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ORIGINAL ARTICLE

Optimal beam angle selection and knowledge-based planning significantly reduces radiotherapy dose to organs at risk for lung cancer patients

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ABSTRACT

Background: Lung cancer patients struggle with high toxicity rates. This study investigates if IMRT plans with individually set beam angles or uni-lateral VMAT plans results in dose reduction to OARs. We investigate if introduction of a RapidPlan model leads to reduced dose to OARs. Finally, the model is validated prospectively.

Material and methods: Seventy-four consecutive lung cancer patients treated with IMRT were included. For all patients, new IMRT plans were made by an experienced dose planner re-tuning beam angles aiming for minimized dose to the lungs and heart. Additionally, VMAT plans were made. The IMRT plans were selected as input for a RapidPlan model, which was used to generate 74 new IMRT plans. The new IMRT plans were used as input for a second RapidPlan model. This model was clinically implemented and used for generation of clinical treatment plans. Dosimetric parameters were compared using a Wilcoxon signed rank test or a 1-sided student's t-test. $p < .05$ was considered significant.

Results: IMRT plans significantly reduced mean doses to lungs (MLD) and heart (MHD) by 1.6 Gy and 1.7 Gy in mean compared to VMAT plans. MLD was significantly ($p < .001$) reduced from 10.8 Gy to 9.4 Gy by using the second RapidPlan model. MHD was significantly ($p < .001$) reduced from 4.9 Gy to 3.9 Gy. The model was validated in prospectively collected treatment plans showing significantly lower MLD after the implementation of the second RapidPlan model.

Conclusion: Introduction of RapidPlan and beam angles selected based on the target and OARs position reduces dose to OARs.

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Lung cancer; knowledge-based planning; treatment planning; optimization; beam angle selection; IMRT; VMAT

Introduction

Radiotherapy treatment of lung cancer is challenged by high local failure and toxicity rates [1–3]. Reduction of dose to organs at risk (OARs) such as the lungs, heart and esophagus is therefore of utmost importance. Former studies have shown a high degree of variability in treatment planning depending on human skills and resources [4–7]. The dose to OARs is influenced by beam angle selection for IMRT and configuration of arcs for VMAT, respectively. Beam angles selected based on the target and OAR position in the individual patient may thus be an effective way to reduce toxicity, but not a straightforward one in the routine of a busy clinic.

In some patient groups, knowledge-based planning has been shown to result in reduced dose to the OARs [8–11] and more standardized treatment plans [4,7]. The RapidPlan model was introduced in the Eclipse treatment planning system (VMS, Palo Alto, CA) and was tested in a variety of anatomical sites and for varying treatment techniques [8]. For lung cancer, significant reduction in dose to lungs, heart and esophagus was seen by application of the RapidPlan model [9]. It semi-automates the treatment planning process based on a family of treatment plans used as input for the model. Thus, the dose to the OARs depends on the consistency and goodness of the user-supplied input to the model. Furthermore, a reliable model depends on the input plans having sufficient coverage of the anatomic variations in size and position of the target and OARs. This demands inclusion of a high number of lung cancer patients to cover the large variety in position and size of both primary and lymph node targets in locally advanced lung cancer. Since the output of the model depends on the input plans, the model should be built on plans fulfilling the clinical disease-specific recommendations. Furthermore, a possible scenario is that a sub-optimal model is obtained. Then, the question is whether it may be further improved by a second, refined family of treatment plans, possibly derived from results of the prior model. This was found in a study on head and neck cancer patients using an iterative process to obtain a refined RapidPlan model which allowed for generation of plans with improved quality [12]. In this study, we built and optimized a RapidPlan model with the aim of reducing dose to the lungs and heart. First, we investigated whether IMRT with beam

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angles selected based on the position of the target, lungs and heart or VMAT resulted in lowest dose to OARs. Second, we created a RapidPlan model using the best set of plans. Third, we tested if a consecutive refinement of the model improved its performance. Finally, the model was validated prospectively and the impact of the model on dose to OARs was quantified. Additionally, we investigated if the use of a RapidPlan model could reduce the dosimetric impact of the beam angles selected for planning.

Material and methods

Patients

CT-scans and delineations of 74 consecutive lung cancer patients treated between December 2016 and August 2017 were used to generate the RapidPlan model. The patient group included 49 NSCLC patients treated by 60-66Gy in 30–33 fractions and 25 SCLC patients treated by 45 Gy in 30 fractions. Patients with stage IB to IV were included. Fifteen patients were treated for a primary tumor only, 50 patients had a primary tumor and malignant lymph nodes and nine patients had malignant lymph nodes only. The combined median [interquartile range (IQR)] gross tumor volume (GTV) of the primary tumor and malignant lymph nodes was 30.6 [11.5–65.8]cm^3 and planning target volume (PTV) was 258.8 [137.2–369.5]cm^3. These patients comprise cohort 1.

The validation study was based on CT-scans of 49 consecutive NSCLC patients and 25 consecutive SCLC patients treated between March 2018 and November 2018. Median combined GTV was 23.8 [10.0–85.7]cm^3 and median PTV was 227.7 [130.3–378.3]cm^3. These patients comprise cohort 2.

Retrospective data collection was approved by the Danish Data Protection Agency and the Danish National Board of Health (sagsnr. 3-3013-2756/1).

Treatment planning for clinical delivery

For each patient in cohort 1, a clinical plan (CP0) with 4–8 coplanar or noncoplanar IMRT fields was made. The beam angles were individually set for each patient. The target was covered by a homogeneous dose distribution (95–107%) and the plans should comply with the constraints and priorities in Table S1 (see Supplementary Materials). Clinical protocols with pre-set constraints for target and OARs were used. No rules for the beam angle selection were given in the guidelines. However, for patients with mean lung dose, MLD $<$ 13Gy conformal plans was preferred, whereas dose to the total lung volume (denoted lungs) had highest priority for plans with MLD $>$ 13Gy. The CP0 plans used for treatment were made by eight dose planners.

The RapidPlan model

The RapidPlan model is based on geometric and dosimetric information from a user-supplied library of treatment plans for construction of a model, predicting the range of dose volume histograms (DVHs) for prospective patients. The model is generated from a regression plot of a principal component analysis of the dosimetric and geometric parameters of target and OARs obtained from the input treatment plans [12,13]. For selected OARs, automatic optimization objectives are generated on the lower side of the predicted range of the DVH and are henceforth used to guide the actual plan optimization. Thus, the achievable range for an OAR depends on the consistency and goodness of the user-supplied input to the model.

Input to the RapidPlan model

The input plans to the RapidPlan model were created aiming for the lowest possible dose to the lungs and heart, while maintaining full coverage of the PTV. In cohort 1, we investigated dosimetric parameters for three different plan types: clinical IMRT plans used for treatment (CP0), IMRT plans with beam angles re-tuned so that dose to the lungs and heart was minimized (BA0) see Figure 1, and VMAT plans with two extended uni-lateral arcs (209°) arcs depending on tumor location (V0). An example of the V0, CP0 and BA0 plans was shown for one patient in Figure 2. Naming conventions were quoted in Table 1. The plan type yielding the minimal dose to the lungs and heart was selected as input for generation of the RapidPlan model. All plans were made in the Eclipse treatment planning system (version 13.7) using the Acuros algorithm and 6 MV photons [14].

The V0 and BA0 plans were made retrospectively by one experienced dose planner. The aim was to compare the influence of technique and beam angle selection on dose to lungs and heart. For V0 and BA0 plans, the optimization constraints and priorities were selected to ensure minimization of dose to the lungs and heart and were iteratively changed during the optimization process. For all plan types, homogeneous coverage of the PTV was prescribed. The plans should comply with the constraints and priorities in Table S1, irrespective of fractionation dose. The OARs were delineated according to the Danish national guidelines outlined by Møller *et al*. [15]. Dose to the lungs and heart was minimized, still ensuring full target coverage ($PTV_{V95\%}$$>$99%) and minimizing 95% dose outside PTV by use of a normal tissue objective.

RapidPlan generation and optimization

The IMRT plans with re-tuned beam angles produced the lowest dose to lungs and heart (see Results), and were used to generate RapidPlan model 1 (M1). The OARs included in the model were the lungs, heart, esophagus, bronchi and trachea.

The RapidPlan M1 was applied to ten plans in cohort 1 in order to find the optimal priorities for target and OARs to be applied during optimization. Line constraints were used for lungs, heart, esophagus, bronchi, and trachea. Upper limits on the dose/volume point constraints were set for lungs just below 5 Gy/60% and 20 Gy/35%, for heart below 20 Gy/30%, for esophagus below prescribed dose/0%, for spinal cord and spinal cord plus 5 mm isotropic margin below 45 Gy/0%

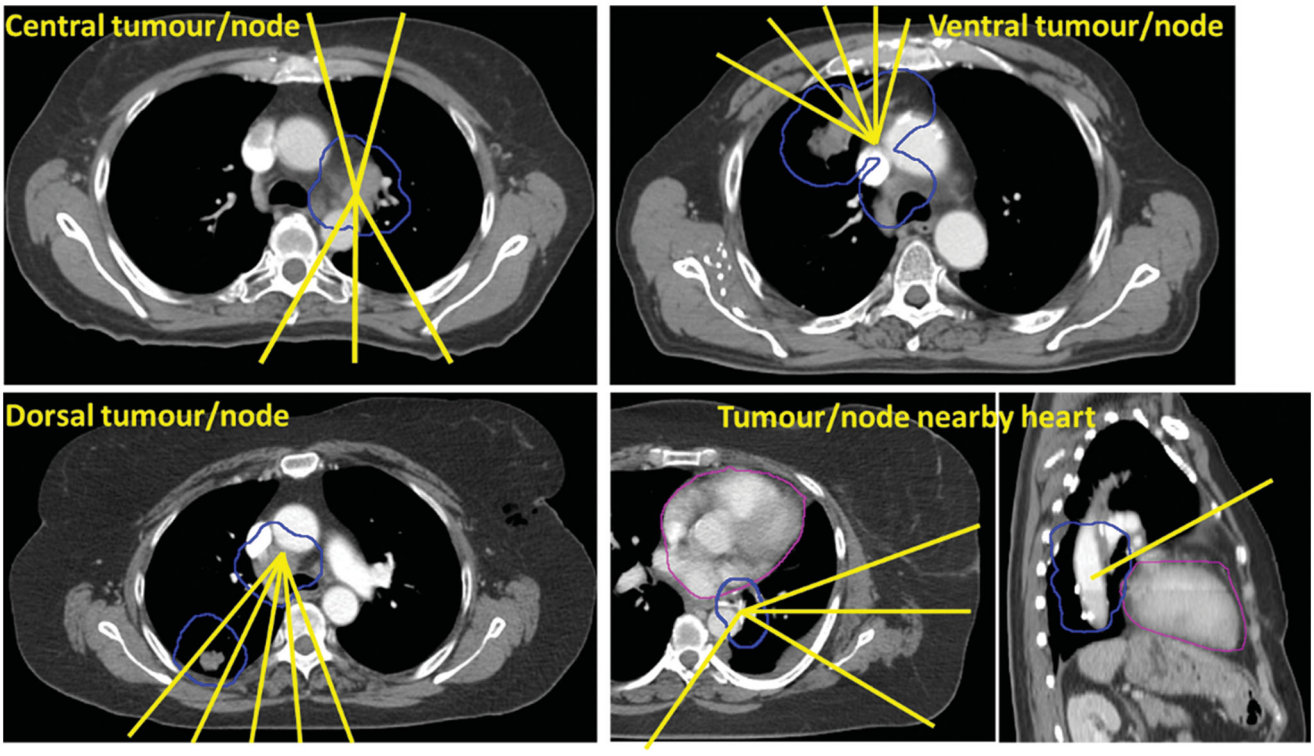

Figure 1. Examples of beam angle selection (lines) depending on tumor/node location. The beam angles were set individually for all target locations, depending on the actual position of tumor and lymph nodes. PTV is outlined in all CT slices.

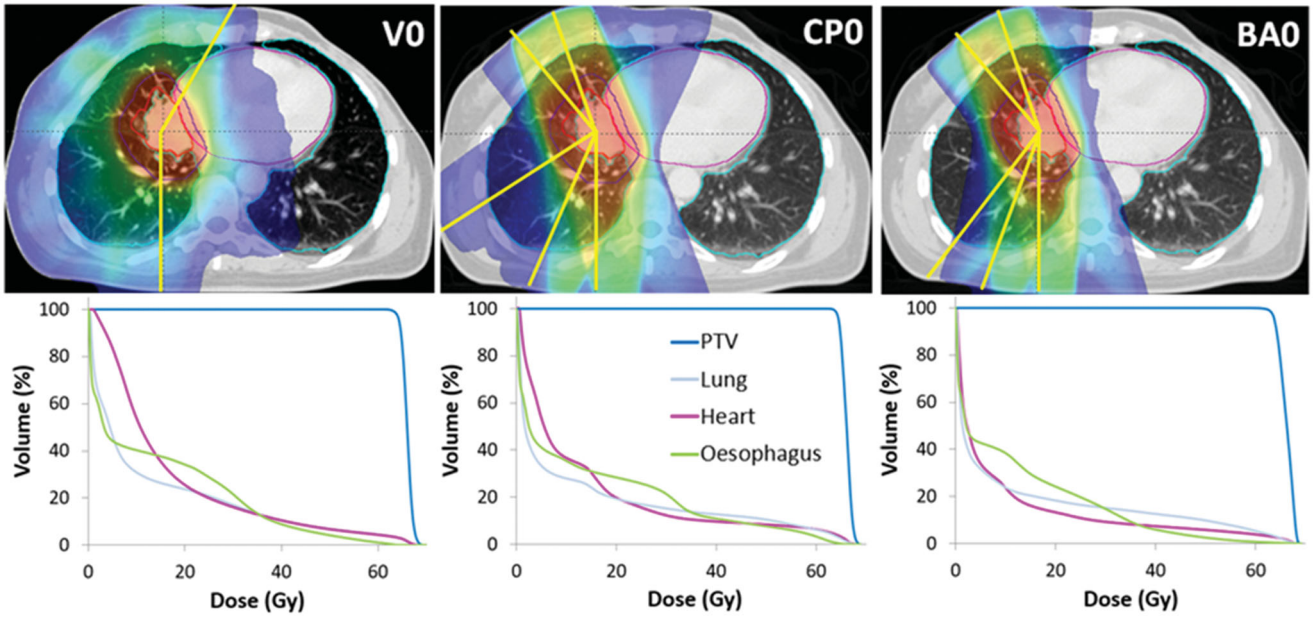

Figure 2. VMAT plan (V0), clinical plan (CP0) and beam angle optimized plan (BA0) for one patient. Upper panel: Dose distributions are shown as dose color wash for all doses > 10 Gy. Beam angles or end of arcs are shown as lines. Lower panel: Dose volume histograms showing dose to PTV, lungs, heart and esophagus.

Table 1. Treatment plans used in the study.

Treatment plan	Plan no	# Dose planners	RapidPlan model	Abbre-viation	Purpose
Clinical IMRT plan		8	No	CP0	Compare technique and beam angle selection, no model
Beam angle optimized IMRT plan	1	1	No	BA0	Compare technique and beam angle selection, no model
VMAT plan	2	1	No	V0	Compare technique and beam angle selection, no model
Clinical IMRT plan	3	1	1	CP1	Compare clinical plan and beam angle selection for M1
Beam angle optimized IMRT plan	4	1	1	BA1	Compare beam angle selection for M1 and no model
Beam angle optimized IMRT plan	5	1	2	BA2	Compare RapidPlan M1 and M2
Clinical IMRT plan	6	8	2	CP2	Investigate results of clinical implementation of RapidPlan

and 50 Gy/0%, respectively. For PTV, a lower constraint was set at prescribed dose and an upper constraint at 107%. A normal tissue objective beginning 1 cm outside the PTV border with a fall-off steepness of 0.05 was applied for doses between 105% and 50% of prescribed dose. Subsequently, RapidPlan M1 was used to generate 74 plans (BA1) using the same beam angles as for the plans with re-tuned beam angles. If target coverage or conformity was unacceptable, the plans were manually adjusted, e.g. regions receiving dose >95% of the prescribed dose outside PTV could be manually delineated in order to decrease dose in these regions in a subsequent optimization.

Generation of RapidPlan model 2

The BA1 plans were used as input for generation of RapidPlan model 2 (M2) to test if a consecutive refinement of the model improved its performance.

New optimal priorities were determined for RapidPlan M2 (see Table S6) and the model was applied to the 74 plans maintaining the original re-tuned beam angles (BA2).

Comparison of clinical plans and plans with re-tuned beam angles

In order to compare the effect of re-tuning the beam angles, the RapidPlan M1 was used to generate 74 clinical plans (CP1), maintaining the original beam angles from the clinical plans. The CP1 plans were compared to the BA1 plans.

Clinical validation

The RapidPlan M2 was implemented for clinical use in March 2018 and all clinical treatment plans were prospectively generated using the RapidPlan M2 and the beam angle selection method sketched in Figure 1. Eight dose planners made the treatment plans. Dose metrics of 74 clinical plans (CP2) from cohort 2 generated after the clinical implementation were collected.

Model evaluation

For both RapidPlan models, selected parameters from the training log providing the goodness-of-estimation statistic were reviewed to evaluate the model quality. Furthermore, the regression and residual plots for each modeled OAR were reviewed. The regression and residual plots can be used for verifying geometric and dosimetric data in the model, respectively [13].

The size and anatomical position of the lung cancer targets differs amongst the patients and for all patients, the position of the PTV classified into ventral, central or dorsal combined with less than or more than 2 cm from the heart were assessed. These different PTV positions were added to the regression and residual plots of the lungs and heart obtained from RapidPlan M2 in order to investigate if some of the categories separate as different groups of point hereby indicating that a unified model cannot be created.

Plan comparison and statistics

In total, six different treatment plans for each patient in cohort 1 were used for modeling, optimizing and testing the RapidPlan model, while one plan for each patient in cohort 2 was used in the validation study, see Table 1.

Selected dose metrics including conformity index $CI = Body_{V95\%}/V_{PTV}$, volume outside PTV receiving $\geq$ x% dose $(Body\text{-}PTV)_{Vx\%}$ and heterogeneity index $HI = (D_{2\%}-D_{98\%})/D_{50\%}$ were compared between plans. In addition, the total number of monitor units (MU) was compared. Data is quoted using median [IQR] and mean values.

The statistical significance of any difference between dose to any structure was assessed using the Wilcoxon signed-rank test for plans created on patient scans before clinical implementation of the RapidPlan model. A p-value of $<.05$ was considered statistically significant.

Dosimetric parameters were compared in terms of PTV size and mean dose to the lungs, heart and esophagus (denoted MLD, MHD and MED, respectively) using a 1-sided student's t-test. A p-value of $<.05$ was considered significant.

Results

For all plans, full target coverage was achieved and all maximum dose limiting constraints for spinal cord, esophagus, and body were respected. For the V0 plans, the upper constraint for MLD, $Lung_{V20Gy}$, and, $Lung_{V5Gy}$ was not respected in four, four and ten patients, respectively. For all six plan types, $Heart_{V20Gy}$ was not respected in one patient. In all other plans, all OAR constraints (Supplementary material, Table S1) were met.

Model building

The median value of R^2 and mean X^2 for the regression plots of the five OARs in M1 was 0.947 and 1.086, respectively, see Supplementary materials Table S4. For M2, the median values were quite similar being 0.904 and 1.124, respectively (Table S5). These values were close to one, showing a high quality of the model [13].

The classification of PTV into ventral, central or dorsal position combined with heart position (Table S2) was added to the regression and residual plots of the lungs and heart in the Supplementary materials Figures S1 to S4. No clustering was seen, showing that one unified RapidPlan model had been obtained.

In Figure 3, box plots of MLD, MHD, and MED were shown. Results for V0, CP0 and BA0 were shown in column one to three for in each plot. The V0 plans led to significantly ($p < .001$) higher MLD and MHD and significantly lower MED compared to the CP0 plans. Re-tuning of beam angles led to a significant decrease ($p < .001$) in MLD, MHD and MED from CP0 to BA0. Additionally, the volume of the lungs receiving low doses (5 Gy) decreased significantly ($p < .001$) from V0 to BA0. The region outside PTV receiving >95% dose $(Body\text{-}PTV)_{V95\%}$ was significantly lower ($p < .001$) for V0 than for both CP0 and BA0, while $(Body\text{-}PTV)_{V5Gy}$

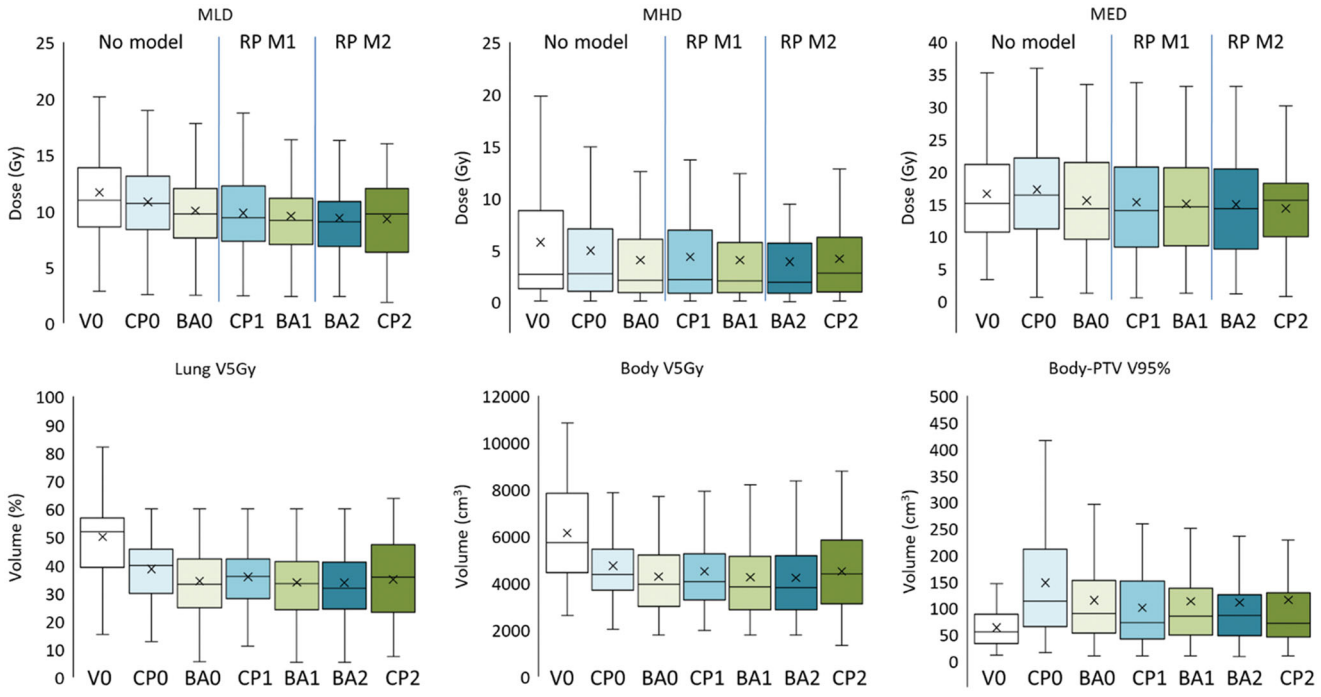

Figure 3. Comparison of selected dose metrics between V0, CP0, BA0, CP1, BA1, BA2 and CP2 plans. Box plot: median (horizontal line), 1st and 3rd interquartile ranges (box), min/max (whiskers), and mean (x).

decreased significantly from V0 to CP0 and from CP0 to BA0 ($p < .001$). Based on these findings, the BA0 plans were selected as input for the RapidPlan M1.

Boxplots for CP1, BA1 and BA2 were shown in column four to six (Figure 3). Significant decrease in MLD from BA0 to BA1 was seen for plans generated with the RapidPlan M1 ($p < .001$). Further significant reduction from BA1 to BA2 was seen for plans generated with the RapidPlan M2 compared to M1 ($p < .001$). Combination of re-tuned beam angles and application of RapidPlan M1 showed significantly reduction of MLD from CP1 to BA1 ($p < .001$). Overall, MLD was reduced from 10.8 Gy ± 3.7 Gy (CP0) to 9.4 Gy ± 3.6 Gy (BA2). For the heart, no significant change between BA0 and BA1 was seen for MHD ($p = .159$). MHD was significantly reduced from BA1 to BA2 ($p = .002$) and from CP1 to BA1 ($p = .019$). Overall, MHD was reduced from 4.9 Gy ± 5.3 Gy (CP0) to 3.9 Gy ± 4.5 Gy (BA2). For the esophagus, overall reduction in mean esophagus dose (MED) from 17.2 Gy ± 8.4 Gy (CP1) to 14.9 Gy ± 8.3 Gy (BA2) was seen. In Figure 4, a plot of the mean DVH for all 74 CP0 and 74 BA2 plans showed that re-tuned beam angles combined with plan optimization using the RapidPlan M2 led to deceased dose for all dose values.

The mean values of MLD, MHD and MED were more similar between the CP1 and BA1 plans (difference:0.3 Gy, 0.3 Gy and 0.2 Gy, respectively) than between the CP0 and BA0 plans (difference:0.7 Gy, 0.9 Gy and 1.4 Gy, respectively), showing that the plans generated by the RapidPlan model were less sensitive to the input beam angles than plans optimized without use of the model.

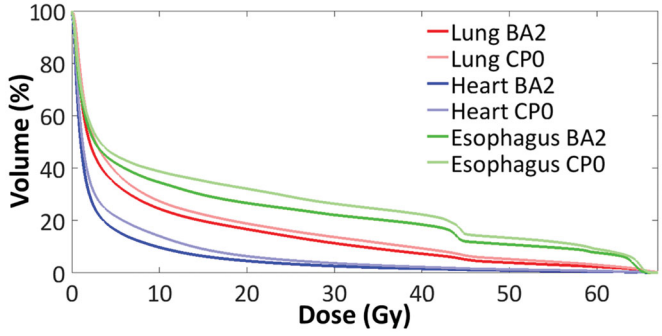

Figure 4. Dose volume histogram showing mean of all clinical plans (CP0) or plans with re-tuned beam angles optimized using RapidPlan M2 (BA2) for lungs, heart and esophagus.

Validation

As a clinical validation, MLD, MHD and MED were compared for CP0 and CP2, see Figure 3. MLD decreased from 10.8 Gy ± 3.7 Gy to 9.3 Gy ± 3.5 Gy for the CP0 plans compared to the CP2 plans. MED decreased from 17.2 Gy ± 8.4 Gy to 14.3 Gy ± 8.0 Gy. The mean value of MHD decreased from 4.9 Gy ± 5.3 Gy (CP0) to 4.1 Gy ± 3.8 Gy (CP2), but it was not significantly different ($p = .132$). MLD, MHD and MED were not significantly different between CP2 and BA2 plans. The PTV volume was not significantly different ($p = .195$). This shows, that the dosimetric benefit obtained by using the RapidPlan model for plan optimization in the modeling part of this study (cohort 1) was maintained for clinical plans created by different dose planners after the clinical implementation of the RapidPlan M2 (cohort 2).

The mean number of MUs increased significantly from 536 ± 180MUs for CP0 to 763 ± 228MUs for CP2. For the CP2 plans, the mean number of MUs was 785 ± 232, not significantly different from the BA2 plans ($p = .187$).

Discussion

In the present study, clinical IMRT plans, VMAT plans and IMRT plans with beam angles selected based on the position

of the OARs were compared. Significant dose reductions to lungs, heart and esophagus were seen for the BA0 plans. The V0 plans led to the highest MLD and MHD, being 1.6 Gy and 1.7 Gy higher in mean than for the BA0 plans. In former studies comparing IMRT and VMAT, dose to lungs and heart was in favor of VMAT [16–19]. However, in these studies fixed beam angles were used for IMRT. In the present study, beam angles were set individually for the IMRT plans enabling selection of beam angles leading to reduced dose to the lungs and heart. A planning study on 20 rectal cancer patients, showed reduced dose to the small bowel and peritoneal space when avoidance sectors were used during VMAT planning [20]. Therefore, five patients were selected for VMAT re-optimization using avoidance sectors at $90^{\circ} \pm 20^{\circ}$ (or $270^{\circ} \pm 20^{\circ}$). Only minor differences (maximum 2%) were found after re-optimization, presumably due to a high priority set for the lungs and heart in the VMAT plans optimized without use of avoidance sectors.

A dosimetric benefit of using RapidPlan was shown in the present study in accordance with the findings of former studies [8–12]. Comparison of the CP1 and BA1 plans, showed that the BA1 plans had significantly lower doses to the lungs and heart than the CP1 plans, pointing out that plans generated by the RapidPlan model did not get the lowest possible dose. Selection of beam angles based on target and OAR positions further pushed down the dose. Therefore, the optimal RapidPlan model should be based on high quality plans.

A user-supplied library of treatment plans is used to construct the RapidPlan model. Thus, the achievable dose range for an OAR depends on the consistency and goodness of the user-supplied input to the model. To test the possibility to further improve the outcome plans generated by the RapidPlan model, a second model was build based on plans optimized using RapidPlan M1. Significant dose reduction was seen for both MLD and MHD, showing that it is possible to improve the RapidPlan model by this iterative process using RapidPlan M1 during optimization and entering these plans into a new RapidPlan model (M2). This agrees with the finding by Fogliata et al. in a study on head and neck cancer patients [12]. Whether this effect depends on the quality of the initial set of plans or is of a general nature cannot be answered here.

For the clinical validation of the RapidPlan M2 combined with beam angles selected based on the position of the lungs and heart, dose metrics of 74 patients treated after the clinical implementation were investigated. The MLD and MED was significantly lower for the CP2 plans than the CP0 plans. The MHD was lower after the implementation, but not significant. This may be due to the limited number of patients as the heart dose is highly dependent on the target position and the patient population was only matched on the number of NSCLC and SCLC patients.

The IMRT approach allows for probing the stability of the RapidPlan model for varying beam geometries. A large heterogeneity in the target position and size is seen for locally advanced lung cancer. Therefore, a high number of patients are needed for generation of a RapidPlan model unifying all target positions and sizes. The regression and residual plots for lungs and heart showed no clustering of targets with specific positions, indicating the applicability of the unified model Furthermore, creation of a new RapidPlan model based on plans from M2 with omission of the last ten patient plans yielded only slightly worse values for R^2 and X^2 of 0.93 and 1.07 for the lungs and 0.84 and 1.08, for the heart. This indicates that addition of plans to the model will only slightly increase the performance of the model. Review of the goodness-of-estimation statistic showed median R^2 and X^2 values close to one, implying good performance of the regression model. The numbers obtained for both M1 and M2 are comparable to or better than the number obtained in a recent study on head and neck cancer [21].

The use of the RapidPlan model occasioned more stringent plan optimization criteria yielding much more modulated plans delivering significantly more MUs. However, for all clinical plans portal dosimetry was performed for quality assurance as part of our clinical routine. Global Gamma evaluation with suppression of doses below 5% was used. The requirement was that 95% of points must fulfill a gamma evaluation with dose difference, $\Delta D \leq 3\%$ and distance to agreement, DTA $\leq$ 3mm. No CP0 or CP2 plans fail this rather strict evaluation.

In conclusion, IMRT plans with beam angles selected to minimize dose to the lungs and heart lead to significantly lower doses to lungs and heart compared to VMAT plans. Introduction of a RapidPlan model for plan optimization significantly reduced dose to lungs, heart and esophagus. Further reduction was seen by creation of a second RapidPlan model in an iterative process. The model was validated in prospectively collected treatment plans showing significantly lower dose to lungs and esophagus for patients treated after clinical implementation of the model compared to treatment plans created before the implementation. The heart dose was reduced but not significantly.

Disclosure statement

No potential conflict of interest was reported by the authors.

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