Designing IMRT for lung cancer

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Chapter 5

THE THEORETICAL BENEFIT OF BEAM FRINGE COMPENSATION AND FIELD SIZE REDUCTION FOR ISO-NTCP DOSE ESCALATION FOR LUNG CANCER

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Abstract:

*Purpose:* Because of the broad beam fringe (50% - 90%) of high-energy photon beams in low-density tissue, the use of intensity modulation to sharpen the beam fringe may be especially beneficial when irradiating lung tumors. We used a numerical simulation of geometrical errors to assess the gain in probability of tumor control by using intensity modulation to sharpen the beam fringe. This gain has been assessed under constraint of a constant complication probability of the lungs, both with and without allowing dose inhomogeneity in the target volume.

*Methods and materials:* Irradiation of a 50 mm diameter lung tumor located centrally in a lung-equivalent phantom was modeled. Treatment plans were designed, varying in number and direction of beams, with and without the use of intensity modulation to sharpen the beam fringe. Field size and prescribed dose were varied under the constraint of a constant mean lung dose (MLD), an indicator for the normal tissue complication probability of the lungs. Using numerical simulation, the effect of setup errors and patient breathing was investigated. Treatment plans were evaluated by means of the equivalent uniform dose (EUD) of the moving clinical target volume (CTV).

*Results:* When the minimum dose in the CTV is limited to 95% of the prescribed dose, the maximum EUD of the CTV using non-intensity modulated beams is 71 Gy for a MLD of 20 Gy. Using a two-segment step-and-shoot technique or a technique with an infinitely sharp beam fringe increases the maximum EUD to 87 and 104 Gy, respectively. Allowing dose inhomogeneity in the CTV by systematically reducing field sizes, the EUD can be further increased to 115 (non-intensity modulated), 113 (two-segment) and 125 Gy (infinitely sharp beam fringe), respectively. These results were obtained for non-coplanar treatment plans.

*Conclusions:* When dose homogeneity in the CTV is pursued, use of intensity modulation for sharpening the beam fringe allows a large increase in prescribed dose and therefore in the probability of tumor control. Without the dose homogeneity constraint the ratio between the probability of tumor control and NTCP of the lungs, can be further increased but the benefit of sharpening the beam fringe decreases.
Gain of beam fringe sharpening in treating lung cancer

1. Introduction

Currently applied dose levels in radiotherapy of non-small cell lung cancer (NSCLC) result in a poor clinical outcome (1-3). An increase in prescribed dose while maintaining dose homogeneity over the target volume is expected to improve tumor control. A strategy of dose-escalation is, however, limited by toxicity of organs at risk like the heart, spinal cord, esophagus and lungs. The dose in most of these normal tissues can be limited using 3-D treatment planning and choosing angles of beam incidence avoiding these organs at risk. The lungs, however, are an organ at risk that surrounds the target. To reduce the normal tissue complication probability (NTCP) of the lungs, for which the mean lung dose (MLD) is an estimate (4), a strategy of reduction of field sizes needs to be pursued. Intensity modulated radiotherapy (IMRT) may provide the means for such a field size reduction.

Mohan et al. (5) showed that, for a prostate treatment, a sharp increase in fluence near the field edge allows the reduction of margins between target volume and field edge while improving target dose homogeneity and reducing the dose in organs at risk. This method of intensity modulation could be especially useful for field size reduction in lung cancer treatments because of the broad beam fringe (distance between 50% and 90% isodose level) in low-density lung tissue (6-11). Without the use of intensity modulation, this broad beam fringe necessitates the use of large margins between the target volume and the beam edge, leading to a high dose in organs at risk thus limiting dose-escalation.

Lind et al. (12) described a method of incorporating random uncertainties in patient alignment into the desired shape of the dose distribution in the target volume. This method resulted in beams that were either not intensity modulated but considerably widened, or slightly widened and overcompensated near the beam edges. The latter method is advantageous for lung cancer treatments, since it not only corrects for patient mis-alignment but also for patient breathing during irradiation. Furthermore, overcompensation at the beam edges leads to a sharpened beam fringe.

Some groups have reported on the reduction of lung dose using step-and-shoot IMRT techniques using either a treatment planning (13,14) or an experimental approach (15,16). In these studies, however, the aim was coverage of the planning target volume (PTV) with a selected isodose level (i.e. 95%) in order to ensure a homogeneous dose in the CTV. In a previous study we described the feasibility of escalating the probability of control of lung tumors by allowing a larger target dose inhomogeneity (17). In that study we modeled a non-intensity modulated AP-PA irradiation of a lung tumor. Tumor movement, characterized by set-up errors and patient breathing was taken into account through numerical simulation. We showed that by reducing field sizes, the prescribed dose could be increased under constraint of a constant mean lung dose (MLD), leading to an increase in the probability of tumor control despite the increase in target dose inhomogeneity. This approach of field size reduction in combination with escalation of the prescribed dose was also shown to be effective for a multiple beam, non-intensity modulated, co-axial irradiation of a non-small cell lung cancer patient.
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The simulation in this previous study represented a worst case scenario because tumor movement was assumed to be in a direction perpendicular to the central beam axis, i.e. in the direction of the penumbra region of both beams in the treatment plan. In a multiple beam (non-coplanar) treatment plan, this is hardly ever the case. In the present study we will simulate irradiation of a lung tumor for multiple non-coplanar beams with and without intensity modulation. The aim of this work is to show the maximum gain in the probability of tumor control achievable by using intensity modulation to sharpen the beam fringe and to counter the effects of tumor motion, instead of using non-intensity modulated fields for the irradiation of lung tumors. Geometrical errors were taken into account by numerical simulation using a distribution of random and systematic errors. The prescribed dose was varied as a function of field size with a constant NTCP of the lungs as a boundary parameter.

Figure 1: Cross-section of the inhomogeneous phantom in a schematic way simulating a spherical tumor in lung for a six field co-axial irradiation. The thick dashed line indicates the extension of the lung volume, which is constant for all treatment plans. The central gray area indicates the GTV. Also indicated is the expansion of the GTV into a CTV.
2. Methods and materials

2.1. The phantom

In Figure 1 a cross-section of the virtual phantom is shown. The phantom consists of a spherical tumor located centrally in a spherical lung volume with a diameter of 190 mm which is indicated by the thick dashed line. The gray areas indicate tissue with unit density, the central white area indicates lung tissue. For each change in the number and direction of beams in a treatment plan the outer contour of the phantom is reshaped in such a way that any beam is incident on a perpendicular surface while the lung volume is identical for all treatment plans. This may seem somewhat artificial. The emphasis of this study is, however, on the improvement in dose to the tumor when using intensity modulation to sharpen the beam fringe. The phantom geometry as shown in Figure 1 is for a six field coplanar irradiation. The gross tumor volume (GTV), indicated by the solid circle at the center of the phantom, has a diameter of 50 mm. The GTV is expanded with 5 mm into a clinical target volume (CTV), according to clinical practice at The Netherlands Cancer Institute. The relative clonogenic cell density was assumed to be unity inside the GTV, and a factor of 10 lower in the region from GTV-edge to CTV-edge. We are not using the PTV-concept and therefore did not delineate a PTV, but instead evaluate the dose to the moving CTV, as explained in our previous study (17).

2.2. Treatment plan design

Dose distributions in the phantom were reconstructed for a large variety of treatment techniques. The plans differed in the number of beams, field sizes, and the use of intensity modulation or not. For each treatment plan the isocenter and ICRU reference point were located at the geometrical center of the phantom. The treatment plans can be summarized as follows:

- **Irradiation techniques**: Either the use of non-intensity modulated fields (indicated as the OPEN-technique), use of non-intensity modulated fields in combination with a single segment in order to sharpen the beam fringe and increase the dose near the beam edge (indicated as the SEGMENT-technique) or the use of a hypothetical beam profile with an infinitely sharp beam fringe (indicated as the SHARP-technique).

- **Number of beams**: 2, 3, 4 or 6 uniformly angled coplanar beams, or a 4-field non-coplanar `box` technique (Couch at 0°, gantry at 140° and 220°; couch at 90°, gantry at 40° and 320°). All fields in a single treatment plan have the same size and shape.

- **Field sizes**: Varying between 60 and 110 mm in diameter, with a step size of 2 mm.
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Although it is impossible to actually create a dose profile with an infinitely sharp beam fringe (i.e. a beam fringe width of 0 mm) in a patient or a phantom, use of this profile will provide insight into the maximum gain achievable by sharpening the beam fringe. For both the SEGMENT and the SHARP-technique, the dose near the field edge was raised to a level higher than the prescribed dose to compensate for the effects of random set-up errors and patient breathing on the dose in the CTV. This is a combination of the two approaches of intensity modulation as suggested by Mohan et al. (5) (sharpening of the beam penumbra) and Lind et al. (12) (increase of dose near the field border). In our work this combination is not only evaluated for respiration-induced tumor motion and random errors, but also for a probability distribution of systematic errors.

Figure 2: Dose profiles for: a) a non-intensity modulated field; b) a non-intensity modulated field with increased dose at the beam edge; c) a hypothetical intensity modulated field with an infinitely sharp beam fringe. The dose profiles are through the beam isocenter and have been normalized at the center of the beam. The dashed line in each graph represents the dose profile when blurred for both random setup errors (1 SD = 3 mm) and patient breathing (breathing amplitude; 10 mm peak-to-peak).
Gain of beam fringe sharpening in treating lung cancer

The four field non-coplanar technique is a compromise. Although using six fields a true box technique with a box-shaped high dose region can be devised, such a beam set-up will not be feasible when irradiating a patient. The four field non-coplanar technique, in which the beam axes form two x-shaped figures that are rotated 90 degrees with respect to each other, can be reproduced on a patient.

For the construction of the dose in the phantom for the OPEN-technique, we used a dose profile as measured with radiographic film for a 10x10 cm² 8 MV beam at a depth of 10 cm in cork with a 2 cm build-up layer of polystyrene (the solid line in Figure 2a). The 3-D dose distribution in the phantom for a single beam is assumed to be circularly symmetric with respect to the central beam axis. The field size is characterized by the position of the 50 % isodose level. Simulation of other field sizes could be performed by shifting the 50 % isodose level with respect to the central beam axis. The dose profile for the SEGMENT-technique (solid line in Figure 2b) is the addition of the profile used for the OPEN-technique and a profile of a 10x1 cm² 8 MV beam measured under the same conditions. The weight and position of the segment have been optimized to result in the sharpest beam fringe after blurring for random errors and patient breathing, while limiting the maximum dose of the summed profile to 107 % of the central axis dose value in order to prevent hot spots and high dose regions. In this optimum, the center of the segment was located 6 mm inwards with respect to the field edge of the conformal beam while the absolute dose at the segment center was 20 % of the dose on the central beam axis of the conformal field. Using segments with widths different from 1 cm did not result in a sharper beam fringe after blurring. For construction of the dose in the phantom using the SHARP-technique, we used a hypothetical dose profile as shown in Figure 2c (the solid line). The relative dose is again 100 % at the field center with an increase in dose near the field border, which is again limited to 107 %. The width of 1 cm of the area of increased dose was chosen to be the same as the optimal width of the SEGMENT-technique.

Some assumptions were made in creating the dose distribution for either irradiation technique. A constant dose gradient in the direction parallel to the central beam axis was assumed. For a phantom with a density of 0.25 g/cm³ with a 2 cm build-up layer (density 1 g/cm³) and a 10x10 cm² 8 MV beam at an SSD of 88.5 cm, the dose gradient at the isocenter is about 2.8 % per cm. For simplicity we assumed non-divergent beams. In our simulations we neglected build-up and build-down effects at the interface of tumor and lung and assumed the dose gradient in the tumor to be equal to the dose gradient in the lung. This will lead to a small inaccuracy in our calculations. Although presence of the unit density GTV in low-density lung will influence the dose distribution in the CTV, this effect is small. In a previous study we showed that, for a systematic set-up error of 10 mm, the inaccuracy in the calculated EUD of the CTV is less than 0.5 % when assuming that the dose distribution is invariant to tumor movement (18).
2.3. **NTCP of the lungs**

The mean lung dose (MLD) can be used as an indicator for the probability of radiation pneumonitis (4). We used this MLD as a boundary parameter for dose-escalation when reducing field sizes. The relative MLD (rMLD, relative to the prescribed dose in the ICRU reference point) for a specific field size and irradiation technique (either OPEN, SEGMENT or SHARP) was calculated over the lung volume, excluding the GTV. With the rMLD, the prescribed dose for a specific field size was chosen to result in a MLD of 20 Gy. This value results in a predicted NTCP of about 10 % (4). Beyond this value the dose-effect relation rises rapidly. Because of the symmetry of the phantom, the rMLD is independent of the number of beams used and is only dependend on field size. Thus, increasing the number of beams does not influence the prescribed dose, but it may lead to a more homogeneous dose in the target volume.

One might expect that the assumption of a constant dose gradient in the direction parallel to the central beam axis, i.e. no increased attenuation in the GTV due to its higher density, will influence the MLD. To test to what extent this is the case, the phantom geometry was reproduced in the Pinnacle TPS\(^1\) and the rMLD was calculated for different field sizes with a tumor density of either 0.25 or 1.0 g/cm\(^3\). The difference was within a few percent for the smallest field sizes and rapidly decreasing with increasing field sizes.

![Figure 3: Respiration-induced tumor displacement in the cranial-caudal direction as a function of time during the breathing cycle (20).](image)

2.4. **Breathing motion and setup errors**

Clinically relevant values for the tumor motion parameters were extracted from data gathered at our institution. The 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 (17). For the systematic component these values are: 1.5, 1.8 and 1.3 mm (1 SD), respectively after application of our correction protocol (19). By adding an assumed

\(^1\) ADAC Laboratories, version 5.2g
2.5 mm standard deviation in systematic errors due to other sources (i.e. GTV delineation and tumor motion during CT-scanning), these values become: 2.9, 3.1 and 2.8 mm, respectively.

Furthermore, we assumed tumor motion due to patient breathing with a peak-to-peak movement of 10 mm to be in the cranial-caudal direction only, i.e. in the direction perpendicular to the central beam axes in the co-axial treatment plans. This amplitude of breathing motion is typical for middle lobe tumors, as found at The Netherlands Cancer Institute. The displacement of the tumor during a breathing cycle is asymmetric as a function of time (20) and was simulated by

\[ d_{\text{breath}}(t) = \cos^6(t) - 0.31 \]  

with \( t \) time and \( d_{\text{breath}}(t) \) the displacement in cm from the mean tumor position at time \( t \) (Figure 3). The offset ensures that the mean tumor position is zero.

### 2.5. The concept of equivalent uniform dose (EUD)

For evaluation of a treatment plan we used the minimum dose in the CTV as well as the EUD-concept according to the formula provided by Niemierko (21):

\[
EUD = \frac{D_{\text{ref}} \ln \left( \sum_i V_i \rho_i S_{F_2}^{\alpha/D_{\text{ref}}} \left( \sum_i V_i \rho_i \right) \right)}{\ln SF_2}
\]  

Summation is performed over all voxels \( i \) in the CTV, with \( V_i \) the volume of voxel \( i \) receiving a dose of \( D_i \) and \( \rho_i \) the clonogenic cell density. The reference fraction dose, \( D_{\text{ref}} \), is 2 Gy and \( SF_2 \), the surviving fraction of clonogenic at this reference dose, is set to 0.5.

The EUD is defined in such a way that homogeneous irradiation of a target volume with this EUD results in the same clonogenic cell kill as irradiation of the target volume with the inhomogeneous dose distribution represented by the DVH. The EUD model is closely related to the TCP model developed by Webb and Nahum (22). The TCP of a DVH is the same as the TCP of the EUD of that DVH.

When comparing two different DVHS, the corresponding TCP-values will give an estimate of the difference in tumor control probability, provided one knows the initial number of clonogenic cells and the linear term in the linear-quadratic model of cell survival, \( \alpha \) (23). The difference in EUD between the two different DVHS is approximately the escalation in prescription dose necessary, in order to increase the clonogenic cell kill of the plan with the lowest TCP to the clonogenic cell kill of the plan with the highest TCP. Thus, an increase in EUD represents an increase in clonogenic cell kill and thus an increase in the probability of tumor control.
2.6. The simulation

Each treatment plan (differing in either treatment technique, number of beams, field size and corresponding prescribed dose) was assessed with respect to the probability of tumor control using in-house software developed by the group of van Herk and colleagues (24). With this software, numerical simulation of random errors and patient breathing is used to blur the dose distribution. After blurring the dose distribution, systematic errors are simulated by taking 5000 random samples from the distribution of systematic errors as determined for a previously treated patient population. For each systematic displacement of the tumor with respect to the blurred dose-distribution, we determined the dose to 104 points, randomly positioned inside the CTV. This data was used to determine the minimum dose in the CTV and the EUD of the CTV.

It is important to notice that for our simulation the probability for an EUD to occur is equal to the probability of the corresponding systematic setup error, which is known from the distribution of systematic setup errors of the patient population. In other words, the probability distribution of EUDs is found from the probability distribution of geometric errors. Using the 5000 EUD values that are calculated for a treatment plan, it was possible to create an EUD-population histogram. This histogram expresses the probability that a particular patient will receive a certain EUD for the designed treatment plan, given the distribution of systematic set-up errors. Population histograms for the minimum dose in the CTV were determined in a similar fashion.

3. Results

3.1. Dose blurring

In Figure 2a, dose profiles are shown for a single non-intensity modulated field in the cranial-caudal direction, either unblurred (static tumor) or blurred as a function of random set-up errors and patient breathing. In Figures 2b and c, similar dose profiles as presented in Figure 2a are shown for the SEGMENT- and SHARP-technique, respectively. Although we assumed an infinitely sharp dose gradient at the beam edge for the SHARP-technique, both random set-up errors and patient breathing cause blurring of the 3-D dose distribution in the patient. This leads to a less steep dose gradient as 'experienced' by the tumor. It is clearly seen that the difference between the blurred and unblurred profile is greater for the SEGMENT-technique and the SHARP-technique when compared with the OPEN-technique, especially when looking at the position of the 95% isodose level with respect to the field edge (50% isodose level). The effect of blurring is small for the OPEN-technique because the dose gradient is already shallow without the occurrence of patient breathing and setup errors due to the presence of low-density material.
3.2. **Escalation of the prescribed dose**

If the field diameter is decreased, the prescribed dose can be escalated while maintaining a constant mean lung dose. Because the fields are circular and because the GTV is excluded from the computation of the rMLD, a reduction in field diameter leads to a reduction in rMLD which is more than proportional to the reduction in field diameter. Therefore, for fields of 60 mm diameter, the prescribed dose can be more than 200 Gy for the SHARP-technique, compared with a dose of about 80 Gy for fields of 92 mm in diameter (Figure 4). For the SEGMENT-technique, addition of the segment to the non-intensity modulated field does not change the location of the 50% isodose level but increases the dose near the edge of the field. This means that addition of the segment leads to an increase in rMLD for a certain field size when compared with the OPEN-technique. Hence the lower prescribed dose as a function of field size.

![Graph showing prescribed dose as a function of field size](image)

*Figure 4: Prescribed dose as a function of field size under constraint of a constant mean lung dose when using non-intensity modulated fields (solid line), non-intensity modulated fields in combination with a single segment near the edge of the non-intensity modulated field (dotted line) or when using of a hypothetical beam profile with an infinitely sharp beam fringe (dashed line).*

3.3. **EUD and minimum tumor dose as a function of field size**

As an example, dose-population histograms are shown for three different treatment plans using the OPEN-technique and a field size of 70 mm diameter in Figures 5a and b. For this field size, the prescribed dose is about 145 Gy. The shape of the EUD-population histogram (Figure 5a) depends on the number and
direction of the beams in a treatment plan. In Figure 5b, dose population histograms of the minimum dose in the CTV are shown for the same treatment plans. Similar to the situation for the EUD, the probability of a certain minimum dose depends on the number and direction of beams in the treatment plan. Because of the small field size of 70 mm diameter, the minimum dose in the CTV, which has a diameter of 60 mm, can drop to very low values. This reduction mainly depends on the magnitude and direction of the systematic error. In a similar way, dose population histograms are constructed for other techniques and field sizes.

Figure 5: Dose-population histograms of: a) the EUD of the CTV; b) the minimum dose in the CTV. Histograms are for the OPEN-technique for three different beam setups. Histograms are for a field size of 70 mm diameter, which corresponds with a prescribed dose of 145 Gy. The horizontal lines indicate the 90% probability level.
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From the dose-population histograms we extracted the EUD- and 'minimum dose'-value with a 90% probability. In Figure 6 these values are shown as a function of field size for the OPEN-technique and the SHARP-technique for some treatment plans that have been simulated.

![Graphs showing prescribed dose, EUD of the CTV and minimum dose in the CTV as a function of field size for several beam setups for both the OPEN (non-intensity modulated fields) and SHARP-technique (infinitely sharp beam fringe). Plotted values are for a probability level of 90%, taking into account respiration-induced tumor motion, random errors and systematic errors.](image)

Figure 6: Prescribed dose, EUD of the CTV and minimum dose in the CTV as a function of field size for several beam setups for both the OPEN (non-intensity modulated fields) and SHARP-technique (infinitely sharp beam fringe). Plotted values are for a probability level of 90%, taking into account respiration-induced tumor motion, random errors and systematic errors.
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The two upper frames show the result for irradiation with two parallel opposing beams. For both techniques the prescribed dose, EUD of the CTV and minimum dose in the CTV at 90 % confidence are shown. Although the prescribed dose increases continuously with decreasing field size (Figure 4), both the EUD and the minimum dose at 90 % probability have a maximum value. The maximum achievable EUD is larger for the SHARP-technique when compared with the OPEN-technique. Furthermore, the EUD decreases more rapidly for the SHARP-technique if too small field sizes are chosen, i.e. field sizes smaller than the optimum field size. The shape of the EUD-curve is closely related to the minimum dose in the CTV, as can be deduced from the resemblance in shape between the EUD-curve and the minimum dose-curve for small field sizes. The other frames in Figure 6 show similar graphs for other field setups. The curves for the 3 and 6 fields co-axial treatment plans are almost identical to the curves for the 4 fields co-axial treatment plans and are therefore not shown in Figure 6. The curves for the SEGMENT-technique are also not shown in Figure 6, but the most important results are given in Table 1.

Table 1: Maximum EUD of the CTV for three irradiation techniques (OPEN, SEGMENT and SHARP) with and without the dose homogeneity constraint that 90 % of the patients receives a minimum dose in the CTV of 95% of the prescribed dose. The maximum values are achieved by choosing optimum field sizes under constraint of a constant mean lung dose of 20 Gy.

<table>
<thead>
<tr>
<th># beams (direction)</th>
<th>OPEN no constraint (Gy)</th>
<th>SEGMENT no constraint (Gy)</th>
<th>SHARP no constraint (Gy)</th>
<th>OPEN 95% minimum dose (Gy)</th>
<th>SEGMENT 95% minimum dose (Gy)</th>
<th>SHARP 95% minimum dose (Gy)</th>
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</thead>
<tbody>
<tr>
<td>2 (co-planar)</td>
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<td>97</td>
<td>110</td>
<td>60</td>
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<td>94</td>
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<tr>
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<td>115</td>
<td>62</td>
<td>82</td>
<td>97</td>
</tr>
<tr>
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<td>102</td>
<td>114</td>
<td>61</td>
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<td>97</td>
</tr>
<tr>
<td>6 (co-planar)</td>
<td>100</td>
<td>102</td>
<td>115</td>
<td>62</td>
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</tr>
<tr>
<td>4 (box)</td>
<td>115</td>
<td>113</td>
<td>125</td>
<td>71</td>
<td>87</td>
<td>104</td>
</tr>
</tbody>
</table>

3.4. The benefit of beam fringe sharpening

The benefit of sharpening the beam fringe depends on the constraints that are used in the design of a treatment plan. In Table 1, the maximum achievable EUD is listed for all treatment techniques both without constraints on the dose homogeneity in the CTV and with the constraint that 90 % of the patients receives at least 95 % of the prescribed dose while limiting the maximum dose to 107 %. In Table 2, the field sizes are given that correspond with the maximum EUD-values as shown in Table 1. The values for the EUD without the dose-homogeneity constraint are the maximum values of the EUD as a function of field size, i.e. the maximum of the EUD curves such as shown in Figure 6 (EUD_{max}). With the dose homogeneity constraint, the EUD values were determined from the same graphs.
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Table 2: Optimum field diameters with respect to a maximum EUD of the CTV, for three irradiation techniques (OPEN, SEGMENT and SHARP) with and without the dose homogeneity constraint that 90% of the patients receives a minimum dose in the CTV of 95% of the prescribed dose. The values shown are rounded to the nearest even number.

<table>
<thead>
<tr>
<th># beams (direction)</th>
<th>OPEN constraint (Gy)</th>
<th>SEGMENT constraint (Gy)</th>
<th>SHARP constraint (Gy)</th>
<th>OPEN minimum dose (Gy)</th>
<th>SEGMENT minimum dose (Gy)</th>
<th>SHARP minimum dose (Gy)</th>
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As can be seen in Table 1, the use of the SHARP-technique leads to the highest EUD$_{\text{max}}$ for each combination of beams in the treatment plan. Use of the SHARP-technique also results in the maximum EUD values if the dose homogeneity constraints of the CTV are applied. The difference between using the SEGMENT- and OPEN-technique is on average 19 Gy and 1 Gy with and without the homogeneity constraint, respectively. Between the SHARP- and OPEN-technique the differences are 34 Gy and 14 Gy, respectively. For the treatment plans that result in the highest EUD$_{\text{max}}$, i.e., the 4 field box technique, the difference is only 10 Gy. With the homogeneity constraint, the SEGMENT-technique results in EUD-values that are considerable higher than when using the OPEN-technique, but also considerably lower than when using the SHARP-technique, having an infinitely steep beam fringe. Without the dose homogeneity constraint, however, the SEGMENT-technique results in more or less similar EUD-values as the OPEN-technique. The SHARP-technique still leads to a much higher maximum in the EUD.

4. Discussion

The possibility of dose escalation using intensity modulation to sharpen the beam fringe and to compensate for random errors and respiration-induced tumor motion has been assessed for irradiation of lung tumors by means of a numerical simulation using an inhomogeneous phantom. The simulation was performed using a basic tumor geometry and some simplifications regarding the dose calculation were applied. In our simulation a constant mean lung dose, a parameter indicating the probability of radiation pneumonitis (4), was used as a boundary condition for escalation of the prescribed dose while systematically reducing field sizes. This reduction in field sizes leads to an increase in dose inhomogeneity in the target...
volume. However, although the minimum relative dose (relative to the prescribed dose) decreases, the minimum absolute dose increases because of the large increase in prescribed dose, as indicated in a previous study (17).

4.1. The simulation

Blurring the dose distribution for random errors and patient breathing was performed by means of convolution, i.e. we assumed that the number of treatment fractions was infinite. Some authors, e.g. Craig et al. (25), argue that the limited number of fractions that is delivered to a patient in clinical practice may have consequences for the probability of tumor control. Others, e.g. McCarter et al. (26), demonstrate that a convolution-based method to take random variations into account is a valid approach as long as more than 15 fractions are given. This constraint is easily met for curative irradiation of NSCLC patients. It is, however, not valid when very large dose gradients are present. For our SHARP-technique the dose gradient is infinite and blurring for different sets of an equal number of random errors leads to different dose distributions. To investigate the effect of a limited number of fractions, we repeatedly blurred the dose profile of the SHARP-technique with 40 random setup errors. This results in a variation in blurred profiles as shown in Figure 7. We assumed that the differences between the 5 profiles shown are small enough to be able to use convolution for our study. This may lead to a small error in the data presented in this study.

For evaluation of our treatment plans we use the EUD model which has not yet been validated. In our study, however, the minimum absolute dose in the CTV increases also with decreasing field size. For the plan with the highest EUD, the minimum dose in the CTV is even larger than the maximum dose of the treatment plan in which dose inhomogeneity in the CTV is limited to -5%. For such a situation, a tumor control probability model is not needed to appreciate which plan will result in the highest probability of controlling the tumor. In our simulation, the surviving fraction at the reference dose of 2 Gy, was set to 0.5. Although this value is debatable, the EUD is rather insensitive to changes in the surviving fraction. Furthermore, there is no definite clinical knowledge about the clonogenic cell density in the rim of the CTV. Our assumption that this clonogenic cell density is ten times lower than in the GTV may be either an overestimate or an underestimate. We repeated the simulation for different values of the surviving fraction (over a range of 0.3 to 0.7) and for different values of the clonogenic cell densities in the rim of the CTV (over a range of 1 to 0.001 times the cell density in the GTV). The EUD-curves retained a maximum but the value and position of this maximum could change.

Some authors use the lung volume receiving a dose of more than 20 Gy as a parameter in estimating the complication probability of the lung (27). Repeating our simulations with this parameter as a boundary constraint instead of the MLD, has shown that in this case the prescribed dose can also be escalated when reducing field sizes. Although the prescribed dose for each field size will differ from the values shown in Figure 4, the global shape of the EUD-curves remains the same, i.e. they all have a maximum.
In our previous study (17) we argued that the AP-PA irradiation used was a worst case scenario because tumor movement was assumed to be perpendicular to the central beam axis of both beams in the treatment plan. The data in Table 1 supports this assumption.

4.2. The benefit of beam fringe sharpening for lung tumor irradiation

Previous studies, e.g. (13-16), have already demonstrated the feasibility of using intensity modulation for sparing organs at risk and thus allowing dose-escalation in the treatment of lung tumors. These approaches were focused on achieving a homogeneous dose distribution in the PTV (and therefore in the CTV). In accordance with these studies, our approach also shows a large gain in the probability of tumor control when using intensity modulation, if one aims at dose homogeneity. When the dose homogeneity constraint is abandoned, tumor control can be increased further, but the difference between the use of intensity modulation to sharpen the beam fringe and the use of classical non-intensity modulated fields, decreases (Table 1). With the dose homogeneity constraint, the difference between the three techniques (OPEN, SEGMENT and SHARP) is due to the fact that sharpening of the beam fringe allows reduced field sizes while maintaining target dose homogeneity. For the four field non-coplanar technique, the optimum field sizes for the OPEN-, SEGMENT- and SHARP-technique are 96, 84 and 80 mm diameter, respectively (Table 2). The reduced field sizes allow a large increase in prescribed dose, resulting in an increased probability of tumor control. Without the dose homogeneity constraint, the difference in optimum field sizes, and therefore the difference in prescribed dose, reduces. Now, optimum field sizes are 68, 70 and 74 mm diameter for the OPEN-, SEGMENT- and SHARP-technique, respectively. Without the dose homogeneity constraint, sharpening of the beam fringe leads to a gain in EUD because the minimum dose in the CTV is raised, i.e. there is less target dose inhomogeneity. The extra segment near the beam edge for the SEGMENT-technique also leads to an increase in relative minimum dose in the CTV with respect to the OPEN-technique. This extra segment, however, also leads to an increase in dose in the lungs which necessitates a reduction in prescribed dose counteracting the effect of the increase in relative minimum dose.

The benefit of using additional beam segments to increase the dose at the beam edges is almost negligible when allowing dose inhomogeneity in the CTV. This benefit may, however, increase for the co-axial treatment plans if these segments are only applied to the cranial and caudal edges of the beams (16). Such an approach, i.e. no segments in the lateral direction, allows an increase in prescribed dose that may outweigh the increase in target dose inhomogeneity.

It is remarkable to notice that the maximum EUD for coplanar treatment plans, using either the OPEN-, SEGMENT- or the SHARP-technique, is similar when using 3, 4 or 6 beams. Apparently, for our symmetrical phantom, the dose distribution that can be created using three equi-angled fields, can hardly be 'improved' when using more beams. For the more complex density distribution in a NSCLC patient, this need not be the case.
Chapter 5

Allowing non-coplanar beam incidences may lead to an increase in the probability of tumor control (Table 1) with respect to the use of multiple coplanar fields, as is also indicated in other studies, for instance by Graham et al. (28). For the coplanar treatment plans, the minimum dose drops because of a reduction in minimum dose in the CTV due to too small field sizes in the cranial-caudal direction, i.e. the region where all beam penumbrae overlap. Using non-coplanar beam incidences, there is no region for which all beam penumbrae overlap. This leads to an elevated minimum dose in the CTV over an increased range of field diameters (Figure 6) when compared with the coplanar treatment plans. The use of non-coplanar treatment planning furthermore allows more sparing of other organs at risk like the heart, esophagus and spinal cord. Non-coplanar treatment planning may, however, also introduce an extra uncertainty because of inaccuracies in patient position due to rotation of the couch. These extra uncertainties in patient set-up may compromise the benefit of non-coplanar treatment planning. However, using the methods described in this paper, the effect of these extra uncertainties can be investigated if enough data become available.

We have shown that the use of very small field sizes leads to a more pronounced decrease in EUD and minimum dose when using intensity modulation to sharpen the beam fringe (Figure 6). This can be explained by the steep dose gradient at the beam edge which leads to a more rapid decrease in the minimum dose in the CTV when the field sizes are too small. As long as the CTV-edge is not too close to a beam edge, use of intensity modulation to sharpen the beam fringe leads to a high minimum dose in the CTV. However, the minimum dose in the CTV will drop severely when the CTV approaches the beam edge.

Underestimation of tumour motion parameters as well as a choice of too small field sizes for a known combination of tumor motion parameters leads to a reduction in EUD and minimum dose with respect to the optimum. This reduction is more pronounced both when intensity modulation is used to sharpen the beam fringe and when dose inhomogeneity in the target volume is allowed. This indicates that the importance of patient setup verification, e.g. using portal imaging, increases when either approach is used to spare the lungs.

Both random set-up errors and patient breathing lead to blurring of the dose distribution, which is more severe with an increasing sharpness of the beam fringe prior to blurring and hardly important for the shallow beam fringe of a high energy beam in low-density lung tissue (compare the difference between the unblurred and blurred profiles in Figure 2). Control of patient breathing during irradiation, e.g. (29-31), or a strategy of tumor tracking (32) is therefore not very useful when the tumor is entirely surrounded by tissue of lung-density, except when the amplitude of respiration-induced tumor motion is much larger than 10 mm (18) or when intensity modulation is used to sharpen the beam fringe. This exception especially holds when dose homogeneity in the CTV is pursued, since then the effect of the change in the high dose region (i.e. a shift in the 95 % isodose level with respect to the beam edge) as a result of random set-up errors and patient breathing, is very large. Less blurring of the dose distribution allows a large reduction in field size and sparing of organs at risk, and thus allows a large escalation of the prescribed dose.
and an increase in the probability of tumor control. Of course, tumor tracking also reduces systematic errors. This is very beneficial since any reduction in systematic errors allows the decrease of field sizes. This decrease in field size is independent of the use of intensity modulation or not.

In our simulation we did not take into account other organs at risk (OAR) that should be spared and we allowed complete freedom in directions of beam incidence. In a treatment plan of a lung cancer patient, the presence of other organs at risk will set limits on the beam directions that can be used in a treatment plan, especially if one does not use intensity modulation. Using beam intensity modulation to ‘block out’ OARs in the beam’s eye views will allow more freedom in choosing angles of beam incidence while still being able to spare organs at risk like the spinal cord and heart. Thus, when designing patient treatment plans, the benefit of intensity modulation could well be larger than the gain that can be derived from the data shown in Table 1.

4.3. Clinical implications

The results shown in this work are only an estimate of the possible gain in radiotherapy of lung cancer patients since other organs at risk, like the heart and the spinal cord, were not taken into account in our simulation. Also, in lung cancer patients the surroundings of the target volume will not be so homogeneous and symmetrical as in our phantom. Consequently it may be that the decrease in relative minimum dose in the CTV is not countered by a more than proportional increase in the prescribed dose when reducing certain field margins, e.g. for field edges that run through the mediastinum. Introduction into clinical practice of treatment planning using the approach of iso-NTCP dose escalation, in combination with intensity modulation to sharpen the beam fringe, will therefore be a trial and error process towards the optimum treatment plan. Simulation of all possible errors and uncertainties in patient setup and organ tumor motion is necessary to allow a safe introduction.

For all treatment techniques shown in this study, the optimum choice of field sizes corresponds with a very high prescribed dose. For the 4-field non-coplanar SHARP-technique for example, the optimum field sizes are 74 mm in diameter for our 60 mm diameter CTV, leading to a prescribed dose of 128 Gy while the minimum dose in the CTV at 90 % confidence is only 70 % of this value. We realize that one will be reluctant to use such high dose levels and large dose inhomogeneities for irradiation of a patient. Especially since the increased dose levels may lead to complications, for instance blood vessels, that have a low occurrence when using conventional dose levels. The results of the simulations in this study should, however, not be interpreted as absolute data but only as an upper limit of the possible gain in the probability of tumor control when using intensity modulation to sharpen the beam fringe in combination with iso-NTCP reduction of field size. The prescribed dose levels and resulting EUD-values in this study are typical for our phantom geometry, i.e. they depend on the tumor size and the symmetry of our phantom. Each patient has a different geometry, density distribution and location of the tumor with respect to the lung. Using intensity
modulation to sharpen the beam fringe for the irradiation of lung cancer patients will therefore not necessarily lead to the same high dose levels as indicated in this study. Our present study also shows the further benefit of allowing target dose inhomogeneity with respect to the probability of tumor control under constraint of a constant mean lung dose, i.e. a constant NTCP of the lungs, something already indicated in a previous study (17). The fact that an increase in dose inhomogeneity leads to increased tumor control sounds counterintuitive and one may be reluctant to let go of the old principle of 'conforming the 95 % isodose level to the PTV while limiting the maximum dose to 107 %'. However, the reduction in the minimum relative dose (relative to the prescribed dose) when reducing field sizes is countered by a more than proportional increase in the prescribed dose, leading to an increase in minimum absolute dose.

5. Conclusions

Both the use of non-coplanar treatment techniques and of intensity modulation to sharpen the beam fringe and compensate for random errors and respiration-induced tumor motion, allow an increase in the probability of tumor control for lung tumors under the constraint of a constant NTCP of the lungs. The advantage of using intensity modulation for this purpose is large when dose homogeneity in the CTV is pursued but it reduces when dose inhomogeneity in the CTV is allowed. Then, use of a single extra segment near the beam edge to sharpen the beam fringe leads to only a marginal gain in tumor control with respect to the use of non-intensity modulated beams. This signifies that, if one aims at maximizing the probability of tumour control, the largest benefit of using IMRT in the thoracic region is not because of the possibility to sharpen the beam fringe and spare the lungs, but because of the possibility to spare OARs other than the lungs.

References

Gain of beam fringe sharpening in treating lung cancer

