CT scan at the mid-ventilation time-percentage is reconstructed at the CT scanner console, which is subsequently sent to the treatment-planning system. However, if the image quality of this MidV CT scan is insufficient to delineate the tumor (due to extensive breathing irregularities), the BH CT scan is used as backup procedure. In this case, delineation of structures such as lung, still has to be done on the MidV scan since deformation of these structures in the breath-hold scan is too large with respect to the “average state”. A soft-tissue (rigid) registration is then performed to match the tumor region in the BH and the MidV scans. The resulting translation of the tumor will then be applied to shift the contours of the tumor to the position in the MidV CT scan. The MidV CT scan is used for dose calculations, however, since small geometrical errors have little influence upon the calculated dose [62, and Chapter 6].

The backup procedure using BH scans generates a relatively high workload. More important, the MidV CT scans can contain errors due to hysteresis, distortions and image noise (Chapter 5). Therefore, we are currently implementing the MidP method (Chapter 5) into the clinic in order to reduce the incidence of such a backup procedure and improve the quality of the treatment-planning scan. After 4D CT acquisition a deformation vector field (DVF) to transform of each frame to the reference frame (generally exhale) is computed from the 4D CT scan. The DVF is recomputed giving the transformation to the time-weighted average position (as new reference) and subsequently, the MidP scan is computed. After verification of the image integrity, this higher quality planning scan is sent to the treatment-planning system. To perform the image integrity check, an additional motion-compensated (“MidP”) scan will be
reconstructed at the roughly estimated mid-ventilation position (a frame closest to the MidV time-percentage, for example frame 20%) instead of the time-weighted mean position. This MidV-"MidP"-scan can then be compared directly to the MidV (frame 20% as example) frame of the 4D CT.

Finally, in the TPS, the expansion of the CTV to the PTV needs to be calculated. A simple spreadsheet in Microsoft Excel is created to compute the necessary anisotropic CTV-to-PTV margin, which includes contributions of the patient’s individual tumor motion, patient group depended baseline variation, institute dependent setup errors, and currently also (patient group and institute dependent) delineation errors (Chapter 4).

Four-dimensional scanning including contrast is performed in clinical thirty minutes time-slots. Scan reconstruction and MidV or MidP analysis can be performed afterwards in the background, keeping the CT scanner available for next patients.

5. **Clinical issues of the mid-ventilation approach**

5.1. **Mid-ventilation and stereotactic body radiotherapy**

The mid-ventilation approach was primarily developed for use in conventional fractionated radiation schemes with offline error correction protocols. For these treatments with many fractions (> 30), reducing systematic errors is essential. However, patients with stage I and II disease in the periphery and no nodal involvement currently receive hypo-fractionated radiation schemes (Stereotactic Body RT - SBRT) in 3 to 5 fractions. Online verification and correction procedures are used for these patients based on a tumor (soft-tissue) registration between planning CT and a 4D CBCT scan. However, a distorted anatomy and structures cannot be corrected. This implies that accurate MidV scans continue to be essential for treatment-planning and arbitrary phases of a 4D CT scan or even a free-breathing 3D CT scan cannot be used for this purpose. Moreover, geometrical errors cannot be corrected simultaneously if multiple targets or lymph nodes are involved and the planning scan represents an “extreme” patient geometry (e.g., deep inspiration breath-hold).

The margin recipe (from CTV to PTV) accounting for systematic and random errors [15], is developed for conventional fractionation schemes which have a large number of fractions. Therefore this recipe might not valid for hypo-fractionation. However, when using 4D CBCT to correct online for systematic and random day-to-day variations, relatively small errors from respiratory motion remain. Since the remaining errors are small in relation to the size of the penumbra [63,63], the margin recipe can still be used for hypo-fractionated treatments, as long as the uncertainty data are derived from the same low number of fractions.
5.2. **Mid-ventilation and dose constraints**

Patients with large tumors or with their tumor close to critical structures often reach their maximum dose constraints for the organs-at-risk (OAR). In these cases, online corrections on the tumor might result in overdosage of the OAR when the OAR shifts towards the high-dose region. To prevent this, limits can be set on the maximum allowed translations in the correction procedure [64]. These limits can be found empirically by shifting the optimized beam geometry towards the OAR and computing the dose until the constraints are exceeded. It is clear that a representative scan (i.e., mid-ventilation) is needed to determine these limits, defining correct “average” distances between organs and target during respiration.

For correct use of dose criteria, the dose to the OAR needs to be determined accurately. For example, the current criteria of the mean lung dose (MLD) and V20 (the lung volume that receives more than 20 Gy) have been determined using “old” free-breathing CT data. It is expected that these criteria can still be used for MidV or MidP CT scans, since the respiratory-induced organ position errors in free-breathing scans will average out when combining results of large number of patients. Although the criteria are valid for the patient group, for the individual patient, the image artifacts in conventional free-breathing CT scans might result in incorrect MLD or V20 values (and probably also similar to other critical organs). These might cause wrong decisions in treatment options (such as the dose level given). Note that MLD and V20 should never be derived from maximum intensity projection (MIP) CT scans (in combination with ITV; see Section 1-8 and Chapter 6), since MIP reconstructions result in a reduced lung volume and an increased tumor volume, making them tumor motion amplitude depended and incompatible with criteria in the literature.

5.3. **Mid-ventilation and lymph nodes**

Unfortunately, frequently lymph nodes are involved and should be included in the treatment field resulting in a large PTV and a high lung dose. In these cases it is important to use a representative “average” geometry (mid-ventilation) of the tumor and lymph nodes for planning. Currently, a fixed margin of 12 mm in all directions is used for the lymph nodes at the NKI-AVL. A (small) reduction of the PTV can be achieved by using locally determined motion for lymph nodes and tumor separately to determine the uncertainty margins (lymph nodes and primary tumor can move differently [65,66]). This local motion information can be obtained by a deformable registration algorithm as described in Chapter 4. In addition, online correction of the setup errors can further reduce the PTV. Ultimately, changes of the configuration of nodes and tumor will have to be corrected using an adaptive radiotherapy approach (see next section).
5.4. **Adaptive radiotherapy**

The 4D CT scan and the derived mid-ventilation planning scan is a snapshot at a certain moment of a variable patient, introducing a systematic error. On- and offline setup correction protocols using (4D) CBCT scans are developed to correct for these systematic errors. However, one cannot correct for local anatomical changes due to treatment (e.g., tumor shrinkage or growth) and differential motion between multiple targets (e.g., tumor and lymph nodes). To deal with these errors, adaptive radiotherapy strategies have been developed [67,68]. Adaptive radiotherapy is a feed-back approach used during the course of radiotherapy, detecting change in anatomy (e.g., as a result of treatment response), and subsequently adapting the plan before delivering the treatment fraction. To do this for radiotherapy of lung cancer, 4D CBCTs instead of conventional 3D CBCTs could be acquired daily in the first week of treatment and weekly thereafter. From each CBCT, the mid-ventilation frame is selected and deformable registered to the MidV planning scan, yielding a fraction specific DVF. The average of the DVF series can be computed and applied to the original MidV CT scan. Finally, the original treatment plan can be modified to correct for the geometrical changes, resulting in an up-to-date treatment plan tailored to the temporally changed patient anatomy, i.e., a representative “average of the average” treatment plan.

6. **Future research and development**

6.1. **Mid-ventilation and PET for proton therapy**

Several studies (e.g., [69]) have reported possible benefits of proton therapy for lung cancer patients. Using proton therapy the integral dose to normal tissues and the dose to critical structures can be reduced considerably compared to photon based radiotherapy, whilst preserving target dose homogeneity. However, protons are sensitive to variations in tissue density making reproducible position and shape of the structures within the treatment beam of extreme importance. Recent literature [70,71] reports the necessity of a full 4D dose accumulation approach (such as described in Chapter 6) to handle respiratory density variation in proton therapy. On the other hand, Engelsman et al. [71] conclude that 3D mid-ventilation is an acceptable alternative to the complete 4D approach to estimate and optimize the actual dose distribution (also) for proton treatment although a full 4D dose optimization would gain in tumor coverage and sparing of healthy tissue. Recent studies have demonstrated the feasibility of dose and range verification for proton therapy using PET-CT [72-74]. During proton radiotherapy, several positron emitters (e.g., $^{11}$C and $^{15}$O) are produced. PET scanners can detect the produced annihilation photons of the positrons in a patient either during (online) or shortly
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After (offline) treatment. Conversion from PET-activity to dose is not straightforward. However, planned and delivered doses can be compared by computing the distribution of positron emitters in the irradiated body from the treatment plan using Monte-Carlo simulations [75] to the actual measured activity.

Respiration affects this approach twice: Firstly during treatment, blurring the “actual” deposited dose; and secondly during post-treatment verification, resulting in a blur of the “measured” distributed dose. Remedies for the first influence are gated, tumor-tracking or 4D optimized treatments, but not considered in this thesis. To resolve the second issue, 4D imaging techniques in combination with deformable registration are necessary. As a result, the 4D PET scan is not blurred due to respiration but the signal-to-noise ratio of the separate frames is possibly too low to be used for quantification of the dose. Using a mid-position approach (as already described in Section 8-1.4) after deformable registering the 4D PET scan to the time-weighted mean position a scan can be obtained that is suitable for quantitative use, i.e., with a high signal-to-noise ratio and without the image blur.

6.2. **Mid-ventilation and tumors in the upper-abdominal region**

Four-dimensional imaging and gated delivery described in this thesis can also be applied to reduce the effects of respiratory motion of tumors in the upper-abdominal region (liver, kidneys, stomach, pancreas) [59]. However, due to small density differences and high photon attenuation in the abdomen, image contrast is poor compared to lung images. Standard 4D CT images are therefore often not suitable to delineate the tumor since dose per frame is generally lower than a diagnostic breath-hold scan (Chapter 2). Applying the image enhancement technique to 4D liver images as described in Chapter 5 gave a considerably improved signal-to-noise ratio (Figure 8-8). Mid-ventilation can also be applied to abdominal tumors. In doing so, PTV volume decreases due to reduction of the systematic respiratory error in the treatment-planning images. The systematic and day-to-day random errors (setup, baseline) can be reduced even more by an online-correction protocol using CB.
imaging. Accurate registration of the abdominal tumor in CBCT to the (planning) CT is therefore important [76]. However, motion-compensated imaging techniques for CBCT (Chapter 5, Section 8-1.1 and [4]) are necessary to enable tumor registration in the abdomen.

Finally, due to the steeper penumbra in liver compared to lung [77], gated treatment or tumor-tracking techniques may lead to somewhat larger reduction in PTV (if performed “perfectly”), especially in the presence of irregular breathing [78].

6.3. Recovering 3D PET and SPECT scans from motion-blur

Although respiration-correlated 4D imaging techniques could be applied to resolve the respiratory motion-blur in 3D PET and SPECT scans, these techniques are not always available. In addition, acquisition of such scans for the thorax region have to be performed after the whole-body (3D conventional) scan. Therefore, it would be helpful if motion-blur could be removed without using 4D acquisition techniques. A few preliminary experiments (for 3D PET) in this direction are described below.

Consider the blurred 3D image as a latent non-blurred image that is convolved with a location-dependent point spread function (smoothing kernel) determined by the respiratory motion. The latent image could, in principle, be recovered using a deconvolution process if the smoothing kernel is known, assuming regular respiration during PET scanning. Since respiratory motion data are not available in the blurred 3D image, the DVF derived from a 4D CT scan could be used as an a-priori estimate. A locally defined point spread function (smoothing kernel) can be computed from this DVF. As deconvolution algorithm, iterative Richardson-Lucy algorithm [79] can be used since this method is robust to statistical image noise (PET and SPECT images are noisy) and has already been successfully applied to recover PET images from spatial burring due to positron emission range effect [80]. The algorithm is generally applied to use a fixed smoothing kernel for the entire image but could be adapted to use the location depended smoothing kernel. However, it is expected that this

![Blurred 3D PET](image1.png) ![Deconvolved 3D PET](image2.png) ![Single frame of 4D PET](image3.png)

Figure 8-9. Preliminary example of de-blurring by deconvolution of a 3D PET image using a (fixed) blurring kernel, which represents the point spread function of the respiratory motion. It can be seen that the blur is reduced considerably, preserving the shape of the tumor.
deconvolution method is computationally intensive. An example of the 3D PET scan deconvolution is shown in Figure 8-9 using a fixed kernel determined by the respiratory motion of the tumor.

6.4. From diagnosis to treatment and treatment response

Generally, new lung cancer patients are currently diagnosed using 3D breath-hold CT and 3D free-breathing PET scans, augmented by (free-breathing 3D) SPECT and sometimes MRI if necessary. In case radiotherapy is applied, a new (4D) planning CT scan is made using a flat table top and arm support like in treatment. Additional respiration-correlated 4D PET scans have to be acquired (preferably in treatment pose) if PET data are needed to delineate the target or accurately define the SUV (see Section 8-1.4). Finally, in principle also SPECT and MRI data have to be repeated in treatment pose for use in treatment-planning. This workflow is inefficient and results in abundant number of scans. The total number of acquired scans may be limited by using the different modalities acquired for diagnoses in treatment-planning. As patients will never be exactly in the same position throughout scanning [81], diagnostic scans have to be transformed to represent the patient in treatment position. Deformable registration, compensating the discrepancies between the different scans, is therefore essential to enable image fusion and reuse of scans. Because multi-modality registration is generally less accurate than uni-modality registration (see Section 8-2.3), different modalities to be registered should be acquired as much as possible under the same conditions. The future workflow might become as follows: Breath-hold CT, free-breathing PET, SPECT and MRI images are acquired according to the diagnostic protocols. However, if (suspicious) tracer uptake is visible in the whole-body PET image, an additional 4D PET of the thorax region is acquired immediately thereafter. Due to the low image resolution of the SPECT it is questionable whether 4D SPECT is valuable. Deformable registration could then be applied to register each of the modalities to the diagnostic CT scan, for example according to the suggestions given in Section 8-2.3. In case of radiotherapy, a low dose 4D CT scan is acquired to obtain the local DVF (motion) and to reconstruct the mid-position CT scan. Note that a short time-span between diagnostic imaging and treatment-planning is necessary. Subsequently, the diagnostic CT scan is registered to the mid-position CT scan using deformable registration (assuming no anatomical changes of the soft tissue; Section 8-2.3b), yielding a MidP CT scan of breath-hold quality. Subsequently, transformation to the mid-position treatment pose may be done using the computed transformations, making these scans available for use in treatment-planning. Possibly, the diagnostic SPECT scan used to measure lung function, could be omitted since this information can also be extracted from the 4D CT as will be discussed in Section 8-6.6.
Finally, treatment response can be observed by comparing multiple repeated (4D) CBCT scans, acquired during the course of treatment, to the mid-position planning scan (Figure 8-10). Deformable registration is then used to match corresponding structures over time. Note that registration of corresponding structures in the presence of changing anatomy is, however, an unsolved problem (see Section 8-2.3).

6.5. PET, tumor response and pathology

Multi-modality imaging, in addition to becoming standard practice in the clinic, also has its impact on oncology research. New studies correlating functional and anatomical imaging modalities to pathology [82-84] and gene expressions [85] are reported. Stroom et al. [82] investigated pathology, PET and CT correlation to accurately define the GTV and CTV (including the microscopic tumor extensions). Due to the different representation in pathology compared to CT and PET and strong deformations, a manually selected control-point/feature based deformable registration was applied. Respiration motion was not taken into account by using BH CT scans and 3D PET (only 3D PET images were available). Respiration correlated 4D PET scans can improve the correspondence between pathology and PET images. The advantage of 4D CT over BH CT is limited since image quality of the BH scan is superior. Also, respiration would not change the structure and anatomy representation (resulting in image discontinuities) in the BH CT scan. Van Baardwijk et al. [83] performed a

Figure 8-10. An example to show tumor shrinkage during radiotherapy treatment. 14 respiration-correlated (4D) CBCT scans were acquired on different days. The scans were (rigidly) registered to the vertebra. Possibly, deformable registration could be helpful to detect and analyze local changes.
similar study but acquired PET-CT scans of an ex-vivo specimen after surgery, which simplifies the registration of the images to pathology.

6.6. **Local lung compliance and ventilation**

Lung compliance and ventilation are important measures in respiration physiology and disorders are associated with fibrosis and chronic pulmonary diseases (e.g., COPD). Localized information on these pulmonary parameters can be used in treatment-planning in order to spare well functioning lung tissue or to evaluate the complications or response of the treatment (estimation of the remaining lung capacity of the patient after radiotherapy) [86-88]. Lung compliance is the ability of lung tissue to stretch in reaction to an applied pressure change (Δ Volume/Δ Pressure). Ventilation is defined as the rate at which air enters or leaves the lung (Δ Volume/Δ Time). Since patients may have significantly heterogeneous regional lung function [89], these parameters have to be determined locally.

Local lung function parameters are generally quantified by using SPECT perfusion scans. However, ventilation can be also derived from 4D CT scans, eliminating the need for additional SPECT scans. Lung compliance can also be derived but the pressure change has to be measured externally. The deformable registration method described in Chapter 5 then results in a DVF from which the local volume change over the respiratory cycle can be computed. However, the local volume change depends on the vector gradient, which is very sensitive to noise and (small) image distortions. The occurrence of CT imaging artifacts due to irregular breathing causes local discontinuities in the DVF resulting in deviant volume change values. Moreover, when comparing pre and post treatment ventilation or lung compliance data, normalization with respect to respiration amplitude is necessary. Potentially, lung function parameters derived from 4D CT may have higher resolution than with SPECT.

Volume changes may be calculated alternatively from changes in the fractional air content in pulmonary tissue between matched regions of inhale and exhale CT frames [90].

6.7. **Tumor-tracking during radiotherapy**

As extensively discussed in Chapter 6, respiration gated radiotherapy has several disadvantages. First of all, irradiation is taking place only during part of the breathing cycle resulting in long irradiation times, increasing the chance of intra-fraction movements. However, irradiation times can be reduced by “tumor-tracking” techniques. Here, a multi leaf collimator (MLC) is tracking the respiration-induced moving target regulated by a feedback loop from the respiration signal to a real-time MLC controller [91-94], allowing for continuous irradiation. Another tumor-tracking technique consists of a linear accelerator mounted on a robot in which a feedback loop matches accelerator movements with respiration [95-97].
A more severe issue with tracking is that inaccurate correlation between internal motion and external respiratory gating signal may result in dose delivery errors. This issue might be solved by extracting an internal respiratory signal from online fluoroscopic imaging of the target [18,98,99] but this technique inherently gives an additional dose to the patient. Alternatively a hybrid respiratory signal system using an external signal, correlated and updated on-the-fly to the internal target motion using sparsely acquired fluoroscopic images can be used [97]. Another approach makes use of radiographic markers implanted in the tumor [100,101]; however, most lung cancer patients are physically unable to undergo the implants. Recent developments have shown the feasibility to combine a linear accelerator with MRI equipment [102].

The advantage of this combination is to deliver radiation with high precision based on diagnostic quality MR images (high tissue contrast). Continuous online acquisition of MR images to track the target during respiration might therefore be an alternative for online fluoroscopy (as well as determining intra-fraction motion not related to respiration). Note that for treatment-planning purposes, 4D imaging techniques (possibly simplified by the use of mid-ventilation approach) are still necessary for the correct definition of tumor shape and position.

Although technically feasible, due to its complexity, this MRI-guided tumor-tracking will not be widely available in the near future. In addition, it has been shown that the simplified mid-ventilation concept does not perform inferiorly compared to the “perfect” gating or tracking method, which is true for online and offline correction protocols (Chapter 6). Consequently, MRI-guided tracking techniques will especially be useful for patients with large tumor motion (> 2 cm) or mobile tumors in areas with steep dose gradients (e.g., liver).
Conclusions
The objective of the study described in this thesis was to improve imaging for radiotherapy planning by reducing geometrical uncertainties related to respiration. Improvements have been achieved at the source, resulting in acquisition of 4D CT and PET scans. Subsequently, a framework was proposed and developed, currently in clinical use at the NKI-AVL, providing a patient-specific representative (mid-ventilation) CT scan for treatment-planning. After three years of experience at the NKI-AVL, we may conclude that this approach has resulted in clinically safe treatment plans, enabling treatment of larger tumors with smaller uncertainty margins than with conventional free-breathing CT. The simple mid-ventilation concept was also shown to be superior or equivalent to other reported planning strategies with respect to PTV volumes. The most widely used alternative, ITV, results in larger PTV volumes whereas gated treatment delivery can be cumbersome and technically difficult. Furthermore, 4D verification of the accumulated dose over the respiration cycle has shown that the 3D mid-ventilation approach gives a sufficiently accurate estimate of the delivered dose. Finally, a post-processing algorithm was developed to obtain a high quality mid-position CT scan resolving hysteresis, image noise and artifact issues.

In conclusion, this thesis has proven that the mid-ventilation (and mid-position) approach reduces geometrical errors related to respiration, thereby reducing the PTV volume. The methods described in this thesis are currently in routine use at the NKI-AVL. The proposed methodology may be applied both in advanced hospitals as well as lesser-equipped institutes.
Summary / Samenvatting
Lung cancer is the most common cause of cancer related death. Overall survival is often poor after treatment with conventional radiotherapy. Improvements may be obtained by increasing the radiation dose; however, this can lead to unacceptable complications of healthy organs in or near the irradiation field. The size of the irradiation field is defined by the size of the tumor plus a treatment margin, to allow for geometrical uncertainties during treatment.

The aim of this thesis is to reduce respiration-related geometrical uncertainties by improved imaging, creating patient-specific treatment plans. As a result treatment dose can be increased and/or the risk of complications reduced. For this purpose, four-dimensional imaging acquisition and post-processing techniques were developed and implemented in the clinic.

Technical realization Time-resolved four-dimensional (4D) respiration-correlated image acquisition techniques were developed to reduce respiratory imaging artifacts in conventional 3D free-breathing (anatomical) CT and (functional) PET scans (Chapter 2). Scan-speed is low in this mode, acquiring multiple slices of the same table position, each corresponding to a different breathing phase. Simultaneously, a breathing signal was acquired using a thermometer in the respiratory path of the patient. Using this signal, the acquired CT and PET data were sorted retrospectively to the corresponding respiratory phases, obtaining a set of 3D CT and PET reconstructions, referred to as 4D CT and PET.

The complementary value of both imaging modalities is obtained when viewing the scans in a common reference system. Hybrid PET-CT scanners automatically result in registered PET and CT scans provided that the patient did not move between the two scans (hardware-fusion). In this study, scans were acquired on separate scanners, necessitating development of a post-registration procedure of the PET and CT scans (software-fusion). In addition, a procedure was developed to register the respiratory phase of both modalities correctly.

Clinical implementation Four-dimensional CT scans are not widely used in treatment-planning since systems with 4D capacities are currently hardly commercially available. Therefore, a simple concept was developed to incorporate patient-specific motion information into radiotherapy planning of lung cancer patients, based on 4D CT scans (Chapter 3). This concept uses the frame of the 4D CT scan in which the tumor is represented in its time-weighted mean position over the respiratory cycle. This selected frame is called the mid-ventilation (MidV) CT scan. The most simple approach is clinically used at NKI-AVL since 2005.
**Deformable registration** When registering the vertebra in different (corresponding) scans other structures or organs in the thoracic region are still misaligned since they move differently. Non-rigid methods are necessary to register these entities locally. In Chapter 4 an iterative multi-scale deformable registration technique is described, registering each frame of the 4D scan to a fixed reference frame. The used algorithm derives a linear relation between displacement of image structures and time (between the two scans) from variations in image phase (image intensity transitions from bright to dark and vice versa) between the two scans. The resulting deformation (motion) vector field for every pixel to every 4D CT frame is used subsequently.

**Image quality optimization** The image quality of the MidV CT scan can be poor due to irregular breathing (distortions) and when the patient is obese (noise), yielding unsuitable scan for accurate delineation and treatment-planning. Also hysteresis may cause a small displacement error. A framework is developed to reconstruct a new high quality CT scan resolving the mentioned issues (Chapter 5). For each frame of the 4D CT scan the deformation vector field (DVF) relative to a reference frame is computed using the deformable registration technique. The resulting set of DVFs is (time-weighted) averaged and applied to the 4D CT scan, yielding a transformed set of CT frames with all structures and organs in their mean position over the respiratory cycle. Finally, the image intensities of this transformed set of CT frames were combined, resulting in a 3D mid-position (MidP) CT scan containing less image distortions and noise.

**Treatment-planning evaluation** Four-dimensional CT scanning provides information on respiratory induced tumor motion. To utilize this information, several target volume approaches are described in the literature reducing geometrical uncertainties during radiotherapy treatment-planning and/or delivery (internal target volume, exhale gated radiotherapy and mid-position approach). These approaches were discussed and compared to the conventional free-breathing CT scan approach (Chapter 6). A simulation was performed to compute the uncertainty margins and the corresponding planning target volume (PTV) for the different approaches, covering inter-fractional setup errors, tumor baseline variation and respiratory motion induced geometrical uncertainties. Based on the results of 45 patients, we showed that the internal target volume method resulted in a significantly increased irradiated volume. Gated radiotherapy and mid-position (and mid-ventilation) method resulted in an approximately equal PTV reduction compared to the conventional free-breathing approach. However, real-time tumor localization is essential for gated radiotherapy. The mid-ventilation approach is easier to use in the clinic since it only affects the planning scan part of treatment and not the delivery.
**Dose accumulation and evaluation** In Chapter 7, a dosimetric analysis was performed to investigate the effect of respiration-induced anatomy (geometry and density) variations on the estimated dose to moving structures using the MidV approach.

A treatment plan was designed on the MidV CT scan for each patient, including an appropriate CTV-to-PTV margin accounting for setup errors, baseline variation and respiratory motion. To assess the impact of respiration-induced anatomy variations (geometry and density changes in the 4D CT), this plan was applied to all 10 breathing phases of the 4D CT and dose distributions were recalculated. The dose of each breathing phase was transformed to the MidV geometry using the DVF computed by deformable registration method applied to the 4D CT. The cumulative 4D dose was determined by averaging the transformed dose distributions. Subsequently, the “original” planned MidV dose distribution was shifted according to the respiratory motion, and then accumulated (i.e., blurring of the dose assuming shift invariance), resulting in the 3D MidV dose estimation excluding density variations. Comparing these two accumulated dose distributions showed that the influence of density variation is very small. In addition, it was shown that the 3D dose distribution computed on the MidV CT scan is a sufficient estimate of the full 4D accumulated dose, implying that a full 4D treatment plan optimization is superfluous.
Longkanker is de meest voorkomende kankersoort met de grootste kans op sterfte. De overlevingskansen na conventionele radiotherapiebehandeling zijn in het algemeen klein. Verbeteringen zijn mogelijk door de bestralingsdosis te verhogen, echter, dit kan ook ernstige complicaties veroorzaken aan de gezonde organen die in of nabij het bestralingsveld liggen. De grootte van het bestralingsveld wordt gedefinieerd door de grootte van de tumor plus een extra marge om geometrische onzekerheden tijdens de bestraling te ondervangen.

Het doel van deze dissertatie is om de door ademhaling geïnduceerde (veroorzaakte) geometrische onzekerheden te verkleinen met behulp van betere beeldvorming. Hiermee kunnen patiëntenspecifieke bestralingsplannen (bundelvorm en richtingen e.d.) worden gemaakt en kan de bestralingsdosis worden verhoogd en/of de complicatierisico’s worden verkleind. Om dit te bereiken zijn vierdimensionale beeldacquisitie- (beeldopname) en verwerkingsmethoden ontwikkeld en geïmplementeerd in de kliniek.

**Technische realisatie** Om beeldverstoringen door ademhalen in conventionele driedimensionale (3D) vrijeademhaling CT (anatomisch) en PET (functioneel) scans te verminderen, zijn vierdimensionale (4D) ademhalingsgecorreleerde beeldvormende technieken ontwikkeld (Hoofdstuk 2). Bij dit soort beeldvormende technieken is de beeldopnamesnelheid laag, waarbij meerdere (2D) plakken (dwarsdoorsnede van de patiënt) worden verkregen bij eenzelfde tafelpositie. Echter, elke plak correspondeert met een andere ademhalingsfase. Tegelijkertijd wordt het ademhalingssignaal van de patiënt gemeten met behulp van een thermometer geplaatst in de ademhalingsluchtstroom. Dit signaal wordt vervolgens gebruikt om na beeldopname de verkregen CT en PET plakken te sorteren naar de verschillende ademhalingsfasen. Hiermee wordt een set van 3D CT en PET scans (4D CT en PET) verkregen.

De toegevoegde waarde van de verschillende beeldmodaliteiten wordt verkregen door beide scans in een gezamenlijk referentiestelsel te bekijken (fusie). Hybride PET-CT scanners leveren automatisch geregistreerde (dat wil zeggen het bepalen van de afstand tussen twee beelden) scans indien de patiënt niet tussen de twee scans bewogen heeft (hardware-fusie). In deze studie zijn de scans verkregen op aparte scanners waardoor een postregistratie procedure voor de CT en PET moest worden ontwikkeld (software-fusie). Tevens is een procedure ontwikkeld om de verschillende ademhalingsfasen van beide modaliteiten juist aan elkaar te koppelen.

**Klinische implementatie** Vierdimensionale CT scans worden nog niet algemeen gebruikt bij radiotherapieplanning aangezien planningssystemen met 4D mogelijkheden op dit moment nauwelijks commercieel verkrijgbaar zijn. Daarom is
een eenvoudig concept ontwikkeld die patiënt specifieke bewegingsinformatie (uit 4D CT scans bepaald) gebruikt in de radiotherapieplanning van longkankerpatiënten (Hoofdstuk 3). Dit concept selecteert het desbetreffende frame van de 4D CT scan waarin de tumor zich het dichtst bij de tijd gewogen gemiddelde tumorpositie bevindt (over de gehele ademhalingscyclus). Dit geselecteerde frame wordt de mid-ventilatie (MidV) CT scan genoemd. Deze uiterst eenvoudige methode wordt tegenwoordig klinisch gebruikt op het NKI-AVL.

**Deformeerbare registratie** Wanneer de ruggenwervels in verschillende scans worden geregistreerd, komen andere structuren (zoals bloedvaten e.d.) en organen in de thorax nog steeds niet met elkaar overeen. Deze misregistratie komt omdat deze structuren en organen een andere beweging hebben dan de ruggenwervels. Om de structuren en organen lokaal te registreren zijn niet-rigide methoden nodig. In hoofdstuk 4 wordt een iteratieve deformeerbare registratietechniek beschreven waarbij ieder frame van de 4D CT scan lokaal wordt geregistreerd aan een vast referentieframe bij verschillende resoluties. Het gebruikte algoritme leidt een lineaire relatie af tussen de verplaatsing van beeldstructuren en de tijd (tussen twee scans) uit de variatie in beeldfase (beeldintensiteit overgangen van licht naar donker en vice-versa) tussen twee scans. Het resulterende deformatie (bewegings-) vectorveld voor elke pixel (beeldelement) naar ieder 4D CT frame zal in deze dissertatie worden gebruikt.

**Optimalisatie van de beeldkwaliteit** De beeldkwaliteit van de MidV CT scan kan slecht zijn vanwege onregelmatige ademhaling (verstoringen) en bij gezette patiënten (ruis). Deze scan is onbruikbaar om organen in te tekenen en de radiotherapieplanning op uit te voeren. Ook hysterese (d.w.z. het traject van inademen is niet gelijk aan uitademen) kan een kleine verplaatsingsfout veroorzaken. Er is een raamwerk ontwikkeld om een nieuwe scan van hoge kwaliteit te reconstrueren die de genoemde problemen oplost (Hoofdstuk 5).

Voor elke frame van de 4D CT scan wordt het deformatie vectorveld (DVF) ten opzichte van een vast referentieframe berekend met behulp van de deformeerbare registratietechniek uit deze dissertatie. De resulterende verzameling DVF’s wordt (tijd gewogen) gemiddeld en gebruikt om de 4D CT scan te transformeren naar een nieuwe set CT scans waarbij alle structuren en organen in hun gemiddelde positie in de ademhalingscyclus zitten. Tenslotte worden de pixelwaarden van de getransformeerde frames van deze 4D CT scan gecombineerd, wat resulteert in de mid-positie (MidP) CT scan. Deze MidP CT scan bevat minder verstoringen en ruis.
**Evaluatie van de therapieplanning** Vierdimensionale CT scans geven informatie over de ademhalingsgeïnduceerde tumorbeweging. In de literatuur zijn verschillende doelvolume-strategieën beschreven die de geometrische onzekerheden tijdens de radiotherapieplanning en/of -bestraling reduceren (interne doelvolume, gating radiotherapie tijdens de uitademfase en de mid-positie benadering). Deze benaderingen worden vergeleken ten opzichte van de conventionele vrijademhaling 3D CT scan benadering en bediscussieerd (Hoofdstuk 6).

Om de onzekerheids marges te berekenen, met de daarbij corresponderende planning doel volume (PTV) voor de verschillende benaderingen, is een simulatiestudie uitgevoerd waarbij rekening is gehouden met inter-fractie set-up fouten, tumor basislijn variatie en ademhalingsgeïnduceerde geometrische fouten.

Op basis van de resultaten van 45 patiënten hebben we laten zien dat de interne doelvolume methode resulteert in een significant toegenomen bestraald volume. Gating radiotherapie en MidP (en MidV) resulteerde in een ongeveer gelijke PTV reductie ten opzichte van de conventionele vrijademhalingsbenadering. Echter, prompte tumorlokalisatie is essentieel voor gating radiotherapie. De MidP (en MidV) benadering is gemakkelijker te gebruiken in de kliniek omdat het enkel van invloed is op het planningsdeel van de behandeling.

**Dosis accumulatie en evaluatie** In hoofdstuk 7 wordt een dosimetrische analyse uitgevoerd om het effect te bepalen van de ademhalingsgeïnduceerde anatomie (d.w.z geometrisch en dichtheid) variaties op de geschatte dosis in de bewegende structuren bij gebruik van de MidV benadering.

Voor elke patiënt was een radiotherapieplan gemaakt op basis van de MidV CT scan, inclusief een geschikte CTV-naar-PTV marge voor de set-up, basislijn variatie en ademhalingsbewegingsfouten. Om de invloed van de ademhalingsgeïnduceerde anatomie variaties (geometrie en dichtheidsveranderingen in de 4D CT) te bepalen, is plan toegepast op alle tien frames (ademhalingsfasen) van de 4D CT scan. Vervolgens is voor ieder frame de dosisdistributie herberekend. De dosis in elke ademhalingsfase werd getransformeerd naar de MidV geometrie met behulp van de DVFs die voor de 4D CT scan waren berekend. De cumulatieve 4D dosis werd verkregen door de getransformeerde doses te middelen. Vervolgens werd de originele MidV dosis verschoven volgens de ademhalings-geïnduceerde tumorbeweging en dan geaccumuleerd (dat wil zeggen dat de dosis verschuivingsinvariant is), resulterende in een de geschatte 3D MidV dosis zonder het meenemen van de densiteit variaties. Door deze twee geaccumuleerde doses te vergelijken kan worden gezien dat de invloed van dichtheidsvariaties erg klein is. Tenslotte liet deze studie zien dat de 3D dosisdistributie, berekend met behulp van een MidV CT scan, een voldoende juiste schatting is voor de volledig 4D geaccumuleerde dosis. Dit impliceert dat een volledige 4D radiotherapie planning optimalisatie overbodig is.
Biosketch

Jochem Willem Heiko Wolthaus was born in Leiden, The Netherlands on 8 September, 1976. He attended secondary school at the Bonaventura College in Leiden. In 1994, he began his Masters degree in Applied Physics at the Delft University of Technology. His final project was undertaken at the Department of Radiation Oncology, at the Netherlands Cancer Institute (NKI-AVL) in Amsterdam. The project was titled ‘Automatic three-dimensional position verification for patient setup in radiotherapy of lung cancer patients’. In June 2002, he received his degree of Master of Science in Applied Physics. Following one year of research work at NKI-AVL, exploring four-dimensional imaging, he started his Ph.D. project on ‘Four-dimensional imaging in Radiotherapy for lung cancer patients’.

In September 2008 he began his Medical Physicist residency at the University Medical Center, Utrecht, The Netherlands.
Biografie


Sinds september 2008 is hij werkzaam als klinisch fysicus in opleiding (klifio) op de afdeling Radiotherapie van het Universitair Medisch Centrum Utrecht. Jochem is getrouwd met Renske Bakker en samen hebben zij een dochter Saar.
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List of abbreviations

1D, 2D, 3D, 4D One, two, three, four-dimensional
AP Anterior-posterior
CB Cone beam
CC Cranio-caudal
Conv Conventional
CRT Conventional radiotherapy
CT Computed tomography
CTV Clinical target volume
DVF Deformation/displacement vector field
EPID Electronic portal imaging device
EUD Equivalent uniform dose
GTV Gross tumor volume
Gy Gray (dosimetric unit)
ICRU International Commission on Radiation Units and Measurements
IGRT Image-guided radiotherapy
IMRTIntensity modulated radiotherapy
ITV Internal target volume
LR Left-right
MidP Mid-position
MidV Mid-ventilation
MIP Maximum intensity projection
MLC Multi leaf collimator
MLD Mean lung dose
MRI Magnetic resonance imaging
MV Mega voltage
NKI-AVL Netherlands Cancer Institute – Antoni van Leeuwenhoekhospital
NTCP Normal tissue complication probability
PET Positron emission tomography
PTV Planning target volume
SBRT Stereotactic body radiotherapy
SD Standard deviation
SPECT Single photon emission tomography
TCP Tumor control probability
TM Tumor motion
TPS Treatment planning system
V20 Lung volume exceeding 20 Gy
V50 A nice car