Designing IMRT for lung cancer
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OPTIMISING RADIATION TREATMENT PLANS FOR LUNG CANCER USING PERFUSION INFORMATION

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Chapter 6

Abstract

Purpose: To study the impact of incorporation of lung perfusion information in the optimization of radical radiotherapy (RT) treatment plans for patients with medically inoperable Non-Small Cell Lung Cancer (NSCLC).

Materials and methods: The treatment plans for a virtual phantom and for 5 NSCLC-patients with typical defects of pre-RT lung perfusion were optimized to minimize geometrically determined parameters as the mean lung dose (MLD), the lung volume receiving more than 20 Gy (V20), and the functional equivalents of the MLD and V20, using perfusion-weighted dose-volume histograms. For the patients the (perfusion-weighted) optimized plans were compared with the clinically applied treatment plans.

Results: The feasibility of perfusion-weighted optimization was demonstrated in the phantom. Using perfusion information resulted in an increase of the weights of those beams that were directed through the hypo-perfused lung regions both for the phantom and for the studied patients. For patients with one hypo-perfused hemithorax, the estimated gain in post-RT lung perfusion was 6% of the prescribed dose compared with the geometrically optimized plan. For patients with smaller perfusion defects, perfusion-weighted optimization resulted in the same plan as the geometrically optimized plan.

Conclusion: Perfusion-weighted optimization results in clinically well applicable treatment plans, which cause less radiation damage to functioning lung for patients with large perfusion defects.
1. **Introduction**

For patients with medically inoperable non-small cell lung cancer (NSCLC), local control remains poor after treatment with conventional radiotherapy doses [25] up to 74 Gy [21-23]. In the study of Martel *et al.* [18] based on tumor control probability model calculations, it was found that the dose required to achieve a better (50%) tumor control at 3 years is probably in the order of 85 Gy. Because the incidence of grade II radiation pneumonitis was found to be relatively low for prescribed standard doses up to 65 Gy [2], dose escalation studies are ongoing in our and other institutions to increase the tumor dose while keeping lung toxicity within certain limits [1,3,8,8,19,24]. In these studies two parameters are used to estimate the incidence of radiation pneumonitis for a patient and to guide optimization of the dose-distribution. The first parameter uses the mean lung dose (MLD) and the second the relative volume of lung receiving more than 20 Gy (V20) [7]. The parameters to estimate the incidence of radiation pneumonitis from the MLD and the V20 are based on patient data of large (multi-center) studies [7,12].

Besides the development of radiation pneumonitis, reduction in overall pulmonary function or lung perfusion due to the treatment can be a complication as well. The amount of pulmonary function loss is especially important for patients with medically inoperable non-small-cell lung cancer who often have a reduced lung function prior to treatment because of chronic obstructive pulmonary disease (COPD), intra-thoracic tumor or because they are heavy smokers. The extent of damage to the lung due to these pre-existent diseases is not always reflected in CT images. Single Photon Emission Computed Tomography (SPECT) lung perfusion scans then provide additional information in three dimensions about local functionality of lung tissue and might give additional benefit to design the plan that minimizes the complication risk for perfusion damage for an individual patient [16,17]. The effect of inhomogeneous dose distributions on lung perfusion can be predicted using a dose-effect relation for perfusion damage [26]. Changes in overall lung perfusion are correlated with reduction in pulmonary function tests for patients with breast cancer and malignant lymphoma [27,28]. The group of Marks *et al.* [15] suggested that the perfusion weighted dose-volume histogram (where the volume receiving a certain dose is weighted with the average perfusion in that dose-region) could be a valuable tool in designing the optimal RT plan.

In this paper we investigated whether the additional information of including functional information obtained by SPECT lung perfusion scans in the treatment planning process resulted in better treatment plans for patients with inoperable non-small cell lung cancer.

2. **Methods and materials**

Perfusion-weighted optimization was first simulated on a phantom as a proof of principle and then applied to a number of representative lung cancer patients.
To apply perfusion-weighted optimization, the automatic beam weight optimization method of the University of Michigan was used. With this method, a set of randomly distributed points was generated for the PTV, lung (= CT-defined lung volume minus the GTV) and spinal cord. The dose per beam was calculated in each point. To allow perfusion-weighted optimization, the dose in each of the randomly distributed points in the lung was weighted with the normalized pre-treatment perfusion of that point (see Appendix). Fast simulated annealing [14,20] was used to optimize the weights of the beams by minimizing user-defined cost functions (costlets). These costlets were composed for each relevant organ (target and organs at risk). The costlets can be defined as a function of an evaluator, such as a point in a dose-volume histogram or a dose parameter (e.g., the mean lung dose). The total cost of a certain dose distribution is then computed by summation of the costlets. The details of the algorithm are published elsewhere [10,11]. The constraints used to optimize the treatment plans for the PTV were: a minimum dose of 95 %, a maximum of 107 % and an average of 100 % of the prescribed dose (according to the ICRU [9]). When violating the constraints a proportional cost was applied. For the spinal cord the applied dose was not allowed to be higher than 50 Gy.

For a phantom and 5 patients, beam weights were optimized by (individually) minimizing 4 different lung parameters besides the constraints for the PTV and the spinal cord. These lung parameters were the mean lung dose (MLD), the relative volume of lung receiving more than 20 Gy (V20, a DVH-point), or the mean perfusion-weighted lung dose (MpLD) and the perfusion weighted volume receiving more than 20 Gy (Vp20), using perfusion-weighted dose-volume histograms. The MpLD is a measure for the perfusion damage when the local dose-effect relation for perfusion changes is linear, while the Vp20 is an approach for a step-like local dose-effect relation (see Appendix). The optimized beam weights for the different plans were re-entered into the U-MPlan treatment planning system and the full 3-D dose distribution of each optimized plan and the averaged remaining perfusion after treatment was calculated. For the phantom the dose distributions and the dose-volume parameters were compared with the treatment plan with the highest conformity.

2.1. Phantom

A virtual phantom was constructed in the treatment planning system (U-MPlan, University of Michigan treatment planning system version 339, [6]). The phantom consisted of three concentric cylinders: one inner cylinder with a radius of 2.5 cm consisting of unit density material representing a lung tumor, one with a radius of 8 cm, density 0.3 g/cm³, representing lung tissue and an outer cylinder with a radius of 10 cm of unit density representing the patient's body contour (Figure 1A).

Seven beams (8 MV) at equally spaced angles were set up around the tumor. The gross tumor volume (GTV) plus 0.5 cm margin yielded the planning target volume (PTV). All the beams could be wedged in two directions. The margin between PTV and field edge was adapted in such a way that the 95 % isodose line was fitted as close as possible around the PTV (Figures 1B and 2A). A hypo-
Perfusion-weighted optimization

perfusion region was constructed representing 29% of the total lung volume (dark grey area in Figure 1A).

![Diagram](image)

**Figure 1.** A) Cross section of the phantom consisting of three concentric cylinders: one with a radius of 2.5 cm consisting of unit density material representing the tumor, one with a radius of 8 cm, density 0.3 g/cm³, representing lung and one with a radius of 10 cm, unit density representing the patient contour. The PTV is a 0.5 cm expansion of the GTV. The right upper quarter of the lung has no perfusion (function = 0, dashed area), while the other part of the lung is functioning 100%. B) Beam setup consisting of 7 coplanar 8 MV photon beams (all may be wedged) at equally spaced angles.

### 2.2. Patients

To investigate the value of perfusion-weighted optimization for real treatment plans, we performed a planning study using chamfer matched CT and normalized SPECT lung perfusion scans [26] of patients with non-small cell lung cancer. The lung perfusion patterns of 116 patients could retrospectively be divided into 6 groups (See Results section). The subdivision in groups was based on the overall appearance of their perfusion pattern, the localization and size of the perfusion defect and the localization of the perfusion defect relative to the spinal cord. Left and right-mirrored perfusion defects were put in the same group.

The clinically applied treatment plan of a representative patient from each group was compared with perfusion-weighted optimized plans, with and without varying the number of beams and beam incidence directions. The prescription dose was 70 Gy, according to the treatment planning protocol that was used at the time these patients were treated. The beams were shaped using a multi-leaf collimator to conform field shape to the PTV in the beam's eye view. The isocenter, chosen near the center of the PTV is the ICRU reference point, which receives the prescribed dose. For the patients the dose constraint for the spinal cord of 50 Gy was included in the optimization procedure. The treatment plans created with (perfusion-
weighted) optimization were calculated retrospectively in this study. All patients were treated with conventional plans.

### 2.3. Dose calculation

CT-based dose calculations were performed as described previously [4], using a 3-D treatment planning system (U-MPlan) in which the clinically applied Octree/Edge model with tissue inhomogeneity correction (equivalent path length algorithm) is incorporated.

### 2.4. (Perfusion-weighted) dose per beam

For the phantom and all tested patients, the MLD and MpLD per single beam were calculated. These values represent the geometrical and functional usefulness of using that beam for the treatment plan: when the MLD of a beam is low compared with others, this beam irradiates a relatively small lung volume. The values for the MLD per beam are determined by the geometry of the lungs. When the MpLD of a beam is low compared with others, this beam irradiates a relatively small perfused lung volume. The values for the MpLD per beam are determined both by the geometry of the lungs and the perfusion distribution of the particular patient: when a large amount of lung is irradiated by a particular beam, but most of the lung tissue in the beam's-eye-view of that beam is not perfused, the value for the MpLD will be low.

The ratio of the MpLD and the MLD per beam indicates the gain for that beam of using perfusion information and is independent of the lung geometry. If the ratio is small, the extra perfusion information is useful, when the ratio is larger, the beam irradiates well-perfused lung and thus is not favorable. When the ratios for all beams are comparable, the perfusion-weighted optimization will not give other results than non-weighted optimization. When the ratio is small for one or more beams, the perfusion-weighted optimization will prefer the use of these beams to create an optimal plan. However, the use of less favorable beams can sometimes be necessary to create a homogeneous dose distribution in the target.

![Figure 2](image)

*Figure 2. A) Dose distribution of the plan with the highest conformity to the PTV. All beams have the same weight (no wedges); 100, 95, 50 and 29 % (20 Gy) iso-dose lines are represented (the prescribed dose is 70 Gy). B) Dose distribution optimized for the MpLD. C) Dose distribution optimized for the V20. D) Dose distribution optimized for the Vp20.*
3. Results

As a proof of principle the method of (perfusion-weighted) optimization was first applied to the cylindrical phantom (Figure 1). Optimizing the mean lung dose yielded a wide range of beam weight combinations with a varying number of beam weights equal to 0, with the same mean lung dose and a similar tumor coverage. One of the solutions was a plan with all beam weights equal to 1 (Figure 2A). Minimizing the V20 resulted in an approximation of a plan-parallel irradiation. In this dose-distribution the V20 is as small as possible (Figure 2C). The MLD for this plan is about the same as any of the plans optimized on the MLD. Because of the symmetry of the phantom, rotation of the dose distribution resulted in the same V20.

When perfusion information was considered during optimization, the choice of a certain dose distribution became better determined. The MpLD and the Vp20 were minimal in the configurations as shown in Figures 2B and D, respectively. In both cases, the beams with the highest weights were directed through the lung region that had no perfusion. The opposed beam ensured a better PTV coverage. The other beams with a smaller contribution to the absolute dose were necessary to ensure a homogeneous PTV dose. For a smaller tumor (2.5 cm diameter), similar beam weights were obtained.

Figure 3. Each patient is assigned to a group according to the characteristics of the perfusion pattern. The white ellipses represent the tumor. Group 1: hypo-perfusion at the site of the tumor (44 %). Group 2: hypo-perfusion adjacent to the tumor (5 %). Group 3: hypo-perfusion ventral of the tumor (13 %). Group 4: hypo-perfusion dorsal of the tumor (9 %). Group 5: hypo-perfusion of the entire ipsi-lateral lung (16 % of the patients). Group 6: miscellaneous (13 %): including patients with bullae and emphysema, the patterns of hypo-perfusion were inhomogeneous for these patients.

3.1. Patients

In the cylindrical phantom no other organs at risk were considered besides lung. To apply the optimization method in more realistic situations, perfusion-weighted optimization was applied to representative NSCLC-patients with different kinds of perfusion defects. The 116 patients were divided into groups according to Figure 3, based on the size and appearance of their perfusion pattern (group 1-5) and the location of their tumor with respect to the spinal cord (group 3 and 4):

Group 1: hypo-perfusion at the site of the tumor (44 % of the patients).
Group 2: hypo-perfusion adjacent to the tumor (5 % of the patients).
Group 3: hypo-perfusion ventral of the tumor (13 % of the patients).
Group 4: hypo-perfusion dorsal of the tumor (9% of the patients).
Group 5: hypo-perfusion of the entire ipsi-lateral lung (16% of the patients).
Group 6: miscellaneous (13% of the patients): including patients with bullae and emphysema. The patterns of hypo-perfusion were inhomogeneous for these patients.

From group 1 to 5, one representative patient who had an average sized tumor was chosen for perfusion-weighted optimization (Figures 4-8). For every representative patient, next to the beams of the clinically used plans (in the C panels of Figures 4-8), 2 to 4 additional beams were set up around the tumor for the optimization.

Figure 4. A) The beam set-up for a patient of group 1. All six beams could be wedged in two directions. B.) The pre-RT perfusion pattern of this patient, hypo-perfusion is present only at the site of the tumor. C) The 3 field clinically applied treatment plan, the 20, 35, 50, 66.5 (95%) and 70 Gy (100%) isodose lines are shown in solid, dashed, solid, dotted, and solid lines, respectively. The PTV and GTV are delineated in solid lines. In all figures the beam numbers of the beams that were used for the plans are indicated. D) A treatment plan optimized for the MLD. E) Including perfusion information yielded a dose distribution very similar to the plan in Figure 4D, when optimized for the MpLD. F) Treatment plan optimized for the V20. Including perfusion information did not change the dose distribution. The arrow indicates the lower conformity in the V(p)20 optimized plan.
Figure 5. A) The beam set-up for a patient of group 2. All six beams could be wedged in two directions. B) The pre-RT perfusion pattern of this patient, hypo-perfusion is present at the site of and adjacent to the tumor. C) The clinically applied treatment plan with five fields. Note the relatively high dose in the contra-lateral lung at the arrow that is reduced in the optimized plans. D) A treatment plan optimized for the MLD. Including perfusion information did not change the dose distribution. E) A treatment plan optimized for the V20. Including perfusion information did not change the dose distribution.

Figure 6. A) The beam set-up for a patient of group 3. All beams could be wedged in two directions. B) The pre-RT perfusion pattern of this patient, hypo-perfusion is present at the site and ventrally of the tumor. C) The 3-field clinically applied treatment plan. D) A treatment plan optimized for the MLD. E) A treatment plan optimized for the MpLD. F) A treatment plan optimized for the V20. Including perfusion information did not change the dose distribution. Although the dose distributions are a little different, the lung volume parameters as the M(p)LD and V(p)20 were not different for all four plans.
Figure 7. A) The beam set-up for a patient of group 4. All seven beams could be wedged in two directions. B) The pre-RT perfusion pattern of this patient, hypo-perfusion is present at the site and dorsal of the tumor. C) The 3-field clinically applied treatment plan. D) A treatment plan optimized for the MLD. Note the higher conformity to the PTV. E) A treatment plan optimized for the MpLD. The arrow indicates the higher dose in the poorly perfused area. F) A treatment plan optimized for the V20. The 20 Gy isodose line is similar to that of plan E, however, the 50 % isodose line (arrow) encompasses a much larger volume. Including perfusion information yielded the same dose distribution as Plan E.

Figure 8. A) The beam set-up for a patient of group 5. All 6 beams could be wedged in two directions. B) The pre-RT perfusion distribution of this patient, almost the entire right lung is hypo-perfused. C) The clinically applied 4-field treatment plan. D) A treatment plan optimized for the MLD. E) A treatment plan optimized for the MpLD, V20 or Vp20, these parameters yielded the same dose-distribution.
Table 1. Dose-volume parameters (in % of the prescribed dose) for the plans optimized for the different parameters for 5 patients. The parameters that were optimized are bold.

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3.1.1. Group 1

For the patient of group 1 (beam set-up in Figure 4A) with homogenous perfusion throughout the lungs and hypo-perfusion only at the tumor site (Figure 4B), all optimized plans improved compared with the clinical plan (Figure 4C) when considering all dose-volume parameters (Table 1), except for the plan optimized for the MpLD: the V20 was 1 % higher than in the clinical plan. There is, as expected, almost no difference between perfusion-weighted and MLD-optimization (Figures 4D and E). Because the hypo-perfused region is located only at the tumor site, and the mean lung dose and the mean perfusion-weighted lung dose are calculated based on the lung volume minus the gross tumor volume, the MLD and the MpLD are equal. Optimizing the V20 resulted in a different treatment plan that was more AP-PA and less conformal (see the 95 % isodose line at the arrow in Figure 4E) than the plan in Figure 4D. Including perfusion information did not alter the V20 optimized plan.
3.1.2. Group 2

The perfusion patterns of patients of group 2 show hypo-perfusion adjacent to the tumor similar to the patient shown in Figure 5. Six beams were set up (Figure 5A) around the tumor. The lateral beam directed through the hypo-perfused lung adjacent to the tumor in the clinical plan (Figure 5C, beam 3) exited in the contra-lateral (well perfused) lung (arrow). The beam incidence direction of this beam that seemed to be smart at first sight, attributed to damage to the healthy contra-lateral lung. All optimized plans improved compared with the clinical plan (Table 1). For the optimization on the MLD and the MpLD, the beam incidence directions through hypo-perfused parts of the lungs coincided with the best beam incidence directions chosen as optimal for a low mean lung dose (Figure 5D). For this patient there was very little difference between the MLD-optimized and perfusion-weighted optimized treatment plans. Using the V20 as the optimization parameter, a slightly different dose distribution was obtained (Figure 5E). The V20 of this plan was equal to that of plan D, however, the values for the MLD and MpLD are a little higher (Table 1). Optimizing on the Vp20 did not alter the dose distribution as obtained by minimizing the V20.

3.1.3. Group 3

The representative patient of group 3 (Figure 6A) had a hypo-perfused region located ventrally of the tumor (Figure 6B). The clinically used treatment plan consisted of three fields (Figure 6C). Optimization on the MLD (Figure 6D) and MpLD (Figure 6E) resulted in two plans, almost identical to the clinically used plan. Beams that were passing through a large volume of lung tissue were turned off in the optimization. The remaining 3 beams were directed through the smallest possible lung volume to ensure adequate tumor coverage and a minimal MLD and V20. Although using the perfusion information yielded a slightly different dose-distribution, the plans were identical with regard to MLD, V20, MpLD, Vp20 (Table 1) and tumor coverage.

3.1.4. Group 4

In Figure 7A seven different beam incidences are shown for a patient with a hypo-perfused posterior part of the lungs (Figure 7B). Compared with the 3 fields of the clinical plan (Figure 7C), the dose distribution optimized for the MLD (Figure 7D) is more conformal. In all optimized plans, the dose-volume parameters improved compared with the clinical plan (Table 1). When perfusion information is included in the optimization, the high dose area was transferred a little into the hypo-perfused region (Figure 7E, arrow). Optimizing on the V20 and Vp20 yielded a different dose distribution: note the 50% isodose line that encompasses a larger area than in the other dose distributions (Figure 7F, arrow).
3.1.5. Group 5

For a patient of group 5 the beam weights of 6 different beams (Figure 8A) were optimized. All the beams could be wedged in both directions. The entire right lung of this patient was hypo-perfused (Figure 8B). The left lateral beam that was used in the 4-field clinical plan (Figure 8C) was turned off in the optimization for the MLD, resulting in the dose distribution displayed in Figure 8D. Also for this patient, in all optimized plans, the dose-volume parameters improved compared with the clinical plan (Table 1). When the V20 was minimized, also the right lateral beam was turned off, resulting in plan E (Figure 7E). The V20 of plan D is 37.5 %, compared with 21.5 % in plan E. The relatively higher dose in lung tissue anterior of the tumor in plan E might intuitively appear unfavorable because it is not conformal to the PTV, but these high local doses do not contribute to a higher MLD compared with plan D. Both dose distributions resulted in almost the same MLD (26 % of the prescribed dose). Both plans have a similar tumor coverage. The maximum dose in the spinal cord remained below 50 Gy by using beam 4 in plan E.

When the 3-D perfusion information of this patient was included (the pre-RT SPECT perfusion pattern is shown in Figure 8B: the entire right lung was hypo-perfused), the lateral beams were turned off again because these beams would irradiate too much functional lung. When the remaining constraints for the PTV, spinal cord and MLD were met, a plan equal to plan E was obtained. The mean perfusion-weighted lung doses of plans D and E are 19 % and 13 %, respectively. Plan E resulted thus in the combination of the lowest MLD, the lowest V20 and the lowest MpLD with adequate tumor coverage and no violation of the spinal cord constraint for this particular patient.

The effect of plans D and E on the post-RT perfusion is visualized in Figure 9, based on two different dose-effect relations (a linear and a step dose-effect relation). The plan optimized for the MLD (plan D) resulted in a perfusion pattern with gradual perfusion damage (Figure 9A) when the linear dose-effect relation was used and in sharp edged perfusion damage when a step dose effect relation was used (Figure 9B). When plan E was applied on the pre-RT perfusion, both dose-effect relations did not lead to visible perfusion damage (Figure 9C).

3.1.6. Group 6

Because the perfusion patterns of these patients were very diverse and complex, it was not possible to select a single representative patient. Due to the inhomogeneity of the perfusion pattern of these patients, it was very difficult to select the smartest beam incidence direction prior to automatic optimization using the current methods.
3.2. (Perfusion-weighted) dose per beam

For the phantom and all tested patients, the MLD and MpLD per beam (normalized on 100 % in the isocenter) were calculated (Figure 10). For the phantom the values for the MLD per beam are equal. The values for the MpLD and the ratio between the MpLD and MLD varied with the amount of non-perfused lung in the beam's-eye-view. For the patient of group 1 the ratio did not vary more than 10 %. Only beam 6 had a small ratio. However the absolute values for the MLD and MpLD for that beam were larger than for the other beams so that in the optimization this beam will be omitted. For the patient of group 2 the ratio did not vary much for beams 1, 2, 3 and 6. Beams 4 and 5 had a high ratio, indicating that, although beam 4 was placed through the hypo-perfusion adjacent to the tumor, a relatively well perfused lung region is irradiated in the contra-lateral lung. For the patient of group 3, beams 4 and 6 had a low ratio, but also a low value for the MLD and the MpLD by itself, meaning that these beams were both geometrically as functionally advantageous. For the patient of group 4 beam 1, 2 and 5 have a lower ratio than the other beams and also the values for the M(p)LD are lower or comparable to the other beams. For this patient especially beam 5 was already preferable in the non-weighted optimization and became even more preferable when the perfusion information was included. This beam got a higher weight in the MpLD optimized treatment plan.

Although beam 5 for the patient of group 5 had a high MLD compared with the other beams, in the optimization for the MLD this beam was chosen to ensure a homogeneous irradiation of the PTV. In the perfusion-weighted optimization beam 5 was omitted and the 3 beams with the lowest MpLD/MLD ratio remained.
Perfusion-weighted optimization

Figure 10. The relative mean (functional) lung dose per beam and the ratio between MpLD and the MLD per beam for the phantom (A) and the 5 tested patients (B-F).

4. Discussion

The feasibility of using perfusion information for optimization of radiotherapy treatment plans for patients with Non-Small Cell Lung Cancer (NSCLC) has been studied in a phantom and for patients with different types of perfusion defects. Including perfusion information did not yield different treatment plans for patients with small perfusion defects. Only for the patient with one hypo-perfused hemi-
Chapter 6

Thorax, the perfusion-weighted optimization made a difference of 6% of the prescribed dose on the remaining lung perfusion after treatment.

Optimization on the MLD or the V20 yielded different dose distributions, resulting in a more parallel-opposing treatment plan for the V20 constraint, with a dose distribution that was less conformal to the PTV.

4.1. Clinical relevance and patient selection

When the treatment plans for the 5 representative patients were functionally optimized, it appeared that the functional gain for the patient was small in certain cases. Planar V/Q images, made before applying the technique, can help to select patients with one hypo-perfused lung that benefit most from the 3-D perfusion-weighted optimization.

Based on the following factors, the usefulness of perfusion-weighted optimization for an individual patient can be estimated:

4.1.1. Geometrical considerations

Lateral beams directed through hypo-perfused lung adjacent to the tumor usually exit in contra-lateral (well-perfused) lung. To take maximum advantage of the perfusion-weighted optimization, beams that only pass through ipsi-lateral (hypo-perfused) lung are preferred, for example in an AP-PA setup. However, these beams often deliver their dose to the spinal cord where the maximal prescribed dose is restricted to 50 Gy (2 Gy/fraction). One has also to consider organs at risk such as the heart and esophagus, which further limit the beam incidence directions that can be chosen. For central tumors, the beam direction with the shortest path through lung is preferred in the optimization because these beams will result in the lowest mean lung dose. This is in general coinciding with the region where hypo-perfusion is situated, as hypo-perfusion often is located distally from the (central) tumor [16,26]. For more distally located tumors, the region of hypo-perfusion is often very small and will not contribute significantly in the optimization.

4.1.2. Tumor size

Large tumors require large treatment fields and thus the damage to (perfused) lung tissue will also be large. In these cases perfusion-weighted optimization will be important in terms of functional outcome for the patient, especially because the pre-RT lung function that is reflected in the perfusion is also more likely to be reduced for patients with large tumors. When the tumor is small, both the tumor and the irradiation affect only a small part of the lungs and therefore the improvement that can be gained by perfusion-weighted optimization is of less significance for the patient.
4.1.3. Sophisticated treatment planning

If perfusion-weighted optimization can be combined with IMRT plans and non-coplanar beam incidence directions, perfusion-weighted optimization might become of more importance for the patient because it will be easier to irradiate through hypo-perfused lung regions which are situated for example in the lung apex or caudal of the tumor. For patients from group 6 with inhomogeneous perfused lungs, perfusion-weighted IMRT and inverse planning techniques may become beneficial because in each beam, segments with a different weight, based on perfusion information, can be determined.

4.1.4. Dose calculation

The Octree/Edge dose calculation algorithm incorporated in the treatment planning system used in this study does not take lateral scatter adequately into account and therefore in lung tissue the dose is not calculated correctly. This algorithm underestimates beam penumbra in lung; film measurements show a flattening of the beam penumbra [5]. This means that in the penumbra region where more than 50% of the dose is planned, a lower dose is delivered than predicted by the treatment planning system. Because the actual dose is lower in the high dose regions and on the edge of the PTV, larger fields are necessary to ensure adequate tumor coverage. Due to these larger fields the mean functional lung dose will rise and thus the gain of perfusion-weighted optimization may be of more importance for the patient. The effect of the underestimation of the beam penumbra on (perfusion-weighted) treatment optimization is the subject of future studies.

4.1.5. Pre-RT perfusion and re-perfusion

Especially for patients with an impaired lung perfusion prior to treatment it is important to consider perfusion damage during optimization of the treatment plan.

Re-perfusion, which can be caused by tumor-regression, might reduce the adverse effect of the irradiation [26]. Re-perfusion occurs even in regions where a high dose was given [26]. In the studied patient group however, the measured re-perfusion was not followed by improvement in lung function as measured with classical lung function tests [K. De Jaeger, personal communication]. Therefore re-perfusion was not considered in the perfusion-weighted optimization.

4.2. MLD vs V20

Optimization of the MLD and V20 will lead to very different dose-distributions in some cases. In the clinic, two 'schools' are present: one uses the V20 parameter [7] while the other adheres to the MLD for the estimation of the incidence of radiation pneumonitis [12]. The methods differ in the 'inferred' underlying dose-effect relation between locally absorbed dose and the development of local lung damage resulting in radiation pneumonitis. In the V20 model a step local dose-effect relation is assumed while the MLD model assumes a linear relation [13]. For the 116 NSCLC-patients in this latter study the V20 of their clinically applied treatment plan is plotted.
as a function of the MLD in Figure 11 (triangles). In this patient group the V20 is highly correlated to the MLD ($r^2 = 0.9$). The correlation between the MLD and V20 makes it difficult to discriminate between the V20 and the MLD as the best predictor for radiation pneumonitis. To be able to discriminate between the two methods, patient data are needed in which there is no correlation between V20 and the MLD. To illustrate this we have added the MLD and V20 values of plan 1 and 3 of the phantom to Figure 11. For these two plans the MLD is equal while the V20 varies substantially. To collect more clinical data for a reliable discrimination between the V20 and the MLD method, for example half of the number of patients with the same tumor location should be treated with plans optimized on the MLD and the other half with plans optimized on the V20. The reason why patients in our institution are not treated with plans optimized on the V20 is that in these plans the volume of the high dose region is not conformal enough to be clinically applicable (for example the 95 % isodose line in Figure 8E encompasses a much larger region than the 95 % isodose line in Figure 8D).

Figure 11. Scatter-plot of the mean lung dose (MLD) and the volume irradiated with more than 20 Gy (V20) of the clinical treatment plans of NSCLC-patients. The solid triangles represent patients who developed radiation pneumonitis grade 2 (SWOG) or higher. The circles represent the MLD and V20 for two different plans for the phantom. For these two plans the MLD is the same while the V20 is different.

5. Conclusion

Only for patients with a large pre-treatment perfusion defect, perfusion-weighted optimization resulted in clinically well applicable treatment plans, which would have caused less radiation damage to functioning lung, compared with treatment plans.
that were optimized on the mean lung dose and a homogeneous target dose alone. For patients with small perfusion defects, perfusion-weighted optimization yielded a treatment plan equal to the non-perfusion-weighted optimized plan. Because the gain of perfusion-weighted optimization depends on the pre-RT perfusion pattern, planar V/Q scans can be used to select patients that may benefit from 3-D perfusion-weighted optimization.

Reference List

16. Marks L.B., Spencer D., Bentel G., Ray S., Sherouse G., Sontag M., Coleman R., Jaszcza R., Turkington T., Tapson V. The utility of SPECT lung perfusion scans in minimizing and assessing...


Appendix:

To be able to include functional information in the optimization, two steps have to be taken: the first is to define a parameter, which is predictive for the functional outcome of the treatment (using for example a local dose-effect relation for changes in lung perfusion). The second is to find a way to incorporate the functional information into the optimization module.

The *mean lung dose* and the *mean perfusion-weighted lung dose* of a treatment plan can be calculated by

\[
MLD = \frac{1}{N} \sum_{n=1}^{N} D_n
\]

and

\[
MpLD = \frac{1}{N} \sum_{n=1}^{N} C_n \cdot D_n
\]

where \(N\) is the number of voxels and \(D_n\) is the local dose in voxel \(n\). \(C_n\) is the local number of perfusion counts before treatment in voxel \(n\), representing local functionality, normalized using:

\[
C_n = \frac{C_{ts_n}}{\left( \sum_{n=1}^{N} C_{ts_n} / N \right)}
\]

with \(C_{ts_n}\) the counts in voxel \(n\). In each voxel \(n\) we could predict the remaining perfusion at 3 months after treatment by calculating

\[
Perf_n^{predicted} = Perf_n^{pre} \cdot \{1 - E(D_n)\}
\]

where \(E(D_n)\) is a local dose-effect relation for perfusion damage and

\[
Perf_n^{pre} = \frac{C_n}{\left( \sum_{n=1}^{N_{wp}} C_n \right) / N_{wp}}
\]

is the local perfusion normalized on the well perfused (WP) lung region that has a perfusion better than 60% of the maximum perfusion in the lungs. The average perfusion homogeneity prior to treatment (PHpre) is the average perfusion throughout the lungs:

\[
Perf^{pre} = \frac{1}{N} \sum_{n=1}^{N} Perf_n^{pre} = PHpre
\]
The average perfusion after treatment is calculated by:

\[ PH_{predicted\ post} = PH_{pre} \cdot \left\{ 1 - E(D_n) \right\} \]

To ensure the maximum possible lung function for a patient after radiotherapy, this value should be maximized by varying the number of beams, the beam incidence directions and the beam weights. We used two different local dose-effect relations that represent extreme shapes of a dose-effect relation for perfusion damage:

1.

\[ E(D_n) = cD_n \]

which is a linear dose-effect relation. With this dose-effect relation the remaining perfusion after treatment can be calculated by:

\[ PH_{predicted\ post} = PH_{pre} \left\{ 1 - c \cdot MpLd \right\} \]

2.

\[ E(D_n) = \Theta(D_n - D_{th}) = \begin{cases} 
0 \text{ for } D_n < D_{th} \\
1 \text{ for } D_n \geq D_{th} 
\end{cases} \]

which is a step dose-effect relation with \( D_{th} \), a threshold dose of, for example, 20 Gy. For local doses less than the threshold dose there is no perfusion damage and for doses higher than the threshold dose, the local perfusion damage is 100%.

The perfusion-weighted equivalent for a threshold dose \( D_{th} \) of 20 Gy is:

\[ Vp_{20} = \frac{1}{N} \sum_{n=1}^{N} C_n \cdot \Theta(D_n - D_{th}) = \frac{pV_{D_{th}}}{V_{tot}} \]

The remaining perfusion homogeneity after treatment can be calculated by:

\[ PH_{predicted\ post} = PH_{pre} \left\{ 1 - c \cdot Vp_{20} \right\} \]

In the optimization for an individual patient \( PH_{pre} \) and \( c \) are constant, the \( MpLd \) or \( Vp_{20} \) vary, thus if \( MpLd \) or \( Vp_{20} \) are minimal, \( PH_{predicted\ post} \) is automatically maximized.