A New Margin Concept to Compensate for Breathing Motion during Stereotactic Treatment of Lung Tumours

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der RWTH Aachen University zur Erlangung des akademischen Grades einer Doktorin der Naturwissenschaften genehmigte Dissertation

vorgelegt von

Dipl.-Phys.
Carolin Schubert geb. Bornemann
aus Minden

Berichter: Univ.-Prof. Dr. rer. nat. Achim Stahl
Univ.-Prof. Dr. med. Michael J. Eble

Tag der mündlichen Prüfung: 9. September 2015

Diese Dissertation ist auf den Internetseiten der Universitätsbibliothek online verfügbar.
Abstract

In radiotherapy, dose distributions are optimized patient individually to ensure high dose to the tumour while preserving the surrounding healthy tissue as much as possible. Treatment planning and dose calculation are performed using static image data sets of the patient. Due to breathing, lung tumours are subject to regular movements. The magnitude of motion affects the applied dose to the tumour leading to dose blurring and underdosage in the tumour region. To compensate for motion during treatment, margins around the tumour are applied to account for motion induced effects on dose distributions. By applying the margin, the irradiated volume is increased to ensure that the tumour is irradiated even under motion.

In this work, the compensation of motion by applied margins is methodically analysed based on dose calculations using the treatment planning system. This is done for stereotactic treatments of lung tumours using the 3D conformal treatment planning technique.

A new optimized margin concept is developed leading to a margin formula to calculate an optimized margin for motion compensation. The optimized margin concept is different from existing margin concepts by taking into account tumour size in motion direction beside motion amplitude as parameters having an impact on the margin.

The optimized margin concept is evaluated by measurements using an in-house developed robotic 4D motion phantom and film measurements. Due to this measurements it is demonstrated that the optimized margin compensates for motion induced effects on applied dose distributions. The dose to the tumour is ensured by preserving the surrounding tissue at the same time due to highly conformal dose distributions.
Zusammenfassung

Bei der Anwendung einer Strahlentherapie wird die Dosisverteilung für jeden Patienten individuell optimiert. Der Tumor wird dabei mit einer hohen Dosis versorgt, während das umliegende, gesunde Gewebe so gut wie möglich geschont wird. Der Vorgang der Bestrahlungsplanung und die damit verbundene Dosisberechnung basiert auf einem statischen Bilddatensatz des Patienten. Durch die körpereigene Atembewegung sind Lungen-tumoren aber nicht statisch, sondern unterliegen einer wiederkehrenden Bewegung, die die im Tumor applizierte Dosis beeinflusst. Dies führt zu einer Verschmierung der Dosis und damit schließlich zu einer Unterdosierung der Tumorregion. Um den Einfluss der Bewegung zu berücksichtigen und zu kompensieren, werden um den Tumor herum Margins angewendet. Durch die Verwendung eines Margins wird das bestrahlte Volumen um den Tumor herum vergrößert. Damit wird der Tumor bestrahlt, auch wenn er sich bewegt.


Das neue Margin Konzept für einen optimierten Margin wird anhand von Messungen validiert. Dazu werden ein eigens entwickeltes 4D Bewegungsphantom und Filmmessungen verwendet. Anhand dieser Messungen kann gezeigt werden, dass die Verwendung des optimierten Margins den Einfluss der Bewegung auf die applizierte Dosisverteilung kompensiert. Durch die hohe Konformität der applizierten Dosisverteilung wird die Dosis im Tumor sichergestellt, während das umliegende Gewebe gleichzeitig geschont wird.

III
## Contents

1 Introduction ........................................................................ 1

2 Clinical Background .......................................................... 3
   2.1 Radiotherapy ................................................................. 3
      2.1.1 Computed Tomography (CT) ........................................ 3
      2.1.2 Respiration-Correlated Computed Tomography ........... 4
      2.1.3 Medical Linear Accelerator ....................................... 5
      2.1.4 Course of Radiotherapy .......................................... 7
   2.2 Radiobiology ................................................................. 9
      2.2.1 Linear-Quadratic Formula ........................................ 9
      2.2.2 Biologically Effective Dose (BED) ............................. 10
      2.2.3 Fractionation ....................................................... 10
      2.2.4 Radiation Effects ................................................ 11
   2.3 Stereotactic Treatment of Lung Tumours .......................... 12
      2.3.1 Incidence ............................................................ 12
      2.3.2 Stereotactic Body Radiotherapy (SBRT) .................... 12
      2.3.3 Outcome and Side Effects ....................................... 16
   2.4 Lung Tumour Motion due to Respiration ......................... 16
      2.4.1 Motion Amplitudes .............................................. 17
      2.4.2 Motion Model .................................................... 17

3 State of Research ............................................................. 19
   3.1 Application of Margins ................................................ 19
   3.2 Margins to Compensate for Breathing Motion ................. 21
      3.2.1 Internal Target Volume ......................................... 21
      3.2.2 Further Margin Concepts ..................................... 22
   3.3 Motivation for Research ................................................ 23
4 Material and Methods
   4.1 Treatment Planning .............................................. 25
      4.1.1 Treatment Planning System ............................. 25
      4.1.2 Treatment Planning Techniques ....................... 26
   4.2 Film Dosimetry .................................................. 27
      4.2.1 Gafchromic EBT3 Films ................................ 27
      4.2.2 Scanner ..................................................... 28
      4.2.3 Film Data Processing .................................. 28
      4.2.4 Reference Measurement System for Film ............ 29
   4.3 4D Motion Phantom .............................................. 30
   4.4 Linear Accelerator .............................................. 32
   4.5 4D-CT ............................................................. 32

5 Development of the Margin Concept ............................ 33
   5.1 SBRT Treatment Planning ..................................... 33
   5.2 Application of Margins ....................................... 35
   5.3 Integration of Motion ......................................... 36
   5.4 Determination of Ideal Margins ............................. 38
   5.5 Development of the Margin Formula ....................... 43
      5.5.1 Sources of Error ....................................... 46

6 Evaluation of the Measurement System ....................... 49
   6.1 Characterising the Phantom ................................. 49
      6.1.1 Reproducibility of Static Positioning ............... 49
      6.1.2 Reproducibility of Motion Pattern .................. 50
      6.1.3 Accuracy of Motion Pattern ........................... 52
   6.2 Determining the Image Data Set for Treatment Planning . 53
   6.3 Characterising Gafchromic EBT3 Films ................... 54
      6.3.1 Film Calibration ......................................... 54
   6.4 Reproducibility of the Evaluation Process .............. 56

7 Evaluation of the Margin Concept ............................. 59
   7.1 Preparation Process .......................................... 60
   7.2 Evaluation ...................................................... 64
      7.2.1 The Motion Compensation with the Optimized Margin 64
      7.2.2 Optimized Margin in Comparison with ITV .......... 65
   7.3 Performance for Symmetric Motion Profiles ............. 68
   7.4 Performance for VMAT Treatment Technique ............. 70
   7.5 Assessment of Spared Lung Tissue ......................... 71
8 Conclusions and Outlook 73

A Film Calibration Function 77

B 4D Motion Phantom Target 79
Chapter 1

Introduction

Ionizing radiation transmits energy to matter while interacting. This is utilised in the medical field of radiotherapy to treat cancer patients. Thereby, the course of disease can be decelerated or patients can be cured. Irradiating human tissue leads to biochemical changes inside the cells. By doing so, tumour cells are irreversible damaged. To reach the aim of therapy the tumour is covered with a high dose. At the same time, the surrounding healthy tissue has to be preserved as much as possible. For this reason, a treatment plan is generated for each patient individually offering an optimized dose distribution.

Tumour motion during treatment affects the applied dose leading to dose blurring and under dosage in the tumour region, respectively. Some tumours are subject to regular movements produced naturally in the body like breathing motion, heart beat or peristalsis. This kind of motion appears during the treatment and is called intrafractional motion. Motion can also occur between different treatment days (interfractional motion). This work focuses on the effect of recurrent tumour motion due to breathing on applied dose distributions.

To ensure the prescribed dose to the tumour, tumour motion has to be taken into account during radiotherapy. By using respiration-correlated imaging techniques instead of static imaging tumour motion can be visualized over the whole breathing cycle. But treatment planning and dose calculation are based on a static image data set of the patient. When motion occurs during the applied dose distribution does not match the calculated dose distribution. To compensate for motion induced effects on applied dose distributions margins are applied during the treatment planning process. According to the margin the irradiated volume is increased to ensure that the tumour is completely irradiated even under motion.
This thesis focuses on the application of margins to compensate for breathing motion induced effects on applied dose distributions. The Internal Target Volume (ITV) margin concept is recommended by the International Commission on Radiation Units and Measurements (ICRU) when motion dominates other uncertainties [1 2]. Here, the full motion amplitude is taken as margin in motion direction to account for the tumour motion. Publications focussing on margins to account for motion [3 4 5 6] report the ITV concept to overcompensate motion effects leading to excessive dose in the surrounding tissue. Different approaches for determining a motion compensating margin which better spares the surrounding tissue are offered. But motion amplitude is considered to be the only important parameter for margin calculation.

It is motivated in the context of this thesis that motion amplitude as well as tumour size in motion direction are important parameters for the effect of motion on applied dose distributions and for determining a motion compensating margin. Therefore, a new optimized margin concept is developed taking tumour motion amplitude and size in motion direction into account. The concept is designed for stereotactic treatment of lung tumours using the 3D conformal treatment technique. The application of the margin is validated in the context of this work. The optimized margin is supposed to ensure the prescribed dose to the tumour and to preserve the surrounding tissue as much as possible, at the same time.

The clinical background related to the context of this thesis is described in Chapter 2 representing an overview of the stereotactic treatment of lung tumours as well as lung tumour motion due to respiration. In Chapter 3, applications of margins in radiotherapy are presented in general and especially to compensate for motion. The need for research is motivated and the aims of this work are specified. Material and methods used for developing and evaluating the optimized margin are described in Chapter 4. The development of the margin concept and the resulting margin formula to calculate the optimized margin are represented in Chapter 5. Before evaluating the margin concept, the measurement system used to evaluate the margin concept is characterized in Chapter 6. Finally, the newly developed margin concept is evaluated. Results are shown in chapter 7. Conclusions and outlook are given in Chapter 8.
Chapter 2
Clinical Background

2.1 Radiotherapy

Radiotherapy stands for the clinical application of ionising radiation to treat patients. The therapy aims to cure a disease, alleviating patients’ pain, improving quality of life or extending life time. Therefore, a target (tumour) is irradiated with a high dose while surrounding tissue is spared as much as possible. Fitting the dose distribution to the shape of the tumour is named conformal radiotherapy. Treatment planning is based on computed tomography imaging. For external beam therapy high energy photons are used in the majority of cases. Radiation is generated and shaped by medical linear accelerators.

2.1.1 Computed Tomography (CT)

Computed tomography (CT) imaging is the basic imaging technique used in radiotherapy. On the one hand, images are used to visualize the patients anatomy and identify tumours and also organs at risk (OAR), to make a diagnosis first and define the regions of interest for radiotherapy treatment later. On the other hand, the treatment planning process is based on CT image data which provide the mass attenuation coefficients of tissue for calculating the dose to the patient.

For CT imaging the patient lies on a couch surrounded by the CT gantry containing an x-ray tube and opposed detector. While the gantry rotates around the patient, the attenuation of photons by the patient is measured from many directions. During this scanning process the patient table moves continuously through the gantry. This is called helical CT imaging. Based on the measured attenuation profiles, the spatial distribution of attenuation co-
efficients of the scan object can be reconstructed. This information is stored into a 3D image composed of single slices with an adjustable thickness. As the measured attenuation coefficients vary with different photon energies for the same scan object, a scale normalized to water was introduced. The units of the scale are called Hounsfield Units (HU), illustrated in grey values. HU for water and air are fixed by definition.

2.1.2 Respiration-Correlated Computed Tomography

Some organs are subject to permanent motion due to e.g. breathing or heartbeat. For that case modern CT machines are capable to account for motion induced effects on reconstructed images. For respiration-correlated CT (4D-CT) data acquisition, the patient is fitted with a breathing belt around his chest. The surrogate signal of the breathing belt is recorded synchronously during CT scanning. Retrospectively the signal of the breathing belt is divided into a selectable number of phases, usually ten. The measured attenuation profiles are sorted by the signal of the breathing belt and a complete CT image data set is reconstructed for each phase with a part of the raw data only. Afterwards ten CT image data sets are generated allowing to visualize motion induced effects to the anatomy of the patient and to determine tumour motion and motion amplitude.

Figure 2.1: Ten reconstructed images generated by respiration-correlated CT imaging.

Additionally a mean CT image can be generated using all measured raw data for image reconstruction without respiration correlation. Furthermore, a maximum-intensity-projection (MIP) can be generated by assigning each voxel the maximum HU found in all ten images for each voxel. For lung tumours, this image data set can be used to identify the magnitude of motion
or rather all tumour positions during respiration in one image data set.

For high image quality, the scanning time and also dose applied to the patient is extended compared to normal CT imaging. The pitch factor, representing the ratio of table movement per gantry rotation time and number of detector slices times slice thickness, has to be chosen in an optimal way to ensure high image quality and less dose to the patient at the same time.

2.1.3 Medical Linear Accelerator

To generate the photon treatment beam electrons are accelerated, focussed and bent onto a target made of tungsten. Thus bremsstrahlung is produced. Then the photon beam is formed with a flattening filter for homogenous irradiation of the treatment field and with filters for beam hardening. Afterwards, the beam is shaped with collimators to conform the radiation field to the tumour.

Figure 2.3 shows the external setting of a medical linear accelerator in principle. The treatment unit consists of four parts: the radiation treatment head with treatment detector on opposite side and perpendicularly arranged, the imaging head with opposed imaging detector. The radiation head contains
all components to generate and shape the treatment beam, compare Figure 2.2. The treatment detector on the opposite side is a semiconductor detector for high energy photon imaging using the treatment beam. The system composed of imaging head and corresponding detector is called cone beam computer tomography (CBCT). The imaging head contains an x-ray tube which generates a cone beam of x-rays. By rotating the treatment unit during x-ray imaging, the patient volume is scanned similar to a computed tomography (CT).

The treatment unit can rotate continuously or step-by-step around the axis shown in Figure 2.3 as dotted blue line, and therefore, around the patient. The beam axis is shown as a dotted yellow line, the imaging axis as a dotted green line. All three axes intersect at one point, called isocenter point. The idea of radiotherapy treatment is to position the isocenter in a central part of the tumour. By rotating around the patient, the tumour is treated continuously but the surrounding tissue can be preserved because different

![Diagram of radiation treatment head and imaging head](image)
regions are irradiated from different directions. Simultaneously the beam is shaped to the tumour from every direction or to create a highly conformal dose distribution inside the patient, respectively.

2.1.4 Course of Radiotherapy

Prior to radiotherapy treatment, a patient is informed of the diagnosis of cancer which is confirmed by several imaging techniques like computed tomography (CT), positron emission tomography (PET) or magnetic resonance imaging (MRI). The clinical classification is done by biopsy or blood count for example. Based on all this information radiotherapists, surgeons and oncologists together decide which interdisciplinary treatment concept is appropriate for each patient individually according to national and international guidelines.

If radiotherapy is chosen as treatment, the patient passes through the radiotherapy workflow as described and shown in figure 2.4.

![Radiotherapy Workflow Diagram](image)

Figure 2.4: Schematical illustration of the radiotherapy workflow.

Patient Preparation and Imaging

CT imaging is done to identify size, shape and position of the tumour and the surrounding tissue. For more detailed information, this can be combined with MRI or functional imaging like PET.

The patient is positioned on the CT scanner couch in a selected and beneficial position to ensure that the surrounding tissue is spared well while treating the tumour with radiation. To treat the tumour with high precision and reproducibility, patient fixation systems are used for immobilization. For patients with a head and neck tumour mask systems are used, for example, but the fixation system depends on the tumour location.

The patient is positioned in the same way during the whole treatment course.
Contouring and Treatment Planning

The radiotherapist contours the tumour and the organs at risk (OAR) on the CT image data set and prescribes the dose to the tumour. Dose limits are defined for the organs at risk, too. Patients get the total dose in one, few or many (up to 38) treatment sessions. This is called fractionation and it is based on radiobiology (cf. chapter 2.2).

Based on the CT data set and the contours, an individual treatment plan is calculated for each patient. The dose distribution is optimized in the way to give the prescribed dose to the tumour while sparing the OARs as much as possible. Typically, the tumour is treated with a homogeneous dose.

![Dose distribution](image)

Figure 2.5: Dose distribution optimized with two prescribed dose levels (red and orange coloured) and viewed for three orthogonal planes.

Treatment plan evaluation is performed by visually controlling the calculated dose distribution and evaluating the dose conformity to the tumour but also by using dose-volume histograms (DVH). This way the dose to the tumour as well as the dose to the OARs can be evaluated and recorded.

When the treatment plan is accepted by a physicist and a physician and
the quality assurance procedure is successfully completed, it can be used for treatment.

Pre-Treatment Verification and Delivery

Right before treatment, the patient is positioned on the treatment couch in the same position as during imaging. Pre-treatment imaging is done via CBCT imaging to localize the tumour and the OARs. The current position is compared with the position in the CT used for treatment planning to ensure that the tumour and the organs at risk are in the right position for treatment. Differences can be adjusted. This verification process is called image-guided radiation therapy (IGRT). Afterwards the treatment delivery can start.

2.2 Radiobiology

Tumour cells are mutated cells, capable of unlimited cell division. Malignant tumours spread in the body, infiltrate normal tissues and form secondary tumours there (metastasis). Finally, by infiltration the normal organ function is damaged leading to death. Treating tumours with ionising radiation aims to destroy all tumour cells and leading to local tumour control. Due to the interaction of ionising radiation with the tissue, the constituent atoms are ionised and excited. Thereby, molecular bonds are separated or free radicals are produced which react with other molecules.

This leads to biochemical changes inside exposed cells [2] such as:

- mutagenic changes inside the DNA by single/double-strand breaks
- inhibition of cell division
- metabolic changes

Most cells will not die immediately after exposure even if they are lethally damaged. But they have lost their ability for unlimited cell division and die during consecutive cell divisions. [10]

2.2.1 Linear-Quadratic Formula

To determine the effect of radiation dose to human cells, cell lines are irradiated. The surviving fractions $S$ are counted. $-\ln(S)$ can be considered to be
the effect of radiation. Cell survival decreases with increasing dose and is well described by the linear-quadratic (LQ) model \[ E = -\ln S = D \cdot (\alpha + \beta d) \] (2.1)

where \( D \) is the total dose and \( d \) is the dose per fraction. \( \alpha \) and \( \beta \) describe the linear and quadratic components and are tissue specific parameters. The \( \alpha/\beta \)-ratio is defined as the dose at which the two components (linear and quadratic) are equal. The value is determined from experiments with different cell types \[11\].

For fraction doses higher than 8-10 Gy the LQ model is not intended \[11\] but it is widely used for comparing different fractionation schemes \[12, 13\].

2.2.2 Biologically Effective Dose (BED)

Dividing equation 2.1 by \( \alpha \) gives the biologically effective dose (BED)

\[ BED = D \cdot (1 + \frac{d}{\alpha/\beta}) \] (2.2)

with the total dose \( D \) and the dose per fraction \( d \) \[14\]. The factor in parentheses is called relative effectiveness (RE).

The biologically effective dose depends on both physical dose and fractionation scheme and tissue (represented by the corresponding \( \alpha/\beta \)-ratio). It is used to calculate the effect of different fractionation schemes and also the effect of dose to different biological tissues.

2.2.3 Fractionation

The linear-quadratic model offers the understanding and the potential to optimize dose fractionation in radiotherapy. But fractionation is clinically used today because it was empirically discovered \[10\]. Giving a daily dose over a time period of many days instead of treating with a single dose provided good tumour control with fewer side effects.
When multiple fractions are used cells recover between fractions. Then a higher cumulative dose is needed for the same surviving fraction. But normal tissues could be spared better because they have got higher repair capacity then most tumours [10]. Fraction doses of 1.8-2 Gy are commonly used in clinical practice. Reducing the number of fractions and increasing the fraction dose is called hypofractionation.

2.2.4 Radiation Effects

There are non-stochastic effects which occur when the radiation induced damage exceeds a specific limit. Therefore, a dose limit exists for a non-stochastic effect. Below this limit there is no effect, above the limit the effect depends on the dose. For stochastic effects no dose limit exists. The incidence increases with dose but not the severity. Stochastic effects are mutagenic changes inducing secondary tumours or leukaemia. [9]

Controllable factors for radiation effects are the total dose, treatment volume and fractionation schemes. But there are also uncontrollable factors like patient age, condition, genetics, comorbidities, lifestyle that can lead to reduced tolerance [10].

Tissues can be differentiated by their response to irradiation. There are early-responding tissues like skin, intestines and bone marrow. Here, radiation induced effects appear within a few weeks after irradiation, but they tend to recover. Late-responding tissues like lung, kidneys or spinal cord show effects within months or years after irradiation. Late damage tends to be more permanent and are the main limiting factor for the maximum dose which can be given to the tumour. [10]
2.3 Stereotactic Treatment of Lung Tumours

In this section, the stereotactic treatment of lung tumours is described. In section 2.3.1 the clinical incidence is described and the need for stereotactic treatment is motivated. In section 2.3.2 the definition of stereotactic treatment and essential characteristics are itemized. Outcome and side effects are mentioned in section 2.3.3.

It is important to account for breathing-induced tumour motion during stereotactic treatment of moving tumours. Lung tumour motion due to respiration is described in section 2.4.

2.3.1 Incidence

Lung cancer is the most frequent cause of death by cancer and is distinguished into two groups: non-small cell lung cancer (NSCLC) and small cell lung cancer. Stereotactic body radiotherapy (SBRT) is a treatment modality for early stage NSCLC which make up about 80-85 % of all lung cancers. [14]

For medical care, surgery is the therapy of choice in treating NSCLC with 90 % local control leading to 60-80 % overall survival after five years [15]. But if certain comorbidities exist, surgery is not possible for 25 % of the patients. Then NSCLC is treated by radiotherapy.

In the past, conventional fractionated radiotherapy was used irradiating 60-66 Gy in 2 Gy per fraction. However, the results were unsatisfactory. The majority of patients still died from lung cancer, most by local recurrences. [15]

So it became evident that the applied dose was not sufficient for local control. For increasing the dose to the tumour, a high precision treatment method was developed to improve local control and therefore overall survival.

2.3.2 Stereotactic Body Radiotherapy (SBRT)

Stereotactic radiotherapy was originally developed as high precision treatment for small brain lesions at Karolinska Hospital, Sweden and was advanced there later to treatments of the body [16].

Stereotactic method literally means that the tumour is precisely localized by an external coordinate system which is rigidly connected to the patient per stereotactic frame. A frame for the body was developed at Karolinska Hospital, Sweden [16] in 1994. It is pictured in Figure 2.7.

The patient is positioned in the body frame, then a CT image is generated in this treatment position for treatment planning. The tumour can be easily
localized on the CT slices. To transfer this position to the coordinate system of the frame, indicators inside the walls of the frame, visible on the CT slices, are used. Therefore the tumour inside the patient can be localized from outside by using the external coordinate system of the frame.

Nowadays stereotactic frames are no longer in use, because the tumour position can be easily and precisely localized by the internal coordinates of the image-guidance systems of modern treatment machines. Right before treatment the tumour position is localized by CBCT imaging. Then the planned

![Figure 2.7: Schematic view of the body frame which was developed to offer the stereotactic coordinate system for tumour localization [16].](image)

![Figure 2.8: IGRT: Controlling the tumour position inside the body right before treatment via images determined by planning CT (reference) and CBCT (current position). Image fusion is used to correct for the current tumour position.](image)
and the current, localized positions are compared and can be matched to the tumour position (Figure 2.8). If the tumour position fits to the position related to the planned treatment beams, the treatment can be applied. Due to these advantages of the technical progress, the name stereotactic treatment is no longer correct but still in use. To rethink the definition of this treatment method the Stereotactic Radiotherapy Working Group of the German Society of Radiation Oncology (DEGRO) summarizes the similarities in the definition of SBRT given by several national working groups, leading to the following conclusion [12]:

SBRT is characterized by

- Application of external beam therapy
- Extracranial target
- High accuracy
- High dose per fraction given in one or few fractions

In the following paragraphs, the characterizing items of SBRT are described and also illustrated according to SBRT applied in the Clinic of Radiotherapy and Radiooncology at the University Hospital Aachen.

**Application of External Beam Therapy**

The concepts of SBRT are applicable for both particle and photon therapy. In our department, SBRT is performed with a medical linear accelerator with cone beam CT (CBCT) for image-guidance.

**Extracranial Target**

This work focuses on lung targets. SBRT can also be applied to tumours of liver, adrenal, prostate and spinal metastases.

**High Dose per Fraction Given in One or Few Fractions**

In conventional fractionated radiotherapy the uniform dose given to the tumour was not sufficient and local control failed. Doses up to 66 Gy in 2 Gy per fraction result in a BED of 79.2 Gy, using an $\alpha/\beta$-ratio of 10 Gy for lung tumour [11]. This BED was clearly not high enough. To increase the BED a hypo-fractionated dose concept was applied combined with an inhomogeneous dose distribution. Giving higher dose per fraction
in fewer fractions leads to an increased BED. In addition, the dose in the central part of the tumour can be increased by using small beam diameters creating inhomogeneous dose distributions. Thereby, the dose outside the tumour can be kept almost as low as in the case of using homogeneous dose distributions without central maximum. This approach was first presented by Lax [17].

In our department, the following fractionation schemes are used for lung SBRT. BED is calculated with an $\alpha/\beta$-ratio of 10 Gy for tumours [11] according to equation (2.2) with the total dose $D$ and the dose per fraction $d$. According to [18], an inhomogeneous dose distribution with a maximum dose of 150 % in the central part of the tumour is allowed while giving 100 % dose to the tumour border.

<table>
<thead>
<tr>
<th>$D$</th>
<th>$d$</th>
<th>$\text{BED}_{\text{Border}}$</th>
<th>$\text{BED}_{\text{Centre}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 Gy</td>
<td>8 Gy</td>
<td>72 Gy</td>
<td>132 Gy</td>
</tr>
<tr>
<td>45 Gy</td>
<td>15 Gy</td>
<td>112.5 Gy</td>
<td>219.4 Gy</td>
</tr>
<tr>
<td>26 Gy</td>
<td>26 Gy</td>
<td>93.6 Gy</td>
<td>191.1 Gy</td>
</tr>
</tbody>
</table>

For local tumour control, a BED greater than 100 Gy is needed [19], [22]. Further increasing the dose does not improve local control [19], [15]. The dose to the tumour border was found to be the important parameter on local tumour control [19]. Therefore, the dose prescription in SBRT refers to the tumour encompassing isodose, the minimum dose which is given to the tumour border. Due to dose calculation uncertainties, the prescription dose has to encompass only 98 % of the tumour volume and is named $D_{98\%}$.

**High accuracy**

In SBRT high doses per fraction are applied in fewer fractions using small treatment fields. To apply these highly conformal dose distributions a high accuracy is mandatory. The precision of the overall system has to be evaluated and ensured by quality assurance tests for e.g. the used imaging devices, the treatment planning and the treatment machine. To ensure a highly accurate treatment, precise patient immobilization and accurate positioning verification (IGRT) have to be assured.

Applying SBRT to a moving target like lung or liver tumour is challenging. Because high accuracy is needed for applying high doses it is important to account for the motion during the whole treatment process from imaging, treatment planning to pre-treatment verification and delivery.
2.3.3 Outcome and Side Effects

Outcome after SBRT is summarized by [15]. An excellent local tumour control of above 84% is reported for all presented studies. Therefore, SBRT is superior compared to conventional fractionated radiotherapy [15]. For medically inoperable patients, SBRT is the standard of care. For elderly patients, SBRT offers a non-invasive and safe treatment modality and reduces the number of untreated patients in this age group [15].

Side effects like radiation-induced pneumonitis, rib fractures and chest wall pain occur in up to 10% of the patients depending on tumour size and location [12]. Lung function and quality of life are not degraded by the treatment [15].

2.4 Lung Tumour Motion due to Respiration

Some tumours are subject to motion produced naturally in the body. On the one hand there is motion between different treatment fractions which defines a day-to-day difference. This so-called interfractional motion is caused by different organ fillings or tumour shrinkage or growth for example. On the other hand there is motion during treatment. This motion can be caused by breathing or cardiac motion and is called intrafractional motion. This work focuses on intrafractional motion of lung tumours due to respiration.

![Figure 2.9: Lung tumour motion projected to tumour position in lung [20.](image)]

Lung tumour motion vary with position in lung and has a main motion direction. Tumour positions and corresponding amplitudes were investigated
by Seppenwoolde et al. [20] and Liu et al. [21]. Their conclusions are summarized in this section.

Superior-inferior (SI) direction is the main motion direction. As depicted in figure 2.9 tumours in the lower part of the lung move more in SI direction than upper-lung tumours. Tumour motion is connected to diaphragm motion in SI direction. Magnitude of motion in anterior-posterior (AP) and lateral (L) direction is small and independent of the position in the lung. For tumours attached to the chest wall motion is small in all directions, even in SI direction.

According to [21], lung tumour motion decreases with bigger tumour sizes and early-stage tumours have a higher tendency of mobility than stage III or IV NSCLC.

Respiration varies from patient to patient due to the course of disease [21]. According to Stevens et al. [22], lung tumour motion is patient individual and not predictable. To account for motion induced effects on dose application in radiotherapy tumour motion therefore has to be determined for each patient, individually.

### 2.4.1 Motion Amplitudes

Seppenwoolde et al. [20] measured tumour motion peak-to-peak amplitudes about 12 mm and up to 25 mm in SI direction via fluoroscopy imaging for unfixed tumours close to the diaphragm. Rietzel et al. [23] evaluated tumour motion by comparing contours on 4D-CT data sets. For light breathing during CT imaging, peak-to-peak amplitudes up to 10 mm were obtained for lung tumour motion. According to van Herk et al. [24], peak-to-peak amplitudes of 20 mm are characteristic of lung tumours close to the diaphragm.

Some lung tumours show hysteresis, but the magnitude is small compared to motion amplitude in SI direction. Hysteresis was measured by [21] to be 1-2 mm for the most cases. Only for two cases hysteresis was up to 5 mm.

### 2.4.2 Motion Model

Highest magnitude of lung tumour motion occurs in the lower part of the lung where diaphragm motion is associated with tumour motion. Therefore, diaphragm motion was modelled by [24] assuming a fixed motion period. Organ motion in SI direction can be parametrized by an asymmetrical model

\[
z(t) = z_0 - b \cdot \cos^2n \left( \frac{\pi t}{\tau} - \phi \right)
\]

(2.3)
with $b$ describing the motion amplitude, $z_0$ the position at exhale, $\tau$ the period of the breathing cycle and $\phi$ the phase. Parameter $n$ describes the shape, the magnitude of asymmetry of the motion profile. Seppenwoolde et al. [20] fitted this model to measured tumour motions and determined the corresponding parameters. Accordingly typical breathing cycles have periods of 3-5s. Parameter $n$ was fitted as 1 or 2. Measured amplitudes are mentioned before in section 2.4.1.
Chapter 3

State of Research

In this chapter, the applications of margins in radiotherapy are described. The first part deals with the concept of margins in general. The second part focuses on margins for motion compensation. Different publications on margin calculations are presented. In the third part, the need for further research is motivated.

3.1 Application of Margins

There are various applications of margins in radiotherapy treatment planning. The definitions are well described by reports of the International Commission on Radiation Units and Measurements (ICRU).

Figure 3.1: According to ICRU Report 50, margins are applied: GTV, CTV and PTV contours illustrated for a lung tumour case.
Gross Tumour Volume (GTV)

The GTV is defined by ICRU Report 50 [25]:

The Gross Tumour Volume is the gross palpable or visible / demonstrable extent and location of malignant growth. Size, shape and location may be identified by diagnostic methods like clinical examinations and various imaging techniques. The reasons for determining the GTV are to make sure that the GTV receives an adequate dose to control the tumour and to assign tumour response.

Clinical Target Volume (CTV)

In fact, malignant growth is not that sharply delimited as it can be seen in a CT image for example. It is to be expected that there is already microscopic involvement outside the GTV, which is not that dense that it can be determined with imaging techniques. Therefore, an additional margin has to be applied to the GTV accounting for subclinical microscopic extensions. The CTV is defined by ICRU Report 50 [25]:

The Clinical Target Volume is a tissue volume that contains a demonstrable GTV and/or subclinical microscopic malignant disease, which has to be eliminated. This volume thus has to be treated adequately in order to achieve the aim of therapy, cure or palliation.

Planning Target Volume (PTV)

Due to intra- and interfractional movements the position, size and shape of the CTV can change during treatment. This is considered by enlarging the CTV to the PTV, which is defined by ICRU Report 50 [25]:

The Planning Target Volume is a geometrical concept, and it is defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all possible geometrical variations, in order to ensure that the prescribed dose is actually absorbed in the CTV.

Variations are caused by movements of the tissue which contains the CTV (e.g. respiration), different organ fillings and movement of the patient, too. Also variations in beam characteristics like beam sizes and directions are included. The penumbra is not included in the PTV. [25]
The PTV can be similar to the CTV (e.g. pituitary tumours) or much larger (e.g. lung tumours). This depends on the clinical parameters like patient condition and tumour site and is also connected to the chosen treatment technique. The CTV to PTV margin must not be uniform in all directions, it is based on the inducing movement in a certain direction. The PTV is used for treatment planning and for dose prescription.

3.2 Margins to Compensate for Breathing Motion

This section outlines only margins to compensate for motion induced effects on dose distributions. The Internal Target Volume (ITV) concept is a margin concept to account for internal motion during radiotherapy. It is defined by ICRU as well.

3.2.1 Internal Target Volume

For determining margins, ICRU Report 62 advises to differentiate between internal and set-up margins. The Internal Margin (IM) must be added to the CTV to account for physiological variations in size, shape and position but not for external uncertainties. According to the ITV margin, only internal margins are considered in the following. The Internal Target Volume describes the volume of the CTV and the encompassing internal Margin.

![Figure 3.2: Two examples for measured tumour motion by 4D-CT imaging. CTVs are coloured in orange and are displayed for max. inhalation/exhalation. The ITV (yellow) contains all CTV positions during breathing. PTV (ITV plus set-up margin) is shown as red contour.](image-url)
In accordance with ICRU Report 83 [2], the ITV concept is recommended as an optional tool for cases in which variations in tumour position dominate external uncertainties.

Motion-correlated imaging techniques are needed to identify different tumour positions due to motion. To account for breathing induced tumour motion, respiration-correlated CT imaging enables to visualize tumour motion during respiration. 4D-CT imaging offers a set of reconstructed images (so called phases) equally spaced in time. These phases can be used to determine the magnitude of tumour motion and the mean tumour position. On the one hand CTVs can be contoured on each phase and superposed to create the ITV. This procedure is published e.g. by [26], [27], [21] and [28]. On the other hand only extreme tumour positions for maximum inhale and maximum exhale can be combined [28], [23] or a maximum intensity projection (MIP) of the CT data can be used to define the ITV [29], [23]. In all approaches the full amplitude of motion is used as margin here to compensate for breathing induced tumour motion.

3.2.2 Further Margin Concepts

There are several publications focussing on margins to account for motion which show the ITV concept to overcompensate the influence of motion. Only the first of the following publications gives a margin recipe to calculate a margin for motion compensation based on motion amplitude. Results are briefly summarized in this section and assessed in the next section to motivate the need for research.

- Van Herk et al. [3] modelled the effect of respiratory motion in superior inferior direction according to [24] with a motion profile of $\sin^6$. Motion induced blurring effects on a hypothetical, homogenous dose distribution were calculated. Associated changes in isodose positions are used as indication for a motion compensating margin leading to a linear, but asymmetric margin recommendation of

$$\text{Margin} = 0.25 \cdot A \text{ (caudally)}; \quad 0.45 \cdot A \text{ (cranially)}$$

when respiration dominates other uncertainties. A is the amplitude of motion. This margin recipe counts for internal uncertainties due to respiration combined with 3 mm set-up uncertainty.
3.3. MOTIVATION FOR RESEARCH

- Engelsman et al. [4] and Sonke et al. [30] reported a non-linear relation between margin and peak-to-peak amplitude but no margin recipe was offered. Calculations were based on hypothetical, homogenous dose profiles here, too.

- Mutaf et al. [3] evaluate the effect of motion to conformal dose distribution for one spherical phantom case and 11 patient cases based on treatment plans. Optimum margins were determined for the phantom case but no margin recipe was concluded. For patient cases the influence of motion was calculated only for one peak-to-peak amplitude of 10mm. Here, a most probable average optimum margin of 1.5mm was determined. Finally, the authors just conclude an optimum margin being less than the full motion amplitude.

- Guckenberger et al. [2] calculated motion compensating margins on patient 4D-CT image data sets. A quadratic relationship between motion amplitude and margin (as increase of field size in motion direction) was found offering a margin smaller than the full motion amplitude. Margins of 2.4mm and 6mm were determined for motion amplitudes of 10mm and 20mm (peak-to-peak). However, no calculation function was published.

3.3 Motivation for Research

As demonstrated in the publications mentioned in section 3.2.2 the ITV margin overcompensates the effect of motion on dose distributions. Instead of that, a margin formula enabling to calculate an optimized margin for motion compensation taking into account patient individual parameters is desirable. So far the only margin recipe offering a margin calculation and being different from ITV is in accordance to Van Herk et al. [2]. But the validity of this concept is connected to 3mm setup uncertainty and homogenous dose distributions and therefore limited. All concepts mentioned in section 3.2.2 consider motion amplitude to be the only important parameter for margin calculation. But it is easy to realize that the effect of motion with a well defined amplitude is different for different sized objects. This is outlined in figure 3.3. When differently sized targets move with similar amplitudes related to an irradiation field, the percentage of the volume which completely leaves the field area is not identical and depends on the target size. Therefore, tumour size in motion direction is an important parameter, too.

None of the approaches in section 3.2.2 analyse the influence of motion systematically. For developing a new margin concept for motion compensation
the influence of motion and the compensation effect of margins have to be researched systematically for a well-defined range of amplitudes and tumour sizes in motion direction under real treatment conditions (e.g. inhomogeneous dose distributions). Furthermore, none of the approaches in section 3.2.2 have been evaluated and verified by subsequent measurements. A newly developed margin concept has to be evaluated by measurements verifying the compensation effect of applied margins for different amplitudes and tumour sizes.

The aim of this work is to:

- Systematically analyse the influence of motion on calculated dose distributions for various motion amplitudes and tumour sizes in motion direction for stereotactic treatment of lung cancer.
- Systematically analyse the compensating effect of applied margins for various motion amplitudes and tumour sizes in motion direction for stereotactic treatment of lung cancer.
- Develop a new patient individual margin concept for an optimized motion compensating margin as function of motion amplitude and tumour size in motion direction for stereotactic treatment of lung cancer.
- Evaluate this margin concept by subsequent measurements to validate the motion compensating effect for stereotactic treatment of lung cancer.

The idea of an individual margin taking into account motion amplitude and tumour size in motion direction was developed based on research carried out at the beginning phase of this work [31, 62, 33].
Chapter 4

Material and Methods

In this chapter the material and methods are described which are used to develop and to evaluate the margin concept. For developing the margin concept, the influence of margins and motion on dose distributions is calculated using a treatment planning system (TPS). The applied treatment planning techniques are briefly introduced. For evaluating the margin concept, radiosensitive films are used for dose measurements inserted into an in-house developed 4D motion phantom. Afterwards, the medical linear accelerator and the imaging device are described which are used for measurements and CT/4D-CT image data acquisition, respectively.

4.1 Treatment Planning

For determining a new optimized margin concept for lung SBRT treatments dose calculations are evaluated using the clinical treatment planning system.

4.1.1 Treatment Planning System

The radiation therapy planning system Pinnacle³, version 9.4 (Philips Medical Systems) was used. The entire treatment planning process is supported by this software application offering several modules for the consecutive steps. Organizing patient data and image data sets is supported by a data management module. During the treatment planning process the target volumes and also the OARs have to be defined by physicians on the CT image data set used for treatment planning. This is supported by a contouring module offering tools for segmentation, adaptation and processing of contours. Afterwards the treatment planning is performed by medical physicists using
tools e.g. for beam modification (forward planning) or inverse optimization. Before the parameters of the generated treatment plan can be exported to the treatment machine and the record-and-verify systems, the plan has to be evaluated by a physician and a physicist and has to pass quality assurance tests. These steps are supported by the Pinnacle³ TPS, too.

For dose calculation the model-based collapsed cone convolution superposition algorithm is used. Parameters of the model are adapted by comparing calculated dose distributions to measured ones. Due to this process the model is fitted to the used medical linac. Furthermore technical parameters of the linac are stored in a database which is administrated by the physics tool of the software. For all used CT machines, corresponding HU-density-calibration tables are stored here, too. They are needed for dose calculation.

### 4.1.2 Treatment Planning Techniques

In this section, the applied treatment planning techniques are introduced. For developing the margin concept only treatment plans based on 3D conformal planning were used. For evaluating the margin concept it was investigated in addition if the application of the developed margin can be transferred to a different treatment technique. This was analysed for the new treatment technique volumetric-modulated arc therapy (VMAT).

Differences are shown in figure 4.1 and described in table 4.1.

![Figure 4.1: Exemplary treatment plans for lung SBRT generated via 3D conformal planning (left) and VMAT (right). The PTV contour is shown as red line. Dose distribution is represented as colour distribution. Isodose levels and corresponding colours are shown in the legend. The yellow green isodose level defines the prescribed dose level. Due to the stereotactic dose prescription, this isodose surface has to encompass 98% of the PTV volume.](image-url)
Table 4.1: Differences between 3D and VMAT planning are briefly summarized.

<table>
<thead>
<tr>
<th>Planning</th>
<th>3D Conformal</th>
<th>VMAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beam Directions</td>
<td>Forward Planning</td>
<td>Inverse Planning</td>
</tr>
<tr>
<td>Field Configuration</td>
<td>Single directions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>here: 6 beams</td>
<td>Continuous arc, here: segment of a circle</td>
</tr>
<tr>
<td>Field Configuration</td>
<td>Conformal to tumour projection from each direction</td>
<td>Not conformal, optimized to create conformal dose</td>
</tr>
<tr>
<td>Dose rate</td>
<td>Constant</td>
<td>Modulated</td>
</tr>
<tr>
<td>Delivery time</td>
<td>Longer than VMAT</td>
<td>Shorter than 3D Conformal</td>
</tr>
</tbody>
</table>

Dose Prescription, patient positioning and pre-treatment verification are identical for both treatment techniques. The great advantage of VMAT is a reduced treatment delivery time along with highly conformal dose distributions due to the inverse optimization. But the treatment fields are not conformal to the tumour shape from every direction any more. For moving targets this can lead to motion induced interplay effects between tumour motion and leaf motion and therefore affects the dose applied to the tumour.

### 4.2 Film Dosimetry

To measure the effect of target motion on applied dose distributions with and without motion compensating margins radiosensitive films are used. These nearly tissue equivalent detectors are easy to handle for dose measurements and offer high spatial resolution for evaluation purposes.

Gafchromic EBT3 films are used for dose measurements and digitised by a commercial flatbed scanner. For conversion of measured transmission to absorbed dose the software package FilmQAPro 2014 (Ashland Advanced Materials) is used \[34\] which was kindly provided by the manufacturer for this research work.

#### 4.2.1 Gafchromic EBT3 Films

EBT3 is the updated version of radiochromic films manufactured by Ashland Advanced Materials, especially for radiotherapy application. Films are made of an active layer symmetrically coated by polyester. The active layer contains radiosensitive molecules which form blue polymers by being irradiated.
Therefore, due to dose absorption the film changes colour and transmission respectively. The active layer also contains a yellow marker dye for uniformity enhancement. Polyester layers protect the active layer from surficial damage. EBT3 can be handled under room light which offers easy handling during measurement and digitalization. No film-developing process is needed after irradiation, the films are self-developing. The measured dose distribution is digitalized by scanning the film using a commercial flatbed scanner. Films are scanned only 24h after irradiation to minimize effects of post-exposure changes due to the self-developing process [35]. EBT3 allows for dose measurements in a wide dose range, up to 40 Gy. [36]

For all measurements films from lot number A10121201 are used. These films are named EBT3+ but they are identical to EBT3 except for a special cut to easily separate a band for using the one scan protocol with FilmQA Pro software. But this feature was not used here.

### 4.2.2 Scanner

Transmission of irradiated films are measured with an Epson Expression 10000XL flatbed scanner (Seiko Epson Corporation) with transparency unit. Light intensity transmitted by the scan object is measured by a charge-coupled device in RGB mode with opposed xenon lamp and displayed as pixel value PV. Transmission T is calculated for each colour channel according to equation 4.1

$$ T = \frac{PV}{65535} $$

(4.1)

with 65535 being the maximum pixel value obtained without absorbing scan object.

The scanner is operated by Epson Scan software version 3.04G (Seiko Epson Corporation). Scans are taken in 48 bit RGB mode, with all colour corrections disabled. Films are placed centred and in portrait orientation on the scan area. For reproducible positioning on the scan area a frame made of black opaque paper is used to align the films with two sides to the frame. The chosen image resolution is 72dpi.

### 4.2.3 Film Data Processing

Digitized film measurements are imported to FilmQAPro 2014 software (Ashland Advanced Materials) for data processing. The software is used for dose calibration and for converting measured colour values to dose. The software
uses all three colour channel information of a film scan to calculate three calibration functions. Thus non-uniformities in the thickness of the active layer can be corrected for, by using the signal of the yellow marker dye measured in the blue colour channel. [57]

Colour values are converted to dose for each colour channel and exported as a matrix (dose map) to be further processed and evaluated with MATLAB 7.12.0, R2011a (The Mathworks). This way, dose maps for the three colour channels are averaged. The mean dose is evaluated.

### 4.2.4 Reference Measurement System for Film Calibration

Before measuring absolute dose with Gafchromic EBT3 films the films have to be calibrated against a reference measurement system for absolute dosimetry. An air vented, rigid stem ionization chamber (type 30016, PTW Freiburg) with a sensitive volume of 0.3 cm$^3$ is used as reference chamber. A radioactive check device is used for air density correction. Measured dose values are corrected with energy dependent correction factor and replacement correction factor. [58]
4.3 4D Motion Phantom

The 4D motion phantom is an in-house developed phantom for analysing motion induced effects on radiotherapy treatment delivery and medical imaging. The phantom was engineered in collaboration with the Institute of Automatic Control, RWTH Aachen University [39]. First measurements and clinical feasibility tests have been performed and presented on conferences [40] and [41]. Before using the 4D motion phantom for dose measurements, it is improved in the context of this work.

The phantom consists of a box made of acrylic glass with a target insert which is connected via target mount with robotic driving mechanics. Thus, the target can be moved by three axes for 3D translational motion execution. Motion is controlled by a user interface, where stored motion patterns can be chosen from a library and then be executed by the phantom. Meanwhile, the phantom controller provides real-time information about phantom status and target position. This information is visualized on the user interface additionally. [42]

The phantom is advanced in the context of this work related to the target. The original target consists of two concentric spheres. The inner one is made of acrylic glass, the outer one is made of cedar wood. Therefore, the target represents a tumour insert (acrylic glass) surrounded by less dense material (cedar wood) like it is the case for lung tumours.
To perform dose measurements inside the target the spheres are sliced. Radiosensitive films can be placed between the slices for dose measurements in
five concurrent planes. Using a cover made of acrylic glass the slices and films are held together and the target can be connected to the target mount.

For evaluating a margin concept depending on motion amplitude and tumour size in motion direction the adaptation of these two parameters has to be offered by the corresponding measurement system. Therefore, the target was redesigned to achieve these requirements. At the same time, changes are applied to simplify handling and processing of the inserted films. The new target is shown in figure 4.4. For easy handling and processing the target is built as cube, not as sphere anymore. As the target is built as cube, slices can be inserted in different orientations enabling for dose measurements in all three directions in space. The target is manufactured with three different sized tumour inserts and corresponding cedar wood slices. Maximum diameters in the middle of the tumour inserts, parallel to the film are 26 mm for the small (s), 33 mm for the medium (m) and 40 mm for the large (l) tumour. Additional information about the target are given in the appendix [3].

The target enabling for dose measurements can be replaced by an optical target (reflective marker) e.g. for validating optical tracking systems on the one hand. On the other hand a CT/PET target can be used instead, consisting of a hollow sphere made of acrylic glass which can be filled with water or radioactive tracer fluids for proving 4D-CT / 4D-PET. Therefore, the
phantom box can be filled with water or water-tracer-mixtures to simulate background activity in PET imaging.

In addition to the inner target motion, an outer one-dimensional motion can be generated by a simple lifting platform. The outer motion has a fixed phase relationship to the inner motion. By attaching a breathing belt to the moving platform the measured signal can be used as surrogate signal for motion-correlated phantom measurements in 4D-CT imaging or motion-correlated treatment techniques like gating.

4.4 Linear Accelerator

Measurements are performed using an Elekta Axesse linear accelerator (Elekta Oncology Systems) generating 6MV photons. This treatment machine is equipped with the Agility head offering 160 multi leaf collimators for shaping the treatment field with 5mm width projected to the isocenter plane. An integrated x-ray volume imaging system (XVI) is used for cone beam computed tomography for phantom positioning right before treatment.

4.5 4D-CT

CT and 4D-CT measurements are performed using a Gemini TF16 machine (Philips Medical Systems). CT image data sets are generated with 3mm slice thickness for scanning the 4D motion phantom without performing motion. For scanning the phantom with moving target 4D-CT image data sets are generated with 3mm slice thickness using a small pitch of 0.0042. For analysing motion the breathing cycle is divided into ten phases, equally spaced in time. CT image data sets are reconstructed for each phase.
Chapter 5

Development of the Margin Concept

In this chapter, the development of the new margin concept is described. First, the effects of motion and applied margins on SBRT dose distributions are calculated using the treatment planning system. As discussed in section 2.4, motion is dominant in SI direction. Therefore, only motion in SI direction is considered for developing the margin concept. Afterwards the motion compensation effect of applied margins is evaluated and ideal margins are calculated. Finally, the calculated ideal margins are parameterized as function of amplitude and tumour length in motion direction leading to a formula for calculating an optimized margin for given amplitude and tumour length in motion direction.

The procedures described in section 5.1 - 5.4 were presented as a poster on ESTRO 33 conference and published in Radiother Oncol 111, Suppl. 1, 349-350 (2014) [13].

5.1 SBRT Treatment Planning

41 SBRT treatment plans are generated in the context of this work using patient image data sets (3D CT) with 3mm slice thickness.

Contours
The CTV and OARs are contoured by a physician. For the purpose, no setup margin is applied (PTV=CTV). No margin for motion compensation is applied here. For adapting the multi leaf collimator positions of the treatment fields to the PTV, the PTV contour is expanded by 1mm in L and
AP direction and 3 mm in SI direction. The adaptation of the treatment fields to this expanded volume is needed to achieve the prescribed dose even in the boundaries of the PTV due to the dose fall off in the surrounding tissue.

**Points of Interest**

The beams’ isocenter is placed in the centre of the PTV volume and in the middle of a CT slice.

**Beams**

6 MV photons are used for treatment. Six treatment beams are used, each 30 degrees apart. The treatment fields are shaped conformally to the PTV projection from each direction (3D conformal treatment technique). MLC options are set to minimum adjustment. Collimator positions are set to 0 except for using wedged fields.

For a start, equal beam weights are assigned to the beams. But during the planning process beam weights are optimized by hand to create highly conformal dose distributions and to fulfill the objectives for the PTV and OARs.

**Dose**

The dose grid is set to 3x3x3 mm³ and therefore adapted to the CT slice thickness. Dose calculation is performed using the collapsed cone convolution superposition algorithm. The prescribed dose is given to 98 % of the PTV volume and the maximum dose to the PTV is not allowed to be more than 150 % of the prescribed dose at the same time.

![Lung SBRT dose distribution and beam configuration](image)

Figure 5.1: Lung SBRT dose distribution and beam configuration is shown exemplarily in the transversal plane. The DVH is used for evaluating the dose to PTV (red) and lungs (blue). The dose prescription is indicated with black arrows: 45 Gy is given to 98 % of the PTV volume (PTV $D_{98\%}$).
Evaluation
The treatment plans generated in the context of this work are evaluated to be clinically acceptable concerning the dose to the PTV and the dose to the OARs.

The treatment plans generated under static conditions are referred to as static treatment plans in the scope of this work. They represent the ideal treatment situation and ideal dose distribution when there is no motion occurring.

5.2 Application of Margins

Margins are applied to the static treatment plans by increasing the treatment field size in motion direction. For each margin application the static treatment plan is duplicated and the treatment fields are adapted to the margin.

For a 3 mm margin the PTV contour is expanded by 3 mm in SI direction for example. Afterwards the PTV plus margin contour is expanded by 1 mm in L and AP direction and 3 mm in SI direction for treatment field adaption like it is done for the static treatment plan, too. When the shape of the treatment fields is changed to the new contour, the dose is recalculated to determine the effect of applied margins on the dose distribution. Beam weights persist.

The plan with applied margin is normalized to the static plan such that the dose at isocenter point is the same as in the static plan.

Dose distributions for treatment plans without and with applied margins are shown in figure 5.2. The static PTV is pictured as red contour.

Figure 5.2: Treatment plans with applied margins (M) are calculated by increasing the field size in motion direction (SI). Dose distributions are shown in the coronal plane for three different applied margins.
The light green coloured isodose represents the prescribed dose. The high dose region or rather the volume of the prescribed isodose level is increasing in margin direction by increasing the applied margin.

Margins (M) are applied from 0 - 18 mm in 3 mm steps in SI direction only.

5.3 Integration of Motion

Motion is integrated into treatment planning by moving the isocenter of the treatment beams in SI direction with respect to the static isocenter position or rather the tumour position. In fact, the tumour is moving with respect to the isocenter position but this cannot be simulated by using a static CT image data set for treatment planning. Therefore, motion is applied using the inverted situation.

To account for real patient motion according to section 2.4 the motion profile is a symmetrical $\cos^4$ function. From one motion period ten positions are extracted, equally spaced in time. These positions are projected to the SI direction of the treatment plan to determine ten new isocenter positions for motion integration, symmetrically oscillating around the static isocenter position.

![Figure 5.3: Motion pattern of a $\cos^4$-function shown for two amplitudes and associated projection to the SI direction. Instead of assigning one static isocenter position to the treatment beams ten isocenter positions are used to move the treatment beams with respect to the tumour position and to integrate motion into treatment planning.](image)
5.3. INTEGRATION OF MOTION

For each motion integration the static plan is duplicated and the beams isocenter is adjusted. For ten isocenter positions in the motion case, each beam has to be duplicated to exist ten times but with ten different isocenter positions. Therefore, the beam weights have to be split into ten equal parts to contribute to the dose as much as one corresponding single beam in the static treatment plan. This is done for all six beams of the static treatment plan. Afterwards the dose is recalculated with integrated motion to determine the effect of motion on the dose distribution.

Integrating motion into treatment planning this way is a time-consuming process, especially when it is done by hand. Therefore, to avoid mistakes during implementation of this procedure and to assure constant quality for all cases, the process of motion integration is automated by the use of Pinnacle3 Scripting.

Dose distributions for treatment plans without and with integrated motion are shown in figure 5.4. The static PTV is pictured as red contour. The light green colored isodose represents the prescribed dose. The volume of the prescribed isodose level is decreasing with increasing motion amplitude A and the dose is blurred more and more. This becomes apparent in the broadened dose distribution in SI direction with smaller high dose region in the centre.

Motion is applied with amplitudes (A) from 0-18 mm in 3 mm steps in SI direction only.

![Figures showing dose distributions](image)

Figure 5.4: Dose distributions in the coronal plane shown for integrated motion in SI direction with different amplitudes (A). As the number of beams for the motion case is ten times higher than in the static plan, more beams are visible here. Dose blurring is visible for integrated motion.
5.4 Determination of Ideal Margins

The application of margins and the integration of motion into treatment planning is described in detail in the sections before. This procedure is now carried out simultaneously for all combinations of margins (M) and motion amplitudes (A) and applied to the 41 static lung SBRT plans.

All dose distributions generated that way are evaluated relating to PTV $D_{98\%}$, the dose which is given to 98% of the PTV volume. This procedure is illustrated in figure 5.5. Dose distributions in the coronal plane and corresponding DVHs are shown for three combinations of integrated motion and applied margins.

At the top, the static treatment plan is represented with the prescribed, light green isodose level shaped conformal to the red PTV contour. The prescribed dose of 40 Gy is given to 98% of the PTV volume as marked in the corresponding DVH.

In the middle, motion with an amplitude of 6 mm is integrated but no margin for motion compensation is applied. The dose distribution is affected by the motion. Dose blurring is visible from the reduction of the high dose region’s size. The isodose level of the planned dose does not encompass the PTV any more. This effect is not symmetrical, as the motion follows the cos² profile. The PTV $D_{98\%}$ is decreased to around 32 Gy and is therefore much smaller than the prescribed dose.

At the bottom, motion with an amplitude of 6 mm is integrated but 6 mm margin is applied, simultaneously. The influence of motion is compensated by the applied margin now. The planned isodose level again encompasses the PTV. By evaluating $D_{98\%}$ of the PTV it becomes apparent that the dose decrease is compensated but $D_{98\%}$ is even higher than in the static case. Thus in this case, the applied margin overcompensates the effect of motion.
Figure 5.5: Dose distributions and DVHs for three combinations of integrated motion with amplitudes (A) and applied margins (M).
Evaluating $D_{98\%}$ of the PTV for all motion amplitudes and margins, ideal margins for motion compensation are determined. Therefore, $D_{98\%}$ of the PTV is plotted as function of the applied margin ($M$) for all amplitudes and as function of amplitude ($A$) for all margins, see figure 5.6.

Figure 5.6: Dose given to 98% of the PTV volume plotted over a) margins for all amplitudes and b) amplitudes for all margins. Therefore, ideal margins for motion compensation can be determined.
5.4. DETERMINATION OF IDEAL MARGINS

When a margin is applied without motion, $D_{98\%}$ of the PTV increases with increasing margin. When motion is integrated without applied margin, $D_{98\%}$ of the PTV decreases with increasing motion amplitude. For applied margins, $D_{98\%}$ of the PTV increases with increasing margin for all amplitudes. For integrated motion, $D_{98\%}$ of the PTV decreases with increasing motion amplitude for all margins. An ideal margin for motion compensation compensates the influence of motion in the way that the same dose is given to $D_{98\%}$ of the PTV as in the static case.

The curves are linearly interpolated and a) the ideal margin for motion compensation is calculated for each amplitude or b) the amplitude compensated by the applied margin is calculated for each margin when the $D_{98\%}$ reaches the dose as in the static case. This is done for all combinations of margins and amplitudes and for all 41 patient data sets. The ideal margin for motion compensation is plotted over amplitude in figure 5.7 a). By comparing the ideal margin to the ITV margin (solid black line) it becomes apparent that the ideal motion compensating margin is smaller than the ITV margin.

In figure 5.7 b) the ideal margin for motion compensation is plotted over the ratio of amplitude to tumour length (TL). Tumour length indicates the half of the tumour size in motion direction, like amplitude being half of peak-to-peak amplitude. Due to this visualization the margin is shown to be subject to the tumour length. Plotted this way, the curves are ordered by the tumour length. Therefore, the ideal margins can be parameterized by the ratio of amplitude to tumour length and the tumour length. This is done in the next section to develop a formula for calculating an optimized margin for motion compensation.
The ideal margin for motion compensation is plotted over a) amplitude and b) ratio of amplitude to tumour length in motion direction for the full range of tumour lengths. Lines are shown to guide the eyes.
5.5 Development of the Margin Formula

According to figure 5.6, ideal margins to compensate a given amplitude and the amplitude which is compensated by a given margin are determined. The results are ideal margins for motion compensation determined for each patient, individually.

Now, the ideal margins are averaged over data sets based on same tumour lengths. Mean and standard deviation of the mean $\sigma/\sqrt{N}$ are calculated and plotted over the ratio of amplitude to tumour length in motion direction. The tumour length is measured in multiples of CT slice thicknesses. The thickness of the CT slices divided by $\sqrt{12}$ is taken as uncertainty on the tumour length. This uncertainty is propagated to the ratio of amplitude to tumour length to calculate the associated error.

The ideal margins $M$ for motion compensation are parametrized as a function of the ratio of amplitude $A$ to tumour length $TL$ using a second order polynomial:

$$M\left(\frac{A}{TL}\right) = p_2 \cdot \left(\frac{A}{TL}\right)^2 + p_1 \cdot \left(\frac{A}{TL}\right)$$  \hspace{1cm} (5.1)

The polynomial produces a continuously increasing margin for increasing amplitudes. The constant parameter $p_0$ is fixed to zero because an amplitude of 0 mm needs no margin for compensation. The coefficients of the fitting function are shown in table 5.1 for all tumour lengths with 68% confidence bounds. The parameter $p_2$ increases with TL, while $p_1$ shows small variations. To evaluate fit quality $\chi^2/df$ values are shown. The large $\chi^2/df$ value for 12 mm tumour length is caused by a data point close to zero with a very small uncertainty.

Table 5.1: Coefficients for parametrizing the ideal margin as function of the ratio of amplitude to tumour length using a second order polynomial.

<table>
<thead>
<tr>
<th>TL</th>
<th>$p_2$</th>
<th>$p_1$</th>
<th>$\chi^2/df$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 mm</td>
<td>1.22 ± 0.13</td>
<td>3.06 ± 0.25</td>
<td>3.68</td>
</tr>
<tr>
<td>9 mm</td>
<td>1.49 ± 0.17</td>
<td>4.23 ± 0.27</td>
<td>4.28</td>
</tr>
<tr>
<td>10.5 mm</td>
<td>2.22 ± 0.21</td>
<td>4.35 ± 0.30</td>
<td>3.15</td>
</tr>
<tr>
<td>12 mm</td>
<td>2.27 ± 0.14</td>
<td>6.11 ± 0.17</td>
<td>61.15</td>
</tr>
<tr>
<td>13.5 mm</td>
<td>3.91 ± 0.45</td>
<td>4.82 ± 0.49</td>
<td>3.53</td>
</tr>
<tr>
<td>15 mm</td>
<td>3.80 ± 0.26</td>
<td>7.17 ± 0.26</td>
<td>6.13</td>
</tr>
<tr>
<td>16.5 mm</td>
<td>5.34 ± 0.43</td>
<td>6.21 ± 0.39</td>
<td>4.27</td>
</tr>
<tr>
<td>19.5 mm</td>
<td>7.92 ± 0.65</td>
<td>6.38 ± 0.49</td>
<td>7.00</td>
</tr>
<tr>
<td>24 mm</td>
<td>13.89 ± 0.81</td>
<td>3.77 ± 0.50</td>
<td>3.33</td>
</tr>
</tbody>
</table>
In a second step, the parameters $p_1$ and $p_2$ are parametrized as a function of the tumour length using again a second order polynomial. Uncertainties of the parameter values are taken from the previous fit. The uncertainty of the measured tumour length is determined as before.

The result of the parametrization is

$$p_1(TL) = a_2 \cdot TL^2 + a_1 \cdot TL + a_0$$

$$p_2(TL) = b_2 \cdot TL^2 + b_1 \cdot TL + b_0$$

Table 5.2: Fit parameter resulting from the parametrization of $p_1$ and $p_2$ as function of TL.

$$\begin{array}{l|l|l}
  a_2 = (-0.042 \pm 0.010) & a_1 = (1.379 \pm 0.330) & a_0 = (-5.159 \pm 2.492) \\
  b_2 = (0.043 \pm 0.003) & b_1 = (-0.604 \pm 0.183) & b_0 = (3.666 \pm 1.465)
\end{array}$$

Data and fit functions with corresponding $\chi^2/df$ are shown in figure 5.9.
5.5. DEVELOPMENT OF THE MARGIN FORMULA

Figure 5.9: Fit functions for the two parameters $p_1(TL)$ and $p_2(TL)$ as function of tumour length.

Inserting the parametrization of $p_1(TL)$ and $p_2(TL)$ into equation [5.1], an optimized margin for motion compensation can be calculated from the amplitude and tumour length.

$$M\left(\frac{A}{TL}, TL\right) = p_2(TL) \cdot \left(\frac{A}{TL}\right)^2 + p_1(TL) \cdot \left(\frac{A}{TL}\right)$$

(5.4)

Explanatory Notes

The margin formula is developed for tumour lengths in motion direction from 7.5 - 24mm and amplitudes up to 18mm. For tumour lengths and amplitudes exceeding this range, the formula should not be used. Tumour size in motion direction and motion amplitude are determined from 4D-CT with 3 mm slice thickness. The slice thickness has an impact on the uncertainty of the calculation. The discussion of the uncertainties is valid for this slice thickness only.

Furthermore, the margin concept is based on and developed for the stereotactic treatment of lung tumours in combination with the 3D conformal treatment planning technique. Further studies are needed to apply it to other techniques. One example will be given in chapter 7.4.
5.5.1 Sources of Error

The optimized margin has an uncertainty caused by the uncertainties of the input values and from the parametrizations. To determine the total uncertainty of the optimized margin these sources of error are considered.

Uncertainties of the Input Parameters A and TL to the Calculation

Motion amplitude (A) and tumour length in motion direction (TL) are input parameters. The values are measured for each patient individually from 4D-CT images. Values of TL and A are measured in the CT data set as multiples of CT slice thickness. Thus, they have an uncertainty depending on the slice thickness s, which is 3 mm in this work.

\[ \sigma_A = \frac{s}{\sqrt{12}} \quad \sigma_{TL} = \frac{s}{\sqrt{12}} \]

The uncertainties of amplitude and tumour length are propagated to the uncertainty of the optimized margin using gaussian error propagation. \(\sigma_{M,A}\) describes the uncertainty of M due to the uncertainty of A, the same for TL.

\[ \sigma_{M,A}^2 = (\frac{\partial M}{\partial A})^2 \cdot \sigma_A^2 = \left( \frac{p_1(TL)}{TL} + \frac{2 \cdot A \cdot p_2(TL)}{TL^2} \right)^2 \cdot \sigma_A^2 \]

\[ \sigma_{M,TL}^2 = (\frac{\partial M}{\partial TL})^2 \cdot \sigma_{TL}^2 = \left( \frac{A \cdot (a_1 + 2a_2 \cdot TL)}{TL} - \frac{2A^2 \cdot p_2(TL)}{TL^3} + \frac{A^2 \cdot (b_1 + 2b_2 \cdot TL) - A \cdot p_1(TL)}{TL^2} \right)^2 \cdot \sigma_{TL}^2 \]

Through the margin formula, the values of the uncertainties depends on the values of the input parameters as well. To analyse the contribution of the single components, \(\sigma_{M,A}\) is plotted as function of A for different values of TL and vice versa for \(\sigma_{M,TL}\). Results are shown in figure 5.10.

\(\sigma_{M,A}\) increases with increasing amplitude and reaches its largest values for small tumour lengths. The contribution of \(\sigma_{M,TL}\) behaves differently. For small tumour length, \(\sigma_{M,TL}\) decreases from large values followed by a shallow increase with increasing tumour length. \(\sigma_{M,TL}\) reaches highest values for the largest amplitudes. Therefore, the maximum uncertainty contributed by \(\sigma_{M,A}\) and \(\sigma_{M,TL}\) can be estimated using the smallest tumour length of 7.5 mm and the highest amplitude of 18 mm. For these values the uncertainty is

\[ \sigma_{M,A,TL} = \sqrt{\sigma_{M,A}^2 + \sigma_{M,TL}^2} = 1.6 \text{ mm} \]
5.5. DEVELOPMENT OF THE MARGIN FORMULA

This value is the maximum uncertainty due to the uncertainties of the input parameter.
Calculating the uncertainty for a different case with a TL of 15 mm and an amplitude of 12 mm leads to an $\sigma_{M,ATL}$ of 0.8 mm, quite smaller than the maximum uncertainty calculated for TL of 7.5 mm and an amplitude of 18 mm.

For TL = 15 mm and A = 12 mm: $\sigma_{M,ATL} = 0.8$ mm

The uncertainty due to the input parameters varies with TL and A and has to be calculated for each combination of TL and A, respectively.

Uncertainties of the Parametrization

The formula for the optimized margin results from a parametrization of the ideal margins as a function of amplitude and tumour length. The coefficients of the formula are determined by fitting second order polynomials to the data. Fit qualities are evaluated through the $\chi^2/df$. Good agreements are achieved. Therefore, the uncertainties of the coefficients are not directly propagated to the total uncertainty of the optimized margin.
To evaluate the uncertainty due to the parametrization, the optimized margin is calculated for each patient data which were used to develop the margin concept. The calculated margins are compared to the ideal margins for each patient. The difference of optimized margin and ideal margin is shown in figure 5.11. A gaussian function is fitted to the histogram. The root mean square deviation $\sigma$ of the gaussian function is 0.76 mm. This value is taken as uncertainty of the optimized margin due to the parametrization.
Total Uncertainty

To determine the total uncertainty of the optimized margin, the uncertainty due to the input parameters A and TL and the uncertainty due the parametrization are added in quadrature.

$$\sigma_M = \sqrt{\sigma_{M,ATL}^2 + \sigma_p^2}$$

Because the uncertainty due to the input parameters depends on the values of A and TL, the total uncertainty varies for different values of A and TL. The maximum total uncertainty accounts for the maximum uncertainty due to the values TL of 7.5 mm and A of 18 mm as input parameters.

For TL = 7.5 mm and A = 18 mm : \( \sigma_M = 1.8 \text{ mm} \)

This value is the maximum total uncertainty of the margin. Calculating the total uncertainty for a different case, leads to a smaller total uncertainty due to the smaller value of the uncertainty of the input parameter.

For TL = 15 mm and A = 12 mm : \( \sigma_M = 1.1 \text{ mm} \)

The total uncertainty of the margin varies with the values of amplitude and tumour length in motion direction and has to be calculated for each combination, individually. The maximum total uncertainty is determined to be 1.8 mm using the smallest tumour length of 7.5 mm and the highest amplitude of 18 mm for calculation.
Chapter 6

Evaluation of the Measurement System

Before evaluating the margin concept by measurements with the in-house developed 4D phantom and GafChromatic EBT3 films, the phantom is analysed for accuracy and reproducibility, chapter 6.1.

In section 6.2 the CT image data set for treatment planning is determined which fulfills the requirements for applying the developed margin. Before using EBT3 films for absolute dosimetry the films are calibrated against a reference measurement system. For conversion of pixel values to dose a calibration function is determined, section 6.3.

Finally, the positioning accuracy of the complete measurement system consisting of phantom, film and medical linear accelerator is evaluated in section 6.4.

6.1 Characterising the Phantom

Prior to measuring for margin concept evaluation, the motion performed by the phantom has to be tested with regard to accuracy and reproducibility. Measurements for phantom characterisation are carried out via 3D/4D-CT imaging. The most important parameters which have to be checked are motion amplitude and mid-position of motion.

6.1.1 Reproducibility of Static Positioning

The body of the phantom is positioned on the CT table for CT imaging and aligned to laser markers. The target with the medium sized tumour insert is moved and afterwards taken to central position. In this position, a CT image
of the phantom with slice thickness of $s=1.5\,\text{mm}$ is taken. This procedure is repeated several times.

CT images are transferred to the Pinnacle$^3$ TPS. The tumour inserts are automatically contoured by using the Pinnacle$^3$ threshold based contouring algorithm with 625 HU as threshold. This value is chosen so that the volume of the contour fits the volume of the tumour insert to better than 1%.

A point is placed in the centre of the contoured tumour insert. The coordinates of the centre position are analysed. Thereby, the dominant measurement uncertainty is the slice thickness $s$. For determining the centre position the average over the number of slices building the contour $N_{\text{slices}}$ is calculated. The uncertainty $\sigma$ of the measured centre of mass position is therefore calculated by:

$$\sigma_{\text{slices}} = \frac{s}{\sqrt{12}} \quad \sigma = \frac{\sigma_{\text{slices}}}{\sqrt{N_{\text{slices}}}}$$

(6.1)

The centre of mass position for different measurements are compared. Reproducibility of the static positioning is better than $0.1 \pm 0.3\,\text{mm}$ in every direction.

### 6.1.2 Reproducibility of Motion Pattern

The body of the phantom is positioned on the CT table for CT imaging aligned to laser markers. The target is moving in SI-direction with a motion profile of the $\cos^4$ function, 10 mm amplitude and a motion period of 4 sec. During image acquisition, the breathing belt is fixed around the synchronously moving lifting ramp of the phantom and produces the surrogate signal for 4D-CT imaging (3mm slice thickness). To visualize the target motion ten CT images are reconstructed retrospectively, equally spaced in time. This measurement is repeated five times for the same motion setup. CT images are transferred to Pinnacle$^3$ TPS and tumour inserts are automatically contoured (threshold 625 HU) in all ten image data sets. A point is placed in the centre of the contour. SI coordinates of the centre position in all ten image data sets are plotted over time. The corresponding uncertainty $\sigma$ is calculated according to [6.1]. Uncertainties are small and therefore not visible in figure [6.1]. The preset function

$$SI(t) = -a + 2 \cdot a \cdot \cos^4\left(\frac{\pi}{b}t + c\right) + d$$

(6.2)

is fitted to the data for all five measurements. This describes a symmetric $\cos^4$ function with amplitude $a$, period $b$, phase $c$ and mid-position $d$. Fit parameters are shown in table [6.1] with related fit uncertainties (68% confidence bounds).
Figure 6.1: SI coordinates over time for five \( \cos^4 \) motion patterns, measured via 4D-CT for evaluating reproducibility of motion.

It can be seen in figure 6.1 that motion profiles analysed for five different measurements are highly reproducible. Amplitudes fit well within up to 3 \( \sigma \) uncertainties to the preset value of 10 mm. Periods fit to the preset value of 4 sec within up to 4 \( \sigma \). Amplitude and period of performed motions are reproducible and reliable, too.

The phase of motion \( c \) was not preset, but the determined values agree within up to 2 \( \sigma \) uncertainty for all measurements. The determined mid-position \( d \) of motion for all measurements agree within their uncertainties, too. Thus, the mid-position of motion is stationary for repeating different measurements which is important for treatment planning cf. chapter 6.2.

Table 6.1: Fit parameters for five \( \cos^4 \) measurements to evaluate the reproducibility of phantom motion using the medium tumour insert.

<table>
<thead>
<tr>
<th>Meas</th>
<th>a [mm]</th>
<th>b [sec]</th>
<th>c</th>
<th>d [mm]</th>
<th>( \chi^2/df )</th>
</tr>
</thead>
<tbody>
<tr>
<td>M21587</td>
<td>9.95 ± 0.07</td>
<td>4.04 ± 0.02</td>
<td>0.03 ± 0.01</td>
<td>-43.11 ± 0.08</td>
<td>0.26</td>
</tr>
<tr>
<td>M21588</td>
<td>9.89 ± 0.05</td>
<td>4.04 ± 0.01</td>
<td>0.03 ± 0.01</td>
<td>-43.12 ± 0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>M21589</td>
<td>9.91 ± 0.06</td>
<td>4.00 ± 0.01</td>
<td>0.02 ± 0.01</td>
<td>-43.17 ± 0.07</td>
<td>0.17</td>
</tr>
<tr>
<td>M21590</td>
<td>9.90 ± 0.07</td>
<td>4.04 ± 0.02</td>
<td>0.04 ± 0.01</td>
<td>-43.12 ± 0.08</td>
<td>0.24</td>
</tr>
<tr>
<td>M21592</td>
<td>9.91 ± 0.03</td>
<td>4.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>-43.12 ± 0.04</td>
<td>0.09</td>
</tr>
</tbody>
</table>
6.1.3 Accuracy of Motion Pattern

To determine the accuracy of performed motion pattern 4D-CT measurements according to section 6.1.2 are done for different motion amplitudes 5 mm, 7.5 mm and 10 mm. Again, the centre of mass of the tumour contour is marked with a point for all 10 image data sets. SI coordinates and corresponding errors are plotted over time. Errors are determined according to equation 6.1.

![Graph showing SI coordinates for cos^4 motion profiles measured for different amplitudes to investigate accuracy of performed motion.](image)

Figure 6.2: SI coordinates for cos^4 motion profiles measured for different amplitudes to investigate accuracy of performed motion.

A function according to equation 6.2 is fitted to the data. Measurements and fitted functions are shown in figure 6.2.

Fit parameters and related fit uncertainties (68% confidence bounds) are shown in the subsequent table:

<table>
<thead>
<tr>
<th>Meas</th>
<th>a [mm]</th>
<th>b [sec]</th>
<th>c</th>
<th>d [mm]</th>
<th>(\chi^2/df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M21593</td>
<td>4.93 ± 0.06</td>
<td>4.04 ± 0.03</td>
<td>0.03 ± 0.01</td>
<td>-43.06 ± 0.07</td>
<td>0.14</td>
</tr>
<tr>
<td>M21596</td>
<td>7.41 ± 0.04</td>
<td>4.05 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>-43.11 ± 0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>M21592</td>
<td>9.91 ± 0.03</td>
<td>4.04 ± 0.01</td>
<td>0.04 ± 0.01</td>
<td>-43.15 ± 0.04</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Measured amplitudes and preset values agree within up to 3 \(\sigma\) uncertainty. Periods fit to the preset value of 4 sec within up to 5 \(\sigma\), as the errors are
very small. The phase of motion c was not preset, but the determined values
agree within 1 σ uncertainty for all measurements. Mid-positions agree within
their uncertainties. The mid-position keeps constant even if the amplitude
of motion is varied.
Therefore, the 4D motion phantom is an accurate and reproducible tool to
perform measurements for evaluating the margin concept.

6.2 Determining the Image Data Set for Treatment Planning

The margin concept is based on a motion pattern performed with symmet-
rical amplitude around a mid-position. This is how it was generated by
methodically analysing the influence of motion to applied dose distributions
on static patient CT image data sets.
Thus, for evaluating the margin concept and thereby applying the motion
compensating margins to the moving target, one static CT image of the
phantom is needed for treatment plan generation and dose calculation. For
the phantom just one static CT image could be acquired with the phantom
in central position. This would meet all requirements for data and motion
performed during measurements. But this is not applicable for patients.
Therefore, another solution also adaptable to patients has to be found and
therefore a method to determine the mid-position of a motion pattern is
developed which is described in the following.

![Image](image.png)

(a) Tumour contours on CT image data
(b) Motion pattern of the centre of mass over time plotted
    for three amplitudes. Mid-position of motion is shown in red.

Figure 6.3: The mid-position of motion is used to determine the image data set used for
treatment planning. CT image data sets can be reconstructed for the time when the target
is in mid-position.
4D-CT image data sets are acquired and evaluated according to section 6.1.3. By fitting the coordinates of the centre of mass over time the mid-position d is determined. The mean value of parameter d determined for all three amplitudes (see 6.1.3) is $-43.11 \pm 0.03\, \text{mm}$ and is shown in figure 6.3 as red line. There are two times when the centre of the moving target is located at mid-position. For this points in time/ phases new image data sets are reconstructed. One of these image data sets are used for treatment planning to evaluate the margin concept. This solution is applicable also for patients.

6.3 Characterising GafChromatic EBT3 Films

Before the films are used for absolute dose measurements, they are calibrated against an ionisation chamber as reference measurement system for absolute dosimetry. A calibration function is calculated to determine dose values from measured colour values (CV) for each colour channel.

6.3.1 Film Calibration

Films are calibrated for 6 MV photons. Calibration measurements are performed in an acrylic slab phantom with chamber adaption using 12 mm build-up and 60 mm backscatter material. Chamber and films are irradiated by 10 x 10 cm fields in the same depth, subsequently. For measuring each dose level a separate 4 cm stripe of film is positioned in the centre of the radiation field perpendicular to the beam axis.

Films are irradiated with known doses for determining the calibration function and for evaluating the calibration, respectively. Dose range used for calibration is up to 24 Gy, adapted to the later measurements.

<table>
<thead>
<tr>
<th>Monitor Units [MU]</th>
<th>0</th>
<th>900</th>
<th>1200</th>
<th>1500</th>
<th>2400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meas. Dose [cGy]</td>
<td>0</td>
<td>898.8</td>
<td>1198.1</td>
<td>1497.8</td>
<td>2396.1</td>
</tr>
</tbody>
</table>

Due to the self-developing process and post-exposure changes in colour, calibration films are scanned more than 24 h after exposure and in one scan conforming to FilmQA Pro 2014 user manual [14]. After scanning, the image is imported to FilmQA Pro 2014 software for data processing.

For each dose level, a frame is defined in the centre of the irradiated field. Pixels inside the frame are evaluated for calibration. The mean colour values (CV) of the frames are plotted over dose for each color channel. Rational functions are fitted to the data. The inverse functions are the calibration
functions used for converting measured CVs into dose. They are plotted in figure 6.4. The calibration functions with corresponding fit parameters can be found in the appendix A.

Uncertainties for absolute reference dose measurements are determined by repeated measurements of the same dose value. Standard deviations used to determine variations are less than 0.5 cGy and therefore very small.

Uncertainties of measured mean CVs are also very small, because they are averaged over all pixel inside the frames. Therefore, error bars are not visible in figure 6.4. Residuals are used to evaluate the fit quality of the calibration function. According to a maximum residual of 20 cGy the calibration function fits well to the data.

**Evaluation of the Calibration Function**

The calibration function is further assessed by applying the calibration to measured colour values which were not used for determining the calibration. Films are irradiated with doses which are measured before by an ionisation chamber, too. Measurements and data processing are performed just as for film calibration, see section 6.3.1. The measured colour values are converted to dose for each color channel using the calibration functions. Dose maps are exported in csv-format to be further processed with MATLAB.

Then, doses from all three colour channels are averaged to determine the corresponding dose. Measured and calculated doses are compared in the

![Image: Dose as function of colour value (CV). Calibration data and functions shown for three colour channels RGB.](image)
following table. The absolute difference between measured and calculated
dose is less than 10 cGy. This value is taken as dose uncertainty in the
following. The high accuracy is achieved by averaging over the dose measured
by all three colour channels.

Reproducibility of Film Measurements

In this section, the reproducibility of measurements with GafChromatic EBT3
films is evaluated. Five films are irradiated under the same conditions with
300 MU. Films are processed as described in section [6.3.1] A frame is defined
in the centre of the high dose region. Mean dose of the frame is determined
by using the calibration function to convert CVs into dose. Dose maps are
exported in csv-format to be further processed with MATLAB. Doses from
all colour channels are averaged for each film.
Standard deviation of the five measured doses is less than 3 cGy. Therefore,
measurements with EBT3 films are highly reproducible.

6.4 Reproducibility of the Evaluation Process

Reproducibility of the measurement system and subsequent data process-
ing is analyzed including positioning of phantom and target insert, the film
position inside the target and positioning of the film on the scan area for
measuring CVs and digitalization for data processing. All these parameters
have an impact on the measurement result, especially when comparing the
absolute position of isodose lines and known tumour positions. This is done
for evaluating the margin concept later. So reproducibility and positioning
accuracy of the complete evaluation process have to be determined first.

The phantom is completely reassembled and newly aligned five times on
different days. The target insert is reassembled and mounted each time with
a new film inserted. A single irradiation field (positioning field) conformal
shaped to the tumour contour with gantry and collimator set to 0° is generated
for analyzing reproducibility. The linac is moved between the measurements
6.4. REPRODUCIBILITY OF THE EVALUATION PROCESS

and repositioned each time, too. Afterwards the films are scanned and CVs are converted to dose. The mean dose of all three colour channels is calculated. Isodose line positions are compared for all measurements for three dose levels, 250, 350, 450 cGy.

In addition, a complete treatment plan for the non-moving medium sized tumour was measured two times. The encompassing isodose line of the prescribed dose is compared for both measurements.

Results are shown in figure 6.5. On the left side, one measured dose distribution related to the positioning field is shown. Isodose lines determined from all five measurements are overlaid for three dose levels. Isodose lines for the same level are shown in same colours. On the right side the same is done for the two times measured treatment plan.

Repeated measured isodose lines match very well. The maximum spatial deviation detected between two similar isodose lines is 3 pixels, which is equivalent to 1 mm. Therefore, the maximum uncertainty for reproducible and accurate measurements related to the complete evaluation process is estimated to be 1 mm.

![Figure 6.5](image)

Figure 6.5: Evaluating the reproducibility of measurements and subsequent data processing by using a) a single irradiation field measured five times and b) treatment plan measured two times. Isodose lines for the same level are shown in similar colours. On the right side, the tumour position is visualized as black circle.
CHAPTER 6. EVALUATION OF THE MEASUREMENT SYSTEM
Chapter 7

Evaluation of the Margin Concept

In this section, the margin concept is evaluated by film measurements using the 4D motion phantom. During treatment planning, a margin for motion compensation is applied according to the new developed concept, but also according to the ITV margin concept for comparison. Then, the moving target is irradiated with the calculated treatment plan in each case. Applied doses are measured by films placed between the target slices. The prescribed isodose line on the measured dose distribution is analyzed to encompass the target position and to fit conformal to the target shape. When the isodose line encompasses the target position the margin compensates the motion and ensures that the target receives the prescribed dose. At the same time, the target surrounding tissue have to be spared as good as possible. Therefore, the prescribed isodose line has to fit conformal to the target shape.

Preparation for measurements are described in section 7.1. Subsequently, the optimized margin is evaluated related to the motion compensating effect. Results are described in section 7.2.1. To compare the optimized margin to the ITV concept margin, measurements with applied ITV concept margins are done and compared to measurements with applied optimized margins. Results are shown in section 7.2.2.

In addition to the evaluation of the new developed margin concept, motion compensation of the optimized margin is evaluated for a motion profile being symmetrical and therefore different from the one used to develop the margin concept. Results are shown in section 7.3.

The margin concept is developed using the 3D-conformal treatment planning technique. In section 7.4, the margin concept is used combined with the dynamic arc technique (VMAT) in addition. It is investigated, if the motion compensating margin can be transferred to this treatment technique without further adaptation.
In the last section [7.5] three patient data sets are exemplarily used to calculate how much dose to the lung can be spared by applying the optimized margin instead of the ITV margin.

7.1 Preparation Process

To irradiate the target, treatment plans are generated for the different sized targets assuming different motion amplitudes $A$ of 5 mm, 7.5 mm and 10 mm. To account for target motion during treatment, margins $M$ are applied. No setup margins are used.

- To evaluate the optimized margin concept, margins are applied related to equation [5.4]. They are shown in the following table.

Table 7.1: Optimized margins calculated for different motion amplitudes and three different sized tumors inside the target small (s), medium (m) and large (l).

<table>
<thead>
<tr>
<th>Motion Amplitude</th>
<th>Optimized Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>small</td>
</tr>
<tr>
<td>5 mm</td>
<td>$2.7 \pm 0.9,\text{mm}$</td>
</tr>
<tr>
<td>7.5 mm</td>
<td>$4.3 \pm 1.0,\text{mm}$</td>
</tr>
<tr>
<td>10 mm</td>
<td>$6.2 \pm 1.0,\text{mm}$</td>
</tr>
</tbody>
</table>

- To compare the new developed margin concept and the ITV concept, margins according to the ITV concept are applied. Here, the applied margin is identical to the full motion amplitude, $M = A$.

Figure 7.1: Planned dose distribution for evaluating the margin concept exemplarily shown in the transversal and coronal plane.
Margins are applied in SI direction direction rounded to full millimeters. Therefore, a margin of 2.7 mm is applied as 3 mm for example. The PTV is created by adding the margin in motion direction to the automatically contoured tumour (threshold 625 HU).

Treatment plans are generated just as described in section 5.1 with six 6 MV photon beams. Treatment fields are shaped conformal to the PTV projection and a total dose of 45 Gy is prescribed to 98% of the PTV volume, 15 Gy per fraction according to the clinical dose concept of SBRT.

Treatment plans are transferred to the medical linac. Before treatment, the phantom is positioned at the medical linac and aligned to the laser markers. The positioning is verified via CBCT imaging. Films are inserted in the target in all five slices for correct positioning of the target insert but only the three films in the center are used for dose measurements. The Set-up is shown in figure 7.2.

Measurements and evaluations are performed for evaluating the margin concept.

- **Evaluating the motion compensation of the optimized margin**
  In this part, the motion compensating effect of the optimized margin is demonstrated.
  The target is moving with three different amplitudes and the treatment plan with optimized margin for motion compensation is irradiated. Results are shown in section 7.2.1.

- **Optimized margin in comparison with ITV margin**
  In this section, the optimized margin is compared to the ITV margin to show the advantage of the optimized margin.
  The target is moving with three different amplitudes and the treatment plan with ITV margin for motion compensation is irradiated. This measurements are compared to the measurements performed with optimized margin. Results are shown in section 7.2.2

The optimized margin concept is developed using a preset motion profile and a fixed treatment technique. In addition to evaluating the margin concept in principal, the performance of the applied margin is evaluated for a different motion profile and a different treatment technique, respectively.

- **Performance for symmetric motion profile**
  The treatment plan with applied optimized margin is irradiated but the target is moving with same amplitude but a different, symmetric motion profile. Results are shown in section 7.3
• Performance for different treatment technique

Two treatment plans using VMAT treatment technique are generated using the optimized margin for motion compensation. The target is moving during irradiation. Results are shown in section 7.4.

The target is irradiated with one dose fraction using several settings which were described before. The dose distributions are evaluated with respect to the isodose line of the prescribed dose of 15 Gy for one fraction.

For evaluation purposes, tumour coverage and dose conformity are determined based on the two-dimensional dose measurement. Tumour coverage is defined as the percentage of the tumour area receiving at least the prescribed dose. This percentage determines whether the required dose is applied to the tumour which is important for a successful therapy. Coverage of less than 100 % is acceptable, because the dose is prescribed to only 98 % of the tumour volume. Dose conformity is evaluated as the ratio of the prescribed isodose area and the tumour area. This value is calculated to quantify how good the dose distribution fits to the tumour shape and how much area outside the tumour is irradiated with high dose. It is preferable to fit the prescription isodose as good as possible to the tumour border to spare the surrounding healthy tissue. Therefore, conformities close to one are desirable. Treatment planning is limited by e.g. the finite slice thickness of the image data set used for treatment planning, the dose calculation grid size or mechanical parameters like the size of the collimators used to shape the treatment field. Due to this limitations, conformity is larger than one. Good coverage and conformity have to be achieved at the same time.

Measured dose distributions and related tumour positions are shown in all figures with the tumour in central position. The reproducibility of the evaluation process is within 1 mm, according to section 6.4. This uncertainty has to be considered for tumour coverage. Thus, the tumour position is moved around its center within the range of 1 mm. For each position tumour coverage is determined. Tumour coverage for the central position (coverage) as well as best tumour coverage within the uncertainty (max coverage) are represented and evaluated further. Conformity is not affected by this uncertainty, because only the ratio of the isodose area and the tumour area enters, but not the absolute position.
Figure 7.2: Phantom positioned for measurements at the medical linac. Target motion direction is labeled. Film orientation inside the target and film position related to beaming directions (blue) are illustrated at the bottom.
7.2 Evaluation

7.2.1 The Motion Compensation with the Optimized Margin

Treatment plans calculated with optimized margins for motion compensation are irradiated while the target is moving. This is done for all tumour sizes and for three different amplitudes, respectively. Dose distributions measured with films in slice C are shown for all cases in figure 7.3. Tumour positions related to the measured dose distributions are displayed as black circles, respectively. The prescribed isodose line is illustrated as red line. Tumour coverage and conformity are determined from measured dose distributions to evaluate the compensation effect of the optimized margins. Results are shown in table 7.2.

![Figure 7.3: Dose distributions measured for three motion amplitudes with optimized margins to account for motion. Motion direction is indicated by the black arrow.](image-url)
Table 7.2: Tumour coverage and conformity calculated from measurements with optimized margins.

<table>
<thead>
<tr>
<th>Motion Amplitude</th>
<th>Coverage / Max Coverage</th>
<th>Conformity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>small (s)</td>
<td>medium (m)</td>
</tr>
<tr>
<td>5 mm</td>
<td>99.9/100 %</td>
<td>99.2/99.4 %</td>
</tr>
<tr>
<td>7.5 mm</td>
<td>100/100 %</td>
<td>100/100 %</td>
</tr>
<tr>
<td>10 mm</td>
<td>100/100 %</td>
<td>99.9/100 %</td>
</tr>
</tbody>
</table>

Tumour coverage is above 99% for all cases. Minimum coverage is 99.2%. Maximum coverage is 100% for all cases except for the measurement of the medium tumour size and 5 mm motion amplitude. In this case, the prescribed isodose line and the tumour contour are tangent or overlap in the lateral part of the dose distribution. In motion direction, the isodose line encompasses the tumour. Thus, the applied margins compensate the motion effects and guarantee the prescribed dose to the tumour. At the same time, conformity is close to one, with a worst conformity of 1.6. The dose to the tumour is applied while preserving the surrounding tissue.

To conclude, the motion compensating effect of the newly developed margin concept is well demonstrated. For all tumour sizes and motion amplitudes, the optimized margin compensates motion induced effects and ensures tumour coverage while preserving the surrounding tissue.

**7.2.2 Optimized Margin in Comparison with ITV Margin**

The newly developed margin is meant to be a replacement for the ITV margin. To demonstrate the benefit of the optimized margin, both margins are applied in the treatment planning process. The moving target is irradiated separately with the two generated treatment plans and the measured dose distributions are compared.

Measurements are evaluated for three combinations of target size and motion amplitude. Dose distributions are measured with films in three slices B, C and D for

- Small tumour insert and 5 mm motion amplitude,
- Medium tumour insert and 10 mm motion amplitude,
- Large tumour insert and 7.5 mm motion amplitude.
Figure 7.4: Measured dose distributions to compare the motion compensation effect of the ITV margin and the newly developed optimized margin (here: margin). Motion direction is indicated by the black arrow.
7.2. EVALUATION

Tumour positions related to dose distributions are displayed as black circles. The prescribed isodose is shown as red line.

For all measurements, the prescribed isodose line encompasses the tumour position, but for the applied ITV margin the isodose line is larger in motion direction for all measured combinations of tumour size and motion amplitude. In case of the optimized margin the isodose line fits closer to the tumour shape. In motion direction, the isodose line encompasses the tumour. In the lateral part of the dose distribution, the tumour contour and the prescription isodose are tangent or overlap. Tumour coverage and conformity are calculated to determine the motion compensation effect of the margins and to compare the optimized and the ITV margin.

Table 7.3: Tumour coverage and conformity measured for the small tumour insert and a motion amplitude of 5 mm achieved for ITV and optimized margin.

<table>
<thead>
<tr>
<th>Coverage / Max Coverage</th>
<th>Conformity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITV</td>
<td>Optimized Margin</td>
</tr>
<tr>
<td>B</td>
<td>100/100 %</td>
</tr>
<tr>
<td>C</td>
<td>100/100 %</td>
</tr>
<tr>
<td>D</td>
<td>100/100 %</td>
</tr>
</tbody>
</table>

Table 7.4: Tumour coverage and conformity measured for the medium tumour insert and a motion amplitude of 10 mm achieved for ITV and optimized margin.

<table>
<thead>
<tr>
<th>Coverage / Max Coverage</th>
<th>Conformity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITV</td>
<td>Optimized Margin</td>
</tr>
<tr>
<td>B</td>
<td>100/100 %</td>
</tr>
<tr>
<td>C</td>
<td>100/100 %</td>
</tr>
<tr>
<td>D</td>
<td>100/100 %</td>
</tr>
</tbody>
</table>

Table 7.5: Tumour coverage and conformity measured for the large tumour insert and a motion amplitude of 7.5 mm achieved for ITV and optimized margin.

<table>
<thead>
<tr>
<th>Coverage / Max Coverage</th>
<th>Conformity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITV</td>
<td>Optimized Margin</td>
</tr>
<tr>
<td>B</td>
<td>100/100 %</td>
</tr>
<tr>
<td>C</td>
<td>100/100 %</td>
</tr>
<tr>
<td>D</td>
<td>100/100 %</td>
</tr>
</tbody>
</table>
For the ITV margin tumour coverage is 100% for all measured slices. This can be easily seen by analysing the prescription isodose which fully encompasses the tumour in figure 7.4. For the optimized margin, tumour coverage is higher than 98.7%. Coverage of less than 100% is acceptable due the prescribing the dose only to 98% of the tumour volume. Thus, both margins assure adequate tumour coverage and compensate motion induced effects.

In the case of the ITV margin, conformities are in the range of 1.8 to 2.7. For the optimized margin, conformities are in the range of 1.3 to 1.7. The comparison of the applied doses shows that the conformities are substantially better for optimized margins. For the ITV margin, the prescription isodose is larger in motion direction leading to a conformity much bigger than one. As the optimized margin is smaller than the ITV margin, the isodose line fits closer to the tumour creating a higher conformal dose distribution. Thus, conformity is closer to one.

Due to the high conformity with the optimized margin, the tumour surrounding tissue is protected better against high doses while the tumour is still covered with the prescribed dose. Therefore, the application of the optimized margin is to be preferred over the ITV margin.

### 7.3 Performance for Symmetric Motion Profiles

To study the robustness of the optimized margin the phantom is irradiated with optimized margin while the target is moving with a symmetric profile. In this case, a \( \cos \) function is used as motion pattern which is a symmetric profile instead of the asymmetric \( \cos^4 \) motion used for determining the optimized margin.

Measurements are performed using a motion amplitude of 10 mm for the small and the large target insert, respectively. Dose distributions measured in slice C are shown in figure 7.5 for both tumour sizes. Tumour positions related to the measured dose distributions are displayed as black circles while the prescribed isodose line is illustrated as red line. The isodose line encompasses the tumour position for all measurements.

Tumour coverage and conformity of the dose distribution are determined to evaluate the compensation effect of the optimized margin in the case of a different motion profile. Results are shown in table 7.6. Tumour coverage is above 99% for all measurements. The optimized margin compensates motion.
induced effects on dose distributions for symmetric motion profiles as well. This follows from the determination of the optimized margin during the development of the margin concept. Margins are applied symmetrical in motion direction even if the motion profile is not symmetric. Dose distributions measured in section 7.2.1 visualize this difference. Dose distributions and tumour positions are not centered. This is due to the symmetrically applied margin on non-symmetrical motion profile.

For a non-symmetrical motion profile a non-symmetrical margin could be applied like it is proposed by van Herk et al. [3]. But in this case, the margin is very sensitive to the pre-defined motion profile. To avoid this dependence and to assure reliable coverage for different motion profiles a symmetrical margin is proposed here.

Table 7.6: Tumour coverage and conformity measured for small and large tumour insert with optimized margin for 10 mm amplitude.

<table>
<thead>
<tr>
<th>Motion Profile</th>
<th>Coverage / Max Coverage</th>
<th>Conformity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>small</td>
<td>large</td>
</tr>
<tr>
<td>( \cos^4 )</td>
<td>100/100%</td>
<td>99.4/100%</td>
</tr>
<tr>
<td>( \cos )</td>
<td>100/100%</td>
<td>99.7/100%</td>
</tr>
</tbody>
</table>
7.4 Performance for VMAT Treatment Technique

The VMAT treatment technique is becoming more and more popular. The optimized margin were developed for the 3D conformal treatment technique. Now it is investigated if the optimized margin compensates motion effect for the VMAT technique, as well.

Two VMAT treatment plans are generated for the phantom with medium target insert using full (VMAT1) and half (VMAT2) rotation, respectively. The optimized margin is applied in both cases for compensating motion with 10 mm amplitude. No setup margins are used.

As for the 3D conformal treatment technique, a prescribed dose of 15 Gy per fraction to 98 % of the tumour volume is used for VMAT.

Figure 7.6: Comparison of dose distributions applied using the 3D conformal (Conf) and the VMAT treatment technique, measured for applied optimized margins for the medium target insert and 10 mm motion amplitude, respectively. Motion direction is indicated by the black arrow.
Generated treatment plans are irradiated while the target is moving. Dose distributions measured in slice C are shown in figure 7.5 for the 3D conformal and the VMAT treatment techniques. Black circles represent tumour positions related to the measured dose distributions. The red line illustrates the prescribed isodose line.

Tumour coverage and dose conformity are determined from measured dose distributions to evaluate the compensation effect of the applied margin. Results are displayed in table 7.7. For the 3D conformal treatment technique, highest coverage is achieved. The conformity is 1.3 in this case. With the VMAT technique, the conformity is improved. Values are smaller than in the 3D conformal case. But at the same time, coverage is reduced to a minimum of 90.5%. The motion compensation is not sufficient in this case. Intensity modulation and tumour motion interfere leading to under dosage in the tumour volume.

The optimized margin cannot be applied without adaptation in combination for VMAT treatment.

### 7.5 Assessment of Spared Lung Tissue

The clinical benefit of the optimized margins is the improved dose conformity while sufficient tumour coverage is ensured. For a patient, this means that more of the healthy lung tissue surrounding the tumour can be spared. Less side effects can be expected for the patient. This benefit is quantified by a study of three patient data sets with different sized tumours. Treatment plans are generated according to the procedure described in section 5.1 with applied optimized and ITV margins to compensate motion during treatment with 12 mm amplitude. Corresponding dose volume histograms are evaluated to determine the dose to the lung containing the tumour. The dose to the lung for the applied ITV and optimized margin are compared related to specified dose tolerance limits. Published dose tolerance
limits used for SBRT have been reviewed and summarized by Grimm et al. [45]. For a fractionation scheme like it is used in the context of this work (three fractions) tolerance limits are displayed in the second column of table 7.8. They are summarized by [45] amongst others for the lung containing the tumour. They are used to compare both margin applications and to quantify the clinical benefit of the application of the optimized margin. Results are shown in table 7.8.

Table 7.8: DVH evaluation to compare dose to the lung for the applied ITV margin (ITV) and the optimized margin (Margin). The planning study is performed using margins to compensate motion with 12 mm amplitude and for three different sized tumours. Results are compared to dose tolerance limits [45].

<table>
<thead>
<tr>
<th>Lung</th>
<th>Dose Tolerance Limit [45]</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TL = 9 mm</td>
<td>TL = 13.5 mm</td>
<td>TL = 24 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ITV</td>
<td>Margin</td>
<td>ITV</td>
</tr>
<tr>
<td>(V_{5\text{Gy}})</td>
<td>(\leq 50%)</td>
<td>18.9%</td>
<td>15.4%</td>
<td>38.8%</td>
</tr>
<tr>
<td>(V_{10\text{Gy}})</td>
<td>(\leq 30%)</td>
<td>9.6%</td>
<td>7.3%</td>
<td>19.6%</td>
</tr>
<tr>
<td>(V_{20\text{Gy}})</td>
<td>(\leq 10-20%)</td>
<td>3.7%</td>
<td>2.7%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>

By comparing the percentage of lung volume receiving the doses mentioned in the first column, it becomes apparent that the volumes are smaller for the optimized margin. More of the lung is spared with the optimized margin. The optimized margins are smaller than the ITV margin. Dose to the lung or rather the lung volume receiving a particular dose is increasing with increasing tumour size. Because the radiation has to penetrate the lung to reach the tumour, the penetrated lung volume increases with increasing tumour size. For small tumours it is simple to respect the dose tolerance limits. But for larger tumours the dose tolerance limits can be exceeded. This is the case in the example of patient 3. Tolerances are exceeded for the ITV margin, but are still fulfilled for the optimized margin. \(V_{20\text{Gy}}\) decreases from 21.3\% in the ITV case to only 15\% for the optimized margin. For the patient, this implies a vital reduction of the probability for side effects.
Chapter 8

Conclusions and Outlook

The aim of this work was to develop a new margin concept to compensate for breathing induced tumour motion during the stereotactic treatment of lung tumours.

The effects of motion and applied margins on SBRT dose distributions were calculated based on 41 patient data sets using the treatment planning system. Margins up to 18 mm were applied by increasing the treatment field size in motion direction. Motion was integrated into treatment planning by moving the beams isocenter in motion direction (SI) in relation to the static isocenter position. A symmetrical cos^4 function with amplitudes up to 18 mm was used as motion profile adapted to real patient motion. For all combinations of margins and motion amplitudes, the influence of motion on the calculated dose distribution was determined. The compensating effect of the applied margins was methodically analysed for various motion amplitudes and tumour sizes in motion direction.

For all patient data sets, ideal margins were calculated for all amplitudes. Ideal margins are defined to compensate for motion in the way that the dose which is given to 98% of the tumour volume is the same for the motion case as in the static case. To compensate for motion with a well defined amplitude, a larger margin is needed for a small tumour compared to a larger tumour. Therefore, motion amplitude and tumour length are parameters having an impact on the motion induced effect on dose distributions.

Ideal margins were parametrized as function of motion amplitude and tumour length leading to a margin formula to calculate an optimized margin for motion compensation. The optimized margin concept is different from existing margin concepts by taking into account tumour length beside motion amplitude as input parameters for margin calculation.
Calculated optimized margins were evaluated to compensate for motion induced effects on applied dose distributions using an in-house developed robotic 4D motion phantom and film measurements. Due to these measurements, it is demonstrated that the optimized margin compensates for motion induced effects on dose distributions.

By comparing the motion compensating effect of the applied optimized margin with the ITV margin, it was shown that the optimized margin is to be preferred to the application of the ITV margin due to the conformity of the applied dose distribution. Both applied margins ensure the prescribed dose to the tumour. But the conformity of the applied dose distribution was measured to be in the range of 1.8 to 2.7 for the applied ITV margin. In the case, the optimized margin was applied, conformities were in the range of 1.3 to 1.7. Conformity of the applied dose distribution is essentially smaller for the applied optimized margin. The prescribed isodose line fits better to the tumour shape. Therefore, the tumour surrounding tissue can be spared better while the tumour is covered with the prescribed dose at the same time. Motion effects are compensated by applied optimized margins for symmetrical motion profiles as well, although the margin concept was developed using a non symmetrical motion profile. As an outlook on establishing treatment techniques in radiotherapy, the optimized margin was applied in combination with the VMAT treatment technique although the margin was developed based on the 3D conformal treatment technique. By analysing the measured dose distributions it was demonstrated that the target coverage was reduced in the VMAT case compared to the 3D conformal case. Intensity modulation of the treatment fields and tumour motion interact in a way leading to an under dosage in the tumour region. Therefore, the optimized margin cannot be applied without adaptation along with the use of the VMAT treatment technique.

As clinical outlook, the application of the optimized margin and the ITV margin were clinically evaluated by comparing the dose to the surrounding tissue for patient’s treatment planning. Treatment plans were generated for three different sized tumours and a motion amplitude of 12 mm. Both margins were applied for treatment planning. The dose to the lung containing the tumour was evaluated. For larger tumours the dose to the lung is higher compared to a smaller tumour. Lung volumes receiving a certain dose are smaller for applied optimized margins compared to the ITV margin. For the large tumour case \( V_{20\text{Gy}} \) of 21.3% in the case the ITV margin is applied can be reduced to 15.0% for the applied optimized margin. This leads to reduced side effects for the patient or can make this treatment modality applicable for the patient according to dose tolerance limits.
For the clinical implementation of the optimized margin concept motion amplitude and tumour length have to be determined using 4D-CT imaging. An image data set representing the tumour in the mid-position of motion is used for treatment planning and dose calculation. During treatment planning the optimized margin for motion compensation is applied. Because the applied margin and the treatment plan depend on the amplitude, the motion amplitude has to be verified right before treatment. Modern linear medical linacs offer the possibility for breathing-correlated CBCT imaging with the patient in treatment position. That way, the motion amplitude can be verified right before treatment. As an outlook on future radiotherapy workflow, the motion amplitude measured right before treatment can be used to adapt the treatment plan with a new optimized margin applied to the daily treatment situation. Thereby, the tumour is covered with the prescribed dose while the surrounding healthy tissue is preserved best possible at the same time for each patient, individually.
Appendix A

Film Calibration Function

Calibration functions for converting measured colour values (CV) into dose (D) determined using FilmQA Pro 2014 software (Ashland Advanced Materials). This function is fitted to the data for each colour channel, separately.

\[ D(CV) \ [Gy] = A + B \cdot CV + C \cdot \sqrt{|CV^2 + D \cdot CV + E|} \]

Table A.1: Fit parameters for the calibration function of the red colour channel.

<table>
<thead>
<tr>
<th>( A_R )</th>
<th>( B_R )</th>
<th>( C_R )</th>
<th>( D_R )</th>
<th>( E_R )</th>
</tr>
</thead>
<tbody>
<tr>
<td>-42.982</td>
<td>2090.542</td>
<td>-2090.542</td>
<td>-0.038</td>
<td>-0.002</td>
</tr>
</tbody>
</table>

Table A.2: Fit parameters for the calibration function of the green colour channel.

<table>
<thead>
<tr>
<th>( A_G )</th>
<th>( B_G )</th>
<th>( C_G )</th>
<th>( D_G )</th>
<th>( E_G )</th>
</tr>
</thead>
<tbody>
<tr>
<td>12451.3343</td>
<td>464785.8188</td>
<td>-464785.8188</td>
<td>0.0536</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

Table A.3: Fit parameters for the calibration function of the blue colour channel.

<table>
<thead>
<tr>
<th>( A_B )</th>
<th>( B_B )</th>
<th>( C_B )</th>
<th>( D_B )</th>
<th>( E_B )</th>
</tr>
</thead>
<tbody>
<tr>
<td>32.67</td>
<td>-216.71</td>
<td>261.71</td>
<td>-0.38</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Appendix B

4D Motion Phantom Target

Figure B.1: The wooden slices of the phantom target with the small tumour inserted. For dose measurements films are placed between the slices.

Table B.1: Diameters of the tumours inside the target for all slices.

<table>
<thead>
<tr>
<th>Target Size</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>18.5 mm</td>
<td>26 mm</td>
<td>18.5 mm</td>
</tr>
<tr>
<td>Medium</td>
<td>28 mm</td>
<td>33 mm</td>
<td>28 mm</td>
</tr>
<tr>
<td>Large</td>
<td>35 mm</td>
<td>40 mm</td>
<td>35 mm</td>
</tr>
</tbody>
</table>
Figure B.2: The three different sized tumour inserts of the 4D motion phantom. Corresponding cedar wood slices exists for each tumour size.
## List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Ten reconstructed images generated by respiration-correlated CT imaging.</td>
<td>4</td>
</tr>
<tr>
<td>2.2</td>
<td>Geometric model of the medical linear accelerator head Agility (Elekta Oncology Systems, Sweden)</td>
<td>5</td>
</tr>
<tr>
<td>2.3</td>
<td>Schematic representation of a treatment unit with all modalities equipped.</td>
<td>6</td>
</tr>
<tr>
<td>2.4</td>
<td>Schematic illustration of the radiotherapy workflow.</td>
<td>7</td>
</tr>
<tr>
<td>2.5</td>
<td>Dose distribution optimized with two prescribed dose levels (red and orange coloured) and viewed for three orthogonal planes.</td>
<td>8</td>
</tr>
<tr>
<td>2.6</td>
<td>By using multiple fractions cells recover during the fractions.</td>
<td>11</td>
</tr>
<tr>
<td>2.7</td>
<td>Schematic view of the body frame which was developed to offer the stereotactic coordinate system for tumour localization</td>
<td>13</td>
</tr>
<tr>
<td>2.8</td>
<td>IGRT: Controlling the tumour position inside the body right before treatment via images determined by planning CT (reference) and CBCT (current position). Image fusion is used to correct for the current tumour position.</td>
<td>13</td>
</tr>
<tr>
<td>2.9</td>
<td>Lung tumour motion projected to tumour position in lung.</td>
<td>16</td>
</tr>
<tr>
<td>3.1</td>
<td>According to ICRU Report 50, margins are applied: GTV, CTV and PTV contours illustrated for a lung tumour case.</td>
<td>19</td>
</tr>
<tr>
<td>3.2</td>
<td>Two examples for measured tumour motion by 4D-CT imaging, CTVs are coloured in orange and are displayed for max. inhalation/exhalation. The ITV (yellow) contains all CTV positions during breathing. PTV (ITV plus set-up margin) is shown as red contour.</td>
<td>21</td>
</tr>
<tr>
<td>3.3</td>
<td>Outline to illustrate the influence of motion on differently sized targets.</td>
<td>24</td>
</tr>
</tbody>
</table>
4.1 Exemplary treatment plans for lung SBRT generated via 3D conformal planning (left) and VMAT (right). The PTV contour is shown as red line. Dose distribution is represented as colour distribution. Isodose levels and corresponding colours are shown in the legend. The yellow green isodose level defines the prescribed dose level. Due to the stereotactic dose prescription, this isodose surface has to encompass 98 % of the PTV volume. ........................................... 26

4.2 Scan position of the film on the scan area, the films are aligned to the frame made of black opaque paper. The grey bar on the left side of the scan area displays the park position of the scanner lamp, the grey arrow shows the scan direction. ...... 29

4.3 In-house developed 4D motion phantom. .......................... 30

4.4 Exploded view and section of the new phantom target. ......... 31

5.1 Lung SBRT dose distribution and beam configuration is shown exemplarily in the transversal plane. The DVH is used for evaluating the dose to PTV (red) and lungs (blue). The dose prescription is indicated with black arrows: 45 Gy is given to 98 % of the PTV volume (PTV $D_{98\%}$). ................................. 34

5.2 Treatment plans with applied margins (M) are calculated by increasing the field size in motion direction (SI). Dose distributions are shown in the coronal plane for three different applied margins. .................................................. 35

5.3 Motion pattern of a $\cos^4$-function shown for two amplitudes and associated projection to the SI direction. Instead of assigning one static isocenter position to the treatment beams ten isocenter positions are used to move the treatment beams with respect to the tumour position and to integrate motion into treatment planning. ........................................ 36

5.4 Dose distributions in the coronal plane shown for integrated motion in SI direction with different amplitudes (A). As the number of beams for the motion case is ten times higher than in the static plan, more beams are visible here. Dose blurring is visible for integrated motion. ................................. 37

5.5 Dose distributions and DVHs for three combinations of integrated motion with amplitudes (A) and applied margins (M). 39

5.6 Dose given to 98 % of the PTV volume plotted over a) margins for all amplitudes and b) amplitudes for all margins. Therefore, ideal margins for motion compensation can be determined. 40
5.7 The ideal margin for motion compensation is plotted over a) amplitude and b) ratio of amplitude to tumour length in motion direction for the full range of tumour lengths. Lines are shown to guide the eyes. 

5.8 Averaged margins for same tumour lengths plotted against the ratio of amplitude to tumour length and parametrized using a second order polynomial. 

5.9 Fit functions for the two parameters \( p_1(TL) \) and \( p_2(TL) \) as function of tumour length. 

5.10 Contributions to the total uncertainty: \( \sigma_{M,A} \) as function of \( A \) for different values of TL and \( \sigma_{M,TL} \) as function of TL for different values of \( A \). 

5.11 For determining the uncertainty of the calculated optimized margin, optimized margins and ideal margins are compared. Gaussian function is fitted to the differences. 

6.1 SI coordinates over time for five \( \cos^4 \) motion patterns, measured via 4D-CT for evaluating reproducibility of motion. 

6.2 SI coordinates for \( \cos^4 \) motion profiles measured for different amplitudes to investigate accuracy of performed motion. 

6.3 The mid-position of motion is used to determine the image data set used for treatment planning. CT image data sets can be reconstructed for the time when the target is in mid-position. 

6.4 Dose as function of colour value (CV). Calibration data and functions shown for three colour channels RGB. 

6.5 Evaluating the reproducibility of measurements and subsequent data processing by using a) a single irradiation field measured five times and b) treatment plan measured two times. Isodose lines for the same level are shown in similar colours. On the right side, the tumour position is visualized as black circle. 

7.1 Planned dose distribution for evaluating the margin concept exemplarily shown in the transversal and coronal plane. 

7.2 Phantom positioned for measurements at the medical linac. Target motion direction is labeled. Film orientation inside the target and film position related to beaming directions (blue) are illustrated at the bottom. 

7.3 Dose distributions measured for three motion amplitudes with optimized margins to account for motion. Motion direction is indicated by the black arrow.
84

LIST OF FIGURES

7.4 Measured dose distributions to compare the motion compensation effect of the ITV margin and the newly developed optimized margin (here: margin). Motion direction is indicated by the black arrow. .......................... 66

7.5 Dose distributions measured for two target sizes with same motion amplitude of 10 mm but different motion profile. Motion direction is indicated by the black arrow. ............... 69

7.6 Comparison of dose distributions applied using the 3D conformal (Conf) and the VMAT treatment technique, measured for applied optimized margins for the medium target insert and 10 mm motion amplitude, respectively. Motion direction is indicated by the black arrow. ......................... 70

B.1 The wooden slices of the phantom target with the small tumour inserted. For dose measurements films are placed between the slices. ........................................... 79

B.2 The three different sized tumour inserts of the 4D motion phantom. Corresponding cedar wood slices exists for each tumour size. ....................................................... 80
Bibliography


08.02.2015.


[34] www.FilmQAPro.com, 29.11.2014.


