Title page

Predicting personalised optimal arc parameter using knowledge-based planning model for inoperable locally advanced lung cancer patients to reduce organ at risk doses

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Abstract

Objectives: Volumetric modulated arc therapy (VMAT) allows for reduction of organs at risk (OAR) volumes receiving higher doses, but increases OAR volumes receiving lower radiation doses and can subsequently increasing associated toxicity. Therefore, reduction of this low-dose-bath is crucial. This study investigates personalizing the optimization of VMAT arc parameters (gantry start and stop angles) to decrease OAR doses.

Materials and Methods: Twenty previously treated locally advanced non-small cell lung cancer (NSCLC) patients treated with half-arcs were randomly selected from our database. These plans were re-optimized with seven different arcs parameters; optimization objectives were kept constant for all plans. All resulting plans were reviewed by two clinicians and the optimal plan (lowest OAR doses and adequate target coverage) was selected. Furthermore, knowledge-based planning (KBP) model was developed using these plans as 'training data' to predict optimal arc parameters for individual patients based on their anatomy. Treatment plan complexity scores and deliverability measurements were performed for both optimal and original clinical plans.

Results: The results show that different arc geometries resulted in different dose distributions to the OAR but target coverage was mostly similar. Different arc geometries were required for different patients to minimize OAR doses. Comparison of the personalized against the standard (2 half-arcs) plans showed a significant reduction in lung V_5 (lung volume receiving 5 Gy), mean lung dose and mean heart doses. Reduction in lung V_{20} and heart V_{30} were statistically insignificant. Plan complexity and deliverability measurements show the test plans can be delivered as planned.

Conclusions: Our study demonstrated that personalizing arc parameters based on an individual patient's anatomy significantly reduces both lung and heart doses. Dose reduction is expected to reduce toxicity and improve the quality of life for these patients.

Keywords

Volumetric modulated arc therapy, Avoidance arc treatment, Non-small cell lung cancer, Personalized radiotherapy, Treatment planning optimization, Knowledge-based planning model.

Introduction

The aim of radiotherapy treatment planning is to maximize the therapeutic ratio, that is, to achieve higher tumour control whilst lowering the risk and severity of associated toxicities (Mayles, Nahum and J.C, 2007). This is achieved by minimizing organ at risk (OAR) doses whilst delivering a prescription dose designed to control tumour cells to the target volumes. Treatment planning and delivery techniques have evolved significantly over the years from parallel opposed fields to multiple conformal fields to advanced techniques such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc radiotherapy (VMAT), which have improved overall treatment plan quality. This has led to a relatively larger number of patients receiving the intended tumour dose without exceeding OAR doses.

Three-dimensional conformal radiotherapy (3D-CRT) and VMAT/IMRT treatments reduce higher doses to OARs due to the conformity of the high doses to targets. However, due to the nature of VMAT/IMRT techniques, the low dose bath increases significantly (Marks *et al.*, 2009; Diwanji *et al.*, 2017). Several studies have reported that lower doses to a larger portion of healthy lung volume increased the incidence of grade 3 radiation pneumonitis (Wang *et al.*, 2006; Marks *et al.*, 2009). Additionally, patients undergoing combination chemo-radiotherapy have associated co-morbidities and are more prone to chemo-associated toxicity (Rancati *et al.*, 2003). Finally, increasing the low dose bath in IMRT and VMAT plans could also increase the risk of secondary malignancies (Abo-Madyan *et al.*, 2014). Therefore, it is critical to keep doses to the lung as low as possible.

Several studies have reported that IMRT reduces V_{20} (lung volume receiving 20 Gy) but may increase V_5 (the lung volume receiving 5 Gy) when compared to 3D-CRT plans (Li *et al.*, 2018; Yin *et al.*, 2012). Furthermore, lung V_5 and mean lung dose (MLD) increased in VMAT plans for lower and middle oesophageal cancer plans when compared to IMRT plans, whereas V_{20} of lung and V_{30} of heart decreased slightly in VMAT plans with a comparatively lower treatment time (Yin *et al.*, 2012). Recently, a study reported an increase in grade 3 cardiac toxicities for the oesophagus patients where the mean heart dose is greater than 15 Gy (Wang *et al.*, 2020). Therefore, reducing doses to both lungs and heart are important.

Several treatment planning methods have been studied to reduce lung doses including the use of avoidance sectors in VMAT, 4pi and hybrid planning. Regarding the latter, a study combined 3D conformal fields with IMRT fields and reported that, for lung cancer plans, V_5 increased by 3.7 % in the hybrid IMRT plans compared to the 3D conformal plans and reduced by 4.8 % and 9.8 % for four/five and nine field IMRT plans respectively (Mayo *et al.*, 2008). The V_{20} and MLD were reduced by 4.3 % and 0.5 Gy respectively. However, the same hybrid plans increased heart V_{30} dose by 6.3 % compared to IMRT and 3D conformal plans (Mayo *et al.*, 2008). Another study demonstrated that lung V_5 can be reduced using a hybrid RapidArc (Varian's VMAT) technique compared to a 240^o RapidArc plan but is still increased compared to the 3D conformal plans (Chan *et al.*, 2011). In addition, an increase in total treatment time was reported in the hybrid RapidArc plans (Chan *et al.*, 2011).

Further studies have reported the benefit of RapidArc with avoidance sectors (the linear accelerator switches the beam off in the defined avoidance segment/sector of the arc treatment) for head and neck, abdomen, pelvic and stereotactic ablative body radiotherapy cases (Huang *et al.*, 2015; Dumane *et al.*, 2010; B and ChihYao, 2013; Rana and Cheng, 2013; Pursley *et al.*, 2017). Furthermore, a study performed by Rosca *et al* (Rosca *et al.*, 2012) demonstrated that restricted arc (i.e. arcs with avoidance sectors) plans reduce lung doses but the heart dose increases compared to full arc plans (Rosca *et al.*, 2012). One of the shortcomings of this evaluation was that it only investigated the restricted arc technique for centrally located tumours. Recently, the use of 4 pi technique has been investigated for stereotactic ablative body radiotherapy for lung cancers, this study reported a significant reduction in lung V_5, V_{10} and V_{20} (Dong *et al.*, 2013). The 4 pi technique includes non-coplanar IMRT beams distributed on the 4 pi spherical surface; the beam optimisation begins with a pool of 1162 non-coplanar IMRT beams with 6^o separation in the 4 pi solid angle space. The optimiser then eliminates the beams that could collide with couch/patient and the plan is optimised using the remaining beams (Tran *et al.*, 2017).

All these studies recommended using a single protocolised treatment plan for all patients irrespective of patient anatomy (e.g., fixed restricted arcs or hybrid arcs) for all the patients. However, tumour shape, size and location and its overlap with OAR volumes could vary significantly between patients with locally advanced-stage lung cancer disease. Therefore, a single protocolised, fixed arc parameter approach may not be the most optimal planning method across the patient population. The field size, multi leaf collimator (MLC) sequencing and the isocentre are can be optimised by the planning system for IMRT and VMAT treatments. Here we are addressing arc parameters that are not automatically selected by the planning system or the optimiser, such as, start-stop arc angle and avoidance sectors.

The aim of the present study is to investigate optimal arc geometries using a personalised arc parameter approach for planning inoperable locally advanced stage lung cancer patients treated with curative intent. This strategy hopes to reduce low dose bath and OAR doses whilst maintaining target coverage. Furthermore, a knowledge-based planning model was developed to predict the optimal arc parameter using patient-specific parameters.

Methods

Patients and prescription

In our clinic, all locally advanced stage lung cancer patients are treated using RapidArc (Varian's solution for VMAT), as previously described (Tambe *et al.*, 2020). Treatment plans were produced using the Eclipse™ treatment planning system (V15.6, Varian Medical System). A total of 30 previously treated patients' plans were randomly selected from our database, of which 20 were used as baseline 'training' plans and ten reserved for validation

of the model. Patient demographics are summarized in Table 1. The prescription dose was 55 Gy in 20 fractions (i.e., ≥ 95% of the PTV receives 95% of the prescription dose (see Table 2)).

Imaging and contouring

Lung cancer patients who could maintain regular breathing underwent 4D-computerised tomography (CT) scans which were binned into 10 phases. Patients with irregular breathing underwent free breath scans only, as per local protocol. For 4D patients, the gross tumour volume (GTV) was contoured on at least three phases (max-Inhale, max-exhale and average phases) ensuring full capture of the tumour motion. For some of the 4D patients, GTV and involved nodes were contoured on more phases especially where hysteresis in tumour motion was observed. The target volumes contoured on phased images were accumulated on the average scan (produced from all the phase images) for planning. The Clinical target volume (CTV (for 3DCT patients)) or internal target volume (ITV (for 4DCT patients)) was produced by adding an isotropic margin of 0.6 cm for squamous cell carcinoma and 0.8 cm for adenocarcinoma patients. The planning target volume (PTV) was generated with 0.5 cm isotropic margins for 4DCT patients and 0.9 cm circumferential and 1.2 cm superior-inferior for 3DCT patients. All 4D patients were treated with back-up gating. OAR, lungs-GTV (i.e., total lungs subtracted from GTV), heart, spinal cord and spinal cord planning organ at risk volume (PRV = spinal cord + 0.5cm) were contoured and doses to these structures were reported. (Added which specification were used for the contouring).

Clinical RapidArc ($RA_{Clinical}$) treatment planning and delivery

Two, 6 MV (flattened) photon beam, partial arcs 0 to ±180° avoiding direct entry through the contralateral lung with a collimator angle of 30° and 330° (non-zero collimator angles were used to minimise the effect of tongue and grove leakage). All plans were calculated using the AcurosXB algorithm (V15.6) with a dose grid of 0.25cm and optimized to meet the planning goals described in Table 2. The isocenter was positioned in the centre of the PTV, minimising tracking of the arc fields and any dosimetric complications that could occur due to high demanding leaf motion. Field size was optimised to the PTV volume with x-jaws limited to 16.5cm, which is the limit for the Varian linacs (Huang *et al.*, 2019). The maximum dose rate of 600 MU/minute was set. The Normal tissue objective (NTO) function (with priority set the same as the PTV) and a ring structure (an optimisation structure produced using extract wall function within the planning system with inner margin of -0.5cm and outer margin of 1.5cm from the PTV) were used to reduce dose spread away from the PTV. The NTO parameter, available within the Eclipse™ planning system, was used to limit dose as a function of distance from PTV outer border (Clemente *et al.*, 2013). Automatic/default NTO settings were used with priority set same as the PTV. All 4D patients were treated with backup gating, where the treatment machine holds the beam off if breathing amplitude during treatment goes outside the set threshold limits and when there is a significant difference in the periodicity in the breathing trace. Locally, all the patients treated with VMAT undergoes daily CBCT imaging.

Re-planning with different arc parameters

A total of twenty patients were re-planned, each with the seven different arc parameters (gantry start and stop angles) illustrated in Figure 1; these are shown with and without avoidance sectors. The test plans include a range of active treatment angle arc geometries to minimize entry through whole lungs, or contralateral lung, or heart, and a range of treatment angles from 360° arcs to 90° arcs. The 90° arc was placed in the same quadrant as the PTV. Optimization objectives were kept the same as the original clinical plans so that the effect of change of arc parameter on lung, heart and spinal cord PRV doses could be assessed. In addition to different arc parameters, five patients were planned with three different collimator angle settings, 30° and 330°, 20° and 340° and 10° and 350° to assess their impact, within the study aims, and all other patients were planned with one collimator angle setting (i.e., the collimator angle that reduced overall OAR doses). All the plans, including the original clinical plans, were blind reviewed (i.e., without knowing arc parameters), and a preferred plan was selected for each patient following the pre-defined criteria (see Table 2), including target coverage and OAR doses at specified dose-volume tolerance level (e.g., lung V_5 or V_{20}). The optimal plans were then compared with the original clinical plans (i.e., arc parameter A). In addition, conformity index (CI) and homogeneity index (HI) were calculated as defined in ICRU (International Commission on Radiation Unit and Measurement) report 83 ('Preface,' 2017) for clinical and the test plans (using equation 1 and 2) and compared.

$$\text{Conformity Index (CI)} = \frac{V_{95\%}}{Volume\ of\ PTV} \quad (1)$$

where $V_{95\%}$ is volume of PTV covered with at least 95% of prescription dose.

$$\text{Homogeneity Index (HI)} = \frac{D2\% - D98\%}{D50\%} \quad (2)$$

where $D_{2\%}$, $D_{50\%}$ and $D_{98\%}$ are the doses received by 2 %, 50 % and 98 % of the planning target volume.

Development of knowledge-based planning model

The plans for a training subset of 20 patients were used to develop a knowledge-based planning (KBP) model to predict the optimal arc parameter. A number of patient-specific volumes (i.e., PTV, Lungs, Heart, and overlap of heart with PTV) and location of the volumes/ structures were recorded and used to develop the KBP model. In addition, each arc parameter was numbered from 1 to 8 (see Figure 1: 1 to 8, parameter A to H respectively). The KBP model was developed using Multivariate regression analysis (see equation 3 and 4) to predict arc parameter that will provide the most optimal OAR sparing whilst achieving adequate target coverage for prospective patients. The patient factor was calculated using the patient-specific geometric volumes and the coefficients predicted by the multivariate regression

analysis. The predicted arc parameter was rounded to nearest whole number and compared with the clinician chosen arc parameter, this was required as the model uses continuous functions to predict a discrete parameter..

$$Arc\ Parameter_{predict} = m\ \times Patient\ Factor \quad (3)$$

$$Patient\ Factor = \left[\left(m1 \times \frac{Lungs_{cc}}{PTV_{cc}}\right) + (m2\ \times MSD_{PTV\ and\ Heart}) + (m3\ \times MSD_{PTV\ and\ Contralateral\ Lung})\right] \quad (4)$$

where MSD: mean square difference in centre of mass between the referenced structures

Verification of arc parameter prediction model

The model was verified using ten independent patients; a total of 80 treatment plans including original clinical plans were used for verification. All ten patients were re-planned using all seven geometries (i.e., parameters B to H, see Figure 1) and the preferred plan was selected for each patient using blind review. These calculations and subsequent selection of clinician preferences were done before the knowledge based planning model was used to predict which arc parameter should be utilised. This was done to ensure the exclusion of any potential bias of choice by the clinician. t

Following the selection of the optimal plan, via local protocol/ criteria and then the KBP model was used to predict the clinician selected arc parameter (see equation 3 and 4) and the prediction accuracy of the model was calculated. Furthermore, the target coverage and OAR doses achieved with the optimal plans (i.e., clinician selected arc parameters) were compared with the original clinical plans (i.e., plans produced using arc parameter A).

Plan complexity and deliverability

Treatment plan complexity metrics small aperture score (SAS: calculated as the ratio of open leaf pairs where the aperture was less than a defined criterion (2 mm, 5 mm, 10 mm and 20 mm in our study) to all open leaf pairs (see equation 5) (Crowe *et al.*, 2014)), MU/Gy, MU/control-point, islands < 1 cc) were calculated using an Eclipse ESAPI script and compared with those for the original clinical plans.

$$SAS(x)beam = \sum_{i=1}^{1} \frac{N(x > a > 0)i}{N(a > 0)i} \times \frac{MUi}{MUbeam} \quad (5)$$

where *x* is the aperture criteria, *i* is the number of segments in the beam, *N* is the number of leaf pairs not positioned under the jaw, and a is the aperture distance between opposing leaves (Crowe *et al.*, 2014).

Furthermore, to evaluate the effect of the avoidance sectors on the deliverability of plans, all plans were measured on a TrueBeam linear accelerator and gamma analysis was performed using our standard clinical criteria (i.e., percentage of pixels where gamma is less than or equal to unity using a criteria of 3%/2 mm (global gamma) with a threshold of 20%) by comparing predicted fluence with the measured fluence. The fluence for each beam was measured using an electronic portal imaging device (EPID) and compared in the portal dosimetry software within the Eclipse™ planning system.

Statistical analysis

The studied parameters from both planning techniques were compared using a Student's t-test to assess significance. A *p*-value of < 0.05 was considered statistically significant. Normality of data was tested with Kurtosis analysis (Reinard, 2006). Multivariate analysis was performed to develop a knowledge-based planning model predicting optimal arc parameter.

Results

Effectiveness of arc geometries

The results show that different arc parameters and collimator angles resulted in different dose distributions to OAR volumes, whereas dose to target volume was mostly similar between different arc parameters (see Table 4 and Figure 2). Overall, for all arc parameters, the plans produced using collimator angle of 10^{o} and 350^{o} provided lower OAR doses for similar target coverage. All 240 treatment plans (including the original clinical plans) were reviewed; for each patient, the preferred plans (meeting the local protocol: plans with lowest OAR doses and adequate target coverage) were identified. None of the original clinical plans (i.e., arc parameter A plans) was selected as the preferred optimal plan and, more importantly, different patients required different arc parameters to minimize OAR doses.

The clinician chosen plans were compared with the original clinical plans and the results showed a reduction in OAR doses (see Table 5). The reduction in V_5, mean lung dose, mean heart dose and mean body doses was statistically significant whereas the reduction in lung V_{20} and heart V_{30} was not statistically significant. Furthermore, an increase in the total number of MUs was observed, however, this was not statistically significant.

Validation of knowledge-based planning model

The model was validated using 80 plans (n = 10 patients) outside the model. The model developed to predict optimal arc parameter using equation 3, predicted the optimal arc parameter accurately for 80 % of patients (see Figure 3). OAR sparing achieved with the model predicted arc parameters are displayed in Table 6.

Planning complexity and deliverability analysis

A number of complexity metrics were calculated and are presented in Table 7. Some of the complexity parameters, (MU/Gy, MU/Degree, mean dose rate and mean leaf speed), suggested the optimal plans were more complex than the original clinical plans. The remaining metrics considered did not indicate an increase in complexity.

The selected (clinician chosen arc parameters) plans were measured on a Varian TrueBeam linear accelerator. Gamma comparisons of the measured and predicted beam fluences were performed at 3%/2 mm. The results showed overall good agreement with all plans passing the local accuracy standard, which requires ≥ 98 % pixels with gamma less than or equal to unity with a 3%/ 2 mm criteria.

Discussion

Modern arc-based intensity-modulated radiotherapy treatment planning and delivery techniques enable the reduction of the volume of critical structures (OARs) receiving higher doses but increase the volume receiving lower doses (Marks *et al.*, 2009; Diwanji *et al.*, 2017), which remains a concern. In view of the new knowledge (Wang *et al.*, 2006; Marks *et al.*, 2009; Wang *et al.*, 2020), both dose to lungs and to the heart need consideration, which means our planning job is considerably more difficult and hence the need for new/ individualized approaches. This study investigated the use of full-arcs (i.e., arc parameter H), short-arcs (i.e., arc parameter G), and arcs with multiple avoidance sectors for treatment planning of inoperable locally advanced lung cancer patients, aiming to reduce OAR dose without compromising target coverage.

The technique presented here separates continuous, half and full, arcs into segmented ones with avoidance sectors, in order to avoid direct (incident) irradiation of normal tissues. Whereas from a dose reduction perspective this follows a simple maxim of conventional radiotherapy, in the context of intensity modulation it also reduces the degrees of freedom available to the optimizer to deliver the required dose to the target. Under these circumstances, an unwanted coincidental effect may be a reduction in the control of the dose to the target or larger contributions from 'allowed' directions which may increase the complexity of delivery, possibly significantly.

In this study, we report that deliverable, clinically acceptable VMAT with 'optimised avoidance sectors' plans can be produced using different arc parameters and collimator angles.

Treatment plans produced with different arc parameters and collimator angles provided different amounts of OAR sparing. Clinical review of all plans produced for each patient indicated that, although meeting (OAR dose) acceptability criteria, when using the KBP prediction model more optimal plans were always found in preference to original clinical plans. OAR sparing was relatively higher for collimator angle of 10^{o} and 350^{o} compared to other collimator angles used but this was not significant compared to the OAR sparing achieved with the arc parameters.

It was also noted that patient-specific arc parameters provided the highest OAR sparing without clinically significantly compromising target coverage. This shows the importance of the personalization of arc geometries based on each patient's anatomy. A standardized (i.e., arc parameter A or H) arc parameter may not be the optimal solution for treating these patients especially when there are larger variations in target size, shape and location with respect to the OARs volume. The reduction in lung doses is significantly higher in our study compared to other studies (Chan *et al.*, 2011; Mayo *et al.*, 2008)[, 17], but more notably, our study also reports a reduction in heart doses (significant reduction in mean heart dose), whilst the other studies (Chan *et al.*, 2011; Mayo *et al.*, 2008) reported a systematic increase in heart dose. Additionally, it was noted that personalization of arc parameter also resulted in a reduction in the mean dose delivered to patient.

Various arc geometries were tested and compared to the original clinical plan. These included full arcs (i.e., arc parameter H), short arcs (i.e., arc parameter G) and arcs with different avoidance sectors (i.e., arc parameter B to E) to reduce entry and exit beams through OAR volumes. Different avoidance sectors were used in different arc parameters aiming to reduce entry and exit of radiation beams through OAR volumes, except for three arc geometries (i.e., arc parameter A (the original clinical arc parameter), G and H). For these arc parameters, avoidance sectors were not used. The 90^{o} arcs were placed in the same quadrant as the tumour.

It was interesting that the original clinical plans (i.e., the plans produced using arc parameter A) or plans produced using arc parameter G and H were not selected as the optimal plans for any of the patients. These arc parameters resulted in significantly higher OAR doses compared to the other test plans. A difference in the target coverage in the plans produced using different arc parameters was not clinically significant, except for the four plans produced using arc parameter G where the target coverage dropped below 95.0 %.

Moreover, a number of relatively simple knowledge-based planning models were developed to predict arc parameter using OAR volumes, target volume and their centre of mass location. The KBP model developed using, lungs, PTV and mean square difference in the centre of mass of PTV, heart and contralateral lung predicted optimal arc parameter accurately for 80 % of the patients. This model will improve planning efficiency by predicting optimal arc parameter and help reduce OAR doses whilst maintaining target coverage. For two patients, the predicted arc parameters did not match those selected by the clinician, we considered this

likely due to difference in the tumour geometry for these patients and the model may be improved in any further work. Furthermore, fine tuning the arc geometry (start angle, stop angle, avoidance sector span) may provide further benefit in optimal OAR sparing, however prediction of the 'baseline' arc parameter will potential save many initial 'iterations' in the planning process. For the patients where the model predicted arc parameter did not match the one selected in the blind review, the predicted plan had lower OAR doses compared to arc parameter A, but the doses were slightly higher compared to the plan with optimal arc parameter.

The conformity and homogeneity indices were calculated and compared for the clinical and the test plans. The results showed statistically significant differences between the clinical and the test plans, but differences were clinically not significant. The mean difference in CI and HI was 0.03 and -0.02 and respectively compared to plans with arc parameter A for plans within and 0.07 and -0.02 for outside the model. The CI for the test plans was clinically similar to the original clinical plans (arc parameter A plans) as doses outside the PTV structure were controlled by using a ring structure. During plan optimization, an upper limit was used on the ring structure.

Furthermore, the results from the clinical review showed that arc parameter F was chosen more frequently than the other arc parameters: this arc parameter consists of two full arcs with avoidance sectors (see Figure 1), so it is important to verify gantry clearance prior to treatment delivery to avoid collision issues. In our experience, this will not be a problem for the majority of patients, but for those where the lateral shift is ≥ 10 cm from the midline, verification will be required prior to treatment delivery.

A number of studies reported that plan complexity is dependent on the number of small segments, MU/Gy and number of MU per control point (MU/Degree) and reduction in these parameters could reduce the plan complexity and reduce errors in delivery (Webb, 2003; Abdellatif and Gaede, 2014). An increase in the total number of MU seen in the optimal plans could mean that these plans are more complex to deliver. In order to test this hypothesis, treatment plan complexity metrics were calculated for both plans. The deliverability was assessed by measuring plans on a TrueBeam linear accelerator. The results showed a significant increase in MU/Gy, MU/degree, mean dose rate and mean leaf speed in the test (i.e., optimal) plans, however, the plans were shown to be deliverable within our 'challenging' accuracy acceptable requirements.

The results show significant reductions in lung V_5 with mean lung V_5 reduced below 42 % (a threshold reported by Wang *et al* [4]). Therefore, this approach should significantly limit lung toxicities below grade 3 for these patients. Furthermore, our study reported significant reductions in mean heart dose; this approach would help reducing mean heart dose below 15 Gy, where severe cardiac toxicities reduced significantly (Wang *et al.*, 2020). A reduction in toxicities may improve the quality of life for these patients. Also, reductions in OAR doses can facilitate dose escalation for these patients.

The current version/license of the planning and delivery system at our clinic does not allow the use of non-coplanar arc geometries. Therefore, this was not investigated in this study. Further evaluation would be required to assess if non-coplanar arcs can help reducing OAR doses for inoperable advanced-stage NSCLC patients.

Conclusion

Overall, treatment plans produced using personalized arc parameters were superior compared to the clinical plans. This method not only utilizes the benefits of VMAT planning technique (reducing the volume of healthy lung receiving higher doses without compromising target coverage) but also reduces OAR doses. This could reduce toxicities and improve the quality of life for locally advanced stage lung cancer patients treated with VMAT radiotherapy.

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Table 1: Patient demographics

	Used to develop Model Mean/Frequency/Range	Validation Model Mean/Frequency/Range
Age (mean) +/- SD	70.37 (6.72) Years	71.35 (10.26)
Gender	9 Male/11Female	6 Male/4Female
Staging	T1N1/T4N3	T1N1/T4N2
Laterality	9Right/11Left	5Right/5Left
Location	9UL*/5ML†/6LL‡	3UL*/2ML†/1LL‡
PTV volume (cc)	360.7 (167.7 – 707.0)	340.9 (161.0 – 483.1)
Lungs volume (cc)*	3600.4 (2036.9 – 6267.7)	3463.0 (1926.7 – 4850.5)
Heart volume (cc)	699.7 (417.6 – 1110.4)	685.1 (301.5 – 1043.0)

* Total lung volumes subtracted from GTV, *UL: upper lobe, †ML: middle lobe, ‡LL: lower lobe.

Table 2. Treatment planning clinical objectives and wish-list used for planning advanced-stage NSCLC patients at our clinic.

	Clinical objective		Constraints
	Spinal Cord PRV	Max Dose	≤ 50Gy / 45Gy for 55Gy/20# (Mandatory)
	PTV	$V_{95\%}$	≥ 95%
		Max (1.8cc)	≤ 107% of the prescription dose
	Lungs-GTV	V_{20Gy}	≤ 35% (Mandatory)
		V_{5Gy}	≤ 60% (Mandatory)
	Heart	Mean dose	≤ 26Gy (Mandatory)
		V30Gy	≤ 46% (Mandatory)
Wish-list priority	PTV	$V_{95\%}$	≥ 99% (Optimal)
	Lungs-GTV	V_{5Gy}	< 60% (Optimal)
		V_{20Gy}	≤ 30% (Optimal)
	Heart	Mean Dose	≤ 20Gy (Optimal)
		V_{30Gy}	≤ 30% (Optimal)
	Spinal Cord PRV	Max Dose	≤ 45Gy / ≤ 40Gy for 55Gy/20#
	Lungs-GTV	V_{20Gy}	As low as possible
		V_{5Gy}	As low as possible
	Heart	Mean Dose	As low as possible
		V_{30Gy}	As low as possible
	Spinal Cord PRV	Max Dose	Max (As low as possible)

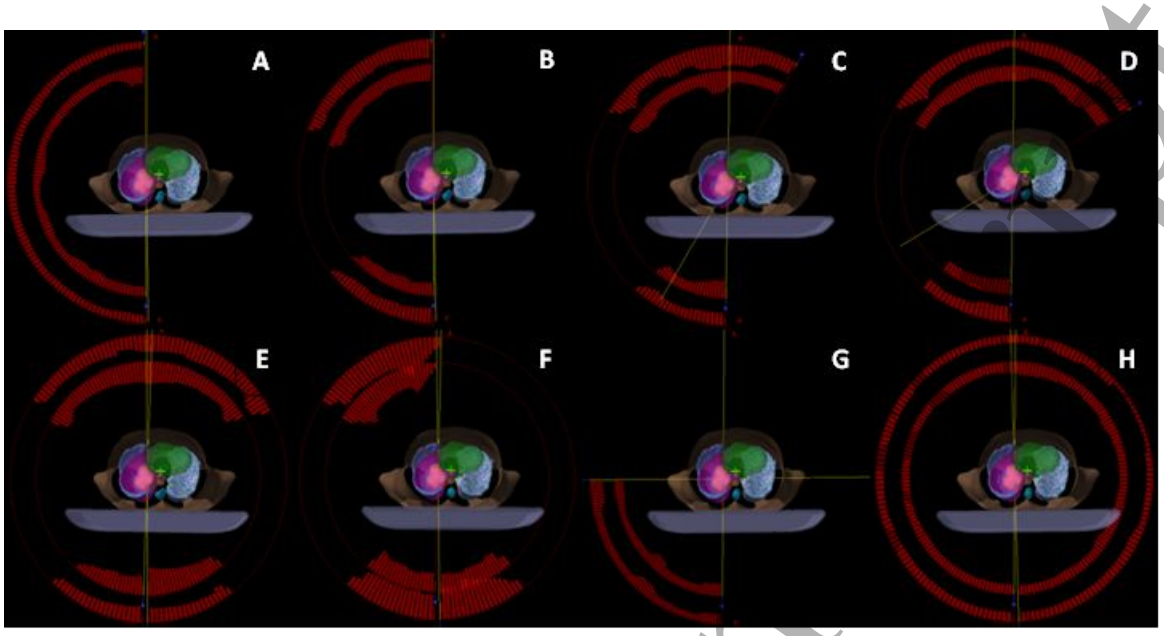
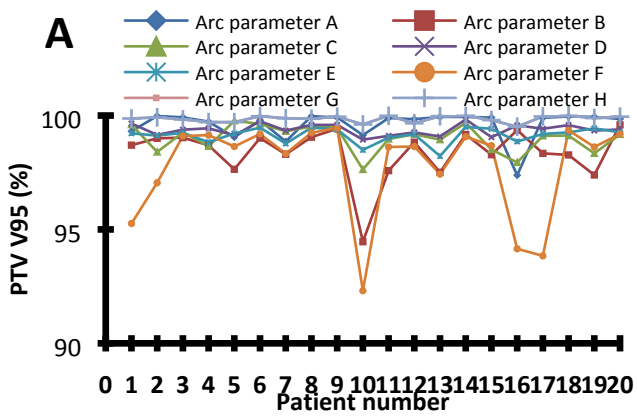
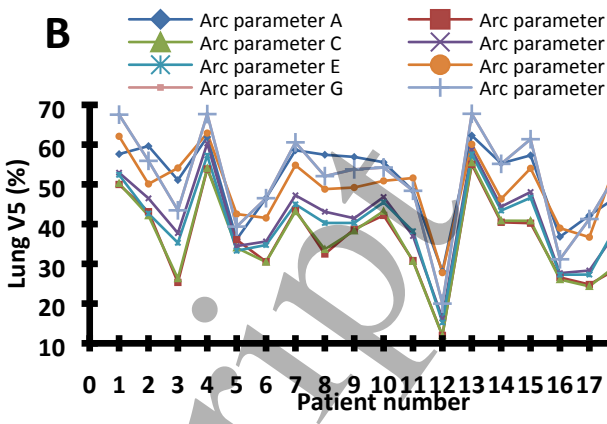


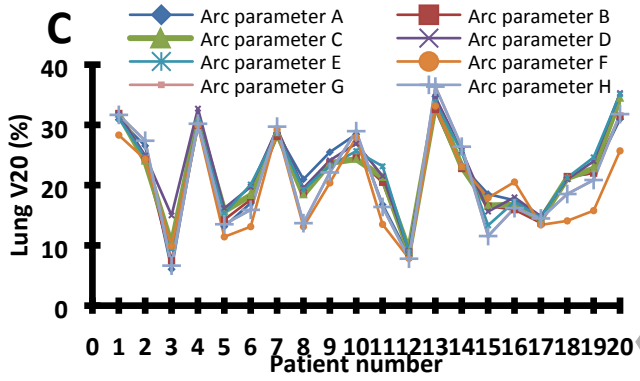
Figure 1. Displays arc parameters for test plans and clinical plans (see Table 3 for description of start and stop angle and avoidance sectors used).

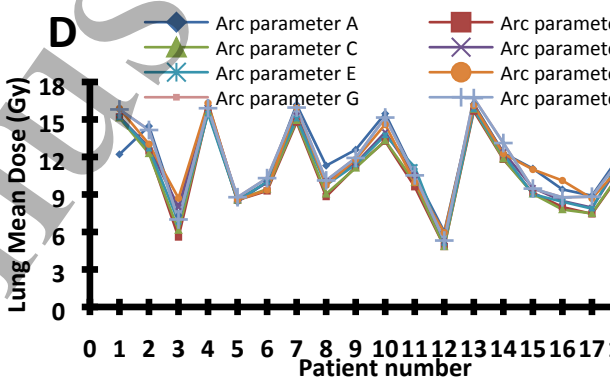
Table 3: Arc parameters used for planning test and the clinical plans (arc parameters are displayed in figure 1).

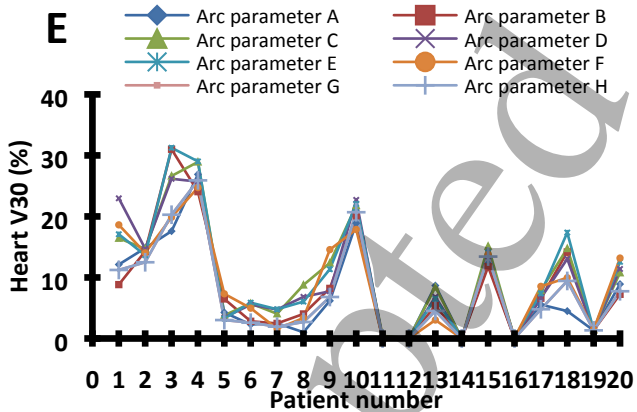
Arc parameter	**Start and stop angle**	**Avoidance sector(s)**
A	0° to ± 180°	None
B	0° to ± 180°	For right sided tumours: 220° to 300° For left sided tumours: 140° to 60°
C	± 30° to ± 180°	For right sided tumours: 220° to 300° For left sided tumours: 140° to 60°
D	± 60° to ± 180°	For right sided tumours: 220° to 300° For left sided tumours: 140° to 60°
E	181° to 179°	220° to 300° and 140° to 60°
F	181° to 179°	For right sided tumours: 220° to 300° and 0° to 140° For left sided tumours: 140° to 60° and 0° to 220°
G	181° to 270° Or 179° to 90° Or 90° to 0° or 270° to 0°	None
H	181° to 179°	None

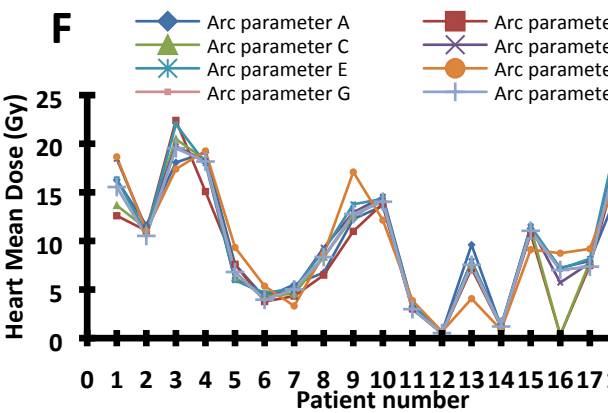


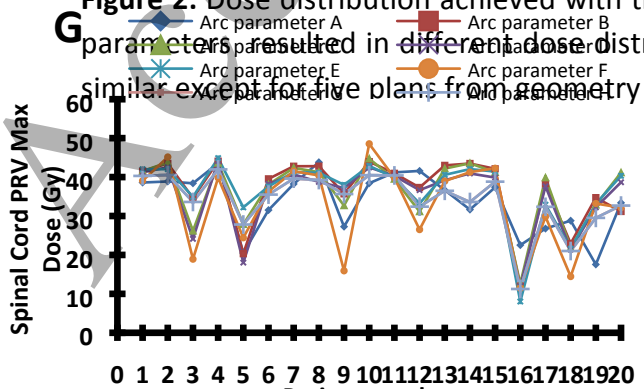












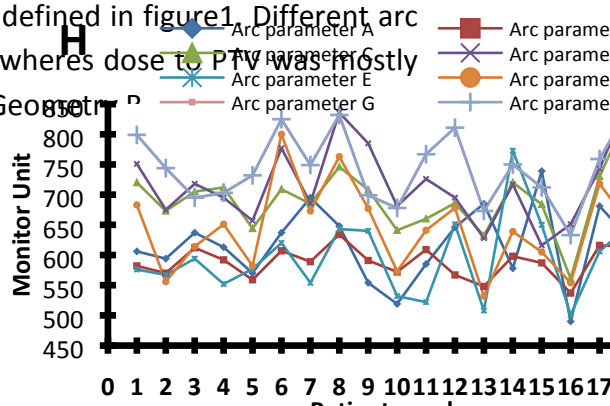


Figure 2: Dose distribution achieved with the different arcs defined in figure1. Different arc parameters resulted in different dose distribution to OAR, wheres dose to PTV was mostly similar except for five plans from geometry F and one from Geometry B.

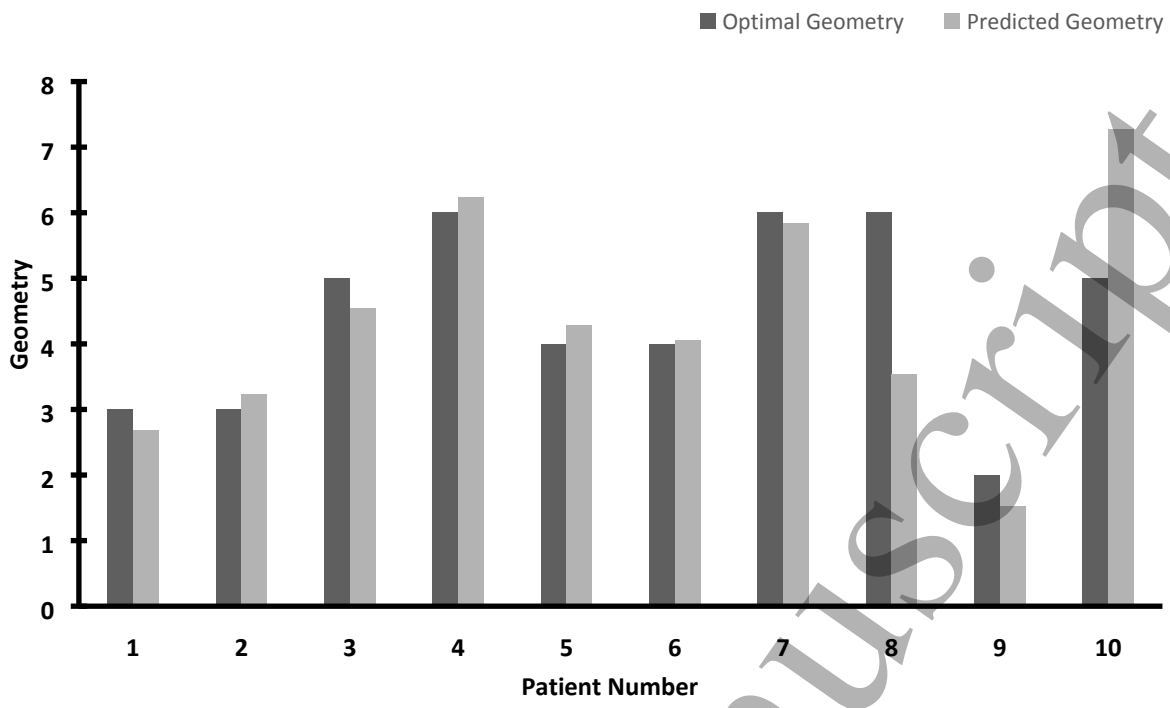


Figure 3. Showing predicted and optimal parameters for the test patients. The arc parameters displayed in the figure 1 were numbered from 1 to 8 (A = 1, B = 2, …, H = 8) to develop the model. The optimal arc parameters were predicted using equation 3 and the predicted parameters were rounded to the nearest number.

Table 4: Dose distribution achieved with different arc parameters compared to the half-arc parameter (A) and p values.

Plan Parameters			A	B	p	C	p	D	p	E	P	F	p	G	p	H	p
PTV	V_{95}	≥ 99%	99.6	-1.2	0.000	-0.6	0.001	-0.2	0.145	-0.5	0.002	-1.4	0.000	-1.8	0.000	0.2	0.061
	V_{107}	< 0	0.0	0.1	0.001	0.1	0.001	0.2	0.014	0.1	0.000	0.2	0.030	0.8	0.010	0.0	0.240
Spinal Cord PRV	$D_{0.01cc}$	< 45Gy	33.8	2.9	0.069	2.6	0.158	1.5	0.381	2.7	0.120	4.5	0.009	-0.8	0.694	0.3	0.803
Lungs-GTV	V_{5Gy}	< 60%	51.6	-13.6	0.000	-14.1	0.000	-9.3	0.000	-10.6	0.000	-14.8	0.000	-1.8	0.165	0.4	0.734
	V_{20Gy}	< 35%	21.8	-0.5	0.224	0.2	0.743	1.2	0.064	0.5	0.439	-0.5	0.340	-2.2	0.006	-0.8	0.195
	MLD	< 20Gy	11.9	-1.0	0.001	-0.9	0.005	-0.3	0.173	-0.5	0.062	-1.0	0.003	-0.2	0.432	-0.1	0.821
Heart	V_{30Gy}	< 46%	6.8	1.0	0.283	2.7	0.002	2.2	0.017	2.8	0.011	1.0	0.208	1.6	0.046	0.0	0.938
	MHD	< 26Gy	9.0	-0.8	0.138	-0.4	0.426	0.3	0.388	0.5	0.259	-1.2	0.014	0.5	0.371	0.0	0.991
Total MU			626.8	-33.8	0.017	69.8	0.000	91.3	0.000	-19.5	0.283	27.2	0.035	13.5	0.497	123.2	0.000
Body (mean Gy)			6.9	-0.5	0.000	-0.5	0.000	-0.2	0.002	-0.3	0.004	-0.5	0.000	-0.2	0.010	0.1	0.082

Table 5: Dose differences between the original clinical plans (i.e. geometry A) and the clinician chosen plans selected for individual patient.

Structures	Clinical Goals	Clinical	SD		Mean	SD	p
PTV	V_{95}	99.61	0.63	-0.78		0.48	0.000
	V_{107}	0.01	0.02	0.09		0.13	0.003
CI[†]		1.19	0.05	0.03		0.08	0.028
HI[††]		0.06	0.02	-0.02		0.01	0.000
Spinal Cord PRV	$D_{0.01cc}$	34.79	6.62	2.31		9.14	0.119
Lungs-GTV	V_{5Gy}	52.17	9.60	-15.05		11.20	0.000
	V_{20Gy}	22.12	7.96	-0.48		7.79	0.348
	Mean Dose	12.06	3.10	-0.97		3.52	0.003
Heart	V_{30Gy}	7.69	7.45	0.53		8.39	0.453
	Mean Dose	9.35	5.30	-1.39		5.23	0.008
Total MU		624.70	69.18	12.10		48.95	0.375
Body (mean Gy)		7.11	1.84	-0.54		1.88	0.000

[†]Conformity index (CI- calculated using equation 1), [††]Homogeneity index (HI- calculated using equation 2)

Table 6: Dose differences between the original clinical plans (i.e. geometry A) and the plans predicted using the knowledge-based planning model.

Structures	Clinical Goals	Clinical	SD	Mean (Predicted Geometry)	SD	p
PTV	V_{95}	99.87	0.63	-0.81	0.08	0.000
	V_{107}	0.02	0.02	0.23	0.02	0.003
CI[†]		1.19	0.05	0.07	0.10	0.095
HI[††]		0.06	0.03	0.02	0.01	0.007
Spinal Cord PRV	$D_{0.01cc}$	30.33	6.62	-1.11	6.19	0.119
Lungs-GTV	V_{5Gy}	49.32	9.6	-13.51	12.36	0.000
	V_{20Gy}	19.34	7.96	1.00	6.73	0.136
	Mean Dose	11.13	3.1	-0.83	2.78	0.033
Heart	V_{30Gy}	5.53	7.45	1.02	7.91	0.090
	Mean Dose	7.39	5.3	-0.41	5.25	0.031
Total MU		662.75	69.18	14.6	57.4	0.559
Body (mean Gy)		5.95	1.84	-0.66	1.70	0.077

[†]Conformity index (CI- calculated using equation 1), [††]Homogeneity index (HI- calculated using equation 2)

Table 7. Plan complexity metrics calculated for both original clinical plans and the test plans.

Complexity metrics	Mean Clinical plans	SD	Mean Test plans	SD	p value
MUperGy	224.65	21.93	242.01	9.95	0.001
MUPerDegree	1.73	0.17	2.36	0.10	<0.001
MeanDoseRate	483.27	38.94	521.97	8.08	<0.001
MeanLeafSpeed	10.82	0.48	7.53	0.39	<0.001
MeanLeafTravelPerMU	0.97	0.09	1.00	0.06	0.144
FractionMUthrough<5cc	0.00	0.00	0.00	0.00	0.056
IslandsPerCP	3.62	1.54	3.66	0.44	0.911
MeanIslandSize	1433.82	694.14	1317.52	201.73	0.410
FractionIslandBelow1cc	0.47	0.18	0.49	0.04	0.674
SAS02	0.17	0.04	0.17	0.02	0.813
SAS05	0.20	0.05	0.20	0.02	0.582
SAS10	0.25	0.07	0.26	0.02	0.292
SAS20	0.36	0.09	0.37	0.03	0.376