CT-PET imaging of lung cancer patients for radiotherapy

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CT-PET imaging of lung cancer patients
for radiotherapy

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CT-PET imaging of lung cancer patients for radiotherapy

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CHAPTER

1

Introduction and outline of the thesis

CANCER INCIDENCE IN EUROPE AND THE NETHERLANDS

In 2006, only in Europe more than 3 million cancer cases were estimated to be diagnosed with an overall mortality of about 53%. The total number of new cases of cancer in Europe has increased by 300 000 since 2004, and ageing of the population will cause these numbers to continue to increase¹. It is thus clear that cancer will remain one of the major health problems in Europe for years to come. One of the most common malignancies is lung cancer (12.1%) and with an estimated 334 800 deaths (19.7% of total cancer deaths), it is currently the most common cause of death from cancer. The overwhelming majority of these lung cancers are caused by smoking tobacco.

In the Netherlands an average increase of 1.5% - 2% new cancer cases is observed each year. In 2005 about 6000 men and 2800 women died of lung cancer. The incidence of lung cancer for men has decreased by one third between 1989 and 2003, but for women the incidence has increased with 80% in the same period. This can be explained by a change in smoking habits between men and women. The increasingly similar smoking habits of men and women have resulted in a convergence of lung cancer incidence between men and women.

Lung cancer can be subdivided in two main pathological subtypes: Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC). The majority (80%) of patients have NSCLC, a disease only rarely diagnosed at an early stage. Five years after the first diagnosis only 10% - 15% of all NSCLC patients are alive (www.ikc.nl), both due to a high incidence of local tumor failure and distant metastases. Research on lung cancer is therefore an important research field aimed at achieving better survival.

Radiotherapy for patients with lung cancer

Surgery remains the treatment of choice for patients with early stage NSCLC. If patients with stage I-II are medically inoperable because of age or co-morbidity (e.g. poor lung function tests), radiotherapy can be curative. For patients with stage III, often referred as locally advanced NSCLC, combined chemotherapy and radiotherapy has evolved as the standard treatment²⁻⁴, resulting in an overall 5 year survival of 5% - 40%^{5,6}.

The two main causes of death in locally advanced NSCLC cancer are distant metastases and lack of local tumor control. Local tumor control with radiotherapy is a function of the total delivered tumor dose in a certain overall treatment time. In addition, improved local control has been shown to yield an improved overall survival^{7,8}. Therefore increasing radiation dose or dose escalation could

lead to better local control and hence improve overall survival⁹. However, dose escalation is hampered by the risk of radiation-induced side effects, like radiation pneumonitis, esophageal damage, spinal cord and heart injury^{10, 11}. The goal of radiotherapy is to find an optimum between local tumor control and these side effects.

To improve local tumor control, NSCLC patients are increasingly treated with innovative techniques such as highly conformal three-dimensional external beam radiotherapy¹², Stereotactic Body Radiation Therapy¹³ (SBRT), Intensity modulated radiotherapy¹⁴ (IMRT), Image Guided Radiotherapy¹⁵ (IGRT) and in-vivo dosimetry using Electronic Portal Imaging Devices (EPID)¹⁶, sometimes called as Dose Guided Radiotherapy (DGRT)¹⁷. To perform these techniques state-of-the-art equipment is used, this means modern linear accelerators equipped with Multi Leaf Collimators (MLC), to shape the radiation beam to the tumor and spare as much as possible the normal tissue, extensive imaging modalities for monitoring the patient's setup in two dimensions (EPID, stereoscopic imaging¹⁸, ...) as well as three dimensions (Kilo Voltage or Mega Voltage Cone Beam CT) and possibilities for four-dimensional (4D) radiotherapy (gated radiotherapy¹⁹). Also a Record and Verify system in combination with unifying digital (DICOM) connections between all used systems is essential to assure a safe patient treatment and to archive and analyze the huge amount of (imaging) data in a systematic central database.

Tumor delineation is one of the weak points of the radiotherapy chain. Large interobserver variations in delineation lung tumors on CT images were reported and especially identification of atelectasis and pathological lymph nodes seems to be difficult²⁰⁻²².

In this thesis two approaches to improve radiotherapy for patients with lung cancer are investigated. The first approach is to better define the target using novel imaging techniques such as 4D-CT and 4D-CT-PET. In the second approach the target is followed during treatment using repeated CT and CT-PET imaging, with the final goal being adaptation of radiotherapy during treatment.

Improving radiotherapy for lung cancer patients by better target definition

One of the most important critical steps in the radiation treatment process is the definition of the tumor and surrounding tissues. Currently a CT scan is widely used to delineate the gross tumor volume (GTV), which consists of all clinically macroscopic disease, including what is visible on imaging modalities^{23, 24}. Safety margins are added to this volume to prevent geographical misses. The clinical target volume (CTV) is created by adding a certain margin to account for microscopic disease. After accurate definition of this GTV and CTV, geo-

metric uncertainties like set-up errors and tumor motion are covered by an additional safety margin to create the planning target volume (PTV). These geometrical errors can be divided into systematic (every fraction the same) and random (varying from fraction to fraction) deviations from the planned situation. Several margin ‘recipes’ are described in literature to calculate the CTV-PTV margin²⁵⁻²⁷. Once the target volume is accurately delineated, treatment fields can be defined and the dose distribution can be calculated and optimized. Optimizing target definition for radiotherapy is therefore extremely important; below are two ways to improve target delineation in lung cancer patients described.

(1) Adding PET to improve GTV delineation

Computed Tomography (CT) with the current multislice scanners is a fast imaging technique which provides anatomical information. This imaging technique is based on the physical principle of attenuation on an X-Ray fan beam through the patient. A three-dimensional representation of the patient is acquired and different densities are visualized as a grey value with a certain Hounsfield unit. These Hounsfield units can be converted to electron densities which are used to calculate the planned dose distribution. Based on the CT scan, Digitally Reconstructed Radiographs (DRR) which is a computer generated fluoroscopic image, can be created and used as a template for the verification of the patient’s position during treatment.

However, CT images are limited to visualize anatomic information only, and they yield no data on intra-tumor heterogeneity. With the advent of Positron Emission Tomography (PET) scanning however, it became possible to visualize and quantify heterogeneities within the tumor. PET is based on the emission of two gamma rays, created by the annihilation of an emitted positron and an electron, which are simultaneously detected. A tracer combined with a radioactive isotope (positron emitter) is injected in the patient. After a rest period, which is needed for the tracer to be diffused within the patient, the patient is imaged. PET images are acquired in several table positions (about 16 cm) of several (2-5) minutes. A whole PET procedure will last between 30-45 minutes. Compared to CT, PET imaging is therefore a slow imaging technique.

The most currently used tracer in PET scanning for radiotherapy is ¹⁸F-fluorodeoxyglucose (FDG). This radiotracer is a measure for the rate of glycolysis in the tumor. FDG-PET has a higher sensitivity, specificity and accuracy for detection of tumor involvement than CT and results in a more accurate staging of malignancies, both for the primary tumor as well as for lymph nodes and distant metastases²⁸. FDG-PET, and more specifically the Standardized Uptake Value

(SUV), can also be very useful for evaluation of treatment response and prediction of recurrence and/or survival after surgery, radiotherapy and chemotherapy^{29, 30}. It has also been proven to be safe to only irradiate PET positive lymph nodes and thus reducing target volume resulting in a higher tumor dose³¹⁻³³.

Interobserver variation in lung cancer delineation is very large using only CT as imaging information, which could be reduced by standardized institutional protocols^{20-22, 34}. Delineation accuracy could be further improved by using PET images which also decrease the observer variation³⁵⁻³⁸. An autocontouring method, based on the Source-to-Background ratio in PET images³⁹, which was validated in laryngeal carcinomas⁴⁰ was applied in NSCLC patients. With this method we also found a good correlation with pathology, currently the gold standard in defining the tumor, both for the maximal diameter of the primary tumor as well as for the involved lymph nodes⁴¹. In addition, the delineation variability amongst observers could be reduced even further with the autocontouring method in NSCLC patients.

Incorporating PET imaging in the treatment planning process seems very promising⁴²⁻⁴⁴ and could for example improve treatment outcome since using this information can lead to sparing of normal tissue and by escalating radiation dose to achieve a higher tumor control probability. Another big advantage of PET imaging is that it can give information on biological characteristics of the tumor and the different areas within the tumor. This might be used in the future to delineate a biological target volume and to adapt radiotherapy treatment. PET imaging is therefore often described as functional or molecular imaging.

Given these benefits, there has been an exponentially growing interest in using (CT-) PET for radiotherapy, as reflected by the number of publications on this subject (Fig. 1).

(2) Adding respiration correlated CT and PET to improve PTV delineation

One of the major challenges when imaging and treating lung lesions is respiration. The current radiotherapy practice is to account for respiration via a safety margin, usually a population based margin applied to all lung cancer patients. However some lung tumors move more than this margin, resulting in part of the tumor receiving a too low dose (geographic miss) while other tumors barely move, resulting in normal tissue being unnecessarily irradiated. Therefore knowledge of the motion for the individual tumor could optimize radiation therapy.

Figure 1: Evolution of the number of publications on PET for radiotherapy. A Medline (www.pubmed.com) search was performed on June 1st 2007 using the terms: [PET AND radiotherapy]. (extrapolated numbers for 2007)

Respiration Correlated CT

With a fast helical multislice CT scanner the tumor is actually freezed at one location. As this is not necessarily the average tumor position, fast CT scanning can cause a large systematic error. Moreover, it can also lead to distortions of the tumor's shape⁴⁵. Efforts should focus on minimizing these systematic errors, rather than controlling the breathing motion during irradiation (gating)⁴⁶. Several strategies have been investigated to solve these problems when imaging and treating moving lung tumors, such as immobilization of the tumor by Deep Inspiration Breath Hold techniques (DIBH), respiratory gating⁴⁷ or Four-Dimensional (4D) CT/Respiration Correlated CT (RC-CT) imaging. Other methods are in detail described in a recent report of the AAPM¹⁹.

RC-CT is an oversampled or low-pitch CT scan during which the respiration signal is recorded. This respiration signal can be measured with different methods, e.g. a thorax band with a pressure sensor^{48, 49}, infrared markers placed on the patient's chest which is visualized with a camera⁵⁰, measuring the flow of warm (expiration) and cold (inspiration) air with a thermocouple in a mouth mask⁵¹, magnetic sensors placed on the patients skin⁵²,... . Afterwards the CT

images can be sorted ('binned') according to the respiration phase or respiration amplitude^{53, 54}. Instead of one CT dataset, several datasets, according to the number of bins, are available for treatment planning. Based on these datasets, movies can be generated in which the motion of the tumor can be measured in all directions.

Incorporating this four-dimensional information into the treatment planning is possible in different ways. Some investigators use Maximum Intensity Projections (MIPs), which reflects the highest data value encountered along the viewing ray for each pixel of volumetric data, giving rise to a full intensity display of the brightest object along each ray on the projection image⁵⁵. Others propose to use only one phase of the respiration, the half-ventilation phase, i.e. the phase where the tumor is at its average position, together with a margin 'recipe' to account for the motion^{49, 56}.

Respiration correlated CT-PET (RC-CT-PET)

As mentioned above, a lung tumor can be much better imaged with the combination of PET and CT, than with CT alone. As RC-CT has also shown to be beneficial to image lung cancer, the effect of respiration on PET and the possibility of respiration correlated CT-PET, needs careful consideration in lung cancer.

PET imaging is a slow imaging technique, several minutes are necessary to achieve an acceptable signal/noise ratio. Therefore multiple respiration periods are covered by the images and this obviously blurs the images. This causes artifacts when matching with fast CT images⁵⁷. Some investigators pose that PET is the ideal imaging technique of lung cancer patients because the respiration is already taken into account in the imaging process and the visible lesion represents an Internal Target Volume (ITV)⁵⁸. Many arguments can be raised against this point of view. First, PET images are extremely sensitive to Window/Level settings, therefore automatic delineation software should be developed. Validation of these methods should occur by correlating these PET images with pathology⁵⁹, which is extremely difficult with blurred PET images. Second, accurate information of several parameters, such as the maximal Standardized Uptake Value (SUV_{max}), is not present in classic CT-PET imaging⁶⁰. Moreover, SUV measurements are only reliable when no or little movements of the target are present. Third, attenuation correction could be wrongly performed when combining the fast imaging technique (CT) with the slow one (PET)⁶¹. Finally, normal CT-PET scanning will represent different intra-tumor heterogeneity due to the respiration, with regard to the tracer uptake. Therefore accurate treatment of these regions, by for example dose painting, is not possible.

Since standard PET procedures, with its respiration blurring, have these limitations in lung cancer, four-dimensional or respiration correlated PET imaging

have been developed. Similar to RC-CT, these techniques rely on the simultaneous acquisition of list-mode PET data and the respiration signal^{51, 62-64}.

Improving radiotherapy for lung cancer patients by target adaptation (Adaptive Radiotherapy)

Nowadays the planned dose distribution is mostly based on a single CT(-PET) scan, taken before the treatment. So the time trends of the tumor are not taken into account in the treatment. Repeated imaging of the tumor during the therapy could give more insight in its dynamics, posing the question if the anatomical and/or biological changes are worthwhile to adapt. A radiation treatment process where the treatment plan can be modified using a systematic feedback of measurements is called ‘adaptive radiation therapy’ (ART)⁶⁵. With repeated 4D-CT-PET images knowledge is gained about tumor volume (CT), tumor motion (4D) and tumor biological/molecular properties (PET). Several groups are now investigating the time trends of several parameters using different imaging modalities like CT⁶⁶, Mega Voltage CT^{67, 68}, 4D-CT^{69, 70}, CT-PET⁷⁰. Haasbeek *et al.* showed that for their patient population the dosimetric consequences were minimal and therefore adaptive treatment planning was of limited value for fractionated stereotactic radiotherapy⁷¹. This information about changes during therapy is not only of interest for the primary tumor but also for the involved lymph nodes, since these are also part of the treatment volumes. Until now, this information was never reported.

Since FDG-PET uptake pre-treatment, and more specifically the maximal standardized uptake value (SUV_{max}), is correlated with outcome^{29, 30}, it is of interest to know the variations of this parameter during treatment. Also an FDG-PET scan post-treatment can predict residual disease and hence outcome in NSCLC patients^{72, 73}. Therefore, the evolution of the FDG uptake may reflect intrinsic tumor characteristics and might finally be useful to adapt and individualize the treatment early during the course of radiotherapy. This could theoretically be done by adjusting the fractionation scheme or by adding other treatment modalities, such as surgery or drugs.

OBJECTIVES AND OUTLINE OF THE THESIS

In this thesis two approaches to improve radiotherapy for patients with lung cancer are investigated. The first approach is to better define the target using novel imaging techniques such as respiration correlated (RC-) CT and respiration correlated CT-PET. These techniques take into account the intra-fraction variations and artifacts due to respiration. In the second approach the target is followed during treatment using repeated (RC-) CT and CT-PET imaging, with

the final goal being adaptation of radiotherapy during treatment and tackle inter-fraction changes.

In **Chapter 2** we investigated how to use the four-dimensional CT information into the treatment planning. More specifically different methods of defining the internal target volume (ITV) were compared with respect to the optimal Clinical Target Volume (CTV) coverage. This was an “in silico” (plannings) study based on real RC-CT patient data.

In **Chapter 3** our first results are described with RC-CT-PET imaging with phantom measurements (a lollipop phantom). It mainly concerned the technical feasibility of acquiring RC-CT-PET images and it also investigated differences in uptake using different CTs for the attenuation correction. The purpose of the study was to investigate the difference in uptake between phased attenuation correction and normal attenuation correction.

A similar study was performed in **Chapter 4**, but now based on real patient data. More different strategies to perform the attenuation correction were studied. Besides the phased attenuation and a fast CT scan we also looked at the average CT data. The influence of tumor motion and tumor location on the SUV recovery was also reported.

Chapter 5 is dedicated to the time trends in tumor volume, tumor motion and breathing frequency of locally advanced lung cancer patients during fractionated radiotherapy. In **Chapter 6**, we also looked at the changes in biological parameters and more specifically the maximum Standardized Uptake Value (SUV_{max}) between metabolic responders and non-responders during and after radiotherapy, for the same patients as in the previous chapter. In the last **Chapter 7**, the time trends in volume and motion are described for the involved lymph nodes.

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CHAPTER

2

An “in silico” clinical trial comparing free breathing, slow and respiratory correlated computed tomography in lung cancer patients

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ABSTRACT

Background and Purpose: To determine which method of internal target volume (ITV) definition based on a respiration correlated CT (RC-CT) allows optimal tumor coverage.

Material and Methods: A free breathing CT (CT_{fb}) and an RC-CT scan were acquired in forty-one lung cancer patients. For twelve patients with a motion > 7 mm in any direction, a detailed analysis was made. The RC-CT scan was used to measure tumor motion and to reconstruct a CT at 10 phases (CT_{10ph}), amongst which the half ventilation CT (CT_{hv}). By averaging the CT_{10ph} , a slow CT (CT_{slow}) was reconstructed. Based on those scans ITVs were delineated and treatments were planned, where for the ITV_{hv} an internal margin of (motion amplitude)/4 was used. The treatment plans for the ITVs were projected on the 10 respiration phases. Doses were calculated and averaged over the ten phases to estimate the actual CTV coverage.

Results: The 3D motion was on average $8.1 \text{ mm} \pm 1.0 \text{ mm}$ (1 SD) for all patients; no statistical difference was found between lower and upper lobe tumors. The ITV_{slow} was the smallest volume on average ($142 \text{ cm}^3 \pm 38 \text{ cm}^3$), followed by the ITV_{hv} ($160 \text{ cm}^3 \pm 40 \text{ cm}^3$), the ITV_{10ph} ($161 \text{ cm}^3 \pm 41 \text{ cm}^3$) and the ITV_{fb} ($250 \text{ cm}^3 \pm 63 \text{ cm}^3$). Mean CTV doses were between 95% and 107% of the prescribed dose for nearly all patients and treatment plans. Analysis of the CTV coverage suggested that underdosage may occur when the CT_{slow} is used and a geographical miss occurred using the CT_{fb} , due to uncorrect localization of the average tumor position.

Conclusions: The CT_{hv} seems to be the optimal dataset for delineation, using an adequate anisotropic internal margin of (motion amplitude)/4.

INTRODUCTION

Non-small cell lung cancer (NSCLC) has a poor prognosis. If surgery is not possible, radiation therapy, alone or in combination with chemotherapy, is the principal mode of treatment, resulting in 5 year survival rates of 5% - 40%^{11, 17-19}. This poor outcome is due to distant metastases and local recurrences. Since an improved local control (LC) results in a better survival^{20, 22}, improvement of local treatment is important. One of the strategies to improve LC, is radiation dose escalation.

Dose escalation, however, is associated with an increased risk of complications, especially from damage to the lung and the esophagus. Therefore it is important to define ways to decrease the volume of irradiated normal tissues allowing dose escalation without undue side effects. In our department, we investigated two complementary strategies in lung cancer: 1) better definition of invaded nodes with CT-PET^{5, 24} and 2) respiratory correlated CT to individualize the margin needed to account for tumor motion and avoiding geographic misses due to respiration (this paper).

Commonly, the PTV margin is split into a set-up margin, to account for daily set-up and machine variations, and an internal margin to account for tumor motion, i.e. with respiration¹. Individualizing the internal margin around the tumor may thus tackle two major causes of local failure: first decreasing for some patients irradiated normal tissue volumes thereby allowing dose escalation and second, by decreasing geographical miss.

Respiratory correlated CT (RC-CT) is a new development^{8, 13} with which the systematic error (geographical miss) can be minimized and the random error (tumor motion during a radiotherapy fraction) can be estimated for an individual patient. With an RC-CT, separate CTs can be reconstructed from multiple phases of the respiration, allowing estimation of tumor motion as well as the selection of a CT with the tumor in its central position (the half ventilation CT).

In our institution, we assume that the tumor moves 7 mm, peak to peak, in all patients. With our known set-up error, standard deviation of 2 mm both for systematic and random error, and the margin recipe²⁵, this assumption results in a 10 mm total PTV margin in all lung cancer patients (see Appendix). However, it is well known that there is a large variation in tumor motion, ranging from 7 mm in most patients but much larger amplitudes in some other^{21, 26}, which illustrates the need for patient-specific measurement of tumor motion and patient-specific PTV margins.

Based on the literature, we hypothesized that the application of RC-CT would offer significant benefits over using free breathing CT by reducing the internal margin but still avoiding geographic misses, thus making radiation dose escalation possible⁴. Furthermore, we expected a benefit of RC-CT over a slow CT^{15, 27} in the delineation of the tumor. With a slow CT the tumor is smeared out due

to the breathing motion. Therefore the contrast for tumors located close to the mediastinum or surrounded by atelactic tissue will decrease compared with the non-blurred RC-CT. In this case the delineation will be more difficult and subject to intra- and interobserver variability.

We therefore set up an “in silico” clinical trial in lung cancer patients to compare four treatment plans based on four different datasets: a free breathing CT (CT_{fb} , with standard margins for motion), a slow CT (CT_{slow} , no margins for motion), the half ventilation CT (CT_{hv} , with margins based on measured tumor motion), and the complete 10-phase RC-CT (CT_{10ph} , no margins for motion). The goal of this study was to evaluate which of these four methods results in the best tumor coverage.

MATERIALS AND METHODS

Patients and CT scans

Forty-one patients, with stage I to IIIB inoperable non-small cell lung cancer, underwent a free breathing CT immediately followed by an RC-CT scan. The RC-CT scan was performed using offline correlation of a 10-slice spiral CT scan (Siemens Sensation 10, Erlangen, Germany) that was modified to enable a low pitch (minimum 0.1), in combination with a respiratory signal obtained by a pressure sensor in a chest belt (AZ-733V, Anzai Medical Corporation, Tokyo, Japan). The raw CT data was reconstructed in 10 phases, from 0% to 100% in steps of 10% of the respiration period starting at end inspiration. In-house developed software with Matlab (Mathworks Inc, Natick, MA) was used to measure the motion of the lesion in all three orthogonal directions by choosing a clearly visible tumor edge and measuring the distance between the extreme positions in an axial, coronal and sagittal movie using the 10 respiratory phases reconstructed from the RC-CT scan. A slow CT was reconstructed by averaging these 10 phases of the RC-CT.

A detailed analysis was performed on patients with a motion in any direction of more than 7 mm, since we currently use an internal margin based on a motion of 7 mm (see Appendix). Since the influence of breathing was assumed to be largest for the primary tumor, only the primary tumor was delineated without taking into account the nodal status.

All patients gave written informed consent before entering this study, which was approved by the Medical Ethical Committee according to the Dutch law.

Target Volume Delineation

The internal target volume (ITV) was defined as the clinical target volume (CTV) with margins for tumor motion based on the ICRU 62¹.

We used four different methods to determine the margin for internal motion, resulting in four ITVs:

1. Free breathing CT: On the CT_{fb}, the gross tumor volume (GTV) was delineated with a window/level setting of 1700/-300 Hounsfield Units (HU), and a 5 mm margin for microscopic disease was added to obtain the clinical target volume (CTV). For the internal target volume (ITV), an 8 mm internal margin in all directions was added to the CTV to account for internal motion of the tumor (see Appendix). This was performed using commercial delineation software (Focal 4.2.0, CMS, St. Louis, USA). This ITV will later be referred to as ITV_{fb}.
2. Slow CT: On the CT_{slow}, the tumor was smeared out, and the resulting visible structure was delineated with a window/level setting of 1700/-300 HU. After adding the 5 mm margin to the GTV for microscopic disease, this was assumed to reflect the ITV_{slow}.
3. Half ventilation CT: With in-house built software, the motion of the tumor in 3 orthogonal directions was measured. Thereafter the CT from the phase with the tumor in its central position (half ventilation CT = CT_{hv}) was selected and exported to the delineation software. On this CT_{hv}, the GTV and CTV (= GTV+5 mm) were delineated. To obtain the ITV_{hv}, the CTV was expanded with an asymmetric margin of A/4, with A being the peak-to-peak amplitude of tumor motion in each of the three orthogonal directions (see Appendix for an explanation of this internal margin).
4. Ten-phase CT: In the same in-house built software, a volume was drawn around the moving visible tumor. This volume was termed the internal gross tumor volume (IGTV). To get the ITV_{10ph}, a 5 mm margin was added to the IGTV for microscopic disease. Finally, this ITV_{10ph} was projected on the slow CT and exported to the delineation software.

Influence of tumor motion on CTV coverage

To compare the influence of tumor motion on the actually delivered dose in the CTV for the four delineation methods, we chose to ignore set-up uncertainties. Therefore, treatment plans were made for the four different ITVs (XiO version 4.2.0, CMS, St. Louis, USA) using a multigrid superposition algorithm. To be able to compare the four methods, the same number of beams and similar gantry angles were used and only field blocking, weight and/or wedge angle were different between the four plans. Criteria for the planning were a dose of 70.2 Gy

(39×1.8 Gy, BID) to the ITV (acceptable inhomogeneity 95% – 107%) and a spinal cord dose below 55 Gy.

To estimate the actually delivered dose, the plans were projected on all the ten phases of the RC-CT. The CTV was contoured on all phases by delineating the visible tumor and 3D-expanding this volume with 5 mm for microscopic disease. For each phase the dose volume histogram (DVH) of the CTV was calculated, and the average dose distribution was calculated over all ten phases, for each of the four ITV treatment plans. From these DVHs, the minimal dose and the mean dose in the CTV was recorded.

Statistical analysis

All results are expressed as mean $\pm$ standard error of the mean (SEM). Statistical differences between paired parameters from treatment plans based on CT_{fb} versus CT_{slow} , CT_{hv} and CT_{10ph} were evaluated using the Wilcoxon signed rank test. The statistical difference in tumor motion between the different tumor locations were evaluated using a student t-test. Differences were considered to be significant if the 2-tailed p-value was less than 0.05.

RESULTS

Patient characteristics

The 3D vector motion of all 41 patients is displayed in Fig. 1. Two different groups were identified according to their location, upper lobe tumors ($n = 27$) versus lower lobe tumors ($n = 14$). The average 3D motion for the entire group was $8.1 \text{ mm} \pm 1.0 \text{ mm}$ (1 SD). There was no statistically significant difference of tumor motion between the tumor locations ($p = 0.136$), although the average motion was somewhat bigger for lower lobe tumors, on average $10.1 \text{ mm} \pm 2.1 \text{ mm}$, compared with the upper lobe tumors, on average $7.0 \text{ mm} \pm 1.0 \text{ mm}$. Fifteen patients (36.5%) showed a tumor motion $> 7 \text{ mm}$ in any direction. Due to technical reasons we could not complete a full analysis for three of these 15 patients. In the remaining 12 patients we performed a more detailed analysis (Table 1). As stated in the methods section, patients with N+ disease (8/12) were planned as if they had no metastatic lymph nodes (N0).

Figure 1: Overview of the 3D vector motion of all 41 patients for different tumor locations. The big markers indicate the patients which were studied more in detail and had an individual motion > 7 mm in any direction.

Table 1: Patient characteristics of the 12 patients with a tumor motion in any direction > 7 mm. The GTV size of the primary tumor was measured on the free breathing CT.

Patient no.	Age	Gender	Stage	GTV Size (cm ³)	Location
1	74	F	T2N0M0	64.9	Right upper lobe
2	56	M	T1N3M0	0.4	Left upper lobe
3	79	M	T2N0M0	65.0	Right lower lobe
4	79	M	T2N2M0	50.9	Right upper lobe
5	79	M	T4N0M0	12.2	Right lower lobe
6	58	F	T2N2M0	272.2	Right upper lobe
7	79	M	T4N2M0	33.5	Right lower lobe
8	60	M	T1N0M0	5.0	Left lower lobe
9	52	F	T2N3M0	79.0	Left lower lobe
10	71	M	T4N2M0	7.3	Right upper lobe
11	61	F	T2N2M0	101.9	Right upper lobe
12	60	M	T1N3M0	7.5	Right upper lobe

Tumor motion

For the 12 patients with a tumor motion > 7 mm in any direction, the mean amplitude for tumor motion was $5.0 \text{ mm} \pm 1.5 \text{ mm}$ (1 SD) in anterior-posterior (AP), $12.5 \text{ mm} \pm 1.7 \text{ mm}$ in craniocaudal (CC) and $3.1 \text{ mm} \pm 1.1 \text{ mm}$ in lateral (LR) direction (Table 2). The maximum craniocaudal motion was 28.5 mm. The quadratic sum of the motion, i.e. the 3D vector motion, was $14.5 \text{ mm} \pm 2.1 \text{ mm}$.

Table 2: Tumor motion (mm) in all three orthogonal directions, Anterior-Posterior (AP), Cranio-caudal (CC), Left-Right (LR) and the quadratic sum (Vector) for the 12 patients with a tumor motion > 7 mm

Patient no.	AP	CC	LR	Vector
1	9.8	28.5	14.7	33.5
2	16.6	18	0	24.5
3	1	15	3	15.3
4	3	15	2.9	15.6
5	0	12	2.9	12.3
6	10.8	12	2.4	16.3
7	0	9	0	9.0
8	2	9	0	9.2
9	2.5	9	2	9.6
10	8,8	9	5.9	13.9
11	6.4	9	3	11.4
12	2.5	7.4	2	8.1
MEAN	5.0	12.5	3.1	14.5
SEM	1.5	1.7	1.1	2.1

ITVs for the four different methods

As shown in Fig. 2, the ITVs based on the CT_{slow} , the CT_{hv} and the $CT_{10\text{ph}}$ were all considerably smaller than the ITV based on the CT_{fb} ($p = 0.002$, $p = 0.002$ and $p = 0.002$ respectively). On average, the ITV obtained from the CT_{slow} was the smallest ($49\% \pm 6\%$ of the ITV_{fb}), the ITV from the $CT_{10\text{ph}}$ and the ITV from the CT_{hv} were comparable, $57\% \pm 6\%$ and $59\% \pm 6\%$ of the ITV_{fb} respectively.

Figure 2: Internal target volumes for four different delineation methods in 12 patients. Volumes are shown relative to the free breathing Internal Target Volume (ITV_{fb}). On average (M) the volumes, ITV_{slow} , ITV_{mv} , and ITV_{10ph} , can be reduced to about 50%. Error bars on the average values show the Standard Error of the Mean.

CTV coverage

The CTV coverage for treatment plans based on the ITVs for the four different delineation methods for all 12 patients is shown in Fig. 3. The CTVs drawn for each technique were projected on all the 10 respiratory phases and the mean dose to the CTV was calculated (100% = 70.2 Gy). The mean CTV doses resulting from the 3 alternative plans were not significantly different from the conventional free breathing plan. Almost all mean CTV doses were between 95% and 107% of 70.2 Gy, suggesting that the margins used were adequate. When looking at the minimum doses per respiration phase, we found that in one patient in one phase the treatment plan based on the CT_{slow} and in one patient the treatment plan based on the CT_{fb} did not reach the 95% minimum dose requirement.

Figure 3: CTV coverage for four different treatment plans in 12 patients. The CTVs delineated on the free breathing scan (CTV_{fb}), on the slow CT (CTV_{slow}), the half ventilation CT scan (CTV_{hv}) and the 10 phases of the RC-CT (CTV_{10ph}) were projected on all 10 phases. For each phase of the respiration and for each technique the mean CTV dose was calculated, where 100% equals 70.2 Gy. In almost all patients good CTV coverage is achieved in all phases for all the four different treatment plans. Only in one patient in one phase the treatment plan based on the slow CT plan, the CTV did not reach the 95% dose requirement, and in one patient in two phases in the CTV_{fb} .

Although the mean CTV doses were thus adequate, localized underdosage in the CTV may occur, since the volumes were drastically reduced with the respiration correlated techniques compared to the conventional CTV_{fb} . Detailed analysis of the minimum doses in all datasets showed that there were several patients who showed a significant underdosage using the CTV_{slow} for treatment planning. To study this issue in more detail, a 3-point moving average was calculated for all minimal doses (for example for phase 2 the mean of the minimum doses of

phases 1, 2 and 3 was calculated). Assuming that cold spots in consecutive phases were located in the same area of the tumor, using the 3-point moving average, a dose less than 83% in three consecutive phases meant that it was likely there was a real coldspot, since a dose less than 83% in three phases cannot be compensated by normal doses in other phases ($((3 \times 83\% + 7 \times 100\%) / 10 \approx 95\%$). In Fig. 4, the 3-point moving average is shown for the minima in the CTV. For several patients it was shown that the CT_{slow} plan results in underdosage.

Figure 4: Representation of possible underdosage of four different treatment plans for 12 patients. The average minimum CTV dose of three adjacent respiration phases are shown for the treatment plans based on the CT_{fb} , the CT_{slow} , the CT_{hv} and the CT_{10ph} . For several patients the CT_{slow} treatment plan shows for almost every respiration phase a dose less than 83%, which strongly suggests a real underdosage. The underdosage in the treatment plan based on the CT_{fb} was due to geographical miss.

A possible explanation of this underdosage is shown in Fig. 5, where one Beams Eye View (BEV) of the treatment plan based on the CT_{slow} scan for a patient is projected on all 10 respiratory phases. It is clearly visible that for some phases the CTV is not adequately covered by the beam settings caudally.

Figure 5: Projection of one (gantry=0°) beam of the treatment plan based on the CT_{slow} scan for the patient with a cranial caudal motion of 15 mm, on all ten phases of the respiration. In blue the CTV is shown on all ten phases. It is clearly shown that in some phases the tumor is not adequately covered by the beam settings.

The underdosage for one patient using the treatment plan based on the CT_{10ph} can be explained by the difficult delineation of the IGTV for this patient without using positron emission tomography information. For some patients also the treatment plan based on the CT_{fb} showed underdosage, caused by the fact that the position of the isocentre, defined as the centre of mass of the ITV_{fb} , was located close to end inspiration instead of half ventilation, thereby causing a “geographical miss”. In Fig. 6, the craniocaudal trajectory is shown for the patient with the largest motion, with the position of the isocentre of the different treatment plans indicated.

DISCUSSION

The internal margin due to respiration has two main contributors in CT based radiotherapy planning. First, CT is a fast imaging technique that captures the

tumor at only one phase of the respiration². If the tumor is not at its central position when it is imaged, a systematic error is introduced possibly resulting in a geographic miss⁶. Second, the motion of the tumor with respiration causes an intra-fractional random error, which cannot be estimated on a single CT. The systematic error has a much larger contribution to the internal margin than the random error²⁵.

Figure 6: Craniocaudal trajectory of the center of mass of the tumor in one patient with a geographical miss. The locations of the isocenter of all treatment plans are indicated.

Respiration correlated CT (RC-CT) scans give information about tumor motion during respiration. Including this information in treatment planning may lead to more optimal treatment plans, avoiding geographical miss and minimizing margins. We showed that by using RC-CT the ITVs were significantly smaller than ITVs delineated in the CT_{fb} , suggesting that considerable dose escalation might be possible. However, analysis of the CTV coverage (see further) suggested that underdosage may occur when the ITV_{hv} is not used, such that the CT_{hv} seems to be the optimal dataset for delineation.

Tumor delineation

We used the RC-CT information to determine the ITV with three different methods, the CT_{slow} , the CT_{hv} and the CT_{10ph} . The smallest volume was obtained using the CT_{slow} scan. This can be explained by the “smear out effect”, which

plays an important role using the CT_{slow} . Regions where the tumor stays for very short time may therefore show a lower density and less contrast, and may therefore not be recognized as tumor. Therefore, the GTV delineation is very dependent on Window/Level settings. Especially the most cranial and caudal parts of the motion path can be missed. Furthermore, particularly in slow CT images, it is sometimes difficult to distinguish tumor from infiltrate.

The delineation of the $ITV_{10\text{ph}}$ for all the different phases of the respiratory cycle was labour-intensive. Although other authors also suggested using only a few phases to determine the ITV , this remains time-consuming and is more subject to variations in delineations¹².

First results, reported by Hugo *et al.*, showed that the mean position (half ventilation) during the treatment course and the breathing pattern remains stable, supporting the use of the half ventilation scan for tumor delineation¹⁰. In addition, in an earlier study we showed that the tumor motion does not change significantly during a course of radiotherapy³.

Internal margins and systematic errors

The internal margin due to respiration applied to the half ventilation CT, $A/4$ (with A the peak-to-peak amplitude), is quite tight, in comparison with other authors^{7,25}. However, the projection of these plans on all the respiratory phases did not show any underdosage, thus this margin recipe for internal motions seems to be valid. The average motion observed in our study was comparable with other studies using CT scans to evaluate tumor motion^{2,16}. In addition, we could not find a significant difference in tumor motion depending on the tumor location, which is in agreement with several other authors^{26,27}.

There was a difference in average tumor position between the different treatment techniques based on the RC-CT and the CT_{fb} scan for some patients. This resulted in a geographical miss when using the CT_{fb} . For patients with a smaller motion (< 7 mm) of the lesion this effect would of course be less pronounced and will probably not be clinically relevant because this systematic error will be covered by additional setup errors.

Tumor coverage

The next step was to study the influence of tumor motion on the CTV coverage for the four different treatment plans. For this purpose, we estimated the actually delivered dose distribution by projecting the treatment plans on all 10 phases of the RC-CT, and by averaging the dose distributions over the 10 phases. This part of the study was difficult, since due to limitations of the planning system it was not possible to summarize the dose volume histograms (DVH) of the different breathing phases. The mean doses in the different CTVs

were not significantly different between the treatment plans, although for one patient the 95% mean CTV dose was not reached (Fig. 4) for the treatment plan based on the CT_{fb} and the CT_{slow} . The minimum doses were more difficult to interpret, because the planning system only gave information about the absolute minimum dose, but it does not provide information about the location of this minimum. Therefore, it is possible that a cold spot (Dose < 95%) observed in one phase of the respiratory cycle is compensated by a higher dose (Dose > 100%) in the same voxel in another phase.

The minimal dose data were analyzed in more detail with the use of a 3-point moving average. Using these strict criteria, in several patients a real underdosage was found when using the CT_{slow} . This would give evidence for the beneficial effect of gated treatment for patients with a large tumor motion, like stated in other articles²³. However, it has to be realized that the analysis of CTV coverage was carried out for treatment plans based on the ITVs. The advantage of this choice was that we could separately analyze the effect of tumor motion on CTV coverage. However, it cannot be excluded that when repeating this analysis of CTV coverage for PTV plans, this would probably show less underdosage.

In conclusion, smaller internal target volumes could be reached using information about breathing and tumor motion. Although the CT_{slow} reduced the ITV the most, the delineation is inaccurate due to the blurring of the lesion at the edges. In addition, the CTV coverage analysis suggested that use of the CT_{slow} for delineation might result in underdosage. Therefore we propose that the treatment plan based on the half ventilation CT, combined with the individual anisotropic margins, is the most suitable method for delineation of lung tumors. This method is easy (only one phase), the tumor is clearly visible (no blurring due to motion) and the reduced margin is adequate.

APPENDIX: CALCULATION OF INTERNAL MARGINS

Internal margins can be calculated using the margin recipe proposed by van Herk²⁵. The total margin (M_{PTV}) can individually be calculated by the following formula:

$$M_{PTV} = 2.5\sqrt{\Sigma_{setup}^2 + \Sigma_{internal}^2} + 0.7\sqrt{\sigma_{setup}^2 + \sigma_{internal}^2} \quad (A1)$$

With Σ_{setup} and $\Sigma_{internal}$ being the standard deviation of the systematic error for setup and organ motion respectively, σ_{setup} and $\sigma_{internal}$ the standard deviation of the random error for setup and organ motion respectively.

Assuming a sinusoidal tumor motion with peak-to-peak amplitude of A , the internal margin can be calculated as follows:

$$\Sigma_{internal} = \sigma_{internal} = \frac{A}{2\sqrt{2}} \quad (A2)$$

Using this in Equation A1 gives:

$$\Sigma_{total} = \sqrt{\Sigma_{setup}^2 + \Sigma_{internal}^2} = \sqrt{\Sigma_{setup}^2 + A^2/8}$$

$$\sigma_{total} = \sqrt{\sigma_{setup}^2 + \sigma_{internal}^2} = \sqrt{\sigma_{setup}^2 + A^2/8}$$

When using a total PTV margin of 10 mm, and using our known set-up error from our institute, i.e. a standard deviation of 2 mm both for systematic and random errors based on EPID measurements, we assumed a tumor motion of 7 mm. The setup errors have been calculated in a previous group of lung cancer patients with the same immobilization method. Since this is the major source of setup uncertainties we could extrapolate these results to our patient group. For a tumor moving 7 mm with respiration, the margin recipe thus prescribes an internal margin of 8 mm for a free breathing CT based plan (setup errors excluded).

In half ventilation CT the systematic error is zero, while the random error $\sigma_{internal}$ of a tumor with motion A is again $A/2\sqrt{2}$. Applying the margin recipe yields an internal margin of $0.7A/\sqrt{8}$ or approximately $A/4$.

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CHAPTER

3

Phased attenuation correction in respiration correlated CT-PET

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ABSTRACT

Purpose: Motion of lung tumors with respiration causes difficulties in the imaging with CT and PET. Since accurate knowledge of the position of the tumor and the surrounding tissues is needed for radiation treatment planning it is important to improve CT-PET image acquisition. The purpose of this study was to evaluate the potential to improve image acquisition using phased attenuation correction in respiration correlated CT-PET, where data of both modalities was binned retrospectively.

Methods and materials: Respiration correlated scans were made on a Siemens Biograph Sensation 16 CT-PET scanner which was modified to make a low pitch CT scan and list-mode PET scan possible. A lollipop phantom was used in the experiments. The sphere with a diameter of 3.1 cm was filled with approximately 20 MBq ^{18}F -FDG. Three longitudinal movement amplitudes were tested: 2.5, 3.9 and 4.8 cm. After collection of the raw CT data, list-mode PET data, and the respiratory signal CT-PET images were binned to ten phases with help of in-house built software. Each PET phase was corrected for attenuation with CT data of the corresponding phase. For comparison, the attenuation correction was also performed with non-respiration correlated (non-RC) CT data. The volume and the amplitude of the movement were calculated for every phase of both the CT and PET data (with phased attenuation correction). Maximum and average activity concentrations were compared between the phased and non-phased attenuation corrected PET.

Results: With a standard, non-RC CT-PET scan, the volume was underestimated by as much as 46% in CT and the PET volume was overestimated to 370%. The volumes found with RC-CT-PET scanning had average deviations of 1.9% ($\pm 4.8\%$) and 1.5% ($\pm 3.4\%$) from the actual volume, for the CT and PET volumes respectively.

Evaluation of the maximum activity concentration showed a clear displacement in the images with non-RC attenuation correction, and activity values were on average 14% ($\pm 12\%$) lower than with phased attenuation correction. The standard deviation of the maximum activity values found in the different phases was a factor 10 smaller when phased attenuation correction was applied.

Conclusion: In this phantom study we have shown that a combination of respiration correlated CT-PET scanning with application of phased attenuation correction can improve the imaging of moving objects and can lead to improved volume estimation and a more precise localization and quantification of the activity.

INTRODUCTION

The combination of CT and PET scanning is the best way to image lung tumors for radiotherapy^{1,2}. However, with the integration of the two modalities in one machine problems may occur because CT-PET combines a fast multi-slice computed tomography (CT) technique with the much slower positron emitted tomography (PET), which should be considered when imaging lung tumors that may move up to 2 cm (peak-to-peak amplitude) with respiration³. A multi-slice CT scan of the thorax is completed in a few seconds and a tumor might be recorded in less than a second. Given the respiration cycle length (3-6 seconds) a moving tumor will most likely not be imaged at its average position in a multi-slice CT scan. The measurement of a single bed position with PET on the other hand takes about 5 minutes, and will represent several full respiratory cycles. On a PET image a moving tumor will thus be smeared out around its average position.

When the tumor movement is considerable these shortcomings of the two separate imaging modalities can lead to a distortion of the combined CT-PET image⁴⁻⁷ resulting in an underestimation of the measured standardized uptake value⁸ (SUV, which is a prognostic factor in lung cancer⁹) or a mislocalization of the tumor. Therefore, in radiotherapy, an isotropic margin of usually 15 mm is added to the tumor volume that is visible on CT-PET images to account for microscopic disease and for the possible mislocalization of the tumor on the CT-PET image and for tumor movement during radiation. Depending on the actual movement of the tumor this margin may be too small or too large leading to an under-dosage of the tumor or an over-dosage of the normal tissue, respectively.

To reduce the influence of movement on tumor location several new techniques have been developed. One of these involves correlation of the respiration signal to the scan data. This technique has previously been studied and shows good results for both CT^{10,11} and PET^{12,13}. In a respiration correlated CT scan (RC-CT) the respiration signal is recorded simultaneously with the acquisition of the CT data. This data is then binned retrospectively according to the respiration phase during which it was acquired. This provides information on the tumor position for each phase of the respiration.

Previous studies with 4D-CT-PET in patients^{14,15} show good results in reducing motion artifacts and increasing maximum SUV. In these studies however, the PET data is acquired in a gated mode and binned prospectively into 10 fractions of, for example, 500 ms. Because the bins have predefined time lengths problems may arise in the case of irregular breathing patterns.

The respiration correlated PET (RC-PET) scanning in the protocol proposed in this study uses continuous acquisition of the data in list-mode and phase binning is carried out retrospectively. In retrospective binning the time length of the bins

is determined individually for each period of the respiration. This way the binning can take into account a varying breathing frequency.

In a CT-PET scanner attenuation correction of PET can be performed automatically with information obtained from the fast CT scan. This CT image represents the position of the lung tumor and surrounding tissues during only part of the respiratory cycle, however, while the PET image contains the information of several full-breathing cycles. The CT image used to correct for attenuation then not fully corresponds to the PET image, thereby introducing motion artifacts¹⁶. After binning the CT and uncorrected PET data into corresponding phases, the tumor and tissue positions on PET and CT match more closely. Therefore an additional advantage of phase binning is the possible reduction of motion artifacts introduced to the PET scan during CT-based attenuation correction. Applying phase correlated attenuation correction will thus, most likely, lead to a more accurate correction and fewer introductions of motion artifacts. A great advantage of an improved attenuation correction would be the possibility of auto-segmentation for delineation of tumors based on the SUV.

For radiotherapy of lung cancer patients the ultimate goal is to adapt the margins needed in delineation of the tumor to the actual movement of the tumor in each patient. The aim of the current study is to show the potential of respiration correlation of PET with retrospective binning and of phased attenuation correction in RC-CT-PET scanning.

METHODS AND MATERIALS

Scans were made on a Siemens Biograph Sensation 16 CT-PET scanner (Siemens Medical Solutions, Hoffmann Estates, IL, USA). For the 16-slice spiral CT scan the following settings were used; 0.125 pitch, 3.0 mm/s table feed, 0.5 s rotation time, 16×1.5 mm scanning slice thickness, 3 mm reconstructed slice thickness, 500 mm transaxial field-of-view. The PET data was obtained in list-mode using a modified list-mode research package originally provided by Siemens. List-mode data were acquired for 10 minutes, retrospectively binned according to the respiration cycle and reconstructed with 3 mm reconstructed slice thickness.

Phantom

For analysis of the accuracy of respiration correlated PET scanning in general and phased attenuation correction in particular, a so-called lollipop phantom was used (Fig. 1).

The sphere at the end of the rod was filled with approximately 20 MBq ^{18}F -fluoro-deoxyglucose (FDG). A sphere with a diameter of approximately 3.2 cm and a volume of 16.0 cc is used (Model ECT/HS/ST, Data Spectrum Corporation (DSC), Hillsborough, NC, USA). The positions 1 to 5 (see Fig. 1a) can be varied in order to get different movement amplitudes. The sphere moved parallel to the cranial-caudal axis. Three longitudinal peak-to-peak amplitude settings were tested of 2.5, 3.9 and 4.8 cm, respectively. The rod was mounted on a disc, which is powered by a motor. The frequency of the motion was set to approximately 18 rotations per minute, corresponding to 0.3 Hz. This is comparable to the average respiration frequency of humans.

The respiration signal was measured with two systems; the first system was synchronized with the CT on time, the second with the PET on time. For CT synchronization the Anzai system (AZ-733V, Anzai Medical Corporation, Tokyo, Japan) was used. This consists of a pressure load cell that is fitted into a chest belt. The signal for the PET data was acquired with a soft, foam-filled sensor (Graseby, UK) connected via a tube to an air pressure detector (BioVET monitoring system, Spin Systems, Brisbane, Australia). This system is based on the flow in the tube caused by pressure on the foam, and not like the Anzai system on the pressure itself.

The belt, in which both cells are fitted, was wrapped around the bottom plate of the phantom and connected to the rod through a rubber band as shown in Fig. 1b.

Figure 1: The lollipop phantom; a) schematically and b) actual.

The maximum movement amplitude found for lung tumors is about 2 cm with an average of 12 mm in cranial-caudal direction³. The sensitivity of the Anzai, however, was not suitable for measurement of amplitudes smaller than the 2.5 cm tested in this study.

For comparison purposes regular non-RC-CT and PET scans were also made. To show the advantage of phased attenuation correction, correction of the phased PET data was also performed with the non-RC-CT scan.

Due to a scanner problem no non-respiratory correlated CT-PET scan was made for the sphere moving with an amplitude of 4.8 cm.

Phase binning

CT

After acquisition, the CT data was binned to ten phases according to the respiration phase during which it was recorded. The respiration signal was synchronized with the CT data by recording the CT on time. Phase binning was performed with a modified version of a software package that was provided by Siemens. Each period was divided into ten bins of 10% each, where phase one was chosen to start at the maximum amplitude.

PET

Phase binning was also performed retrospectively. A trigger could be set at an arbitrary amplitude of the respiratory signal. The trigger signal was used for retrospective sorting of the raw list-mode data into 10 phase bins. The binning was, like the binning of CT data, based on phase only and not on the amplitude. The trigger, and thus phase one, was again chosen to start at the maximum amplitude of the signal.

Attenuation correction

The protocol proposed here required attenuation correction to be applied outside the scanner. Software was therefore developed in-house (Matlab, Mathworks Inc, Natick, MA, USA). The attenuation correction process as described by Kinahan *et al.*^{17, 18} was followed. This correction is based on the following formula:

$$\int_{-\infty}^{+\infty} f(x, y) dy' = e^{-\int_{-\infty}^{+\infty} \mu(x, y) dy'} \cdot p(x', \phi)$$

where the term on the left represents the actual distribution of FDG in the patient, the exponential term stands for the attenuation along the line of response (LOR) at detector position $x'(x, y)$ and projection angle $\phi(x, y)$, and $p(x', \phi)$ is the measured signal.

An overview of the steps in the attenuation correction process is given in Fig. 2.

Figure 2: Overview of the steps in the attenuation correction process.

After the field of view (FOV) and number of pixels have been equalized the map of attenuation correction factors (ACF) can be obtained through forward projection. With forward projection a sinogram is constructed. This consists of the integrals along the LORs. The attenuation correction factors in the sinogram then need to be multiplied by the pixel size to account for the path length. Taking the exponent completed the correction factors.

The raw PET data of the corresponding slice and phase is also converted to a sinogram. If the PET and CT images have matching FOV and the same number of pixels, each element of the PET sinogram has a corresponding element in the ACF sinogram. Multiplying each element of the PET sinogram with the value of the corresponding ACF element will perform the attenuation correction. The corrected PET sinogram can then be converted back to an image through back projection or iterative image reconstruction (OSEM).

The procedure discussed here was applied to the data of every slice and every phase.

Analysis

Maximum activity concentration values in each of the phases obtained with the phased and non-RC attenuation correction were determined and the percentage deviation per phase was calculated.

The accuracy of the respiration correlation was determined by comparing the movement amplitude of the spheres on the PET data to the motion found with RC-CT and to the real amplitude. For the measurements on the CT and PET images, the absolute vertical position of the spheres (centre) was calculated on sagittal images for each of the ten phases. The maximum displacement was calculated as the distance of the minimum and maximum sphere position.

The volumes of the spheres on the PET and CT images were compared to the volume of the actual sphere. This analysis was used to determine both the accuracy of the respiration correlation as well as that of the phased attenuation correction. The PET volume was determined using a 34% threshold in the region of interest, as was determined with in-house experiments following the methods described by Erdi *et al.*¹⁹ and Daisne *et al.*²⁰. The maximum activity concentration (100%) was determined by averaging the nine highest values found within all the phases. This average was taken to account for the influence of extreme values.

The sphere volumes in CT images were determined after manual delineation of the sphere with window width and window level settings of 1000 and 0, respectively.

RESULTS

Fig. 3 gives an example of the phased PET (bottom) and CT (top) images of the experiment with a 2.5 cm amplitude.

In Fig. 4 two images of the same slice and phase of a PET scan from the experiment with a 3.9 cm amplitude are given. On the left the image is shown where attenuation correction of the phased PET scan was applied with phased and RC-CT data. The image in the middle shows the same slice and phase of the same PET scan, but now attenuation correction was applied with the use of a non-RC CT scan. For both images of the phased PET (mid and left, Fig. 4) the same window width and window level settings were used, scaled between 0 to the maximum activity concentration found in the dataset with phased attenuation correction. The image on the right in Fig. 4 is the non-RC PET image of the same experiment. All three images show the same area. Because the amplitude (3.9 cm) is larger than the sphere diameter (3.2 cm) the non-RC PET image (right) shows a region with low activity in the middle.

Fig. 3: 10 phases of the respiration correlated PET (bottom) and CT (top) data for a motion amplitude of 2.5 cm.

Measurements of the maximum activities were performed for the ten phases of both the phased attenuation correction and the non-respiratory correlated attenuation correction.

The dataset obtained with non-correlated attenuation correction showed much larger standard deviations than the dataset with phased attenuation correction. Average maximum activity concentrations of 44864 ± 6054 Bq/ml (13.5%) and 40066 ± 5142 Bq/ml (12.8%) were found for the two experiments with non-correlated attenuation correction, while in the data with phased attenuation correction average maximum activity concentrations were 49431 ± 622 Bq/ml (1.3%) and 49852 ± 771 Bq/ml (1.5%).

In the experiment with a 2.5 cm amplitude the average and maximum difference between the two correction methods were 9.2% and 28.2% respectively. In the second experiment average and maximum deviations of respectively, 19.6% and 30.0% were found between the two correction methods (Table 1).

Figure 4: PET image with phased and respiration correlated attenuation correction (left), with non-RC attenuation correction (mid) and of the non-respiration correlated PET (right). The two phased images were made with the same window width and window level settings; other settings were used for the non-respiration correlated image. All three images show the same area.

Table 1: Percentage difference, for the 10 phases, between the maximum activity concentrations measured in data reconstructed with non-respiration correlated attenuation correction and those measured in data that was reconstructed with phased attenuation correction.

Phase	Experiment 1 (2.5 cm amplitude)	Experiment 2 (3.9 cm amplitude)
1	2.4	-30.0
2	-0.3	-28.7
3	-14.8	-29.7
4	-28.2	-4.6
5	-26.3	-2.5
6	-20.5	-21.0
7	-11.1	-20.2
8	-0.2	-14.5
9	3.1	-16.7
10	4.2	-28.4
average	-9.2	-19.6

The maximum value found in the non-RC PET data of experiment 1 with a 2.5 cm amplitude was 52839 Bq/ml, which is 7% higher than the average maximum activity concentration (49431 Bq/ml) found for the RC-PET data with the same amplitude. In the experiment with a 3.9 cm amplitude a maximum activity concentration of 12316 Bq/ml was found for the non-RC PET data, that is 75% lower than the average maximum activity concentration (49852 Bq/ml) of the RC-PET data of the same experiment.

Motion amplitude

The center positions of the spheres for the different phases of CT and PET, reconstructed with respiration correlated attenuation correction, are plotted in Fig. 5. In Table 2 an overview of the movement amplitudes is given.

Figure 5: Centre position of the sphere at the ten phases on CT and PET, reconstructed with respiration correlated attenuation correction, images for three movement amplitudes of 2.5, 3.9 and 4.8 cm, respectively.

Table 2: Movement amplitudes (cm) measurement accuracy determined for the three experiments in both CT and PET, attenuation correction was performed with respiration correlated CT data, compared to the true amplitude.

Experiment	True	CT	PET
1	2.5 ± 0.1	2.4 ± 0.3	2.1 ± 0.3
2	3.9 ± 0.1	3.9 ± 0.3	3.9 ± 0.3
3	4.9 ± 0.1	4.8 ± 0.3	4.8 ± 0.3

Volume

In Table 3 an overview of the CT and PET volumes, for the clinical and phased data, is given. The actual sphere volume is 16.0 cc.

In the non-RC CT scans the volume was underestimated by 22% and 46% in the two experiments. The PET volume in the non-RC scans on the other hand was overestimated by 156% in the first experiment and by as much as 370% in the second experiment.

The phased scans of CT show that the protocol used here results in measured volumes of 16.1 ± 0.7 , 16.2 ± 0.6 and 16.7 ± 0.9 cc for the three experiments, respectively. The volumes found in the PET images are 16.2 ± 0.6 , 16.5 ± 0.3 and 16.1 ± 0.7 cc, respectively.

The average and maximum deviation from the true volume was 1.4% and 8.1% (experiment 3, phase 4) respectively for PET. The volumes determined with CT have an average deviation of 1.9%. A maximum deviation of 10.6% (experiment 1, phase 8 and experiment 3, phase 1) was found for CT based volumes.

Table 3: Volumes (cc) as determined for the non-respiration correlated CT and PET images and for those recorded with respiration correlation. The true volume of the sphere is 16.0 cc. Due to a scanner problem no non-respiratory correlated CT-PET scan was made for the amplitude of 4.8 cm.

		Experiment 1 (2.5 cm amplitude)		Experiment 2 (3.9 cm amplitude)		Experiment 3 (4.8 cm amplitude)	
		CT	PET	CT	PET	CT	PET
Non-RC CT-PET		12.5	40.9	8.6	75.3	×	×
RC-CT-PET	Phase 1	15.9	16.4	17.2	16.7	17.7	15.6
	Phase 2	16.2	15.6	16.5	16.7	16.3	15.8
	Phase 3	15.3	15.6	15.5	15.9	17.3	15.5
	Phase 4	16.0	16.8	16.3	16.6	16.0	17.3
	Phase 5	15.7	16.9	14.8	16.8	17.6	16.5
	Phase 6	16.6	15.6	16.1	16.5	17.6	16.7
	Phase 7	15.7	15.6	16.4	15.9	16.4	16.1
	Phase 8	17.7	16.3	16.6	16.7	16.2	15.0
	Phase 9	16.0	16.7	16.0	16.6	14.9	15.9
	Phase 10	15.7	15.9	16.2	16.5	16.7	16.2
Average $\pm$ SD		16.1 $\pm$ 0.7	16.2 $\pm$ 0.6	16.2 $\pm$ 0.6	16.5 $\pm$ 0.3	16.7 $\pm$ 0.9	16.1 $\pm$ 0.7

DISCUSSION

This phantom study showed that phased attenuation correction of respiration correlated PET images compared to non-respiration correlated attenuation correction leads to a more accurate localization of the tumor, an improved tumor volume definition, and a more precise determination of the activity concentra-

tion, and more particularly the maximum activity concentration. Respiration correlated scanning and phased attenuation correction will therefore offer new and more precise information of the tumor, thus providing a better basis for radiation treatment planning. With information of tumor motion, internal margins can be determined for each patient individually and adapted to the actual movement in each direction. Moreover, with respiration correlation and phased attenuation correction an SUV determination is more reliable and thus better suited for use in tumor characterization and automatic delineation. To achieve good image quality in respiration correlated PET imaging in patients an optimal acquisition time and number of bins should be further investigated in a patient trial.

In Fig. 4 the image with non-respiration correlated attenuation correction shows that the maximum activity is clearly misplaced. In clinical practice such a motion artifact could result in a mislocalization of the tumor. Moreover the average maximum activity concentration found in the sphere is lower than in the data that was corrected with phased CTs. In a recent study with a gated, prospectively binned, PET protocol Nehmeh *et al.*¹⁵ compared attenuation correction with a non-RC CT to RC-CT. They found that phased attenuation correction led to an improved match of CT and PET data of up to 41%, while maximum SUV was increased by a maximum of 16%. Pevsner *et al.*⁸ found an underestimation of the activity concentration in the sphere between 19 and 75%.

In the current study the difference in average maximum activity concentrations between the two attenuation correction methods reached up to 31%, with an average of about 17% for the two experiments combined. It must be kept in mind however that in our experiments the spheres were simply placed in air, and little actual attenuation will have occurred. One could argue that the difference between phased and non-RC attenuation correction might therefore even be bigger in the presence of more attenuation. However, in the imaging of moving lung tumors, not all the attenuating tissues will move to the same degree as the tumor. The correction of attenuation that was caused by less mobile tissues will therefore not improve distinctly with the use of phased attenuation correction. The benefits of phased attenuation correction will largely depend on the relative contribution to the attenuation by moving tissues as compared to the more stationary tissues and might thus not be as striking as suggested by the results presented in this paper.

The volume of the sphere is greatly underestimated in non-RC CT images in this study, up to 46% deviation from the true volume. Others have found volume deviations between minus 35% and plus 79% in non-RC CT in comparison with RC-CT^{15, 21}. This large range, both underestimating and overestimating the

volume, emphasizes again the importance of using corresponding RC-CT images for attenuation correction.

Volumes determined from the respiration correlated CT and PET images both show only minor deviations from the true volume, 1.9% and 1.4% on average for the respective modalities. This good result demonstrates the accuracy of both the phase binning process and the phased attenuation correction.

Various publications^{15, 22-24} have reported a decrease in tumor volume when using gated PET as compared to non-RC scanning, regardless of their attenuation correction methods. The volumes determined in the current study from the non-RC data confirm that in PET smearing appears with a non-RC scanning protocol (Table 3). When the motion amplitude is smaller than the sphere's diameter, as was the case in experiment 1 with a 2.5 cm amplitude, non-respiration correlated PET data showed a average maximum activity concentration that was 7% higher than the average maximum activity concentration found with the RC-PET data. This high average maximum activity concentration was found in the centre region of the motion, where some part of the sphere was present in every phase. In the 3.9 cm amplitude experiment the average maximum activity concentration found in the non-RC data was 75% lower than found with RC-PET. Since the volume is determined with a threshold of 34% of the maximum activity concentration, the threshold value is set too low and will thus cause an even bigger overestimation of the PET volume than smearing alone. The difference in the ratio between the sphere diameter and the motion amplitude thus can explain the relatively bigger overestimation of the PET volume with the non-RC PET scan in experiment 2, which had a deviation of 370% from the actual volume as compared to a deviation of 156% in experiment 1.

The motion amplitudes found with RC-PET and RC-CT (Table 2) corresponds well with the actual displacement. Taking the measurement error of 3 mm, equal to the slice thickness, and the partial volume averaging effect into consideration the calculated differences will not be significant. This suggests an accurate phase binning for both modalities.

The CT and PET phases in experiments 2 and 3 (motion amplitudes of 3.9 and 4.8 cm, respectively) show good correlation. The determinations of the sphere centre in experiment 1, however, indicate that a slight phase shift was still present. Because the respiratory signals were recorded with different devices the starting point of the first phase bin in CT and PET was determined with different software. For both systems the maximum amplitude of the respiratory signal was set as the starting point. Differences in the respiration measurement techniques of the two systems may have caused the resultant phase shift. Synchronization of both modalities with a single device for respiration correlation will most likely dispose of this resulting phase difference.

CONCLUSION

Valuable information is lost when scans, either CT or PET, are not correlated with respiration. Appropriate attenuation correction is at least as important. Phased attenuation correction not only gives a more accurate overall correction, but perhaps even more important, it provides a better match of PET and CT and results in a more reliable SUV and tumor volume. Combining RC-CT-PET scanning with phased attenuation correction will result in images with less smearing, less motion artifacts and thus in improved volume estimation and localization and quantification of the activity concentration.

In future studies the feasibility of phased attenuation correction in respiration correlated CT-PET for lung cancer patients will be examined.

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CHAPTER

4

Respiratory-Gated CT as a Tool for the Simulation of Breathing Artifacts in PET and PET/CT

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ABSTRACT

Respiratory motion in PET and PET/CT studies blurs the images of tumors and causes attenuation-related errors. In rare instances, this problem even causes localization errors and the disappearance of tumors that should be detectable. Attenuation errors are severe near the diaphragm and can be enhanced when the attenuation correction is based on a CT series acquired during a breath-hold. To quantify the errors and identify the parameters associated with them, we performed a simulation based on respiratory-gated CT studies of five lung cancer patients. Diaphragmatic motion ranged from 8 to 25 mm in the five patients. The CT series were converted to 511-keV attenuation maps which were forward-projected and exponentiated to form sinograms of PET attenuation factors at each phase of respiration. The CT images were also segmented to form a PET object, moving with the same motion as the CT series. In the moving PET object, spherical 20-mm mobile tumors were created in the vicinity of the dome of the liver, and immobile 20-mm tumors in the mid chest region. The moving PET objects were forward-projected and attenuated, then reconstructed in several ways: phase-matched PET and CT; gated PET with ungated CT; ungated PET with gated CT; and conventional PET. Spatial resolution and statistical noise were not modeled. In each case, tumor uptake recovery factor was defined by comparing the maximum reconstructed pixel value with the known correct value. Phase-matched gated PET and CT gave essentially perfect PET reconstructions in the simulation. Gated PET with ungated CT gave tumors of the correct shape, but recovery was too large by an amount that depended on the extent of the motion, as much as 90% for mobile tumors and 60% for immobile tumors. Gated CT with ungated PET resulted in blurred tumors and caused the recovery errors between -50% and $+75\%$. Recovery in clinical scans would be 0% to 20% lower than stated, because spatial resolution was not included in the simulation. Mobile tumors near the dome of the liver were subject to the largest errors in either case. Conventional PET for 20 mm tumors was quantitative in cases of motion less than 15 mm, because of canceling errors in blurring and attenuation, but the recovery factors were too low by as much as 30% in cases of motion greater than 15 mm. Quantitative PET imaging near the diaphragm requires proper matching of attenuation information to the emission information. The problem of missed tumors near the diaphragm can be reduced by acquiring attenuation correction information near end expiration. A simple PET/CT protocol requiring no gating equipment also addresses this problem.

INTRODUCTION

Accurate measurement of tumor standard uptake values (SUV) is an important requirement in many PET applications. In whole-body PET studies SUV is believed to be an indicator of tumor avidity and a predictor of patient survival rates¹⁻⁴, and accurate quantitation is important when autodelineation is used in therapy planning⁵⁻⁸. Indeed, an important requirement for PET in oncology is to detect every tumor that is large enough and has enough tracer uptake to be detectable, even when measurement errors have the potential to cause image-reconstruction errors that result in a missed or mislocated tumor. Respiratory motion is one factor with the potential to reduce quantitative accuracy and to cause missed or misplaced tumors near the diaphragm. For example, the report by Keall *et al.* shows that significant motion is observed in many regions of significance to oncology⁹ and the report by Osman *et al.* indicates the possibility of localization and detection errors near the diaphragm¹⁰. In the state-of-the-art, however, PET and PET/CT reconstruction algorithms are based on the assumption that the patient does not move during the measurement of the emission sinogram and the attenuation factors (AF).

Motion causes two phenomena which lead to image artifacts. First, the tracer distribution moves, blurring the image. Second, the AFs change with time, leading to too much or too little correction for attenuation on some lines of response. The latter problem is severe near the diaphragm and is sometimes enhanced when the AFs are based on a CT series acquired during a breath-hold, with the associated problem that lesions in fusion images of CT and PET, could be mislocated, e.g. from the liver into the lung^{10,11}. One goal of this paper is to indicate clearly, in the case of PET tumor imaging, what kinds of error arise from respiratory motion in conventional PET (CP), considering the complicated interplay between these two sources of error.

Another goal of this paper is to demonstrate the advantages of respiratory gating (RG) in acquisition of the PET or AF information¹²⁻¹⁴. We are interested in respiratory-gated PET (GP), in respiratory-gated CT (GCT), in PET/CT performed with attenuation measurements from non-gated CT, in non-gated PET/CT with gated CT, and in PET/CT in which both modalities are gated. Practical problems are associated with clinical and phantom-based investigations of the benefits of gating. One problem is the low statistics in each phase of GP. Another problem is that laboratory studies are likely to use an unrealistic model of the breathing seen in patients. In this paper, we avoid those problems by using GCT as the basis for a simulated PET emission data set, created with a digital computer. To our knowledge such a simulation has not yet been reported in the literature. A preliminary version of this work was presented earlier¹⁵.

This approach can address the following issues. How well does conventional PET do in the presence of such motion? Does the answer depend strongly on the location of the tumor that is affected by motion? Is phase matching of GP and GCT quantitative? Does GP or GCT by itself solve the motion problem, delivering a quantitative result? What PET/CT imaging protocols, based on technology available today, address respiration-related errors?

METHODS

Our investigation is derived from a set of five GCT studies of lung cancer patients, selected at random from the population of patients receiving GCT at Maastricht Clinic. Patients' breathing was monitored by a strain gauge worn around the abdomen¹⁶. Low-pitch helical CT scans of the chest were performed with a sixteen-slice CT scanner (Sensation 16, Siemens AG, Forchheim, Germany). The data for the five patients were retrospectively reconstructed into images representing a 500 mm field of view sampled by a 512×512 matrix, with 3 mm between slices, and 10 phases of the respiration cycle starting at end inspiration. GCT images were converted to a map $\mu(\vec{b}, r)$ of PET attenuation coefficients¹⁷ at each phase of respiration r and image location $\vec{b}$. These were transformed to a sinogram of AF values at those phases by applying a high-resolution forward projector¹⁸ then rebinned to 168 radial and 168 angular bins. Our equation for this is

$$AF(\vec{d}, r) = \exp(-R\{\mu(\vec{b}, r)\}), \quad (1)$$

where R is the Radon transform and $\vec{d}$ represents a sinogram bin. Related to this quantity is the average attenuation, which, if the patient's breathing pattern were perfectly regular, would be the same as the AF in a high-quality scan in a PET attenuation scan with transmission sources. For us the defining equation in the case of ten gates is

$$AF(\vec{d}) = \frac{1}{10} \sum_r AF(\vec{d}, r). \quad (2)$$

Other related quantities are the sinogram of attenuation correction factors (ACF) in each gate,

$$ACF(\vec{d}, r) = \frac{1}{AF(\vec{d}, r)}, \quad (3)$$

and the ACF corresponding to the average attenuation,

$$ACF(\vec{d}) = \frac{1}{AF(\vec{d})}, \quad (4)$$

The CT series were also segmented to form a simulated PET volume in which a solitary tumor could be imbedded. The PET volumes were defined through a segmentation procedure whose parameters were determined by studying typical whole-body PET/CT studies. First, to enable a smooth segmentation, the volume was smoothed in three dimensions with a gaussian kernel whose full width at half maximum was 3 mm. Next, the segmentation procedure was run. Pixels with CT numbers between -25 and 200 HU, representing soft tissue and marrow, were assigned a SUV of 1.0. Pixels between -300 and -25 HU (fat) were assigned SUV = 0.3. Pixels between -950 and -300 (lung) were assigned SUV = 0.17. Pixels above 200 HU (bone) were assigned SUV = 0.1. This procedure had several unrealistic characteristics. For example, the blood in the ventricles of the heart was treated like soft tissue and clothing and blankets were sometimes treated like fat.

By inspecting coronal and sagittal sections through the sequence of image volumes of each of the five patients, we located the dome of the liver (DOL) in each phase of respiration. We used a model in which the motion of the DOL is entirely in the superior / inferior (SI) direction, the most common direction of tumor motion in the survey of Keall *et al.*⁹ and in the study by Liu *et al.*¹⁹ We simulated a solitary tumor in one of six places: three mobile tumors were simulated on the right side, and three immobile ones in the mid chest. The mobile ones were assigned a position relative to the DOL position in each gate. Each simulated tumor, mobile or immobile, was assigned SUV = 5.0 and a diameter of 10, 20, or 30 mm. A mobile tumor denoted DOL was centered 5 mm below the DOL position. A mobile tumor denoted LRL was defined 25 mm higher than the DOL tumor, in the lower right lung, that is, 20 mm above the dome of the liver. A mobile tumor denoted ULL was defined 15 mm below the DOL tumor, in the upper lobe of the liver. The three immobile tumors were placed in the mid chest and were denoted MC1, MC2, and MC3. Their SI coordinates were set equal to the mean positions of the mobile LRL, DOL, and ULL tumors, respectively. The six tumor locations are indicated by Fig. 1.

Figure 1. Coronal section through a segmented PET object, showing the locations of simulated tumors. The patient is shown at end inspiration. Abbreviations refer to gated lower right lung, dome of the liver, upper lobe of the liver, and mid-chest positions 1, 2, 3.

Because there were in principle three tumor diameters, six locations, five patients, and ten phases of respiration, this procedure should lead to the creation of 900 simulated PET volumes to be processed in our study. However, we processed data for the 10 and 30 mm tumors in only a few cases when it became clear that most of the results could be understood by considering just the 20 mm tumors. The voxelized PET volume in each gate r and voxel $\vec{b}$ is denoted $O(\vec{b}, r)$. We transformed these into unattenuated 2D sinograms, $p_{no_att}(\vec{d}, r)$, using the forward projector referred to above, again with 168 radial and 168 angular samples. The equation for this is

$$p_{no_att}(\vec{d}, r) = R\{O(\vec{b}, r)\}. \quad (5)$$

Attenuated 2D PET sinograms were made by multiplying the PET sinograms by the AF sinograms:

$$p(\vec{d}, r) = AF(\vec{d}, r) \times p_{no_att}(\vec{d}, r). \quad (6)$$

These would be the sinograms measured by a PET scanner with respiratory gating, apart from effects such as limited spatial resolution, scattered radiation, and spatial sensitivity variations. Those effects were not included in the simulation, so that the study could focus exclusively on effects due to motion. We also were interested in the time-averaged sinogram, defined as

$$p(\vec{d}) = \frac{1}{10} \sum_r p(\vec{d}, r). \quad (7)$$

Six types of PET volume were extracted for analysis and comparison. The first of these was $O(\vec{b}, r)$, described above. Second was the time average of these, denoted

$$O(\vec{b}) = \frac{1}{10} \sum_r O(\vec{b}, r). \quad (8)$$

Third was the series derived by reconstructing the gated sinograms with attenuation correction derived from the matched CT gate. These were made with filtered backprojection according to the equation

$$I_{GP-GCT}(\vec{b}, r) = R^{-1} \{ p(\vec{d}, r) \times ACF(\vec{d}, r) \}, \quad (9)$$

where R^{-1} is the inverse Radon transformation. Although iterative reconstruction is now the usual reconstruction method in whole-body PET^{20,21}, filtered backprojection is appropriate in the absence of statistical noise, because it is a gold standard and because there is no question of when to stop the iterations. With the exceptions defined by equations 13 and 14 below, we do not blur the reconstructed images to give a clinical level of spatial resolution.

The fourth PET series to be compared was derived by reconstructing gated sinograms with the average attenuation. This series was associated with the respiratory gate index used for PET reconstruction. It represents, under the assumption of regular breathing, what is achievable when gated PET is used on a PET scanner with a conventional measurement of the attenuation, i.e. a 511-keV transmission scan with rotating rods of ⁶⁸Ge. The defining equation is

$$I_{GP}(\vec{b}, r) = R^{-1} \{ p(\vec{d}, r) \times ACF(\vec{d}) \}. \quad (10)$$

Similarly, the fifth PET series to be compared was obtained when the emission sinograms were time-averaged, i.e. not gated, but the CT was gated. The PET series is associated with the respiratory gate index of the CT that is used for AC. Considering this dataset, one can ask whether a particular state of respiration can be used for attenuation correction. Also, we can investigate what happens when the free-breathing patient is imaged with a very fast CT scan at an arbitrary state of respiration. The defining equation for this case is

$$I_{GCT}(\vec{b}, r) = R^{-1} \{ p(\vec{d}) \times ACF(\vec{d}, r) \}. \quad (11)$$

Conventional PET was the sixth PET series to be compared. In this case, both the emission and attenuation were time-averaged. Again operating under the assumption that one breathing cycle is the same as a long time average, we have the following defining equation.

$$I_{CP}(\vec{b}) = R^{-1} \{ p(\vec{d}) \times ACF(\vec{d}) \} = \frac{1}{10} \sum_r I_{GP}(\vec{b}, r). \quad (12)$$

The seventh, final type of PET image to be compared was the GCT image based on CT acquired at EE or EI. In these cases, and these cases only, we attempted to model the spatial resolution of state-of-the-art PET scanners. Our equations for these images are

$$I_{GCT-EE}(\vec{b}) = I_{GCT}(\vec{b}, r)_{r=EE} \otimes g(\vec{b}), \quad (13)$$

and

$$I_{GCT-EI}(\vec{b}) = I_{GCT}(\vec{b}, r)_{r=EI} \otimes g(\vec{b}), \quad (14)$$

where the symbol $\otimes$ represents convolution and g is a three-dimensional gaussian kernel, whose full width at half maximum was set to 6.4 mm to represent 4 mm instrument resolution and 5 mm smoothing to reduce image noise.

We analyzed each of these PET volumes in three ways, based on a maximum-intensity coronal projection over a 10-mm coronal slice that contained the tumor. First, the SUV of the tumor was defined as the maximum pixel value in the coronal slice containing the tumor. We converted this to a percent recovery figure by dividing by the expected SUV value (the value is 5.0) and multiplying by 100. This maximum-pixel method, and related methods based on regions around the maximum, are used commonly in clinical PET and PET/CT¹⁻⁴. Second, the image of the tumor itself was inspected to see if the correct shape is obtained in the reconstruction. A round shape of the same diameter as the lesion (10, 20, or 30 mm) was expected. Third, the image of the surrounding tissues was inspected visually for artifacts.

RESULTS

The diaphragmatic motion model

The motion of the DOL in our model is characterized in each patient and at each phase of respiration by a single value, the z coordinate used to simulate the positions of the mobile tumors. The total excursions in z (and the root mean square) for the five patients, ranked from least motion to most motion, were: patient 1, 8.4 mm (2.8 mm); patient 2, 11.1 mm (3.4 mm); patient 3, 13.8 mm (4.3 mm); patient 4, 19.8 mm (5.4 mm); and patient 5, 25.2 mm (8.5) mm.

Patients 3 and 5 had actual large tumors in the lower right lung. In both cases, the diaphragm could be visualized in sagittal and coronal sections, allowing us to define the DOL unambiguously. In both cases, our methodology placed the

simulated LRL tumor inside these actual masses. The other three patient studies had no such large masses in the lower right lung.

Typical images

Fig. 2 presents coronal sections through $O(\vec{b}, r)$, $O(\vec{b})$, $I_{GP-GCT}(\vec{b}, r)$, $I_{GP}(\vec{b}, r)$, $I_{GCT}(\vec{b}, r)$, and $I_{CP}(\vec{b})$ for patient 4. The figure also indicates which phases represent end expiration (EE) and end inspiration (EI) as determined from the DOL position. The percent recovery of the lesion SUV in each position is printed in each frame of the picture.

Figure 2. Coronal sections through PET series associated with the 20-mm dome of the liver tumor in patient 4. The figure presents the PET object at each gate, the average object, three gated reconstructed image sequences, and a non-gated reconstruction, as explained in the text. SUV recovery is indicated with a percent value in each frame of the picture. Arrows indicate prominent artifacts. Abbreviations refer to gated PET, gated CT, conventional PET, end expiration, and end inspiration.

In this simulation, the phase-matched reconstructions (GP-GCT) produced correct SUV recovery and created no striking artifacts. Actually, recovered values were in most cases 1% to 2% too high because of reconstruction noise.

Fig. 2 also indicates that the recovery varied from phase to phase when one used the GP and GCT methods. This is discussed in the following sections. Reconstruction artifacts were evident when one used either of those methods. They were particularly noticeable near the diaphragm. These are indicated with arrows in Fig. 2.

Using this approach, we simulated mobile lung lesions 20 mm in diameter in all six of the locations introduced above, and saved the results. We simulated 10 and 30 mm lesions in our earlier analysis¹⁵ of patient 5 and repeated the analysis of the 10 and 30 mm sizes for patient 4. Our study of those two lesion diameters showed that the pattern of artifacts was the same as it was for the larger tumors, except that the 10 mm tumor's SUV recovery was worse than in the case of a 20 mm tumor, presumably because the motion is larger relative to its size, and that, conversely, the 30 mm tumor's SUV recovery was better. Believing that this was a trend, we focused our analysis on tumors with a simulated diameter of 20 mm.

Motion blurring and SUV recovery

The motion-blurring phenomenon is best studied by examining the time-averaged simulated tumor, $O(\vec{b})$. One would expect that respiration should blur edges in the object, and this was borne out by our study of the diaphragm image in $O(\vec{b})$, for example the bottom left corner of Fig. 2. The tumor's image was distended and blurred in the SI direction. Also, the diaphragm's sharp edges were replaced with diffuse ones. In $O(\vec{b})$, the tumor uptake determined as the maximum pixel was 100% in the mobile tumors in patients 1, 2, 3, 4 where the motion was less than the tumor diameter, but uptake was between 69% and 73% in patient 5, where the motion exceeded the tumor diameter.

Fig. 3 illustrates the blurring of the moving tumors. The figure shows the 20-mm tumors at the dome of the liver in patient 2, who had 11.3 mm of respiratory motion, and patient 5, who had 25.2 mm of motion. The figure compares EE and EI, and includes a comparison with the time-averaged object and the conventional PET reconstruction (CP). One will notice a slight flattening at the edges of the sphere, due to our use of a model in which the separation between slices was 3 mm.

Figure 3. Coronal section through a simulated 20-mm tumor in patients 2 and 5 at the dome of the liver, at respiratory phases EE and EI. Averages are also shown. Abbreviations refer to gated PET, gated CT, conventional PET, end expiration, and end inspiration.

The figure shows that phase-matched PET/CT, represented by the GP-GCT images, was in principle capable of generating an essentially perfect replica of the object itself at each phase of respiration. The tumor had the correct shape and was uniformly filled with the correct values. The surrounding tissues were also reproduced well. When the PET was gated but the CT was not, the shape of the tumor was correct but the distribution of activity inside the tumor was non-uniform, and SUV values in the surrounding tissues were wrong. When the CT was gated and the PET was not, the tumor was distorted and the background values were in error. Conventional PET, in these examples, gave nearly the same image as motion blurring alone.

Considering all six tumor locations in patients 1, 2, 3, who had less than 15 mm of breathing motion, and all ten phases of respiration, we found the range of values shown in Table 1. GP-GCT always gave essentially 100% recovery. In

the case of GP, the largest error (overestimation of the recovery) occurred at or near EI and the most negative error (underestimation) occurred at or near EE.

Table 1. Range of SUV recovery for 20 mm lesions in patients 1, 2, and 3 who had less than 15 mm of breathing motion. The average value is presented if the range is less than 5%. The values reported in the table are the smallest and largest recovery values in these three patients, considering all phases of respiration. Abbreviations refer to gated PET, gated CT, conventional PET, the lower right lung, the dome of the liver, the upper lobe of the liver, and three positions in the mid chest.

			GP-GCT	GP	GCT	CP
mobile		LRL	102%	100-110%	97-109%	101%
		DOL	101%	93-145%	90-122%	100%
		ULL	102%	94-114%	94-112%	100%
immobile		MC1	102%	99-108%	97-119%	102%
		MC2	102%	97-111%	99-112%	101%
		MC3	102%	92-115%	93-120%	101%

We also present the recovery values for patients 4 and 5, who had more than 15 mm of motion. These are summarized in Table 2.

Table 2. Range of SUV recovery for 20 mm lesions in patients 4 and 5 who had more than 15 mm of breathing motion. The average value is presented if the range is less than 5%. The values reported in the table are the smallest and largest recovery values in these two patients, considering all phases of respiration. Abbreviations refer to gated PET, gated CT, conventional PET, the lower right lung, the dome of the liver, the upper lobe of the liver, and three positions in the mid chest.

			GP-GCT	GP	GCT	CP
mobile		LRL	102%	100-158%	68-106%	70-89%
		DOL	101%	92-191%	45-120%	76-100%
		ULL	101%	73-134%	55-108%	72-101%
immobile		MC1	102%	100-108%	100-108%	101%
		MC2	102%	85-164%	91-130%	102%
		MC3	102%	85-189%	78-175%	102%

We calculated the SUV recovery for all six tumors reconstructed by the GCT method at EE and EI, with gaussian filtering included, according to Equations 13 and 14. The recovery values are plotted in Fig. 4 as a function of the amount of diaphragmatic motion.

Figure 4. SUV recovery for 20 mm tumors measured with non-gated PET, reconstructed with (a,b) CT at end expiration and (c,d) CT at end inspiration. Six tumor locations are reported: (a,c) lower right lung, dome of the liver, and upper lobe of the liver; and (b,d) positions 1, 2, 3 in the mid chest.

DISCUSSION

A quantitative PET or PET/CT reconstruction procedure requires compensation for the physical effects that distinguish the actual measurement from an ideal measurement based on unattenuated line integrals of the radioactivity density. Those effects include photon attenuation, statistical fluctuations, a background

of scattered radiation, random coincidences, positron range effects, non-colinearity in the two annihilation photons, detector sensitivity variations, and patient motion. In oncological PET, attenuation is normally the largest of these effects, with attenuation factors sometimes in excess of 100 in abdominal and shoulder sections but about an order of magnitude less than that in lung sections. At the level of the diaphragm, this largest effect changes from moment to moment with the patient's breathing. Motion of the radioactive tracer in internal organs is also an important effect in this region in the breathing patient. At the outset of this investigation, it seemed to us that an understanding of the effect of breathing upon PET's accuracy in this anatomical region should include a realistic model of the diaphragm's actual motion in cancer patients. Respiratory-gated CT made this possible, providing measurement of the anatomy of the entire chest.

Our study of respiratory motion effects in PET/CT was driven by GCT series from five patient studies. The range of diaphragmatic motion in this set of five studies was from 8 to 25 mm, with three of the five cases showing motion less than 15 mm. This range of motion is typical of the range seen in a number of clinics around the world^{9,19}. We performed some calculations with 10 and 30 mm tumors but only presented results associated with 20 mm tumors. Large tumors, for example, 30 mm, are less blurred by motion. Although breathing artifacts in the imaging of smaller tumors, for example 10 mm, are of great concern clinically, in actual measurements the limitations of detector resolution, statistical noise, and partial volume effects preclude an accurate measurement of the uptake of such small tumors. Since good SUV recovery is possible for 20 mm lesions, we felt it was appropriate to simplify our presentation by considering mainly this tumor size. The actual resolution in a clinical scan depends on reconstruction parameters, for example the reconstruction method, the number of iterations in the case of iterative reconstruction, and the filtering parameter which is chosen to control statistical noise.

In our simulation, the combination of gated PET with gated CT provided accurate results for each patient and each tumor location at every phase of respiration. This indicates that the Radon transform of the PET object, generated by our forward projector, was correctly inverted by our filtered backprojection algorithm. This is a reassuring check on the correctness of the computational tools that we used.

Gating of the PET alone gave the correct tumor shape but was not quantitative. Gating of the CT alone gave a shape like the shape caused by motion blur alone, and was not quantitative. This was also true of conventional PET. A PET/CT study performed using a CT scan of a free-breathing patient should be similar to gated CT with a random choice of the respiratory phase, provided that the CT scan is performed rapidly enough, i.e. it unavoidably has the same kinds of errors as ungated PET with GCT. A PET/CT study with a CT scan at deep inspi-

ration cannot be modeled by our simulation, since the position of the diaphragm is likely to be outside the range seen in the PET scan of a freely breathing patient.

Mobile tumors were more susceptible to quantitation errors because they were blurred and also subject to attenuation errors. Immobile tumors were subject only to attenuation errors, yet even these tumors cannot be assigned the correct values by GP or GCT alone. In our simulation, CP was more accurate than either GP or GCT in the imaging of 20 mm tumors. This appears to be due to canceling errors in emission blurring (underestimation) and attenuation correction (overestimation). Our limited study of 10 and 30 mm tumors indicated that motion blurring of 10 mm tumors was so great that the attenuation errors no longer compensated for it, whereas recovery for 30 mm tumors in CP was comparable to recovery for 20 mm tumors. In some cases CP had significant quantitation errors in imaging the 20 mm tumors, especially when the tumor was mobile and the motion was large.

When respiration moves a tumor by more than the diameter of the tumor, no PET or PET/CT reconstruction method can be expected to recover the tumor's actual SUV values, unless the method accounts for the motion. In our simulation of this case, no part of the tumor at EE overlapped the tumor at EI. On the other hand, if in our simulation the total motion was less than the diameter, the bottom of the tumor at EE overlapped the top of the tumor at EI. Since we assumed that the uptake was uniform throughout the tumor, this situation creates the illusion that a piece of the tumor did not move. Because we focused our attention on 20 mm tumors, and because SUV values were assigned based on maximum pixel values, motion less than 15 mm had relatively little effect.

The poorest SUV recovery was for tumors close to the dome of the liver. We believe that this was due to large changes, over the course of the respiratory cycle, in attenuation values. The upper lobe of the liver was also strongly influenced by attenuation changes, though the effect was less than at the DOL. Quantitative errors in the lower right lung were of a smaller magnitude and we believe are mostly due to motion-blurring alone, with much smaller attenuation errors.

In many clinics where oncological PET/CT is performed today, the PET data are not gated and a CT scan is performed without special equipment or breathing instructions that would assure data acquisition at a particular, measured phase of breathing. In the case of a freely breathing patient, the phase most likely to be measured by the spiraling X-ray source is EE, because people normally pause between breaths, though the data could be acquired at any phase between EE and EI. We gave special consideration to those two extremes and in Fig. 4 plotted SUV recovery for 20-mm tumors as a function of the extent of the five patients' diaphragmatic motion. In these cases we included a post-reconstruction filter to give a more realistic estimate of the recovery achievable

in an actual PET/CT scanner, considering spatial resolution. The partial volume effects reduced uptake between 0% and 10%.

Fig. 4 illustrates the complexity of respiration's effect upon PET/CT. Part (a) of the figure gives the impression that CT performed at EE gave correct PET/CT results, i.e. errors no larger than 20% in imaging of a mobile tumor in the lower lung, at the diaphragm, and in the upper lobe of the liver. However, part (b) shows that, again with CT performed at EE, immobile tumors at the level of the lower right lung are correctly reconstructed while tumors lower than that are overcorrected by amounts varying from 0% to 60%. In fact, the pattern indicated by part (a) shows that motion blurring, which should lower reconstructed values, is canceled by an overcorrection for the attenuation. The attenuation errors are even larger near the DOL than they are in the mid chest. Part (d) of the figure gives the impression that, with CT performed at EI, the immobile tumors in the mid-chest are reconstructed rather with underestimation in the range from 0% to 30%, apart from effects attributable to a 10% loss in resolution, while part (c) clearly shows that the mobile tumors, again with CT performed at EI, suffer a large undercorrection for attenuation. The pattern in part (d) is explained by the fact that much of the detected radiation from tumors in the mid chest is emitted during the part of the breathing cycle near EI when the lungs are full of air and the attenuation is least; so the EI attenuation correction works fairly well for the immobile tumors. The mobile tumors represented by part (c) move with the diaphragm, and therefore the attenuation varies less through the breathing cycle. In this case, the reconstructed tumor intensity is lowered by three phenomena: inadequate correction for attenuation; motion blurring; and a small loss of resolution. There is no canceling error in this case. When the CT scan is performed during free breathing, tumors near the diaphragm will be overcorrected or undercorrected by an amount that will not be known to the physician reading the images. If the CT data were acquired in an unnatural phase of breathing, for example at full inspiration to afford a good view of chest anatomy, the undercorrection for attenuation should be even larger, and lesions could be completely missed. A practical way of dealing with these problems is discussed below.

Gated CT is relatively new technology, made practical by the introduction of ever faster CT scanners with large numbers of detector rows. In our methodology for simulating a PET/CT acquisition and reconstruction system with breathing motion, gated CT volumes were converted into PET volumes and attenuation sinograms to represent the essential features of respiratory motion. This approach to studying respiration artifacts in PET/CT has benefits not easily achieved in other approaches, for example clinical studies and phantom studies. First, this approach has a gold standard, since one always compares the tumors to the known tumor introduced in the simulation. Clinical studies hardly ever have such a gold standard to compare to. Second, the motions are realistic since

they come from actual patients. In our view, it would be very difficult to create phantom studies in which the motions are modeled with this level of realism. Since actual human tissue is used in our model of the attenuation correction, this approach even includes complex attenuation-related phenomena such as the compression of lung tissue during breathing. Third, we are able to explore the effect of respiratory motion without the confusion of other effects that are present in actual PET studies: limited counts per acquired frame; limits to the detector resolution; three instead of two-dimensional geometry; scattered radiation; and other data corrections. When we want to study motion in isolation from other effects, it is advantageous to be able to turn them off.

Our segmentation procedure had some unrealistic features. Blood in the ventricles of the heart was treated like soft tissue and clothing and blankets were sometimes treated like fat. These problems do not concern us greatly, for two reasons. First, the unrealistic effects did not occur close to the lung lesions, where the motion-related effects were large. Second, we believe that the fundamental lessons of the simulation do not depend on objects in the background.

The respiratory gates were defined at ten equally spaced intervals in the respiratory cycle. A correct physical description of the PET and AF acquisitions would involve integration over all breaths. If we assume a regular and smooth pattern of breathing, the addition of ten phases is nearly the same as time integration, in the sense that a Riemann integral can be approximated with the trapezoid rule. Our model completely ignores motion within each gate. We are not concerned by this because time integration of the motion in such a short frame, which is the appropriate physical model, is well approximated by the average value which we used, given the smooth nature of normal breathing.

The GP/GCT combination gives quantitative PET images in conditions of no statistical noise, and under the assumption that the two modalities can be matched perfectly. Clinically, none of the conditions of this simulation can be met realistically, and in addition cardiac motions in the same territory pose a separate problem that this simulation did not address. Challenges for the future include finding ways of matching the two modalities well enough to achieve quantitative accuracy in essentially every scan, especially in the presence of variable breathing patterns^{22,23}, and finding ways to improve the statistical accuracy of images based on very low statistics per frame.

This simulation can be used to guide practitioners of oncological PET/CT to make the best possible use of existing technology in the face of respiration-related artifacts. The mismatch between the CT and PET images leads to a number of potential problems, including localization and attenuation correction errors. Particularly when a tumor is near the diaphragm in the base of the lungs or in the superior portion of the liver, respiration may result in incorrect localization or even in the tumor being missed because of the undercorrection for attenuation. Fortunately, in a study by Osman *et al.*, the incidence of misposi-

tioning errors was small (less than 2% of cases)¹⁰. Nevertheless, careful attention should be given when reviewing the region near the diaphragm. The review should include PET images made without attenuation correction. Although those images are not quantitative, they are unaffected by attenuation correction errors. In the case of cooperative patients, undercorrection of attenuation due to breathing can be avoided by acquiring the CT scan of the thorax near EE. For patients who are unable to follow breathing instructions, the technologist can acquire two or three fast, low-dose CT scans during free breathing²⁴. The appropriate CT scan for attenuation correction, i.e. the one that most closely corresponds to EE, is identified as the one in which the diaphragm is positioned highest. Such a procedure should reduce the likelihood that tumors near the diaphragm are missed because of respiration artifacts, and would be particularly appropriate for mobile tumors. For stationary tumors, our work indicates that quantitative imaging is more accurate when the attenuation information is derived near EI. A multi-CT protocol like the one mentioned above can also be used to select the scan in which the diaphragm is lowest. This is the breathing phase proposed by Nehmeh *et al.* for tumor imaging¹¹. Therefore, existing technology provides several strategies for tumor imaging in the region near the diaphragm.

SUMMARY

We used gated CT series to provide a realistic basis for simulating errors in PET and PET/CT that are due to respiratory motion. To our knowledge this has not been done previously.

We showed that, in the conditions of the simulation, the combination of gated PET and gated CT was quantitative but other methods were not. In the majority of patients whose breathing motions are less than 15 mm, motion-related errors are in the range of 20% or less in the case of 20 mm tumors. Conventional PET was not quantitative, but there were a remarkable number of cases in our simulation of 20 mm tumors, indeed, nearly all of them, in which canceling errors due to emission blurring and attenuation overestimation led to a nearly correct result in conventional PET, for example in Fig. 2.

We showed that a large amount of motion caused relatively large errors. Although we did not discuss it at length in this report, our simulations showed that 10 mm tumors were blurred to a greater extent by motion. Quantitative imaging of such tumors is in any case challenged by spatial-resolution effects, which could be larger than the motion blurring, depending on processing parameters. Conversely, 30 mm tumors were blurred less by motion. We demonstrated that gated PET by itself gave the correct shape for tumors, but without proper at-

tenuation information gated PET could not be relied upon to give a quantitative image of the tumor.

The largest uptake errors occurred in tumors at the diaphragm. The upper lobe of the liver was another region where large errors occurred. The lower lung was a territory where uptake errors were smaller in most cases, presumably because the attenuation-correction errors are less while the motion blurring was the same.

Although proper alignment of the emission and transmission measurements is necessary for accurate tumor imaging near the diaphragm, the serious problem of a missed tumor can be addressed without respiratory gating, using simple CT protocols to acquire images near end expiration. By using such a protocol, tumor SUV values are overestimated by an amount in the range from 0% to 60%. In cases of suspected tumors near the diaphragm, the physician should review the PET images made without attenuation.

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CHAPTER

5

Intra-patient variability of tumor volume and tumor motion during conventionally fractionated radiotherapy for locally advanced non-small cell lung cancer. A Prospective Clinical Study

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ABSTRACT

Purpose: To investigate the change in tumor volume, motion and breathing frequency during a course of radiotherapy, for locally advanced non-small cell lung cancer.

Patients and Methods: Twenty-three patients underwent CT-PET and Respiration Correlated CT scans prior to treatment, which was repeated in the first and second week following the start of radiotherapy. Patients were treated with an accelerated fractionation schedule, 1.8 Gy BID, with a total tumor dose depending on pre-set dose constraints for the lungs and the spinal cord.

Results: A striking heterogeneity of tumor volume changes was observed at all time points. In some patients the volume decreased $> 30\%$ (3/23) in others the volume increased $> 30\%$ (4/24) but for the majority of patients (16/23) the tumor volume only changed slightly ($< 30\%$). No significant changes in average tumor motion or breathing frequencies were seen during treatment. Although quite some changes in individual tumor motion were seen, only in one patient would this have led to an increase of the internal margin > 1 mm in one direction, one week after the start of treatment, and in three patients for one direction, 2 weeks after the start of the treatment.

Conclusion: A large variability of changes in tumor volume between the patients was observed. This underscores the need for repeated imaging during the course of radiotherapy. However, the changes in tumor motion are small, which indicates that repeated respiration correlated CT does not appear to be necessary.

INTRODUCTION

Radiation therapy, alone or in combination with chemotherapy or surgery, is important in the treatment of lung cancer¹. Nowadays, target volume delineation is often based on sophisticated imaging techniques such as CT and FDG-PET scans, as this improves the diagnostic accuracy and may allow radiation dose escalation²⁻⁵. Breathing induced tumor motion and hence appropriate margins can be taken into account using 4D-CT information from respiration correlated CT (RC-CT) scans. Incorporating this temporal information in radiotherapy planning could also lead to a more accurate delineation of the gross tumor volume. In general, smaller margins can be applied which would make dose escalation or a decrease of normal tissue exposure possible⁶.

However, radiation treatment planning is based on imaging taken at a single time-point before the start of radiotherapy, and therefore any changes of tumor motion, tumor volume or breathing frequency during the course of fractionated radiotherapy are not incorporated in the treatment planning process.

Few data on volume changes during radiotherapy for lung cancer patients have been reported⁷⁻¹⁰, showing conflicting results. Moreover, the evolution of the tumor motion during radiotherapy was only reported in stereotactic radiotherapy for stage I NSCLC patients¹⁰, although this information is important for Adaptive RadioTherapy (ART).

We therefore investigated the changes of tumor volume, tumor motion and breathing frequency during the first 2 weeks of an accelerated course of radiotherapy in patients with locally advanced non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS

Patients

Twenty-three patients with histological or cytological proven non-small cell lung cancer (NSCLC) (UICC stage II-III) were included in this study, from December 2004 until September 2005. Twenty patients received three cycles of carboplatin and gemcitabine chemotherapy before radiotherapy, had a WHO performance status 0-1 and a good lung function ($FEV1 \geq 50\%$ and $DLCO \geq 50\%$). Three patients did not receive chemotherapy due to medical reasons. The response to induction chemotherapy was evaluated using the RECIST-criteria¹¹. No concurrent chemotherapy was given. Patients were treated using our current standard CT-PET simulation, radiation treatment planning, and fractionation schedule, as described below.

The Medical Ethics Committee according to the Dutch law approved the trial. All patients gave written informed consent before entering this study.

Radiotherapy simulation

Patients were simulated in radiotherapy position on a dedicated CT-PET-simulator with both arms above the head and on an immobilization and patient laser marker system. Radiotherapy technologists trained specifically for this purpose always carried out the simulation. The CT-PET scanner used was a Siemens Biograph (SOMATOM Sensation-16 with an ECAT ACCEL PET scanner).

An intravenous injection of ^{18}F -Fluoro-Deoxy-Glucose (FDG) (Tyco Health Care, Amsterdam, The Netherlands) of $(\text{weight} \times 4 + 20)$ MBq was followed by 10 ml physiologic saline. After a 45 minutes uptake period, during which the patient was encouraged to rest, PET and CT images were acquired. A spiral CT with intravenous contrast was performed covering the complete thoracic region.

Radiotherapy planning

Radiotherapy planning was performed on a XiO (Computerized Medical Systems, St Louis, Missouri) treatment planning system, using inhomogeneity corrections, based on a convolution algorithm. For all patients, the Gross Tumor Volume (GTV) and the Planning Target Volume (PTV) were defined, based on CT-PET data, obtained prior to radiotherapy (i.e. post chemotherapy in case of induction chemotherapy). The Clinical Target Volume (CTV) was defined as the GTV with a 5 mm margin incorporating microscopic disease. This CTV was subsequently expanded with 1 cm to draw the PTV to incorporate the internal respiratory motion and setup errors.

For the volume comparison in this study, the CT-GTV was defined as the primary tumor on lung window ($W = 1600$, $L = -800$).

Contouring of the lungs was carried out automatically by the treatment planning system. For the calculation of the mean lung dose (MLD), the volume of both lungs excluding the GTV was used¹². The spinal cord was drawn throughout the whole CT scan and was considered to be at the inner margin of the bony spinal canal.

A 3D conformal treatment plan was calculated on the PTV for all patients according to ICRU 50 guidelines¹³. Dosimetric values were calculated on the basis of dose-volume histograms and dose distributions on each axial CT plan.

Radiotherapy dose and normal tissue constraints

For each patient, the radiation dose was escalated to a mean lung dose (MLD) of 19 Gy while respecting a maximum spinal cord dose of 54 Gy. There were no esophageal dose constraints. As the tumor dose was delivered in 1.8 Gy fractions, a maximum deviation of the constraints of $\pm 4\%$ was allowed. Radiother-

apy was always delivered twice a day (BID), with a minimum of 8 hours between the two fractions, and given 5 days per week.

Respiration Correlated CT scans (RC-CT)

For the patients who gave informed consent for this study, the CT-PET was immediately followed by a respiration correlated CT, using offline correlation of the 16-slice spiral CT scan of the CT-PET system. This had been modified to enable a low pitch (minimum 0.1), in combination with a respiratory signal obtained by a pressure sensor in a chest belt (AZ-733V, Anzai Medical Corporation, Tokyo, Japan). The raw CT data were reconstructed in 10 phases, from 0% to 100% in steps of 10% of the respiration period starting at end inspiration. In-house developed software with Matlab (Mathworks Inc, Natick, MA) was used to measure the motion of the lesion in all three orthogonal directions.

Study design

During the course of radiotherapy, the patients underwent a repeat CT-PET scan and a respiration correlated CT in treatment position, one and two weeks after the start of treatment. At all time points, the primary tumor was delineated using the free-breathing CT rather than on a single phase of a respiration correlated CT, as respiration correlated CT data was not available in all patients (see Table 3). This approach assumes that no blurring of the moving tumor occurs in the free-breathing CT. This assumption was checked and found to be valid as the high-speed 16-slice CT scan protocol, effectively “freezes” the tumor in a single phase during a free-breathing CT. The tumor was delineated for each patient by the same physician to avoid interobserver variability. To study the intra-observer variability, all pre-treatment CT-scans were delineated twice by the same physician, as was the case for ten patients for all time points, with at least a 3 month time interval.

Due to technical and logistical problems, a complete image dataset at all three time points, was not available for all patients. We missed a CT-PET dataset for one patient one week after the start of treatment and for three patients, two weeks after the start of treatment.

Endpoints and statistical analysis

We determined the tumor volumes prior to 1 and 2 weeks, after start of the treatment, based on the GTVs drawn on the free-breathing CT. In addition, we used the respiration correlated CT to quantify the tumor motion at all 3 time points. Tumor motion was expressed as a 3D vector¹⁴, which is the quadratic sum of the motions in the three orthogonal directions. Finally, breathing frequency was recorded at all three time-points during the respiration correlated

CT. All results are expressed as the mean $\pm$ standard deviation (SD). Statistical differences between paired parameters from the three time points were evaluated using the Wilcoxon signed rank test. Differences were considered to be significant when the p-value was less than 0.05.

RESULTS

Patient characteristics

The patient characteristics are shown in Table 1. The mean values of the total tumor dose (TTD) and the corresponding mean lung dose (MLD) were $61.7 \text{ Gy} \pm 9.8 \text{ Gy}$ [range: $46.8 \text{ Gy} - 79.2 \text{ Gy}$] and $16.4 \text{ Gy} \pm 3.4 \text{ Gy}$ [range: $6.8 \text{ Gy} - 20.8 \text{ Gy}$], respectively. The GTV of the primary tumor before radiotherapy was $87.5 \text{ cm}^3 \pm 137.7 \text{ cm}^3$ [range: $0.4 \text{ cm}^3 - 660.2 \text{ cm}^3$].

The first repeat scan was made after the patient received on average a dose of $20.4 \text{ Gy} \pm 4.1 \text{ Gy}$ (about 11 fractions) and the second scan after $38.3 \text{ Gy} \pm 5.1 \text{ Gy}$ (about 21 fractions) (Table 2).

Volume changes of the primary tumor

A striking heterogeneity of the changes in volume of the primary tumor during radiotherapy was observed. Using an arbitrarily chosen cut-off level of 30%, four patients (17%) showed an increase of the tumor volume of $> 30\%$, for sixteen patients (70%) the volume change varied $< 30\%$ while for three patients (13%) the volume decreased $> 30\%$. In Fig. 1 these patients are indicated with a dotted line for the patients with a large increase in tumor volume, a dashed line for those patients with a large decrease and a solid line for the rest of the patients.

Although the average volumes do not reflect the individual changes, we observed a significant increase in average tumor volume in the patients ($n = 22$) for which data at the first and second time point was available, from $90.9 \text{ cm}^3 \pm 139.9 \text{ cm}^3$ to $99.2 \text{ cm}^3 \pm 130.4 \text{ cm}^3$ from the start of radiation to week 1 ($p = 0.049$). For time point at week 2, we missed the CT information for three patients. In the remaining 20 patients the tumor decreased on average from $94.7 \text{ cm}^3 \pm 146.3 \text{ cm}^3$ to $86.4 \text{ cm}^3 \pm 109.8 \text{ cm}^3$ from the start of radiation to week 2 ($p = 0.940$) (Table 2 and Fig. 2).

No significant difference in tumor volume changes was observed between patients with stable disease and partial response to induction chemotherapy.

For the 43 delineations, which were performed twice, we found an average intra-observer variability of $1.2 \% \pm 4.4 \%$, with a maximum deviation of 9.5% .

Table 1: Patient characteristics.

Patient no.	Age (years)	Gender	Stage	Location of the primary tumor	Response chemotherapy	TTD (Gy)	MLD (Gy)	OTT (days)
1	52	F	T1N3M0	RLL	PR	54.0	17.6	17
2	54	M	T3N2M0	RML	SD	54.0	19.3	20
3	75	M	T3N2M0	RUL	PR	54.0	15.2	20
4	71	F	T3N1M0	RUL	no	64.8	20.7	23
5	71	M	T2N3M0	RUL	PR	54.0	14.7	23
6	61	M	T1N3M0	RML	PR	68.4	14.9	22
7	71	M	T2N3M0	LLL	PR	54.0	16.0	19
8	77	M	T4N2M0	RUL	PR	61.2	17.6	22
9	74	F	T2N0M0	RLL	no	54.0	16.3	20
10	79	F	T4N0M0	RLL	PR	57.6	18.3	23
11	57	M	T1N3M0	LUL	PR	64.8	8.5	27
12	68	M	T4N0M0	RUL	PR	54.0	6.8	20
13	63	M	T4N0M0	RLL	SD	64.8	17.3	24
14	59	F	T2N2M0	RML	PR	46.8	20.0	16
15	55	M	T4N2M0	LUL	SD	79.2	16.4	29
16	52	F	T2N3M0	LLL	PR	54.0	15.6	20
17	50	F	T4N2M0	LLL	PR	61.2	20.8	21
18	71	M	T4N2M0	RUL	PR	79.2	13.6	29
19	61	F	T2N2M0	RML	PR	57.6	19.0	21
20	62	M	T2N2M0	RUL	PR	68.4	18.8	27
21	80	M	T2N0M0	LLL	no	61.2	15.2	21
22	56	M	T4N2M0	LUL	SD	79.2	17.8	30
23	54	M	T2N3M0	LUL	SD	79.2	16.1	30
Mean	64.0					61.7	16.4	22.8
SD	9.6					9.8	3.4	4.1

TTD = Total Tumor Dose; MLD = Mean Lung Dose; OTT = Overall Treatment Time
 F = Female; M = Male; PR = Partial Remission as response to induction chemotherapy; SD = Stable Disease as response to induction chemotherapy (RECIST criteria)
 RLL: Right Lower Lobe; LLL: Left Lower Lobe; RUL: Right Upper Lobe; LUL: Left Upper Lobe; RML: Right Middle Lobe

Table 2: Evolution of the Gross Tumor Volume of the primary tumor during radiotherapy.

Patient no.	Volume before RT (cm3)	Corresponding dose after one week of RT (Gy)	Volume after one week of RT (cm3)	Corresponding dose after two weeks of RT (Gy)	Volume after two weeks of RT (cm3)
1	7.9	19.8	4.7	37.8	5.2
2	660.2	18.0	580.3	34.2	455.9
3	53.1	18.0	65.9	NA	NA
4	26.6	19.8	14.7	37.8	2.8
5	97.3	18.0	155.0	36.0	134.6
6	7.5	19.8	4.3	34.2	5.0
7	28.1	16.2	43.8	37.8	36.4
8	3.5	19.8	5.9	41.4	6.0
9	64.9	27.0	35.8	NA	NA
10	12.2	NA	NA	36.0	10.8
11	0.4	19.8	0.5	NA	NA
12	63.2	23.4	64.6	37.8	72.3
13	67.2	19.8	88.6	48.6	42.2
14	272.2	23.4	323.8	41.4	288.9
15	92.9	19.8	104.3	37.8	84.0
16	79.0	21.6	99.7	39.6	83.8
17	92.9	19.8	153.5	37.8	121.1
18	7.3	21.6	6.2	32.4	6.4
19	101.9	16.2	131.2	41.4	80.1
20	24.2	19.8	28.0	37.8	26.7
21	107.7	14.4	114.7	27	105.3
22	73.0	18	75.9	39.6	65.0
23	69.0	34.2	79.9	50.4	95.8
Mean	87.5	20.4	99.2	38.3	84.4
SD	137.7	4.1	130.4	5.1	109.8

p = 0.049 one week vs prior; p = 0.007 two weeks vs one week; p = 0.940 two weeks vs prior

RT: Radiotherapy

NA: Not Assessed because of technical problems

Figure 1: The CT volumes, relative to the volume prior to treatment, were plotted versus the dose. The thick black line is the average relative CT volume together with the standard deviation. The dotted lines represents the patients where the tumor increased more than 30%, the dashed lines those patients with a decrease of more than 30%.

Changes of the motion of the primary tumor

Tumor motion, expressed as a 3D vector, which is the quadratic sum of the motion in the three orthogonal directions and the breathing frequency are shown in Table 3 and Fig. 3. On average, the total vector motion changed from $7.8 \text{ mm} \pm 4.8 \text{ mm}$ initially to $7.8 \text{ mm} \pm 5.9 \text{ mm}$ and $8.0 \text{ mm} \pm 5.6 \text{ mm}$ one and two weeks after the start of the radiotherapy respectively. All differences compared to the initial tumor motion were not statistically different from each other ($p = 0.969$ and $p = 0.582$ respectively).

When we looked at the individual differences for the motion for all directions compared to the initial motion, we observed a maximal absolute difference of 4.5 mm and 6.4 mm one and two weeks after the start of radiotherapy. The maximal difference between week 2 and week 1 after the start of radiotherapy was 5.4 mm. In Fig 3, a histogram of these differences is shown.

If we use the peak to peak amplitude divided by four, as used for the internal margin in van Herk's margin recipe¹⁵, only for one patient, for one direction the

internal margin increased more than 1 mm one week after the start of radiotherapy. Two weeks after radiotherapy the internal margin should have been changed for three patients with more than 1 mm (Fig. 3).

Figure 2: 3D Vector motion, which is the quadratic sum of the motion in three orthogonal directions, plotted versus the dose. The thick black line represents the average tumor motion, together with the standard deviation.

Change of the breathing frequency

The breathing frequency was not statistically different at the three time points. On average, the frequency changed from 18.5 ± 3.6 breathing cycles per minute (BPM) to 19.2 ± 4.1 BPM and 18.3 ± 4.5 BPM ($p = 0.800$ and $p = 0.880$ respectively).

DISCUSSION

For high precision radiation therapy, it is important to have, during a course of radiation therapy, knowledge of the changes of several parameters, such as the tumor volume and tumor motion.

Figure 3: Histogram of the differences (mm) in motion amplitude between all time points. The differences for all three orthogonal directions are shown.

We observed a large heterogeneity of the changes in tumor volume in our patient population. Only a few patients (3/23) showed a large systematic decrease ($> 30\%$) in tumor volume, whereas in the majority of patients (16/23), the tumor volume only slightly changed ($< 30\%$). We even found a large increase in tumor volume for four out of 23 patients. The clinical impact of these volume changes and how to adapt treatment is however still unclear. Further clinical and planning studies need to be done to clarify this problem.

So, in contrast to other investigators^{7,8}, no significant decrease in the tumor volume during the first two weeks of radiotherapy was found. Several differences between the reported studies and our study may explain the differences. In contrast to the present study, in the studies of Kupelian *et al.*⁷ and Erridge *et al.*⁸, patients were treated with a conventional fractionation scheme (2 Gy/day) delivered over an overall treatment time of more than 40 days. In our study, all patients received an accelerated schedule in which 1.8 Gy per fraction was delivered BID, 5 days per week. It may be that the decrease of the tumor volume by radiation-induced cancer cell death was offset by treatment-induced inflammation, which once again increased the volume. The net result may be a stable volume. Comparable results in tumor volume changes on CT scans in the first two weeks due to radiotherapy have been described when high doses per frac-

tions (7.5 Gy – 20 Gy) are used in stereotactic radiotherapy for stage I NSCLC^{9, 10}. We may get more insight in the internal tumor processes by analyzing the FDG distribution in the tumor during the course of radiation. Unfortunately it is still too early to correlate these changes in tumor volume with outcome. These analyses will however be the subject of another paper.

Table 3: 3D Vector motion and breathing frequency before and during the radiation treatment.

Patient no.	Before RT		After one week of RT		After two weeks of RT	
	3D Vector	BPM	3D Vector	BPM	3D Vector	BPM
5	7.7	22.2	9.2	22.2	8.2	25.5
6	8.1	15.5	11.0	12.0	16.0	17.6
7	4.5	24.0	2.9	23.1	3.9	21.6
12	0.5	14.0	0.7	15.0	1.6	12.6
14	16.3	17.5	21.0	17.6	17.8	19.0
15	4.2	12.9	7.3	23.5	4.7	17.1
16	9.5	19.2	6.2	25.5	8.2	21.1
17	4.2	21.6	3.1	21.6	4.0	24.5
19	11.4	22.2	7.4	20.3	9.8	16.1
20	4.5	16.9	1.6	16.3	2.5	16.7
21	15.6	19.7	15.8	17.9	15.1	17.9
22	7.0	16.0	6.9	15.4	4.6	9.9
MEAN	7.8	18.5	7.8	19.2	8.0	18.3
SD	4.8	3.6	5.9	4.1	5.6	4.5
3D Vector: $p = 0.969$ one week vs prior; $p = 0.582$ two weeks vs prior						
BPM: $p = 0.799$ one week vs prior; $p = 0.875$ two weeks vs prior						
BPM: Breathing cycles Per Minute						

To the best of our knowledge, this is the first study dealing with the changes of the motion and the breathing frequency of patients with locally advanced (Stage II-III) NSCLC during a course of radiotherapy. Underberg *et al.*¹⁰ described similar findings for Stage I NSCLC treated with hypofractionated stereotactic radiotherapy. Although we found no significant changes, on average, in tumor motion and breathing frequency, during the first two weeks of radiotherapy, in some patients quite a wide variation was seen. However, even for the largest difference in tumor motion, the clinical implication on the size of the PTV and hence on the treatment fields is limited, since only a fraction of this motion is used for PTV expansion to account for the tumor motion. Only for one patient, for one direction the internal margin increased more than 1 mm one week after the start of radiotherapy. Two weeks after radiotherapy the internal margin should have been changed for three patients with more than 1 mm (Fig. 3). In

this patient group, the respiration correlated CT information will not influence the internal margin that needs to be taken.

In conclusion, our results clearly show that, at least when an accelerated radiotherapy schedule is given, changes in the volume of the primary tumor do occur during the first two weeks of radiotherapy. A large variability among the patients was observed, indicating that repeated imaging during the course of radiotherapy is necessary to know the changes in GTV and to be able to individualize radiation treatment. In contrast, repeated respiration correlated CT imaging during radiotherapy does not appear to be necessary as the changes in tumor motion are small, and will not lead to a change in treatment.

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CHAPTER

6

Time trends in the maximal uptake of FDG on PET scan during thoracic radiotherapy. A prospective study in locally advanced non-small cell lung cancer (NSCLC) patients

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ABSTRACT

Background and purpose: ^{18}F -fluoro-2-deoxy-glucose (FDG) uptake on PET scan is a prognostic factor for outcome in NSCLC. We investigated changes in FDG uptake during fractionated radiotherapy in relation to metabolic response with the ultimate aim to adapt treatment according to early response.

Methods and materials: Twenty-three patients, medically inoperable or with advanced NSCLC, underwent four repeated PET-CT scans before, during and after radiotherapy. Changes in maximal standardized uptake value (SUV_{max}) were described. Patients were treated with accelerated radiotherapy with a total tumor-dose depending on normal tissue dose constraints.

Results: The most striking result was the large intra-individual heterogeneity in the evolution of SUV_{max} . For the total group a non-significant increase in the first week ($p = 0.05$), and a decrease in the second week ($p = 0.02$) and after radiotherapy ($p < 0.01$) was observed. Different time trends were shown for responders (no change during radiotherapy) and non-responders (48% increase during first week, $p = 0.02$ and 15% decrease in the second week, $p = 0.04$). Non-responders had a higher SUV_{max} on all time points investigated.

Conclusions: Time trends in SUV_{max} showed a large intra-individual heterogeneity and different patterns for metabolic responders and non-responders. These new findings may reflect intrinsic tumor characteristics and might finally be useful to adapt treatment.

INTRODUCTION

Thoracic irradiation plays an important role in the management of advanced non-small cell lung cancer (NSCLC). Although the prognosis of these patients has improved, local tumor control is still not achieved in the majority of the patients^{37,44,45}. Local tumor control can be improved by increasing the total radiation dose and the addition of chemotherapy to radiotherapy, but normal tissue toxicity, like esophagitis and radiation pneumonitis, is dose limiting^{3,11,20,30,34,38}. A more individualized prediction of response to a specific therapy is needed in order to avoid needless treatment or to be able to propose an alternative therapy if possible^{29,42,46}. Methods to describe tumor characteristics include imaging techniques, like positron emission tomography (PET). In different tumor sites pre- and post-treatment PET scans have been correlated to outcome^{19,24,57}. Indeed, the maximal uptake of 18F-fluoro-2-deoxy-glucose (FDG) in the primary lung tumor as measured on a PET-scan before treatment was consistently shown to be a significant, independent, prognostic factor for survival in NSCLC, both in case of surgical resection and radical radiotherapy^{1,5,15,18,25,53}. On the other hand, a post-treatment PET scan can predict residual disease and hence outcome in NSCLC^{9,26,32,33,56}. Although there is a paucity on data dealing with the evolution of FDG uptake during fractionated radiotherapy, it is logical to study these time trends as an early predictive parameter, as has been shown for chemotherapy^{12,14,16,22,26}. We hypothesized that changes in uptake might reflect early tumor response during radiotherapy, which might finally allow further individualization and adaptation of treatment before therapy is completed⁷.

The aim of the current study was to describe changes in the uptake of FDG on PET scans during a course of radiotherapy in patients with NSCLC and to investigate whether there are differences in time trends in FDG uptake between metabolic responders and non-responders.

METHODS AND MATERIALS

Study population

From December 2004 to September 2005, 23 patients with medically inoperable or locally advanced NSCLC were enrolled in a phase I study. Patients with localized, histologically confirmed NSCLC, a WHO-performance score of 0 or 1, a weight loss of < 10% in 6 months and a reasonable lung function (a FEV1 > 50% of predicted value and a DLCO ≥ 50%) were eligible. In case of previous chemotherapy, radiotherapy was started after a minimum of 14 days after the last chemotherapy course. The response to induction chemotherapy was evalu-

ated using the RECIST-criteria⁴⁸. No previous radiotherapy to the chest was allowed. Patients were not eligible if they had any other concomitant malignant disease, a recent severe cardiac disease or active peptic esophagitis.

PET-CT-scan

As part of this phase I study repeated PET-CT scans (before start of radiotherapy, on day 7 and day 14 during radiotherapy and 70 days after radiotherapy) were performed in radiotherapy position on a dedicated PET-CT-simulator with both arms above the head and using a laser marker system. The PET-CT scanner used was a BiographTM (SOMATOM Sensation 16 with its ECAT ACCEL PET scanner, Siemens). Patients were fasting for at least 6 h before the examination. FDG (MDS Nordion, Liege, Belgium) was injected intravenously and followed by physiologic saline (10 ml). The injected total activity of FDG depended on the weight of the patient: $(\text{weight} \times 4 + 20)$ MBq. After a rest period of 45 min (time needed for uptake of FDG) PET and CT images were acquired. The CT-scan performed was a spiral CT-scan of the whole thorax, with intravenous contrast. The PET images were acquired in 5-min bed positions, while 2 or 3 positions were needed to scan the thoracic region. The standardized uptake value (SUV) was used to measure the amount of uptake of FDG in the primary tumor. A region of interest (ROI) was drawn on the 3D-images in E-soft (version 5.0.24.5, Siemens, Erlangen, Germany) around the region of the primary tumor. SUV was calculated as activity concentration of FDG uptake divided by injected dose/body weight⁴⁹. To avoid partial volume effects as much as possible, the maximal SUV (SUV_{max}) within this ROI was calculated and used for correlations.

Treatment description

All patients enrolled in this phase I study were irradiated using an individualized prescribed maximal tolerated dose (MTD). This total tumor dose (TTD) was based on normal tissue constraints instead of a classic fixed prescribed dose. For the lungs a mean lung dose (MLD) of 19.0 Gray (Gy) and for the spinal cord a maximal dose of 54.0 Gy were used as dose constraints. The maximal allowed TTD was 79.2 Gy or lower if any of the normal dose constraints were reached. The margin from GTV (gross tumor volume) to CTV (clinical target volume) was 5 mm and for the PTV (planning target volume) another 10 mm for the primary tumor and 5 mm for lymph nodes were added. No elective nodal irradiation was carried out. A 3D conformal treatment plan, using three to six coplanar 10 MV photon fields, was calculated according to the ICRU guidelines²⁷. Calculations were performed using an XiO treatment planning system (Computer Medical System Inc.) with a FFT convolution algorithm for inhomogeneity corrections³⁵. Patients were irradiated on a linear accelerator (Elekta SL 15,

Crawley, United Kingdom). Radiotherapy was delivered twice daily, with at least an 8-h interval (BID scheme) and with a fraction size of 1.8 Gy. Results concerning toxicity and outcome of this phase I study will be reported separately.

Assessment of metabolic response

Metabolic response was measured 70 days after radiotherapy by means of a PET-CT scan. This scan was compared to the pre-treatment scan, following the recommendations of the EORTC (Table 1)⁵⁸. The total group was divided in responders, showing complete metabolic response (CMR) or partial metabolic response (PMR), and non-responders with stable metabolic disease (SMD) or progressive metabolic disease (PMD).

Table 1. EORTC Criteria. Definition of metabolic response on PET-CT scans 70 days after radiotherapy.

CMR	Complete resolution of FDG uptake in tumor, not distinguishable from surrounding tissue
PMR	Reduction of more than 25% in SUV
SMD	Changes in SUV of less than 25%
PMD	Increase of SUV of more than 25% or new (metastatic) lesions

EORTC: European Organization for Research and Treatment of Cancer; CMR: complete metabolic response; PMR: partial metabolic response; SMD: stable metabolic disease; PMD: progressive metabolic disease; SUV: standardized uptake value.

Statistics

The SPSS software (SPSS for Windows, version 14.0, SPSS Inc., Chicago, IL) was used for statistical analysis. Results are expressed as mean $\pm$ SD (standard deviation) for individual results and as mean $\pm$ SE (standard error of the mean) for groups. The paired Student's t-test was used to compare the SUV_{max} on different time points, whereas the Mann–Whitney U-test and the Fisher's exact test was used to compare the different groups. Follow-up was updated and frozen at July 1st of 2006. Survival estimates were calculated using the Kaplan–Meier method and comparison of the survival curves were made using the log-rank test. Patients lost to follow-up were censored from survival data. Two-tailed p-values are provided and p-values less than 0.05 were considered statistically significant.

Ethics

This study has been reviewed and approved by the local Medical Ethical Committee, according to the Dutch law and regulations. All patients gave written informed consent before entering this study.

RESULTS

Patient characteristics

The patient characteristics are depicted in Table 2. Three patients did not receive chemotherapy, while 20 patients received platinum-based chemotherapy (Cisplatin or Carboplatin, combined with Gemcitabin). As a result of induction chemotherapy 15 patients showed a partial remission and 5 patients showed stable disease. The median interval between the last course of chemotherapy and the start of radiotherapy was 35 ± 16 days (range: 14–56 days). The average total tumor dose (TTD) given was 62.5 ± 9.7 Gy (range: 46.8–79.2 Gy) in an overall treatment time (OTT) of 22 days (range: 17–30 days). The first PET-CT scan was performed before start of radiotherapy (median 9 days before start of radiotherapy, range 4–13 days), the second on day 7 of radiotherapy (at a median dose of 19.8 ± 4.1 Gy) and the third on day 14 of radiotherapy (at a median dose of 37.8 ± 5.1 Gy). The fourth PET-CT scan was performed 70 days after the last day of radiotherapy (median: 71 ± 12 days). Because of logistic reasons or technical problems with the PET-scan, no PET information was available for 1 patient on day 7 and for 4 patients on day 14 of radiotherapy. For 3 patients no PET scan was available after radiotherapy, in one because of technical reasons and in 2 patients because of early death after radiotherapy due to a myocardial infarction and a pulmonary infection. The median follow-up (FU) from start of RT was 9.2 ± 3.8 months.

Time trends in maximal SUV

There was a large heterogeneity in the changes in SUV_{max} of the primary tumor during the radiation treatment between patients (Fig. 1). Out of the 22 patients who had a PET-CT at day 7 of radiotherapy, 4 patients (18%) showed a decrease of more than 25% of the SUV_{max} , whereas 41% (9/22) showed an increase of more than 25%. The remainder (9/22) showed a stable SUV_{max} (< 25% change) compared to pre-treatment values.

Table 2: Patient characteristics

patient no.	age (yr)	sex	cTNM	pathology	response to induction chemo-therapy	OTT (days)	TTD (Gy)	Metabolic response 70 days after RT
1	52	f	T1N3M0	adenoca	PR	21	54.0	CMR
2	54	m	T3N2M0	Large cell ca	SD	21	54.0	PMD
3	75	m	T3N2M0	large cell ca	PR	21	54.0	no scan
4	71	f	T3N1M0	scc	no chemo	28	64.8	CMR
5	71	m	T2N3M0	adenoca	PR	21	54.0	†
6	61	m	T1N3M0	scc	PR	27	64.8	CMR
7	71	m	T2N3M0	adenoca	PR	20	60.0	PMD
8	77	m	T4N2M0	large cell ca	PR	22	61.2	CMR
9	74	f	T2N0M0	large cell ca	no chemo	20	54.0	PMR
10	79	f	T4N0M0	large cell ca	PR	24	57.6	PMR
11	57	m	T1N3M0	large cell ca	PR	30	64.8	CMR
12	68	m	T4N0M0	adenoca	PR	21	54.0	CMR
13	63	m	T4N0M0	scc	SD	24	64.8	SMD
14	59	f	T2N2M0	large cell ca	PR	17	46.8	PMD
15	55	m	T4N2M0	adenoca	SD	30	79.2	PMD
16	52	f	T2N3M0	scc	PR	21	54.0	PMD
17	50	f	T4N2M0	large cell ca	PR	22	61.2	PMD
18	71	m	T4N2M0	large cell ca	PR	30	79.2	PMR
19	61	f	T2N2M0	large cell ca	PR	21	57.6	SMD
20	62	m	T2N2M0	large cell ca	PR	27	68.4	CMR
21	80	m	T2N0M0	scc	no chemo	22	61.2	†
22	56	m	T4N2M0	large cell ca	SD	30	79.2	PMR
23	54	m	T2N3M0	large cell ca	SD	30	79.2	PMD

scc = squamous cell carcinoma, PR = partial remission as response to induction chemotherapy, SD = stable disease as response to induction chemotherapy, OTT = overall treatment time of radiotherapy, TTD = total tumour dose, CMR = complete metabolic response, PMR = partial metabolic response, SMD = stable metabolic disease, PMD = progressive metabolic disease. †= patient died within first 70 days after radiotherapy.

For the whole patient group, the SUV_{max} was on average 7.3 ± 0.8 (range: 0.6–16.1) before start of radiotherapy, which increased to 8.9 ± 1.2 (range: 1.3–23.1) on day 7 of treatment ($p = 0.05$). In the second week, a significant decrease was observed to a SUV_{max} of 8.1 ± 1.0 (range: 2.1–17.8) ($p = 0.02$). Seventy days after treatment the SUV_{max} further decreased to a mean level of 4.8 ± 3.3 (range:

1.2–13.4), a significant decrease compared to day 14 of treatment ($p = 0.001$) and compared to pre-treatment levels ($p = 0.005$) (Fig. 2a). Analysing the subset of patients ($n = 16$), who received a PET-CT scan at all time points during radiotherapy, similar results were obtained: SUV_{max} before radiotherapy 7.0 ± 0.9 and at day 7 9.7 ± 1.5 ($p = 0.02$), day 14 8.0 ± 1.1 ($p = 0.02$) and 70 days after radiotherapy 4.7 ± 0.8 ($p = 0.002$).

Figure 1. The absolute (maximal SUV (standardized uptake value) plotted versus time (before start RT, day 7 and day 14 during RT and 70 days after RT) for all individual patients with a CT-PET scan at day 70.

Metabolic responders versus non-responders

In 20 patients a PET-CT scan was performed 70 days after treatment. In 1 patient (with visually a CMR) no SUV_{max} could be calculated, due to a software problem. Eleven patients (55%) showed a metabolic response 70 days after ra-

diotherapy [7 patients CMR and 4 patients PMR], while 9 patients (45%) showed no response [2 patients SMD, 7 patients PMD]. Concerning the PMD group, 4 patients had metastatic disease and 3 patients showed loco-regional progression.

Figure 2. Average change in maximal SUV for the total group of patients (a) and for metabolic responders (complete and partial metabolic response) versus non-responders (stable metabolic disease and progressive metabolic disease) (b), * indicates a significant difference.

Patients with a metabolic response 70 days after thoracic irradiation had a significantly longer overall survival (estimated survival of 100% after 9 months of follow-up) compared to the patients with stable or progressive disease (estimated survival of 63% after 9 months of follow-up) ($p = 0.005$) (Fig. 3). No difference was observed between total radiation dose prescribed ($p = 0.4$) and the overall treatment time of radiotherapy ($p = 0.2$) between metabolic responders and non-responders.

In the group of metabolic responders no change in SUV_{max} was observed during the course of radiotherapy. Only after radiotherapy a mean decrease of 46% of the SUV_{max} was observed from 5.0 ± 0.8 on day 14 during radiotherapy to 2.7 ± 0.4 70 days after radiotherapy ($p = 0.02$; Fig. 2b, Table 3). In contrast to this finding, the group of non-responders showed a significant increase of the SUV_{max} in the first week of radiotherapy. In this group the SUV_{max} before treatment was on average 8.9 ± 1.1 and increased to 13.2 ± 1.7 in the first week ($p = 0.02$). In the second week a decrease was observed to an average level of 11.5 ± 1.3 ($p = 0.04$), with a further decrease after radiotherapy to a mean of 6.9 ± 1.2 ($p = 0.02$). Similar results were obtained for the subset of patients with a PET-CT scan on day 0, 7 and 14: for the responders SUV_{max} did not change during radio-

therapy (before radiotherapy, 5.1 ± 1.1 ; day 7, $5.3 \pm 4.6 \pm 0.8$; day 14, 4.6 ± 0.8), while for the non-responders the SUV_{max} increased during the first week and decreased again during the second week of radiotherapy (before radiotherapy, 8.9 ± 1.2 ; day 7, 14.0 ± 1.7 ($p = 0.01$) and day 14, 11.5 ± 1.3 ($p = 0.04$)).

Figure 3. Actuarial analysis of overall survival (Kaplan-Meier) in months for metabolic responders (n=11) and non-responders (n=9), classified according to EORTC-criteria. p-value of log-rank test.

Not only a difference in time trends in SUV_{max} was observed between responders and non-responders, but the non-responders also showed a significant higher SUV_{max} than the responders at all time points investigated (Fig. 2, Table 3). The number of patients in this study was however too small to test the predictive value of the time trends in SUV_{max} in relation to metabolic response.

Influence of induction chemotherapy

In total 20 patients received induction chemotherapy, of which 18 patients were evaluable 70 days after irradiation. The group of patients achieving a partial remission after induction chemotherapy (13/18) showed in higher percentage metabolic response after radiotherapy (metabolic response rate, 62%) as patients showing stable disease as a result of the induction chemotherapy (metabolic response rate, 20%), although this difference was not significant ($p = 0.3$). The time patterns of the SUV_{max} in relation to metabolic response as described above for the total group were similar in patients having received induction chemotherapy.

This excludes the possibility that the 3 individuals, who did not receive systematic treatment, would have influenced the overall results.

Table 3. Maximal SUV (mean $\pm$ SE) before start of radiotherapy, on day 7 and 14 during radiotherapy and 70 days after radiotherapy for the total group, for patients showing a metabolic response (CMR or PMR) or no metabolic response (SMD or PMD) on radiotherapy 70 days after irradiation. P-value of Mann-Whitney U-test to compare the group of metabolic responders and non-responders.

	Total group			Metabolic responders			Metabolic non-responders			
Maximal SUV	mean	SE	(N)	mean	SE	(N)	mean	SE	(N)	p
Before start of radiotherapy	7.3	0.8	(23)	5.1	0.9	(11)	8.9	1.1	(9)	0.020
Day 7 of radiotherapy	8.9	1.2	(22)	4.8	1.1	(10)	13.2	1.7	(9)	0.001
Day 14 of radiotherapy	8.1	1.0	(19)	5.0	0.8	(9)	11.5	1.3	(8)	<0.001
70 days after radiotherapy	4.5	0.7	(19)	2.7	0.4	(10)	6.5	1.2	(9)	0.002

DISCUSSION

Until now the PET-scan is mainly used before start of radiotherapy for staging purposes, to delineate the primary tumor and/or mediastinal lymph nodes and after therapy to assess the remission status^{2,6,13,17,21,32,33,39,50,52,54}. Similar to early response measurements during chemotherapy, FDG-PET scans performed in the beginning of radiotherapy might give information on the later tumor response

^{14,22,26,41}. However, only limited data on this subject are available in the literature ^{12,16}. We therefore assessed in the present study the time trends of FDG uptake during radiation treatment in NSCLC.

A striking result was the large heterogeneity in the SUV_{max} in serial PET-scans between the individual patients. While some patients showed an increase, others show a stable or decreased FDG uptake after 1 week of radiation. This confirms the findings of Erdi *et al.*, who described serial PET-scans during radiation therapy in 2 NSCLC patients ¹⁶. De Geus-Oei *et al.* investigated repeated FDG-PET scans in patients treated with accelerated radiotherapy with carbogen and nicotinamide (ARCON) for head-and-neck cancer and also showed very heterogeneous changes in SUV_{max} after hyperoxygenation with a median interval of 2 days between the two scans ¹². Investigating the time trends we observed for the total group a trend in increase of the SUV_{max} ($p = 0.05$) during the first week of radiotherapy, followed by a significant decrease in the second week of treatment and in the first 70 days after treatment. Only few other authors described repeated (CT)-PET scans during radiation therapy. Geets *et al.* described re-imaging with FDG-PET scan during radiation treatment in head-and-neck patients ²³. After an average dose of 46 Gy, 18 patients received a repeat PET-scan, which was hard to interpret due to inflammation.

In our patients with NSCLC we did not encounter this problem. de Geus-Oei *et al.* showed in 22 patients with head and-neck tumors a median decrease of relative change of SUV_{max} of 4%, comparing the PET scan after hyperoxygenation to the baseline scan ¹². Lin *et al.* described repeated PET-scans during treatment in cervical patients, but no results concerning the (maximal) SUV were investigated ³¹. In both the study of Lin and Geets, most patients received concurrent chemo-radiation, while in the study of de Geus-Oei *et al.* patients were treated with ARCON.

By using the EORTC criteria to evaluate the metabolic response after 70 days we could confirm the findings of Mac Manus *et al.* that metabolic responders had a better overall survival than the non-responders ($p = 0.005$) ³³. Moreover, a significant difference in the time trends of SUV_{max} during radiotherapy between metabolic responders and non-responders was found. Metabolic non-responders had a higher SUV_{max} at all time points investigated and showed a significant increase in SUV_{max} during the first week of irradiation followed by a decrease. In contrast, the responders showed a stable SUV_{max} during irradiation. The number of included patients was however too small to calculate the predictive value of the changes in SUV_{max} during a course of radiation. The question thus remains what causes the observed time trends and their relation with subsequent response. A first hypothesis is that the increase of SUV_{max} during the first week is due to inflammation, since a rather high median dose of 19.8 Gy (1.8 Gy BID) was already delivered at the time point of the first repeat PET-CT scan. Radiation is known to be a potent inducer of inflammation in several tissues

^{28,43,51}. However, this cannot explain the differences in metabolic responders and non-responders, since one would also expect inflammatory changes in the group of responders. Another possibility is that the SUV_{max} provides information related to intrinsic biological characteristics of the tumor, such as tumor hypoxia. As hypoxia is strongly related to therapy resistance and the occurrence of metastases, this hypothesis is particularly attractive. Hypoxia might play a role in the uptake of FDG, since it leads via the hypoxia inducible factor-1 α (HIF-1 α) pathway to up regulation of glucose transporters. However, contradictory findings concerning the relation between FDG uptake and hypoxia have been published^{8,10,36,40,47,55,59,60}.

Although the radiation dose (range: 46.8–79.2 Gy) could have influenced the response rate, a dose–response relation could not be established in this series, presumably due to the limited number of patients^{11,34}. Another possibility is that the response on induction chemotherapy may also affect the subsequent response to radiation. However, this could not be shown in our study. To fully exclude the influence of induction chemotherapy it would have been best to perform the first PET-CT scan before start of any treatment. Although most of our patients underwent a PET-(CT) scan before start of chemotherapy, most of these scans were performed at different PET-(CT) scanners in affiliated hospitals. Since maximal SUV of different scanners cannot be compared directly, we were not able to encompass maximal SUV before start of chemotherapy into our results.

Lastly, the overall treatment time of radiotherapy might influence response after radiotherapy⁴. We did not find such a correlation between OTT of radiotherapy and the metabolic response rate, but this may be due to a short OTT (less than 5 weeks) in all patients. Our present working hypothesis is that the difference in time trends of SUV_{max} as observed between responders and non-responders might reflect a complex relationship between several factors, like changes in blood flow as well as changes in the extracellular compartment, together with intrinsic tumor properties, which all contribute to the uptake of the FDG tracer. Further in-depth studies, including analysis of several plasma markers at different time points, to address this question are ongoing.

In conclusion, a large heterogeneity in changes in SUV_{max} was observed during thoracic radiation. Differences in time trends of SUV_{max} during radiotherapy were found between metabolic responders and non-responders. Further research addressing the question whether these time trends can predict response, the biological meaning of the different time trends and whether it finally might enable individualized adjustments of treatment is ongoing. The final goal, being prediction of response early during the course of radiotherapy to enable early adjustments, like prescribing a higher total dose, adjusting the fractionation scheme or adding another form of treatment.

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CHAPTER

7

Time trends in nodal volumes and motion
during radiotherapy for patients with stage
III non-small cell lung cancer

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ABSTRACT

Purpose: Knowledge of changes in GTV and motion of GTV during a course of radiotherapy is necessary for accurate treatment delivery. This study describes the time trends in nodal CT volume and nodal motion for patients with locally advanced NSCLC.

Patients and Methods: In a prospective clinical trial 12 patients, with a total of 22 positive nodes, underwent a CT-PET scan prior to treatment, as well as in the first and second week following start of radiotherapy. Volume changes could be measured for all nodes. For 21 nodes, the motion was measured based on a respiration correlated CT (RC-CT) scan. Repeated RC-CT scans were available for 11 nodes to evaluate the change in motion.

Results: In 6/22 (27%) patients the nodal volume increased $> 30\%$ while in 3/22 (14%) the volume decreased $> 30\%$. On average, the nodal volume did not change significantly (from 4.9 to 5.1 to 4.6 cm³). The average motion of the nodal areas was initially 5.6 mm $\pm$ 2.8 mm. This motion decreased slightly during therapy but not statistically significant. However, large inter-patient and inter-nodal motion differences were observed.

Conclusion: A large variability of changes in nodal volume between patients was observed. However, this had limited clinical impact, since volumes and hence volume changes were small. The nodal motion did not change significantly during therapy. However, because of the large inter patient variability of nodal motion prior to treatment, internal margins for nodal areas should be calculated before radiotherapy using RC-CT, such that the margins can be applied for individual patients. Repeated imaging of the nodes seems however to be of limited use, as the observed individual changes in nodal volume and motion tend to fall within the commonly applied margins.

INTRODUCTION

Radiotherapy plays an important role in the management of patients suffering from non-small cell lung cancer (NSCLC). Obviously, accurate definition of target volumes is crucial. Several authors showed that the use of FDG-PET information improves target delineation, as indicated by a reduced interobserver variation. This has been ascribed to the ability of FDG-PET to better discriminate involved from non-involved nodes, tumor from atelectasis and the application of automated contouring systems¹⁻⁸.

Respiration correlated CT (RC-CT) scans have been shown to be able to take into account motion of the tumor^{9, 10}. With this relatively new technique tumor motion can be measured in 3 dimensions, and these data can subsequently be used to apply the internal margins, as defined by the ICRU^{11, 12}.

Besides optimal delineation before the start of radiation, adequate radiotherapy also needs to take into account the changes in volume and motion of target volumes during therapy. Indeed, many research groups have demonstrated striking volume changes during a course of radiotherapy¹³⁻¹⁷. In a previous paper we found that the motion of the primary tumor during a course of radiotherapy on average did not show significant changes, but for individual patients sometimes larger changes in motion were seen¹³. However, all studies presented data on the primary tumor, whereas none described changes of the volume of mediastinal lymph nodes. Even less data are available on the mobility of mediastinal lymph nodes prior to and during a course of radiation therapy. Moreover, only one study used four-dimensional CT scanning to assess nodal motion¹⁸ and other authors used surrogate methods to estimate nodal motion in three dimensions, like repeated CT imaging¹⁹ or orthogonal fluoroscopy of calcified lymph nodes²⁰.

In summary, no data are available on changes of real time nodal motion and nodal volume during a course of radiotherapy. More detailed information on nodal motion and changes in nodal volume and motion would allow to individually adapt the internal margin and thereby allow further optimization of the treatment plans, i.e. to reduce geographical misses whilst mimizing the dose to the normal tissues. Therefore, the aim of the present study was to analyze changes in nodal volumes and nodal motion during the first 2 weeks of an accelerated course of radiotherapy in patients with locally advanced non-small cell lung cancer (NSCLC), using RC-CT scans.

PATIENTS AND METHODS

Patients

Twenty-three patients with histological or cytological proven non-small cell lung cancer (NSCLC) were enrolled in this prospective study, which was part of a phase I trial. Patients were included from December 2004 until September 2005. Five patients had initially no positive lymph nodes (N0), while four patients became node negative on the FDG-PET scan after chemotherapy. Two patients had a primary tumor with direct extensive invasion in the mediastinum, making distinguishing the primary tumor and the involved lymph nodes impossible. This resulted in a total of 12 patients with 22 positive nodal areas. The Naruke/ATS-LCSG standardized mapping system was used to define the anatomical location of the lymph node involvement²¹. No concurrent chemotherapy was given.

The Medical Ethics Committee according to the Dutch law approved this study. All patients gave written informed consent before entering this study.

Radiotherapy simulation

Patients were simulated in radiotherapy position on a dedicated CT-PET-simulator with both arms above the head using an immobilization device and patient laser marker system. Radiotherapy technologists trained specifically for this purpose carried out the simulation. The CT-PET scanner used was a Siemens Biograph (SOMATOM Sensation-16 with an ECAT ACCEL PET scanner). A spiral CT with intravenous contrast was performed covering the complete thoracic region¹³.

Respiration Correlated CT scans (RC-CT)

The CT-PET was immediately followed by a respiration correlated CT, using offline correlation of the 16-slice spiral CT scan of the CT-PET system. This had been modified to enable a low pitch (minimum 0.1), in combination with a respiratory signal obtained by a pressure sensor in a chest belt (AZ-733V, Anzai Medical Corporation, Tokyo, Japan). The raw CT data were reconstructed in 10 phases, from 0% to 100% in steps of 10% of the respiration period starting at end inspiration. In-house developed software with Matlab (Mathworks Inc, Natick, MA) was used to measure the motion of the lymph node in all three orthogonal directions⁹. This was performed manually by measuring the largest distance between the respiration phases on a movie in an axial, sagittal and coronal view.

Radiotherapy planning

Radiotherapy planning was performed on an XiO (Computerized Medical Systems, St Louis, Missouri) treatment planning system, using inhomogeneity corrections, based on a convolution algorithm. For all patients, the Gross Tumor Volume (GTV) was defined based on CT-PET data, obtained prior to radiotherapy (i.e. post chemotherapy in case of induction chemotherapy for the primary tumor and pre chemotherapy for the lymph nodes). For the volume comparison in this study, the CT-Nodal Volume was defined as the FDG-PET positive lymph nodes, as described by the report of nuclear medicine post-chemotherapy, delineated on the CT with a mediastinal window-level setting ($W = 600$, $L = 40$).

Radiotherapy dose and normal tissue dose constraints

For each patient, the radiation dose was escalated to a mean lung dose (MLD) of $19 \text{ Gy} \pm 1 \text{ Gy}$ while respecting a maximum spinal cord dose of 54 Gy. There were no esophageal dose constraints. The maximal allowed total tumor dose (TTD) was 79.2 Gy or lower if any of the normal tissue dose constraints were reached. Radiotherapy was always delivered twice a day (BID), with a minimum of 8 hours interval between the two fractions, and given 5 days per week with a fraction dose of 1.8 Gy.

Study design

Patients underwent repeated CT-PET scans and respiration correlated CT scans in treatment position, before and one and two weeks during radiotherapy. At all time points, the nodal volume was delineated using the free-breathing CT. Although in principle this may have led to blurring artifacts, our high-speed 16 slice CT-scan protocol effectively “freezes” the lesion in a single phase during a free breathing CT-scan. This assumption was found to be valid for the primary tumor and was subsequently extrapolated to the nodal areas. The nodal volume was delineated for each patient by the same physician to avoid interobserver variability. To study the intra-observer variability, seven (32%) nodal volumes were delineated twice by the same physician for all time points, with at least a 3 months time interval. The ratio between the two delineations was calculated and reported as a percentage.

Due to technical and logistical problems, a complete image dataset at all three time points, was not available for two patients. A CT-PET dataset (with in total four nodal areas) two weeks after the start of treatment was not obtained for these two patients.

Endpoints and statistical analysis

We determined the nodal volumes (NV) prior to radiation, 1 and 2 weeks after start of the treatment, based on the NVs drawn on the free-breathing CT. In addition, the respiration correlated CT was used to quantify the nodal motion at all 3 time points. Nodal motion was expressed as a 3D vector²², which is the quadratic sum of the motions in the three orthogonal directions. All results are expressed as the mean $\pm$ standard deviation (SD). Statistical differences between paired parameters from the three time points were evaluated using the Wilcoxon signed rank test. Differences were considered to be significant when the p-value was less than 0.05.

Table 1: Patient characteristics.

Patient no.	Age (years)	Gender	Clinical stage	Involved nodal stations	TTD (Gy)	MLD (Gy)	OTT (days)
1	54	M	T3N2M0	7	54.0	19.3	20
2	75	M	T3N2M0	7, 4R	54.0	15.2	20
3	71	M	T2N3M0	7, 3, 5, 2R	54.0	14.7	23
4	61	M	T1N2M0	7, 4R	68.4	14.9	22
5	77	M	T4N2M0	7, 4R, 10R	61.2	17.6	22
6	57	M	T1N2M0	2R, 4R	64.8	8.5	27
7	59	F	T2N2M0	7, 2R	46.8	20.0	16
8	55	M	T4N2M0	5	79.2	16.4	29
9	52	F	T2N2M0	7, 10L	54.0	15.6	20
10	50	F	T4N2M0	7	61.2	20.8	21
11	71	M	T4N2M0	2, 4R	79.2	13.6	29
12	54	M	T2N3M0	2L	79.2	16.1	30
Mean	61.3				63.0	16.1	23.3
SD	9.6				11.3	3.3	4.5

TTD = Total Tumor Dose; MLD = Mean Lung Dose; OTT = Overall Treatment Time
F = Female; M = Male;

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. The mean values of the total tumor dose (TTD) and the corresponding mean lung dose (MLD) were 63.0 Gy $\pm$ 11.3 Gy [range: 46.8 Gy – 79.2 Gy] and 16.1 Gy $\pm$ 3.3 Gy [range: 8.5 Gy – 20.8 Gy], respectively. The average volume per pathological lymph node before radio-

therapy was $4.9 \text{ cm}^3 \pm 4.4 \text{ cm}^3$ [range: $0.2 \text{ cm}^3 - 19.6 \text{ cm}^3$]. The first repeat scan was made after the patient received on average a dose of $21.2 \text{ Gy} \pm 4.4 \text{ Gy}$ (about 12 fractions) and the second scan after $38.5 \text{ Gy} \pm 5.2 \text{ Gy}$ (about 21 fractions).

Volume changes of the mediastinal lymph nodes

A large heterogeneity of nodal volume changes between patients was observed at all time points (Table 2). In 6/22 (27%) patients the nodal volume increased $> 30\%$, while in 3/22 (14%) the volume decreased $> 30\%$. For the majority of nodal areas (13/22) the volume changed only slightly ($< 30\%$) (Fig. 1).

Figure 1: Nodal volumes (NV), relative to the volume prior to treatment as a function of the dose. The thick black line represents the mean relative CT volume together with the standard deviation. The dotted lines represent the individual patients where the NV increased more than 30%; the dashed lines those patients with a decrease of more than 30%. A solid grey line is used for the remaining patients.

On average the nodal volume changed from $4.9 \text{ cm}^3 \pm 4.4 \text{ cm}^3$ prior to treatment, to $5.1 \text{ cm}^3 \pm 4.1 \text{ cm}^3$ and $4.6 \text{ cm}^3 \pm 4.2 \text{ cm}^3$ 1 and 2 weeks after the start of treatment, respectively. These changes were not significant ($p = 0.897$ prior versus week 1, $p = 0.177$ prior versus week 2 and $p = 0.084$ week 2 versus week 1).

Intra-observer variability in delineation of the mediastinal lymph nodes

For the 21 delineations on three different time points which were performed twice an average intra-observer variability of $11.6 \% \pm 9.4 \%$, with a maximum deviation of 37.4% was found. Since similar volume changes were observed for the second delineation (data not shown) this variability did not influence the results on the volume changes of the mediastinal areas during radiotherapy.

Table 2: Evolution of the Nodal Volume during radiotherapy.

Patient no.	Nodal area	Volume before RT (cm ³)	Volume one week after start RT (cm ³) and relative change (%)	Volume two weeks after start RT (cm ³) and relative change (%)
1	7	11.8	11.2 (-5%)	10.1 (-14%)
2	7	3.5	2.6 (-26%)	NA
	4R	3.1	4.5 (+45%)	NA
3	7	2.2	1.5 (-32%)	1.3 (-41%)
	2R	19.6	16.8 (-14%)	14.9 (-24%)
	3	0.2	0.3 (+50%)	0.3 (+50%)
	5	1.8	0.7 (-61%)	0.7 (-61%)
4	7	6.2	5.9 (-5%)	3.2 (-48%)
	4R	6.1	5.6 (-8%)	3.6 (-41%)
5	10R	3.6	9.5 (+163%)	10.9 (+202%)
	4R	2.9	3.0 (+3%)	2.0 (-31%)
	7	1.8	4.9 (+172%)	8.2 (+355%)
6	2R	9.3	8.2 (-12%)	NA
	4R	6.6	4.7 (-29%)	NA
7	2R	0.6	0.5 (-17%)	0.5 (-17%)
	7	5.7	6.0 (+5%)	6.0 (+5%)
8	5	0.8	0.5 (-38%)	1.0 (+25%)
9	10L	1.5	3.2 (+113%)	1.9 (+27%)
	7	6.1	6.6 (+8%)	5.6 (-8%)
10	7	3.4	4.4 (+29%)	3.8 (+12%)
11	2, 4R	7.6	9.9 (+30%)	6.9 (-9%)
12	2L	2.5	2.7 (+8%)	1.9 (-24%)
Mean		4.9	5.1 (+4%)	4.6 (-6%)
SD		4.4	4.1	4.2
p = 0.897 one week vs prior; p = 0.084 two weeks vs one week; p = 0.177 two weeks vs prior RT: Radiotherapy; NA: Not Assessed because of technical problems				

Motion changes of nodal areas

Nodal motion is shown in Table 3 and Fig 2. For one nodal area it was not possible to measure the motion because of its limited size (0.2 cm^3). The mean initial motion before start of radiotherapy of all nodes was $5.6 \text{ mm} \pm 2.8 \text{ mm}$. The motion was larger in cranial-caudal direction ($4.3 \text{ mm} \pm 3.2 \text{ mm}$) compared with the other directions (ventro-dorsal $1.8 \text{ mm} \pm 1.5 \text{ mm}$ and left-right $2.0 \text{ mm} \pm 1.3 \text{ mm}$). The 3D motion changed to $5.8 \text{ mm} \pm 2.6 \text{ mm}$ and $5.3 \text{ mm} \pm 2.7 \text{ mm}$ one and two weeks after the start of the radiotherapy respectively. All differences compared to the initial nodal motion were not statistically significant different from each other ($p = 0.838$ and $p = 0.221$ respectively).

Table 3: 3D Vector motion before and during radiation treatment.

Patient no.	Nodal area	Motion prior to treatment (mm)	Motion after one week of RT (mm)	Motion after two weeks of RT (mm)
1	7	4.9		
2	7	3.6		
	4R	6.4		
3	7	4.2	4.0	1.4
	2R	2.1	2.2	2.2
	3	NA		
	5	1.4	3.7	1.4
4	7	6.7	9.3	6.1
	4R	6.7	7.8	7.2
5	10R	3.3		
	4R	3.7		
	7	4.3		
6	2R	6.4		
	4R	7.0		
7	2R	12.3	9.2	7.9
	7	6.7	6.3	9.0
8	5	4.3	4.6	3.3
9	10L	9.1	9.1	6.7
	7	3.9	3.6	6.7
10	7	11.0	4.4	6.3
11	2, 4R	7.7		
12	2L	2.1		
Mean		5.6	5.8	5.3
SD		2.8	2.6	2.7

$p = 0.838$ one week vs prior; $p = 0.507$ two weeks vs one week; $p = 0.221$ two weeks vs prior

In order to investigate the influence of the anatomical location of the nodes on its motion, the involved lymph nodes were classified based on their location: infra-carinal ($N = 10$) versus supra-carinal ($N = 12$). The motion was $5.8 \text{ mm} \pm 2.6 \text{ mm}$ versus $5.5 \text{ mm} \pm 3.2 \text{ mm}$ respectively ($p = 0.812$). However, in individual patients, large inter-nodal motion differences could occur (e.g. patient nrs: 2, 7 and 9) (Table 3).

Figure 2: 3D Vector motion (quadratic sum of the motion in three orthogonal directions) as a function of the dose. The gray lines represent the individual patient data, while the thick black line represents the mean tumor motion, together with the standard deviation.

DISCUSSION

To the best of our knowledge, this is the first report about time trends of nodal volume and motion of involved mediastinal lymph nodes in patients with NSCLC during radiotherapy. This information is clinically relevant since changes in size and mobility of all tumor localizations (e.g. the primary tumor and the lymph nodes) during a course of radiotherapy are needed as an input for adaptive radiotherapy approaches.

Our results show that, similar to the volume changes of the primary tumor volumes¹³, the individual volumes of the mediastinal lymph nodes may change considerably during radiotherapy and that a large heterogeneity of nodal volume changes between patients was observed. The nodal volume increased > 30% in 27% of the patients and decreased > 30% in 14% of the patients. In a previous study of our group, for the primary tumor, 17% of the patients showed a large increase of tumor volume and 13% of the patients had a large decrease of the tumor¹³. We did not find a correlation between the tumor increase and decrease versus the change in volume of the involved mediastinal lymph nodes in the same patient. Intra-patient differences were also observed that may be explained by the different location and the size of the nodal areas within the patient.

Intra-observer variability could not explain the time trends of the nodal volume changes. Remarkably, the relative intra-observer variability for delineation of the nodes was substantially larger than the intra-observer variability of the primary tumor ($1.2 \% \pm 4.4\%$)¹³. This can probably be ascribed to the fact that a small intra-observer variation in the small absolute nodal volumes has larger relative effect than small intra-observer variation in the large primary tumor volumes.

However, since the nodal volume was relatively small (average 4.9 cm^3 , range: 0.2 cm^3 - 19.6 cm^3), the clinical impact of the volume changes is probably limited. Assuming that nodes are spherical, the average observed volume change would result in a difference of the radius of 1 mm or less for 85% of the investigated nodes [range: -2 mm – +5 mm]. Only in one patient two lymph nodes showed an increase of respectively 4 mm and 5 mm of the radius. In this case, adaptation of the gross tumor volume might have been appropriate depending on the used treatment technique (e.g. motion adapted) and margins. The motion of those lymph nodes was relatively small (3D vector: 3.3 mm and 4.3 mm respectively). Our clinically applied GTV-PTV margin of 1 cm, consisting of a 3 mm margin for CTV²³ and 7 mm for PTV, would probably have covered most of the change in volume during therapy. This, in contrast with the changes of the volume of the primary tumor during therapy, where in some patients significant changes were observed and adaptive radiotherapy could be beneficial¹³.

The motion of the nodal areas, which are more constrained by surrounding tissue, was smaller than the motion of the primary tumor. Prior to therapy, the 3D vector was on average $5.6 \text{ mm} \pm 2.8 \text{ mm}$ versus $7.8 \text{ mm} \pm 4.8 \text{ mm}$ ¹³ for the nodes and primary tumor respectively. These results are in agreement with Piet *et al.*¹⁸, who also used 4D-CT scans to evaluate the nodal motion. They reported a 3D vector motion of $6.2 \text{ mm} \pm 2.9 \text{ mm}$. Jenkins *et al.*²⁰ used orthogonal fluoroscopic imaging to assess the motion of calcified lymph nodes. These investigators observed the motion during several breathing cycles and therefore have probably taken the maximum respiration excursion. They found a larger nodal motion of $7.0 \text{ mm} \pm 4.7 \text{ mm}$ especially in the cranial caudal direction.

The difference with our results may be due to the motion measurement method and to a different patient population.

Taking into account the peak-to-peak amplitude divided by four in our study to calculate the internal margin ⁹, an average isotropic internal margin of 1.4 mm would suffice, so the 5 mm margin proposed by van Sörnsen de Koste *et al.* ¹⁹, seems rather large. However, since these authors used repeated 3D CT images, other factors like image correlation and intra-observer variations may have influenced their results. In the present study, we found a large inter-patient and inter-nodal difference in motion (range: 1.4 mm – 12.3 mm), indicating that a general internal margin is not appropriate and the motion should individually be measured with an RC-CT. This might improve target definition and hence treatment outcome. In agreement with the other investigators ¹⁸⁻²⁰, we did not observe a difference in motion between the locations of the nodal areas.

On average no change in nodal motion was observed during treatment although for some patients large differences could occur. When using a specific nodal internal margin these motion changes could influence treatment accuracy and adaptive strategies might be developed if the changes extend beyond the applied PTV margins.

Until now respiratory management is mainly focused on the motion of the primary tumor ¹⁰. When extending this high precision treatment technique to the involved lymph nodes, the reported nodal volume and motion changes could play an important role in the accuracy of the treatment.

In conclusion, our results show that a different internal margin should be applied to the nodal areas compared to the primary tumor. This internal margin should be defined individually with a four-dimensional imaging technique prior to therapy. On average the nodal volume as well as the nodal motion did not change significantly during the radiation although large inter patient differences were observed. In contrast to the primary tumor ¹³, repeated imaging of the nodes seems to be of limited use, as the observed individual changes in nodal volume and motion tend to fall within the applied margins.

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CHAPTER

8

General Discussion and Future Perspectives

For stage III non-small cell lung cancer (NSCLC) patients, radiation therapy plays a major role in their treatment with curative intent. Nevertheless, the prognosis remains grim, with most patients still experiencing local and distant tumor relapse.

Local tumor control and hence survival could be improved by delivering higher doses to the tumor in a reasonably short overall treatment time, while at the same time keeping the radiation dose to surrounding healthy tissue tolerable.

Problems to achieve this in clinical practice are respiration artifacts in imaging of the tumor and changes in the tumor during radiation therapy.

Accurate imaging of lung tumors is difficult since respiration causes distorted images. Four-dimensional imaging, with the time being the fourth dimension, is therefore currently a 'hot topic' in radiotherapy. This technique is needed to achieve the accuracy of state-of-the art treatment delivery.

Radiation treatment planning is mostly based on a single pre-treatment CT(-PET) scan, but incorporating the tumor dynamics during a course of radiotherapy into the treatment planning could probably improve treatment accuracy.

Respiration Correlated (RC) or Four-Dimensional (4D) CT

We first investigated how to use the 4D imaging data in the treatment planning. We compared the standard imaging protocol, a free breathing CT, with different methods of generating an internal target volume (ITV) based on the 4D or respiration correlated CT scan. With a free breathing CT, no information about the respiration motion is known. Therefore general population based margins are used to create the planning target volume (PTV). These margins will be too big for some patients, where the tumor will not move that much, but in other patients, with a large tumor motion, the margin will be too small. For the first group, knowledge of the tumor motion in the individual patient could lead to a decrease in treatment fields and hence sparing more normal tissue, resulting in a lower normal tissue complication probability (NTCP). Another possibility would be to keep the same level of toxicity and to escalate the radiation dose to reach these normal tissue dose constraints. For the second group, the treatment fields should be enlarged, thereby reducing geographical misses and increasing the tumor control probability (TCP).

Besides inappropriate margins, free breathing CT also might introduce systematic errors. The free breathing CT, with current fast multislice CT scanners, is actually a snapshot of the patient's anatomy and could be taken at an extreme position near end expiration or end inspiration of the tumor. As such a CT does not represent patient geometry during irradiation, a large systematic error may be introduced, which will have a big impact on the treatment accuracy¹.

One might overcome this problem by acquiring a slow CT instead of the snapshot, free breathing CT. We therefore simulated a slow CT by averaging all the

CTs taken at individual phases, and showed that it was sometimes difficult to delineate the tumor because of the blurred images, especially near the mediastinum or diaphragm. This resulted in too small volumes (Chapter 2) and therefore no optimal coverage of the Clinical Target Volume could be achieved.

Treatment plans based on all the CT datasets (i.e. the full 4D-CT) will have better CTV coverage but this method generated larger volumes than the treatment plan based on the half-ventilation CT scan.

The half-ventilation method seems to be optimal since only one CT has to be delineated, individual anisotropic tumor motion can be incorporated and the proposed margin recipe of the peak-to-peak amplitude divided by four still achieved good CTV coverage (Chapter 2).

The main advantage of using 4D-CT in treatment planning is reducing systematic errors, with the half-ventilation phase, and for some patients decreasing the internal safety margins which make dose escalation possible.

Respiration Correlated CT-PET

CT-PET imaging has proven to be beneficial for radiation treatment planning. It provides a more accurate estimate of the true extent of disease inside the thorax compared to CT and is a sensitive method for detection of distant metastasis outside the thorax². PET can also better identify involved lymph nodes than CT and it has been proven to be safe to only irradiate PET positive lymph nodes³.

However, it is difficult to define the GTV manually on a PET scan, since these images are for instance very susceptible to window level settings. Many suggestions have been made for automatic delineations⁴, but no good three-dimensional validation with pathologic information has been performed. One of the prerequisites of auto-delineation is a quantitative PET, which is a challenge in a tumor moving with respiration. The main problem is the smearing out effect due to the respiration, which makes the intensity of a PET voxel not only a function of glucose metabolism, but also of the respiration. With respiration correlated PET, blurring does not occur, so it should improve target volume definition. Respiration correlated PET might also be very useful to image non-homogeneous tumors. A malignant tumor is not a homogeneous mass, but is composed of regions that differ in radioresistance. This intra-tumor heterogeneity can be visualized with PET imaging and opens new therapeutic possibilities for individualized patient treatment. However, the visualization of this intra-tumor heterogeneity could be distorted if no respiration correlation is performed.

Another consideration when trying to keep PET a quantitative technique, is the attenuation correction. In a CT-PET scanner, the CT information is used for the calculation of the attenuation correction. However, discrepancies between the fast CT and slow PET images could introduce artifacts. We therefore investi-

gated how an RC-PET should be optimally corrected for attenuation in phantom measurements (Chapter 3) and in simulations based on real RC-CT patient data (Chapter 4). To allow reliable quantification of the PET-signal, attenuation related errors should be minimized. These errors depend on tumor location, tumor size and tumor motion. In all simulated cases, the phased attenuation correction yielded the best results.

The binning of the images was based on the phase of the respiration instead of the amplitude of the respiration. The latter method is more accurate but can lead to gaps in the coronal images, depending on the patient's breathing pattern. Phase binning exhibits no gaps but could generate artifacts due to misbinning⁵. For RC-CT, with a relatively short acquisition time, we seldom see irregular breathing patterns. Therefore we believe that phase binning is an acceptable method of reconstruction. For RC-CT-PET, more research on a large patient scale is needed to quantify errors between the two methods.

To allow the use of (RC-) CT-PET suitable for radiotherapy simulation and dose calculation, a flat carbon table should be used, a moveable laser system and the CT Hounsfield units should be calibrated to electron densities. Although this is an initial investment, in the end it will be more cost effective, since in that case no additional CT for radiotherapy planning has to be performed.

In conclusion, the main reasons for making RC-CT-PET scans are: avoiding a systematic error, avoiding image blurring, and improving auto-delineation procedures since it allows quantification of the PET signal when using phased attenuation correction. In addition, the RC-CT-PET also offers unique possibilities for further research on intra-tumor heterogeneity and correlation of CT-PET with pathology data. This indicated that an RC-CT-PET should be the standard procedure for CT-PET imaging of lung cancer patients.

Repeated imaging during radiotherapy

The main purpose of repeat imaging during therapy is to see if the GTV and its motion changes during therapy. We used repeated CT-PET and repeated RC-CT scans to investigate these changes. This has the advantage, over in-room imaging, that the diagnostic image quality is preserved. In addition, apart from anatomical information it allows to investigate metabolic changes. The consequence of anatomical changes could be a change in the size of the treatment fields. But maybe in some cases also the field geometry should be adjusted, when critical organs (e.g. the spinal cord) become dose limiting.

We observed for some patients a large increase in tumor volume during therapy. For those patients tumor control might be improved by enlarging the treatment fields. For the patients with decreasing tumor volumes, more normal tissue can be spared with shrinking treatment fields.

Changes in tumor motion were relatively small, especially when looking at the impact on the internal safety margin, which is only a fraction of the motion (Chapter 5).

The second purpose of repeated PET imaging was to see if we could find a predictive parameter for response early in the treatment and to enable early adjustments, like prescribing a higher total dose, adjusting the fractionation scheme or adding another treatment modality (Chapter 6). With this information we can also investigate if the intra-tumor heterogeneity remains stable during therapy. This information is necessary to develop new treatment options, such as boosting radio-resistant areas within the tumor.

In locally advanced NSCLC, the mediastinal lymph nodes are often involved. Therefore similar knowledge as for the primary tumor is needed for adaptive treatment. When looking at the changes, for the volume as well as for the motion, the clinical impact is relatively small. However, like for tumor motion, there was a large inter-patient variability of nodal motion, even for involved lymph nodes close to the mediastinum (for example: nodal area seven ⁶). The nodal motion was somewhat smaller than tumor motion. Even within the same patient with multiple involved lymph nodes, differences were observed in nodal motion depending on its anatomical location (Chapter 7). This underscores the need of making an RC-CT not only for the tumor but also for the lymph nodes and to use a patient and nodal specific anisotropic internal margin.

FUTURE PERSPECTIVES

Non-small cell lung cancer (NSCLC) is a leading cause of cancer mortality in both men and women. Therefore those patients are a big challenge as they have a very high incidence of both local tumor recurrence and distant failure.

One of the first chains in the radiotherapy process is imaging the patient for target definition. A lot of effort has been made to incorporate PET information for treatment planning. As discussed before, this should be replaced by an RC-CT-PET but currently no institution uses these scans routinely for all patients. Therefore RC-CT-PET scanning protocols should be optimized and standardized to assure good image quality (i.e. a good signal/noise ratio). This includes investigating the benefits of phased attenuation, regarding quantitative parameters like the SUV_{max} , on real RC-CT and RC-PET patient data.

At present, no data are yet available on 3D correlation of PET information with the pathologic information. This could give information about the extent of the tumor and can be used as an input for developing auto-delineation protocols. This would reduce further the interobserver variation and would be less time consuming for the radiation oncologist. It will also facilitate multi-institutional studies when a uniform, preferably automated, delineation protocol is available.

Radiotherapy patients are mostly inoperable and therefore we are currently performing a study to validate RC-CT-PET delineation with pathology in a different, i.e. operable patient population⁷. Another way to tackle this problem is to prospectively investigate the result of autodelineation algorithms by looking at local recurrence patterns.

When resources do not allow to make RC-CT-PET images, another solution is described recently^{8, 9}. Deep inspiration breath hold (BH) CT-PET imaging looks promising and an increased detection and better characterization of lung lesions compared with a standard clinical CT-PET protocol is feasible. This technique is easy to implement in clinical practice and requires only a minor increase in the examination time. It also reduces breathing artifacts, misregistration, and inaccuracies in SUV measurements. Of course treatment should be performed in the same position which will increase treatment time on the linear accelerator and will be more critical to assure similar patient setup during treatment. Another drawback of this approach is the ability of lung cancer patients to hold their breath during scanning and treatment.

These innovative imaging techniques for FDG-PET scanning could also be extrapolated to other tracers, which visualize different biological characteristics of the tumor.

In the near future we will investigate if the information obtained by repeated CT-PET images, is worthwhile to adapt the treatment fields. Calculations will be done for the dose distribution of the tumor and the surrounding tissues. We also need to look more in depth at the biological variations during therapy and try to answer important questions why SUV_{max} changes occurs differently for metabolic responders versus metabolic non-responders. These comparisons will be performed using non-rigid registrations algorithms to minimize deformation artifacts. At all timepoints blood samples were acquired which could give more insight in these tumor dynamics.

Gaining more knowledge of intra-tumor heterogeneity by imaging also implies improving treatment modalities. As the total radiation dose is restricted by virtue of the normal tissue constraints, dose redistribution (higher dose to resistant and lower dose to sensitive areas) within the tumor has a theoretical advantage. This can be done by introducing IMRT (subvolume boosting or dose painting) and delivering a non-homogenous dose to more radioresistant areas within the tumor. Another possibility is to treat the radioresistant zones within the primary tumor with hypofractionation (fraction size of 10Gy – 20Gy) followed by radiotherapy to the whole tumor, with more conventional fraction doses.

Currently, most studies and predictive models, for instance to predict outcome or radiation induced normal tissue injury, are based on planned dose distributions. When the theoretical distribution could be replaced by the actual delivered dose, this will improve accuracy in developing these predictive algorithms. The delivered dose can be measured with repeated imaging using an electronic

portal imaging device (EPID), and research is ongoing of converting the two-dimensional EPID information behind the patient to three-dimensional dose distributions within the patient¹⁰.

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Summary

Radiotherapy plays an important role in the management of treating lung cancer patients. In this thesis two approaches to improve radiotherapy for patients with lung cancer are investigated. The first approach is to better define the target using novel imaging techniques such as respiration correlated (RC-) CT and respiration correlated CT-PET. These techniques take into account the intra-fraction variations and artifacts due to respiration. In the second approach the target is followed during treatment using repeated (RC-) CT and CT-PET imaging, with the final goal being adaptation of radiotherapy during treatment and tackle inter-fraction changes.

In **Chapter 2** we determined which method of internal target volume (ITV) definition based on a respiration correlated CT (RC-CT) allows optimal tumor coverage. Therefore we acquired both a free breathing CT (CT_{fb}) and an RC-CT scan. The RC-CT scan was used to measure tumor motion and to reconstruct a CT at 10 phases (CT_{10ph}), amongst which the half ventilation CT (CT_{hv}). By averaging the CT_{10ph} , a slow CT (CT_{slow}) was reconstructed. Based on those scans ITVs were delineated and treatments were planned, where for the ITV_{hv} an internal margin (margin for tumor motion) of (motion amplitude)/4 was used. The treatment plans for the ITVs were projected on the 10 respiration phases and subsequently the absorbed dose was calculated and averaged over the ten phases to estimate the actual CTV coverage. This was an *in silico* (plannings) study based on real RC-CT patient data. The CT_{hv} seems to be the optimal dataset for delineation, using an adequate anisotropic internal margin.

Since accurate knowledge of the position of the tumor and the surrounding tissues is needed for radiation treatment planning it is important to improve CT-PET image acquisition. In **Chapter 3** we evaluated the potential to improve image acquisition using phased attenuation correction in respiration correlated CT-PET, where data of both modalities was binned retrospectively. After collection of the raw CT data, list-mode PET data, and the respiratory signal CT-PET images were binned to ten phases with help of in-house built software. Each PET phase was corrected for attenuation with CT data of the corresponding phase. For comparison, the attenuation correction was also performed with non-respiration correlated (non-RC) CT data. With a standard, non-RC CT-PET scan, the volume was underestimated by as much as 46% in CT and the PET volume was overestimated to 370% whereas the volumes with RC-CT-PET scanning had small deviations from the actual volume. Evaluation of the maximum activity concentration showed a clear displacement in the images with non-RC attenuation correction. In this phantom study we have shown that a combination of respiration correlated CT-PET scanning with application of phased attenuation correction can improve the imaging of moving objects and

can lead to improved volume estimation and a more precise localization and quantification of the activity.

To quantify the attenuation errors and identify the parameters associated with them, we performed a simulation based on respiratory-gated CT studies of five lung cancer patients in **Chapter 4**. The CT series were converted to 511-keV attenuation maps which were forward-projected and exponentiated to form sinograms of PET attenuation factors at each phase of respiration. The CT images were also segmented to form a PET object, moving with the same motion as the CT series. In the moving PET object, spherical 20-mm mobile tumors were created in the vicinity of the dome of the liver, and immobile 20-mm tumors in the mid chest region. The moving PET objects were forward-projected and attenuated, then reconstructed in several ways: phase-matched PET and CT; gated PET with ungated CT; ungated PET with gated CT; and conventional PET. Phase-matched gated PET and CT gave essentially perfect PET reconstructions in the simulation. Gated PET with ungated CT gave tumors of the correct shape, but recovery was too large by an amount that depended on the extent of the motion, as much as 90% for mobile tumors and 60% for immobile tumors. Gated CT with ungated PET resulted in blurred tumors and caused the recovery errors between -50% and +75%. Recovery in clinical scans would be 0% to 20% lower than stated. Quantitative PET imaging near the diaphragm requires proper matching of attenuation information to the emission information.

Chapter 5 deals with the change in tumor volume, motion and breathing frequency during a course of radiotherapy, for locally advanced non-small cell lung cancer. Twenty-three patients underwent CT-PET and Respiration Correlated CT scans prior to treatment, which was repeated in the first and second week following the start of radiotherapy. Patients were treated with an accelerated fractionation schedule with a total tumor dose depending on pre-set dose constraints for the lungs and the spinal cord. A striking heterogeneity of tumor volume changes was observed at all time points. In some patients the volume decreased > 30% in others the volume increased > 30% but for the majority of patients the tumor volume only changed slightly. No significant changes in average tumor motion or breathing frequencies were seen during treatment. These results underscore the need for repeated imaging during the course of radiotherapy. However, the changes in tumor motion are small, which indicates that repeated respiration correlated CT does not appear to be necessary for the primary tumor.

^{18}F -fluoro-2-deoxy-glucose (FDG) uptake on PET scan is a prognostic factor for outcome in NSCLC. We investigated changes in FDG uptake during fractionated radiotherapy in relation to metabolic response with the ultimate aim to

adapt treatment according to early response (**chapter 6**). The same patient population of the previous chapter was examined. Almost all patients had a 70 days post treatment CT-PET scan. Changes in maximal standardized uptake value (SUV_{max}) were described. The most striking result was the large intra-individual heterogeneity in the evolution of SUV_{max} . Different time trends were shown for responders (no change during radiotherapy) and non-responders (48% increase during first week). Non-responders had a higher SUV_{max} on all time points investigated. Time trends in SUV_{max} showed a large intra-individual heterogeneity and different patterns for metabolic responders and non-responders. These new findings may reflect intrinsic tumor characteristics and might finally be useful to adapt treatment.

Chapter 7 describes the time trends in nodal CT volume and nodal motion. Twelve patients, with a total of 22 positive nodes, underwent a CT-PET scan prior to treatment, as well as in the first and second week following start of radiotherapy. Volume changes could be measured for all nodes. For 21 nodes, the motion was measured based on a respiration correlated CT (RC-CT) scan. Repeated RC-CT scans were available for 11 nodes to evaluate the change in motion. In 27% patients the nodal volume increased $> 30\%$ while in 14% the volume decreased $> 30\%$. These changes had limited clinical impact, since volumes and hence volume changes were small and on average, the nodal volume did not change significantly. The average motion of the nodal areas was initially $5.6 \text{ mm} \pm 2.8 \text{ mm}$. This motion decreased slightly during therapy but not statistically significant. Large inter-patient and inter-nodal motion differences were observed. However, because of the large inter patient variability of nodal motion prior to treatment, internal margins for nodal areas should be calculated before radiotherapy using RC-CT, such that the margins can be applied for individual patients. Repeated imaging of the nodes seems however to be of limited use, as the observed individual changes in nodal volume and motion tend to fall within the commonly applied margins.

Samenvatting

Radiotherapie speelt een belangrijke rol in de behandeling van longkanker patiënten. In dit proefschrift worden twee benaderingen onderzocht om de radiotherapie te verbeteren voor deze patiënten. De eerste benadering is het beter definiëren van het doelvolumen, gebruik makend van vernieuwende beeldvormingstechnieken zoals ademhalingsgecorreleerde CT (RC-CT) en ademhalingsgecorreleerde CT-PET (RC-CT-PET). Deze technieken houden rekening met de intra-fractie veranderingen en artefacten te wijten aan de ademhaling. In de tweede benadering wordt het doelvolumen gevolgd tijdens de behandeling gebruik makend van herhaalde (RC)-CT en CT-PET beeldvorming, met het uiteindelijke doel om de radiotherapiebehandeling aan te passen tijdens de behandeling en om de inter-fractie veranderingen aan te pakken.

In **Hoofdstuk 2** hebben we bepaald welke methode om het interne doelvolumen (ITV) te bepalen, gebaseerd op een RC-CT, een optimale dekking van de tumor toelaat. Daarom hebben we zowel een gewone ‘vrije ademhalings’ CT (CT_{fb}) en een RC-CT scan gemaakt. De RC-CT scan werd gebruikt om de tumorbeweging te meten en om een 10 fasen CT te reconstrueren (CT_{10ph}), waaronder de half-ventilatie CT (CT_{hv}). Door de CT_{10ph} te middelen werd een ‘trage’ CT scan berekend (CT_{slow}). Op basis van al deze scans werden ITVs ingetekend en behandelingen berekend, waarbij we voor het ITV_{hv} een interne marge (marge voor de tumor beweging) van bewegingsamplitude gedeeld door vier werd gebruikt. Al de behandelplannen voor de verschillende ITVs werden geprojecteerd op de 10 ademhalingsfasen en vervolgens werd de geabsorbeerde dosis berekend over alle 10 fasen om de reële dekking van de tumor in te schatten. Dit was een planningstudie gebaseerd op echte RC-CT patiënt gegevens. De CT_{hv} lijkt de optimale dataset te zijn voor intekening, gebruik makend van een voldoende grote anisotrope interne marge.

Nauwkeurige kennis van de positie van de tumor en het omliggende weefsel is nodig voor de radiotherapiebehandelingsplanning en het is belangrijk om de CT-PET beeldvorming te verbeteren. In **Hoofdstuk 3** hebben we de mogelijkheid geëvalueerd om de acquisitie te verbeteren door gebruik te maken van gefaseerde verzwakkingscorrectie in RC-CT-PET, waar beide modaliteiten retrospectief opgedeeld zijn. Na het verzamelen van de ruwe CT gegevens, de list-mode PET gegevens en het ademhalingssignaal, werden de CT-PET beelden opgedeeld in 10 fasen met behulp van zelf geschreven software. Elke PET fase was gecorrigeerd voor verzwakking met de CT gegevens van de overeenkomstige fase. Ter vergelijking was ook de verzwakkingscorrectie uitgevoerd met CT data die niet ademhalingsgecorreleerd was. Met een standaard, niet ademhalingsgecorreleerde CT-PET scan werd het volume onderschat tot 46% in de CT beelden en overschat tot 370% voor het PET volume, terwijl met de RC-CT-PET de volumes konden bepaald worden met kleine afwijkingen ten opzichte

van het reële volume. Het evalueren van de maximale activiteitsconcentratie liet een duidelijke verschuiving zien in de niet ademhalingsgecorrleerde beelden van dit maximum. In deze fantoomstudie hebben we laten zien dat een combinatie van RC-CT-PET beeldvorming met toepassing van gefaseerde verzwakkingscorrectie, de beeldvorming kan verbeteren van bewegende voorwerpen en kan leiden tot een verbeterde volumebepaling en een meer precieze lokalisatie en kwantificatie van de activiteit.

Om de verzwakkingsfouten te kwantificeren en de parameters te identificeren verbonden met deze fouten, hebben we een simulatie uitgevoerd gebaseerd op ademhalingsgecorrleerde CT studies van vijf longkanker patiënten in **Hoofdstuk 4**. De CT werd geconverteerd naar 511-keV verzwakkingsmappen welke voorwaarts geprojecteerd en geexponentieerd werden om sinogrammen te vormen van PET verzwakkingsfactoren voor elke fase van de ademhaling. De CT beelden werden ook gesegmenteerd om een PET object te vormen met dezelfde beweging als de CT data. In de bewegende PET objecten werden bolvormige 20mm bewegende tumoren aangemaakt in de buurt van de top van de lever en niet bewegende tumoren in de buurt van het midden van de borstkas. De bewegende PET objecten werden voorwaarts geprojecteerd en verzwakt en daarna op verschillende manieren gereconstrueerd: gefaseerde PET en CT, gated PET met ungated CT, ungated PET met gated CT en conventionele PET. De gefaseerde gated PET en CT gaf perfecte reconstructies in de simulatie. Gated PET met ungated CT gaf tumoren met de correcte vorm maar de recuperatie van de maximale activiteit was te groot, afhankelijk van de grootte van tumorbeweging, tot 90% voor bewegende tumoren en 60% voor niet bewegende tumoren. Gated CT met ungated PET resulteerde in onscherpe tumoren en veroorzaakte fouten in recuperatie tussen -50% en +75%. In klinische scans zou de recuperatie 0% tot 20% lager uitvallen. Kwantitatieve PET beeldvorming dichtbij het diafragma vereist gepaste matching van verzwakkingsinformatie voor de emissie informatie.

Hoofdstuk 5 gaat over de verandering in tumorvolume, tumorbeweging en ademhalingsfrequentie tijdens een radiotherapiebehandeling voor patiënten met uitgebreid niet-kleincellig longkanker. Drieëntwintig patiënten kregen een CT-PET en RC-CT scan voor de behandeling die herhaald werd in de eerste en tweede week volgende op de start van de radiotherapie. De patiënten werden behandeld met een versneld fractionatieschema met een totale tumor dosis afhankelijk van voorgenomen dosisbeperkingen voor de longen en het ruggemerg. Een opvallende heterogeniteit van de tumorvolume veranderingen werd waargenomen op alle tijdstippen. Voor sommige patiënten werd het volume meer dan 30% kleiner, voor andere werd het meer dan 30% groter maar voor de meerderheid van de patiënten veranderde het volume slechts gering. Geen signi-

ficante veranderingen in gemiddelde tumorbeweging of ademhalingsfrequentie werd waargenomen tijdens de behandeling. Deze resultaten ondersteunen de noodzaak om herhaalde beeldvorming tijdens de radiotherapiebehandeling uit te voeren. De veranderingen in tumorbeweging waren klein, daarom lijken herhaalde ademhalingsgecorrleerde CT scans niet noodzakelijk voor de primaire tumor.

^{18}F -fluoro-2-deoxy-glucose (FDG) opname op PET beelden is een voorspellende factor voor de uitkomst voor patiënten met niet-kleincellig longkanker. We hebben de veranderingen onderzocht in deze FDG opname tijdens gefractioneerde radiotherapie in relatie tot de metabole respons met het uiteindelijke doel de behandeling aan te passen volgens de vroege respons (**Hoofdstuk 6**). Dezelfde patiëntpopulatie als in het vorige hoofdstuk werd onderzocht. Bijna alle patiënten hadden ook een CT-PET 70 dagen na het einde van de behandeling. Veranderingen in de maximale gestandaardiseerde opname waarde (SUV_{max}) zijn beschreven. Het meest opvallende resultaat was de grote heterogeniteit in evolutie van de SUV_{max} tussen de patiënten. Verschillende tijd trends werden gezien voor responders (geen verandering tijdens radiotherapie) en voor niet-responders (48% toename in de eerste week). Niet-responders hadden op ieder onderzocht tijdstip een hogere SUV_{max} . Tijd trends in SUV_{max} lieten een grote intra-individuele heterogeniteit en verschillende patronen voor metabole responders en niet-responders zien. Deze nieuwe bevindingen weerspiegelen mogelijks intrinsieke tumoreigenschappen en kunnen uiteindelijk bruikbaar zijn om de behandeling aan te passen.

Hoofdstuk 7 beschrijft de tijd trends in kliervolume en klierbeweging op de CT scan. Twaalf patiënten, met in totaal 22 positieve klieren, ondergingen herhaalde CT-PET scans voor de behandeling en de eerste en tweede week na de start van de radiotherapie. Volumeveranderingen konden gemeten worden voor alle klieren. Voor 21 klieren was de beweging gemeten op basis van een RC-CT scan. Herhaalde RC-CT scans waren beschikbaar voor 11 klieren om de bewegingsveranderingen te evalueren. In 27% van de patiënten nam het kliervolume toe met meer dan 30% terwijl in 14% het volume daalde meer dan 30%. Deze volumeveranderingen hebben echter weinig klinisch impact gezien de volumes en dus ook de volumeveranderingen klein zijn en gemiddeld veranderde het kliervolume niet significant. De gemiddelde beweging van de klierregio's was initieel $5.6 \text{ mm} \pm 2.8 \text{ mm}$. Deze beweging verminderde lichtjes tijdens de radiotherapiebehandeling maar niet statistisch significant. Grote verschillen in beweging tussen de patiënten en tussen klierregio's binnen dezelfde patiënt werden waargenomen. Vanwege de grote variabiliteit in klierbeweging tussen de patiënten onderling, moeten de interne marges voor deze klierregio's individueel berekend worden voor de start van de behandeling gebruik makend van een RC-

CT. Herhaalde beeldvorming voor de klieren lijkt echter van weinig nut, gezien de geobserveerde individuele veranderingen in kliervolume en klierbeweging lijkt omvat te zijn binnen de huidige toegepaste marges.

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Curriculum Vitae

Geert Bosmans werd geboren op 1 juni 1973 in Hasselt (België) en groeide op in Zonhoven. Zowel lagere als middelbare school doorliep hij in Hasselt en behaalde in 1991 het ASO diploma (Wiskunde-Wetenschappen).

Hierna ging hij natuurkunde (fysica) studeren, de eerste twee kandidaatsjaren aan het toenmalige Limburgs Universitair Centrum (nu Universiteit Hasselt) te Diepenbeek. In 1995 behaalde hij zijn licentiaatsdiploma natuurkunde aan de Katholieke Universiteit Leuven met een thesis in het vakgebied van halfgeleiderfysica.

Vermits de zuivere fysica hem niet kon bekoren volgde hij nog een bijkomende opleiding tot klinisch fysicus, waarvoor het diploma ‘aanvullende studies biomedische en klinische ingenieurstechnieken optie medische fysica’ gehaald moest worden. Hierin was een éénjarige stageperiode omvat die op de radiotherapie afdeling van het UZ Leuven is gebeurd en waarbij ook een thesis over amorf silicium EPID's werd gemaakt o.l.v. Prof. dr. Jan van Dam.

Na een korte werkervaring in de ICT (Cap Gemini Belgium) is hij sinds begin 1998 continu aan de slag als klinisch fysicus radiotherapie. Eerst in het Heilig Hart Ziekenhuis te Roeselare dan in het AZ-VUB te Brussel en tenslotte in het Limburgs Oncologisch Centrum te Hasselt.

De nederlandse lokroep werd echter te groot en sinds oktober 2004 is hij werkzaam in Maastricht Clinic te Maastricht. Na een verkorte opleiding niveau 3 stralingsbescherming is hij vanaf januari 2005 geregistreerd als klinisch fysicus radiotherapie in Nederland.

Zijn voornaamste aandachtsgebieden zijn CT-PET beeldvorming, stereotactische bestralingen en patiëntveiligheid.

Hij is getrouwd met Ann Hendrickx en hebben samen één dochtertje, Janne.

P u b l i c a t i o n s

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