Designing IMRT for lung cancer
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Chapter 7

General discussion
Chapter 7

1 Introduction

In case of lung cancer, dose escalation is necessary since most of the patients treated with radiotherapy have local recurrence at the site of the primary tumour using the currently applied clinical dose levels. Intensity modulated radiotherapy (IMRT) is a useful tool to allow dose escalation for treating any tumour site, but should be an excellent tool in case of lung cancer because it can be used to sharpen the broad beam fringe in low-density lung tissue. This allows a substantial reduction in field size and sparing of the lung and other organs at risk (OARs). The goal of the work described in this thesis is to provide insight in the most important topics to consider when changing from 'classical' conformal radiotherapy of lung cancer on a static volume, i.e. the planning target volume (PTV), to intensity modulated radiotherapy on the 'moving' clinical target volume (CTV), taking into account all uncertainties caused by tumour motion and set-up errors.

2 Tools to enable dose escalation in radiotherapy of lung tumours

2.1 Intensity modulated radiotherapy

There are three general methods of applying IMRT that are feasible for irradiating any tumour site:

First, IMRT can be used to increase the freedom of choice of beam angles. In conventional conformal radiotherapy, beam angles are selected such that OARs are excluded from the beam's eye views (BEVs). In IMRT, however, it will be possible to minimize the dose to OARs that are actually included in the BEV of beams by choosing clever segment shapes. Using a multi-segment technique for a prostate treatment, Damen et al. have shown that the dose in the rectum can be reduced while this OAR is actually included in the beam's eye view of all beams in a treatment plan [7]. A similar approach may be feasible for sparing the oesophagus, heart and spinal cord in case of a thorax irradiation. Derycke et al. have already shown that such an approach is beneficial for sparing the spinal cord in case of lung cancer irradiation [8]. For irradiation of lung tumours the principal OAR, the healthy lung itself, can never be avoided. However, IMRT offers the possibility to freely choose beam directions that minimize the dose to the lung, while simultaneously the dose to other OARs (spinal cord, heart, oesophagus) is minimized and target coverage is maintained by a clever choice of beam segments.

Second, by using IMRT to increase the fluence near the field edges it will be possible to sharpen the beam fringe, allowing a reduction in field size and dose in organs at risk while maintaining target dose homogeneity. Dirkx et al. have shown the benefit of this approach for irradiations in the thoracic region using both a treatment planning [9] and a dosimetric study [10]. By applying a limited number of segments in a co-axial treatment plan, the field margins in both the cranial and
caudal direction could be reduced significantly resulting in a reduced dose in the lungs while maintaining dose homogeneity in the target volume. Using IMRT to reduce field sizes furthermore increases the benefit of including SPECT lung perfusion data in the treatment planning process. Beam directions can be more easily chosen to confound as much dose as possible to the non-functional parts of the lung without minimizing the presence of this OAR in the beam's eye views (Chapter 6). For tumours not located in the lung the method of beam fringe sharpening is only beneficial if the tumour is located very close to an organ at risk, e.g. the rectum in case of prostate cancer, because of the already sharp beam fringe in unit-density tissue.

Third, by increasing the fluence at the edge of the field further, the dose at the border of the target volume can be raised to a level higher than the dose on the central beam axis, in order to compensate for random set-up errors [25]. In case of lung cancer, the same method can also be used to compensate for respiration-induced tumour motion. The overcompensation of the dose at the border of the high dose region ensures that the shift due to blurring of, for example, the 95 % isodose level with respect to the 50 % isodose level (i.e. the field edge) is smaller than without overcompensation. This allows the use of smaller field sizes while ensuring a certain minimum dose in the target. The benefits of this approach will not be obvious as long as a static geometrical shape is used for treatment evaluation. In 'classical' treatment planning, i.e. by applying the PTV concept, this approach does not allow field size reduction and leads to unnecessary extra dose in the PTV and in organs at risk. One needs to simulate random errors and patient breathing and to evaluate the dose in the moving CTV in order to appreciate the benefit of this approach and to safely introduce it in the clinic. The distribution of random set-up errors as acquired from a previously treated patient population should be used since the random set-up errors for an individual patient can not be known prior to treatment planning. The extra merit of this approach compared with the sharpening of the beam fringe has not yet been proven in practice. It can, however, be useful at locations where the CTV is located close to an organ at risk. Then, overcompensation may guarantee a steep dose gradient despite blurring of the dose distribution due to patient breathing and set-up errors, thus ensuring a high enough dose in the target volume while limiting the dose in the organ at risk.

The second and third application of IMRT are particularly suitable for irradiating tumours in the thoracic region because of the broad beam penumbra in low-density lung tissue and the effect of respiration-induced tumour motion on the dose in the CTV. The optimum treatment plan will, however, be a combination of all three methods.

2.2 Dose homogeneity in the CTV: another parameter for treatment optimisation

Irradiation of lung tumours is not only different from the treatment of other tumour sites because of the increased beam penumbra in low-density lung tissue. The situation of an organ at risk (i.e., the lung) surrounding the tumour makes the thorax also an almost unique site. Any reduction in field size near the tumour-lung
interface leads to a large decrease in dose in the lung and, due to the broad beam fringe, only to a relatively small decrease in minimum dose in the tumour. In optimising radiation treatment plans of lung tumours it should therefore be considered whether or not to allow an inhomogeneous dose distribution in the target volume. We have shown that it is beneficial, with respect to the optimum combination of TCP of the CTV and normal tissue complication probability (NTCP) of the lung, to allow dose inhomogeneity, even without the use of intensity modulation (Chapter 4). Combination of this approach with IMRT, however, allows even a further increase in the probability of tumour control (Chapter 5).

Whether or not to use the concept of dose escalation in combination with field size reduction is an important clinical decision. A careful approach is necessary because decades of clinical experience is based on conforming the 95 % isodose level to the PTV. However, due to the use of inadequate dose calculation and inhomogeneity correction algorithms in designing these treatment plans (Chapter 2), patients are in reality already treated with inhomogeneous dose distributions in the CTV (Chapter 3).

The advantage of allowing dose inhomogeneity is that it allows further escalation of the probability of tumour control under constraint of a constant probability of complications of the lung. A disadvantage is, however, that it is more difficult to discriminate between treatment plans. With dose homogeneity, e.g. using the PTV concept, an increase in the prescribed dose will almost certainly result in an increase in the probability of tumour control. Using the PTV concept in which the CTV is supposed to be located within the PTV for most of the treatment time, the dose-volume histogram (DVH) of the static PTV is a close approximation of the DVH of the moving CTV. Allowing dose inhomogeneity, however, one has to use a DVH reduction technique in combination with a radiobiological model such as the EUD [28] or TCP model [41] to assess which treatment plan is best. In the new approach, the cumulative dose distribution in the moving CTV has to be assessed, taking into account set-up errors and patient breathing. In this case a probability based approach of treatment evaluation is needed, as for instance developed by van Herk et al. [39], which is a further difference with 'classical' conformal radiotherapy.

A difficulty with the iso-lung-NTCP approach as used in this work is that it is based on the mean lung dose (MLD) being a good indicator for the NTCP of the lungs. Although patients were scored for MLDs up to about 30 Gy, the application of the MLD has only been tested for prescription dose levels up to 90 Gy [22]. The increase in prescribed dose when dose inhomogeneity in the target is allowed, may lead to 3-D dose distributions in the lung for which the MLD is no longer a representative indicator of the complication probability of the lungs. Regions of high dose may for instance lead to complications with blood vessels. The link between MLD and NTCP of the lungs has only been investigated for radiation pneumonitis grade 2 or higher as an endpoint. For other endpoints, such as necrosis and bleeding, the MLD may not be a representative indicator for the probability of lung complications. The same restriction holds when using the volume receiving a dose
of more than 20 Gy (V20) instead of the MLD, as suggested in Chapter 4, as a dose-limiting parameter in the iso-lung-NTCP approach.

3 Technical aspects of treatment planning and delivery

3.1 Accuracy of dose calculation in lung

Although IMRT is in principle an excellent tool for improving the radiation treatment of lung cancer, clinical application of IMRT is at present applied in only a few institutions. An important reason for this is that only recently algorithms have become available that accurately predict the dose distribution in inhomogeneous media like the thoracic region. Most simple tissue-inhomogeneity correction algorithms do not adequately take into account the increased range of secondary electrons in low-density lung tissue (Chapter 2). Because broadening of the beam fringe in low-density lung tissue is not predicted, too small field sizes are used leading to too low doses in the target volume. Without tissue inhomogeneity corrections, underestimation of the beam fringe in low-density tissue will be at least as large. Therefore, the decision in RTOG 93-11 (dose escalation using conformal radiotherapy) to base dose escalation on dose calculations without inhomogeneity correction, is questionable. Large differences between the calculated and actual dose distribution, of up to 20% (Chapter 2), will be present because penumbra broadening is not taken into account in the choice of field sizes. The errors in the calculated dose distributions will be more or less equal for all participating institutions, but the reported dose distributions in the PTV are not representative for the dose distribution in the tumour.

For the simple inhomogeneity correction algorithms, a large difference between predicted and measured dose distribution is already apparent in case of medium-sized conformal beams with static MLC-shaped fields. For small segments, as will be used in both step-and-shoot and dynamic IMRT, the lack of electron equilibrium at the centre of these small fields will provide an even larger problem. Then, the error in the calculated shape of the dose profile may even be overshadowed by the error in the monitor unit calculation. Use of a convolution-superposition algorithm as incorporated in some commercially available treatment planning systems is expected to lead to a much better prediction of the dose distribution in the thoracic region. It should be noted that Dirkx et al. have designed an IMRT approach for sparing the lungs in irradiation of lung cancer patients [9], although their treatment planning system only has a simple inhomogeneity correction algorithm. Extensive dosimetric verification has allowed them to safely introduce their technique into the clinic [10].

A further problem, as mentioned in Chapter 2, is that the use of a simple inhomogeneity correction algorithm does not only lead to misprediction of the dose in the PTV. It can also lead to an error in the calculated MLD. This has consequences for the choice of prescribed dose values in dose escalation studies.
The actual mean lung dose might be considerably different from the value calculated by a TPS having a simple inhomogeneity correction algorithm. This has consequences for the threshold dose at an MLD of 20 Gy, as used in this study. This dose level is based on a study in which a variety of simple inhomogeneity correction algorithms are used to calculate the MLD for a large patient group [22]. Unpublished data regarding the recalculation of treatment plans of 16 NSCLC-patients with a convolution-superposition algorithm which was verified to accurately calculate the dose in the thoracic region (K. De Jaeger, M.D. personal communication), showed a much lower MLD compared with calculations applying a simple inhomogeneity correction algorithm. Preliminary results show that the threshold dose is close to 16.5 Gy. The fact that the MLD-level of 20 Gy as used in Chapters 4 and 5 is probably a too high estimate does, however, not change the conclusions drawn in these chapters.

3.2 Displacement of the tumour

Set-up errors and tumour motion due to patient respiration have an important influence on the design and evaluation of a treatment plan. When using either the 'classical' approach of pursuing a homogeneous dose in a PTV or when allowing target dose inhomogeneity and conforming a certain dose level to a different structure during treatment planning, knowledge of the amplitude of set-up errors and respiration-induced tumour motion is a prerequisite in order to accurately define field sizes. Too large field sizes will lead to unnecessary radiation dose in organs at risk while too small field sizes will lead to too low doses in the target volume. Especially when using IMRT to sharpen the beam fringe in low-density lung tissue, the minimum dose in the CTV may drop dramatically if the high dose region is conformed too close to the 'static' CTV as delineated on a CT-scan.

In Chapter 3 we have shown that a reduction in systematic errors, random errors and respiration-induced tumour motion will lead to an increase in TCP for a certain treatment. Likewise, reduction of tumour motion will allow the reduction of field sizes thus reducing the dose in OARs while maintaining a certain level of TCP. Knowledge of tumour motion and set-up errors is therefore important but one should also aim at minimizing them. Reduction of systematic errors in patient set-up and target delineation will lead to the largest gain with respect to TCP and NTCP (Chapter 3), followed by a reduction in random (set-up) errors. This is in accordance with data provided by Stroom et al. [36] and van Herk et al. [40], who showed that, for a tumour in homogeneous surroundings, the influence of systematic set-up errors on the required treatment margin is much larger than for random (day-to-day) errors. Although respiration-induced tumour motion is not a random event, movement around a systematic offset has a similar blurring effect on the cumulative dose distribution as random set-up errors. Therefore, patient breathing has only a small effect on the dose in the CTV.

Van Herk et al. [39,40] have argued that error sources that are of influence on the design of a treatment plan can be subdivided in treatment preparation errors (or systematic errors) and treatment delivery errors (or random errors). For each type of error there are a lot of sources. In the next section only some specific error
sources and how to minimize them, will be discussed. Furthermore respiration-induced tumour motion also influences the design and effectiveness of a treatment plan. This motion can, however, be measured for an individual patient and taken into account prior to irradiation and is therefore not an error.

3.3 Measuring and reducing tumour motion and uncertainties in patient set-up

3.3.1 Patient breathing

The effect of patient breathing on the dose in the CTV for a given treatment plan is small (Chapter 3). Short time presence outside the 95% isodoses level, which results in a too low dose in a part of the CTV, will be compensated during another part of the same breathing cycle. It is our opinion that control of patient breathing during irradiation allows only a very small reduction in field sizes, i.e. less than 2 mm diameter reduction for treatment plans based on conformal fields. Although control of patient breathing has a limited effect with respect to field size reduction, it can be beneficial with respect to the NTCP of the lungs. If the patient is only irradiated at full inspiration, the volume of lung within the beam's eye views and the dose in the lungs will be reduced with respect to irradiation during free breathing. If a strategy of selective boosting is applied to deliver an increased dose to a sub-volume of the tumour [37], control of patient breathing during irradiation may be necessary to limit smearing out of the boost dose over the entire tumour. If intensity modulation is used to sharpen the beam penumbra or when the amplitude of respiration-induced tumour motion is very large (>> 10 mm), control of breathing motion during irradiation may become of importance. Some authors, however, argue that control of breathing motion during irradiation allows a substantial reduction in field sizes. Different approaches have been suggested, e.g., using an ABC-device [42], voluntary breath-hold [13] or respiration gating [20,21,29]. Probably the most sophisticated approach is tested and implemented by Shirato et al. [35]. These authors use a 2 mm gold marker implanted in the tumour in combination with four x-ray tubes for real-time tumour tracking in the treatment room. The linear accelerator is only triggered if the gold marker is located within a predefined 'volume'. Thus motion of the tumour can be accounted for with the patient breathing freely and smaller field sizes can be applied allowing sparing of organs at risk. Movement of the marker within the tumour can, however, be a problem.

In fact, the system automatically corrects for day-to-day variations in tumour position. Even random and systematic set-up errors can be accounted for automatically insofar as these errors influence the tumour position with respect to the beam portals. A set-up error in one direction and displacement of the tumour in the opposite direction would not be noticed by the system while it could certainly influence the dose distribution within the patient.
3.3.2 Random errors

The main sources of random errors are patient set-up errors in the treatment room and day-to-day variations in the position of the tumour within the patient. At The Netherlands Cancer Institute portal imaging is performed routinely. For a group of NSCLC-patients the observed standard deviation in random set-up errors are 3.0, 3.4 and 2.2 mm (1SD) in the left-right, cranial-caudal and ventral-dorsal direction, respectively. Data about day-to-day tumour movement are not yet available. In general, random errors are difficult to reduce. They are, however, rather small and have a limited influence on the design of a treatment plan, just as patient breathing.

![Figure 1: Dose profiles for a 100 mm diameter 8 MV beam in cork for a) a conformal field and b) a conformal field with overcompensated fluence near the field edge.](image)

The solid line in Figure 1a indicates an unblurred profile for an 8 MV beam as measured in material of lung-density. The dashed line indicates the same profile blurred for both random errors (3 mm, 1SD) and 5 mm amplitude of respiration-induced tumour motion. Because of the blurring, the 95% isodose level is displaced only 1 mm closer to the central beam axis. This displacement can be compensated
by an increase in field radius of only 1 mm, resulting in a small increase in dose in organs at risk. Because of the already shallow penumbra the positive effect of reducing random errors and control of patient breathing during irradiation is small. If intensity modulation is used to sharpen the beam fringe and to overcompensate the dose near the field edge (Figure 1b) the shift in the 95% isodose level due to blurring increases to 3 mm and control of patient breathing during irradiation might become useful. However, more than half of the shift is a result of dose blurring due to random errors.

3.3.3 Systematic set-up errors

With regard to the irradiation of lung tumours as well as with tumours at other sites, set-up errors in the treatment room can be measured using portal images or an electronic portal imaging device (EPID). For minimizing the systematic component of these set-up errors, an off-line correction protocol using a (shrinking) action level (3-D vector length < 5 mm) as reported by Bel et al. [3] can be applied. This correction protocol is routinely used in The Netherlands Cancer Institute for set-up verification of various tumour sites. In this way, the standard deviation of systematic errors was reduced from 3.0, 4.9 and 2.5 mm in the left-right, cranial-caudal and ventral-dorsal direction, respectively, to 1.5, 1.8 and 1.3 mm, respectively for lung tumour treatments. No patient had a systematic set-up error with a 3-D vector length exceeding 4.5 mm [W. Heemsbergen, personal communication]. Although systematic errors were decreased, the use of this protocol has led to a minor increase in the standard deviation of random set-up errors. However, as mentioned before, these errors have a much smaller influence on the dose in the tumour than systematic set-up errors. Image-guided radiotherapy [e.g. 17,35] can also reduce systematic set-up errors.

3.4 Delineation error

Another systematic error is introduced by the use of a non-representative CT-scan for treatment planning. Patients are breathing freely during acquisition of the CT-scan. This leads to distortions in the CT-scan. Furthermore the tumour may be displaced from the average position at the moment of CT-acquisition, because of respiration-induced tumour motion. As a consequence, there may be a systematic shift between the position of the CTV with respect to the bony anatomy as delineated on a particular CT-scan and how it should have been delineated if the average position on a number of CT-scans was taken. The systematic set-up error in the treatment room is an error in the location of the bony anatomy of a patient with respect to the beam portals. The systematic delineation error is different because it is an error in the location of the CTV with respect to the bony anatomy.

The methods mentioned above regarding control of patient breathing during irradiation can also be used during CT-scanning, ultimately enabling the acquisition of a CT-scan at the average tumour position. One should, however, ensure that the average lung volume in the breathing cycle is the same during CT-acquisition as during irradiation of the patient in order not to introduce an additional systematic
error. When using an ABC-device in which the patient breathes through a relatively small tube, this average lung volume can differ considerably compared with free breathing.

Next to minimizing the systematic error in the position of the CTV, control of patient breathing during CT-acquisition also reduces distortions in the CT-images. This may result in a more accurate overall delineation of the target volume, i.e., a minimum error in the shape of the delineated GTV and CTV. When, however, a lung tumour is attached to the chest wall or surrounded by infiltrate or atelectases, it may still be very difficult to determine the exact shape of the GTV. Use of multi-modality imaging, i.e. combining the information from CT, MRI and PET, may then be helpful, not only in delineation of the primary tumour but also in distinguishing between involved and uninvolved lymph nodes [e.g. 14,24,33]. Target delineation studies can provide insight in the magnitude of the delineation error [e.g. 6,11,30,32]. For lung cancer patients, however, there is only limited experience with delineation variability. Ketting et al. found significant differences between institutions and individual physicians regarding the delineation of the planning target volumes [18]. They argue that this was probably caused by individual and institutional differences in the working definition for the PTV. Senan et al. found, however, that significant inter-clinician variations persist in contouring target volumes in NSCLC-patients, despite the use of an institutional contouring protocol [34].

4 A scenario for clinical implementation of dose escalation in radiotherapy of lung tumours

4.1 Design of a treatment plan

If dose escalation is pursued for the radiation treatment of NSCLC, use of IMRT is advantageous. Especially when target dose homogeneity is pursued, use of IMRT to sharpen the beam fringe will allow a large increase in the probability of tumour control (Chapter 5). Without this dose homogeneity constraint the benefit of using IMRT is slightly less. If, however, not just the dose in the target region and in the lungs is taken into account but also the dose in other OARs, the benefit of IMRT will increase because more and better directions of beam incidence can be chosen when designing treatment plans, while still limiting the dose in OARs. In the next paragraphs, three different methods, with increasing complexity, of treatment plan design will be discussed. Although each approach can also be used without IMRT these types of techniques will not result in an optimum treatment plan. The next paragraphs will mainly concern the future of radiotherapy in general but they are therefore also applicable to the specific future of radiotherapy of lung tumours.

4.1.1 'Classical' approach

Current clinical practice in the irradiation of lung cancer is to pursue a homogeneous dose distribution in the PTV, i.e. the 95 % isodose level is conformed
to this PTV. The PTV is a purely geometrical concept that is primarily used as a planning aid. The CTV is expanded in 3-D into a PTV to account for uncertainties in, e.g. target delineation, patient breathing and patient set-up. The PTV is widely defined in such a way that the CTV is located inside this PTV for the entire course of a radiation treatment, thus ensuring that the entire CTV receives at least 95% of the prescribed dose when the 95% isodose level is conformed to the PTV. The prescription dose is representative for the dose in the CTV. The non-isotropic magnitude of systematic errors, random errors and patient breathing, should result in a non-isotropic expansion from CTV to PTV when following the recommendations of ICRU Reports 50 and 62 [15,16]. In the on-going phase I/II dose escalation study, however, the CTV is expanded with a uniform 3-D margin of 10 mm into a PTV for most of the NSCLC-patients. For some patients, having a large amplitude of respiration-induced tumour motion, the margin from CTV to PTV may be non-isotropic. Since respiration-induced tumour motion has a minor effect on the cumulative dose in the CTV (Chapter 3), only a limited increase in margin from CTV to PTV will be necessary in directions of large amplitudes of breathing motion.

The classical approach is currently applied in the on-going dose escalation study, using conformal fields without intensity modulation. For a typical NSCLC-patient with a relatively small hilus tumour, the current applied prescription dose level is 81 Gy, corresponding with a MLD of approximately 12.5 Gy. Extrapolation to a MLD of 16.5 Gy, i.e. the probable level of mean lung dose at which a sharp increase in lung complications is observed, the highest achievable prescription dose level for this patient will be almost 107 Gy using this classical approach. However, a simple inhomogeneity correction algorithm is currently used for dose calculation. This correction algorithm results in a choice of too small field sizes and misprediction of the MLD. Although the planned 95% isodose level is conformed to the PTV, the actual position of the 95% isodose level is within the PTV. Replanning the treatment of this patient using a convolution-superposition algorithm that does predict broadening of the beam fringe in low-density tissue, shows that the maximum achievable prescription dose level is not 107 Gy but close to 83 Gy for a MLD of 16.5 Gy. The increase in field sizes is necessary to conform the 95% isodose level to the PTV, leading to increased dose in the lung. It is, however, questionable whether such increased field sizes are necessary because the reduction in the probability of tumour control using current clinically applied field sizes is limited (Chapter 3). If intensity modulation is used to sharpen the beam fringe, it is expected that the prescription dose level of 83 Gy can be increased with about 30% while still conforming the 95% isodose level to the PTV (compare the third to last and second to last columns in Table 1 in Chapter 5).

In conclusion: when pursuing the classical approach of conforming the 95% isodose level to the PTV, the maximum attainable dose level for lung tumours when using beam fringe sharpening is about 100 Gy for relatively small tumours and will be lower for larger tumours.
4.1.2 Minimizing complications

The aim of 'classical' treatment planning is to ensure a minimum dose of 95% within the moving CTV. Van Herk et al. [40] have argued that unacceptable field margins are necessary in order to ensure that this constraint is met for all patients in a population. It is a better approach to decide what percentage of the patient population should be treated correctly, e.g. 90%. Furthermore, although the classical approach is straightforward, it is not the optimum approach. The problem is that the PTV is a static geometrical structure while the actual target, i.e. the CTV, is not stationary. As mentioned in a section 3.3.2, the shift in the 95% isodose level (as 'perceived' by the tumour) due to random errors and patient breathing, depends on the dose gradient outside this isodose level. Therefore, the correct position of the planned (i.e. unblurred) 95% isodose level depends on the steepness of the dose gradient outside this isodose level. Even when set-up errors and respiration-induced tumour motion are isotropic, the planned 95% isodose level could be located closer to the 'static' CTV in directions where the dose gradient outside this isodose level is relatively shallow. Some groups, e.g. Dirix et al. [10], used larger margins in the cranial-caudal direction because of the overlap of all beam penumbrae in their co-axial (non-intensity modulated) treatment plans. The dose gradient in the cranial and caudal direction was, therefore, relatively steep. Similarly, the planned 95% isodose level should be located a few mm further outwards at locations where the target volume is embedded in unit-density tissue and is located close to one or more beam edges, resulting in a relatively sharp dose gradient. Treatment plan design for lung cancer irradiations will require anisotropic margins because of the differences in local beam penumbrae [40]. It will therefore be very difficult to devise a general approach for margin recipe-based treatment planning for lung cancer patients.

Using IMRT, the shallow penumbra for a single beam in tissue of lung-density can be sharpened and the desired location of the 95% isodose level may no longer be dependent on the local tissue density. However, even if it would be possible to use IMRT to ensure an equal beam penumbra for all beam edges regardless the local density, the local dose gradient outside the 95% isodose level is still not the same in all directions. The local dose gradient will always depend on the directions of beam incidence in a treatment plan. Optimum margins between the CTV as delineated on a CT-scan and the 95% isodose level depend on the local dose gradient of the entire treatment plan, not just on the dose gradient of a single beam penumbra at that location [5,40]. For this reason, an approach using a margin recipe will still not lead to the design of the optimum treatment plan, although it can be a close approximation.

A process of designing a treatment plan using (dynamic) IMRT under constraint of target dose homogeneity can be (safely) pursued by means of probability-based treatment planning. Van Herk et al. have described a method in which iso-contours are determined for a specific treatment plan [38]. The necessary inputs are the distribution of set-up errors and patient breathing, the planned 3-D dose distribution and the shape and location of the target region (e.g. the GTV and/or CTV) with respect to this dose distribution. The dose distribution is first convolved with the
random errors and respiration-induced tumour motion to obtain an estimate of the cumulative dose distribution. Next, the CTV is displaced with respect to its planned position in all possible directions while computing a parameter of the CTV dose, for example the minimum dose in the CTV. The result is a function of x, y and z. Iso-contours for the minimum CTV dose are shown in a single plane in Figure 2 for a prostate IMRT case.

Figure 2: The contour lines (95 %, 90 %, ..) map the effect of systematic translation on the minimum cumulative CTV dose. By combining them with the probability distribution of systematic errors (the grey blob), the probability of an acceptable CTV dose is computed.

The interaction of the CTV shape with the dose distribution gives the function an irregular shape. In some directions, for instance the +x direction, a systematic error leads to a relatively fast reduction of the dose parameter. Due to the intended rectum sparing, even a small systematic error towards the lower direction (posterior for the patient) leads to a minimum dose in the CTV of less than 95 % of the prescribed dose. The probability that a given dose parameter value is reached is computed by integrating the estimated gaussian error distribution within the iso-contours for this value. Treatment plans can be evaluated with this software and field sizes can subsequently be changed near a location of a too large or too small probability of a cumulative dose in the CTV that is inconsistent with the dose prescription. The software takes the entire 3-D dose distribution and the effects of uncertainties in position of the tumour on the cumulative dose in the target into account. If, for example, a minimum dose in the CTV of 95 % of the prescribed dose
for 90% of the patients is the planning constraint, use of the software will show that a smaller margin between the CTV and the planned 95% isodose level is allowed at locations with a shallow gradient in iso-contours (i.e. a shallow dose gradient prior to blurring) compared with locations with a steeper gradient. Probability-based treatment planning is a flexible approach. If, with respect to tumour control, at some location too small field sizes are necessary because of the presence of an organ at risk, the software can show if the increase in field size at other locations ensures that the planning constraint is still met. This may, however, require a very large increase in field sizes and thus in dose in organs at risk. This can be prevented by using a more flexible treatment planning constraint. Van Herk et al. have suggested an EUD of 98% of the prescribed dose for 90% of the patients. Iso-contours for the EUD (or TCP) can be determined just as simple as for the minimum dose. The advantage of an EUD (or a TCP) constraint is that a low dose in a small sub-volume can be compensated by a too high dose in a large other sub-volume without changing field sizes. In the approach of minimising complications, a slight increase in target dose inhomogeneity can be allowed, thus ensuring that the prescription dose level is representative for the target dose distribution.

One way to implement probability-based treatment planning with iso-contours could be to expand the CTV by anisotropic margins into a geometrical structure to which a certain dose level is conformed using IMRT and computerized optimisation of beam intensity maps. This geometrical structure is different from a PTV in that it will not be used for reporting dose values but only to define a treatment plan. Iso-contours are determined and the CTV can be re-expanded with different margins depending on the local probability of correct target dosage. A new treatment plan will be automatically optimised conforming the same isodose level to the new structure.

Dose escalation will be limited to a certain prescription dose level using the classical treatment planning approach. It is expected that the treatment planning approach described in this section will allow the design of acceptable treatment plans to increased prescription dose levels because the dose in organs at risk can be more effectively minimised while ensuring sufficient coverage of the target volume.

4.1.3 Maximizing tumour control probability

As mentioned in Chapters 4 and 5, pursuing a homogeneous dose in the CTV does not lead to the maximum probability of tumour control for lung tumours. Under constraint of a constant mean lung dose, the probability of tumour control can be substantially escalated by allowing an increased dose inhomogeneity within the CTV. If strict constraints are given by clinicians with respect to the acceptable level of complications of the lungs, heart, spinal cord and other organs at risk, it will be possible to maximize the probability of tumour control under these constraints. It is important to be aware of possible complications with blood vessels because of the high prescription dose levels that may be used in this approach. The essence of the approach is that treatment planning is not determined by prescribing dose but by accepting a certain probability of complications. A large target dose inhomogeneity
is allowed and therefore the use of tumour control models like the EUD and TCP are invaluable in evaluating treatment plans. Optimisation when allowing target dose inhomogeneity will, however, be an elaborate trial and error process because an extra variable, i.e. the prescription dose level, can be altered. There are no strict guidelines, like iso-contours, to help in the trial and error process of finding the best combination of relative target coverage and absolute prescription dose. It is almost impossible to assess a priori whether, for a specific reduction in field size, the reduction in relative minimum dose will be compensated by an increase in absolute prescription dose level. This trial and error process can, however, be automated by, for example, an inverse treatment planning tool [e.g. 1,23,27,31]. An additional benefit of this approach of maximizing the probability of tumour control under constraint of maximum tolerable normal tissue complication probabilities is that it is even more flexible in allowing a reduced dose in parts of the CTV that are located close to OARs. For some geometries in which the CTV is located close to a specific OAR it is simply impossible to achieve sufficient dose coverage of the target without inducing a too high probability of complications using either of the two previously mentioned treatment planning approaches. The best thing to do under these circumstances is to maximise the probability of tumour control within the boundaries set for the normal tissues. The use of dose-population histograms, as described by van Herk et al. [39,40] and in Chapter 5, is very helpful in evaluating treatment plans, especially if dose inhomogeneity in the target volume is allowed.

Using inverse planning for optimisation of treatment plans without a constraint on the minimum dose in the target volume, each treatment plan in the optimisation process has to be assessed with respect to TCP and NTCP. Because the prescribed dose is an optimisation parameter, optimisation needs to be performed in a relative way, i.e. with the dose normalized to 100% somewhere in the tumour. Dose constraints and dose-volume constraints need to be relative as well. After each step in the optimisation, the prescribed dose is determined in such a way that for at least one OAR the tolerance criterion is just met. Next, the dose distribution is blurred for random errors breathing motion and the EUD- or TCP-population histogram of the CTV is determined by means of simulation of all uncertainties in location of the tumour [39]. In the simulation, data for a specific patient regarding tumour motion and set-up uncertainties are used as far as they are known. Respiration-induced tumour motion can, for example, be measured prior to treatment planning. For unknown data, e.g. the systematic set-up error, the characteristic distribution of the patient population parameters will have to be used. Depending on which OAR is limiting the escalation of the prescribed dose, optimisation criteria need to be altered in order to try and improve the treatment plan.

- If a serial organ like the spinal cord is the limiting OAR, one might consider a different choice of beam angles or set a more strict dose limit for this organ in order to allow an increase in prescribed dose as far as this organ is concerned.
- If an organ with a dose-volume constraint like the oesophagus is the limiting OAR, one might set a more strict dose-volume constraint or re-optimise the plan using different beam angles.
- If the mean lung dose is the limiting OAR, it can be beneficial to reduce the field sizes in a direction where a relatively low gradient in the iso-contours exists. Although the reduction in relative dose to the tumour will thus be limited there is, however, no guarantee that this reduction will be compensated by the complementary increase in prescribed dose.

4.1.4 Summary of treatment planning approaches

In this section the main differences between the different treatment planning approaches described in the previous sections are highlighted.

**Classical approach:**
A certain dose level is prescribed by the clinician. In treatment planning, the 95 % isodosse level is conformed to the PTV, which is a static geometrical structure. The PTV is also used for treatment plan evaluation. The aim with respect to the complication probability of organs at risk is to keep it within an acceptable level or even to try to minimize it for one or more organs at risk (e.g. the lung in the dose escalation study).

**Minimising complication probability:**
The clinician sets a prescription dose level but there will only be a certain probability that the tumour will be adequately covered. During treatment planning a certain dose level is conformed to a static geometrical structure but for treatment evaluation it is realised that the target volume is not stationary. The aim of treatment planning is a sufficient probability of correct target dosage while minimising the complication probability of organs at risk. The prescription dose level is representative for the dose in the target volume because only limited dose inhomogeneity is allowed in the target volume.

**Maximising tumour control probability:**
The difference with 'minimising complication probability' is that a certain maximum level of complication probability is prescribed for each organ at risk. The aim of treatment planning is to maximise the probability of tumour control within these constraints. Since very inhomogeneous dose distributions are allowed and since the prescription dose level is used as a variable in the optimisation process, it is no longer representative for the dose in the target volume. Tumour control models like the EUD and TCP are invaluable in evaluating treatment plans in this approach.
5 Can we start with IMRT of the lungs?

The current status of lung cancer treatment as used in the phase I/II dose escalation study is that no intensity modulation is applied. Prior to introducing (step-and-shoot) IMRT into the clinic, several aspects of IMRT still need to be considered.

Dose calculation algorithm:

With current generation convolution algorithms and future generation Monte-Carlo based algorithms, accurate calculation of the 3-dimensional dose distribution in the thoracic region should be possible. At the moment some simplifications are incorporated in these algorithms in order to increase the calculation speed at the expense of accuracy. These inaccuracies are, however, limited and will disappear with the future increase in computer power. A similar study as described in Chapter 2 is currently being performed for the convolution-superposition algorithms as incorporated in the ADAC Pinnacle3, CMS Focus and Helax TMS treatment planning systems. Preliminary results show very good agreement between measured and calculated dose distributions, both within the PTV and the lung.

Target volume delineation:

At The Netherlands Cancer Institute research is being performed in order to determine in what phase of the breathing cycle a representative CT-scan can be obtained. Using an ABC-device, CT-scans are gathered under breath-hold at the inhalation, exhalation and mid-exhalation point in the patient breathing cycle as well as when the patient is breathing freely. This study may lead to improved target delineation and reduction in the systematic delineation error. Also PET-imaging, which can identify regions of increased tumour activity, is used more and more in order to facilitate delineation of the target volume and to verify involvement of lymph nodes. A target delineation study has been started to gather insight in the overall accuracy of target delineation in the thoracic region.

Optimisation of a treatment plan:

Especially when allowing target dose inhomogeneity, optimisation of a treatment plan will be an elaborate process. Furthermore, computerised optimisation of treatment plans requires a score function that can be minimized. Whether to use biological parameters, physical parameters or a combination of both, still has to be investigated. Some inverse treatment planning systems are currently available that automatically optimise fluence maps for multiple beam directions using a user-defined cost function. Most of these systems use, however, a very simple dose calculation and inhomogeneity correction algorithm in the optimisation process in order to save large amounts of time. Therefore these systems are yet not very useful for inverse treatment planning in the thoracic region.

For most currently available computerized optimization algorithms, conversion of optimised fluence maps to leaf trajectories or to multiple segments that can be delivered in a step-and-shoot like way, is the final step in the optimisation process. Most difficulties concerning this conversion, due to e.g. the limitations in movement
Chapter 7

of the leaves and back-up jaws and radiation leakage through and between the leaves [e.g. 2,12,26] have been solved. However, the conversion will nonetheless introduce a difference between the optimised fluence map and the actually delivered fluence distribution. Therefore, conversion of optimised fluence maps to leaf trajectories should be taken into account during the optimization process. Most currently available computerized optimization algorithms do not have this capability.

Delivery of a treatment plan:

Intensity modulated radiotherapy can be applied using both dynamic IMRT and step-and-shoot IMRT. In step-and-shoot IMRT the requested intensity distribution of a beam is approximated by a limited number of fixed beam segments. The advantage is that the treatment plan can be considered to exist of a manageable number of conventional treatment 'fields'.

The advantage of dynamic IMRT is that it allows relatively fast delivery of highly intensity-modulated fluence profiles. However, dynamic IMRT requires more quality control than the use of step-and-shoot IMRT. It still has to be proven whether the additional gain in probability of tumour control and reduction in NTCP of organs at risk when using dynamic IMRT is worth the additional resources for verification.

Evaluation of a treatment plan:

The software that can be used to evaluate a treatment plan by means of iso-contours and dose-population histograms is still only used as a research tool. In order to have optimum benefit from intensity modulation in the clinic, such software should be available during treatment planning.

Verification:

In two other projects that are on-going, i.e. 'Dose verification and dose optimisation using portal imaging' and 'Patient set-up and treatment verification for conformal therapy using dynamic beam intensity modulation', studies are underway to design procedures for on-line verification of dose delivery using an EPID and for quality control of intensity modulated radiotherapy with respect to verification of dynamic leaf movement. It is still a question whether, and what kind of, additional quality control procedures are necessary in case IMRT is used for irradiations in the thoracic region.

6 Conclusions

In order to maximise the probability of tumour control in the thoracic region, the aim of treatment planning should be changed. Instead of prescribing dose and ensuring a homogeneous dose distribution in a static geometrical structure (i.e. the PTV), one should aim at prescribing an acceptable level of complication probability for each organ at risk and maximising the probability of tumour control of the CTV under these constraints. The increased dose levels may, however, lead to
complications, e.g. with blood vessels, that have a low occurrence when using conventional dose levels. In treatment plan design and optimisation, all possible uncertainties in location of the CTV should be taken into account. Knowledge and control of all errors, e.g. in set-up and delineation, and uncertainties, e.g. in parameters describing organ motion, is a prerequisite to allow the safe introduction of optimised treatment plans into clinical practice. An accurate dose computation algorithm, that takes into account the effects of low-density tissue on photon attenuation and secondary electron transport, is indispensable in designing these optimised treatment plans for conformal radiotherapy of NSCLC and even more so if IMRT is applied.

If the concept of dose homogeneity within the target region (i.e. the CTV) is pursued, use of IMRT to sharpen the beam fringe allows substantial reduction of field sizes and dose in organs at risk. This allows escalation of the prescribed dose, which is needed to improve local control. The benefit of IMRT to sharpen the beam fringe is reduced if an increased target dose inhomogeneity is allowed. A simple approach of reducing field sizes under constraint of a constant complication probability of the lungs allows a substantial increase in the probability of tumour control, both with and without the use of IMRT to sharpen the beam fringe. Now, use of IMRT is beneficial because it allows sparing of organs at risk other than the lungs, for instance by means of a smart choice of beam segments, rather than because it allows sharpening of the beam fringe.

The effect of respiration-induced tumour motion on the cumulative dose in the CTV is small. Control of patient breathing during irradiation only allows a minor reduction of field sizes at the tumour-lung interface because of the already shallow beam fringe. The need for controlling patient breathing during irradiation increases if IMRT is used to sharpen the beam fringe or for treatment of patients with a very large amplitude of respiration-induced tumour motion (>> 10 mm). Control of patient breathing is much more useful during CT-acquisition. This allows the acquisition of a representative CT-scan with the tumour in the average position, thus reducing the systematic delineation error. Furthermore, distortions in the CT-images are reduced.

Future investigations are aimed at using the results presented in this thesis in designing optimised treatment plans that can be used clinically. As the imaging sensitivity and specificity increase, IMRT may also be used to vary the dose distribution in the target volume(s) depending on, for instance, the relative clonogenic cell density or the level of hypoxia. Furthermore, set-up errors and patient breathing do not only influence the dose delivered to the CTV but also the cumulative dose distribution in organs at risk. This has not been taken into account in this thesis, but will be addressed in future projects.

References


