Four-dimensional imaging in radiotherapy for lung cancer patients
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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 $^{99m}$Tc 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

![Figure 1-3. Construction of target volumes: Light red is the visible tumor (gross Target Volume; GTV). Mid red: The margin to cover the microscopic extensions representing the Clinical Target Volume (CTV). Deep red: Additional margin to cover the geometrical uncertainties, representing the Planning Target Volume (PTV).](image-url)
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
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

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**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: $M_{\text{CTV-PTV}} = 2.5\Sigma + 0.7\sigma$, 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


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