Title page:

Predicting personalised and progressive adaptive dose escalation to gross tumour volume using knowledge-based planning models for inoperable advanced-stage non-small cell lung cancer patients treated with volumetric modulated arc therapy

Type of manuscript: Full paper

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Declaration of funding source and conflicts of interest:

NST was supported in part by a University of Hull PhD studentship. The authors thank Varian Medical Systems for providing Velocity software for this research.

The authors declare no potential conflicts of interest.

Abstract

***Objectives*:** Increased radiation doses could improve local control and overall survival of lung cancer patients, however, this could be challenging without exceeding organs at risk (OAR) dose constraints especially for patients with advanced-stage disease. Increasing OAR doses could reduce the therapeutic ratio and quality of life. It is therefore important to investigate methods to increase the dose to target volume without exceeding OAR dose constraints.

***Methods*:** Gross tumour volume (GTV) was contoured on synthetic computerised tomography (sCT) datasets produced using the Velocity adaptive radiotherapy software for eleven patients. The fractions where GTV volume decreased compared to that prior to radiotherapy (reference plan) were considered for personalised progressive dose escalation. The dose to the adapted GTV ($GTV_{Adaptive}$) was increased until OAR doses were affected (as compared to the original clinical plan). Planning target volume (PTV) coverage was maintained for all plans. Doses were also escalated to the reference plan ($GTV_{Clinical}$) using the same method. Adapted, dose-escalated, plans were combined to estimate accumulated dose, D_{99} (dose to 99%) of $GTV_{Adapted}$, PTV D_{99} and OAR doses and compared with those in the original clinical plans.

Knowledge-based planning (KBP) model was developed to predict D_{99} of the adapted GTV with OAR doses and PTV coverage kept similar to the original clinical plans; prediction accuracy and model verification were performed using further data sets.

***Results*:** Compared to the original clinical plan, dose to GTV was significantly increased without exceeding OAR doses. Adaptive dose-escalation increased the average D_{99} to $GTV_{Adaptive}$ by 15.1Gy and 8.7Gy compared to the clinical plans. The KBP models were verified and demonstrated prediction accuracy of 0.4% and 0.7% respectively.

***Conclusion*:** Progressive adaptive dose escalation can significantly increase the dose to GTV without increasing OAR doses or compromising dose to microscopic disease. This may increase overall survival without increasing toxicities.

***Keywords*:** Volumetric modulated arc therapy, Dose escalation, Non-small cell lung cancer, Personalized radiotherapy, Treatment planning optimization, Knowledge-based planning model.

Introduction

Lung cancer is the third most common cancer in the UK accounting for 21% of cancer-related deaths (1). Approximately 85% of these patients are diagnosed with non-small cell lung cancer (NSCLC) and 30% or more NSCLC patients have inoperable locally advanced disease at diagnosis (1). Until recently, the standard of care for advanced-stage inoperable NSCLC patients was chemo-radiotherapy; survival of these patients remains poor with a 5-year overall survival of only 15% (1). Recent clinical trials showed improvement in overall survival in the patients receiving immunotherapy (2, 3).

Several studies have reported that high radiation dose could improve local control and hence the overall survival compared to low dose radiotherapy for NSCLC patients (4-14). However, dose escalation is often restricted by the presence of critical healthy structures in close proximity to the target volume. A significant increase of radiation dose to these organs at risk (OAR) could increase toxicities to an unacceptable level, especially when treating inoperable advanced-stage tumours (15, 16). Additionally, it has been suggested that dose escalation could stimulate immune checkpoint inhibitors (ICI) that could considerably increase pneumonitis (17). Therefore, there are multiple pathways towards toxicity and so it is crucial to limit OAR doses as low as possible whilst escalating the tumour doses.

A number of methods have been proposed to escalate doses for advanced lung cancer patients, including conventional fractionation or hypo-fractionated regimes. However, dose escalation with conventional fractionation increases overall treatment time allowing further scope for tumour repopulation before the tumour is controlled (18-22). This has a detrimental effect on local control and overall survival (18-22). Therefore, dose escalation with standard-dose fractionation cannot be considered a standard of care (23) and it is recommended to shorten the overall treatment time to improve survival (4-6, 8, 9, 11-14, 24, 25). Additionally, stereotactic ablative radiotherapy studies reported significant improvement in survival for limited-stage peripheral NSCLC patients (26). Clearly, the hypofractionation technique also introduces efficiency and better utilisation of expensive clinical resources.

Different techniques have been studied to facilitate dose-escalation, such as using positron emission tomography (PET) scans for contouring the boost volume (8), enabling specific targeting of volumes expected to benfit from higher doses, whilst other studies used inhomogeneous dose escalation to $GTV_{Clinical}$ (i.e., gross tumour volume contoured on planning CT) (9, 12). In addition, Higgins *et al* (13) and Doyen *et al* (27)studied combinations

of conventional fractionation radiotherapy with stereotactic ablative body radiotherapy. Higgins *et al* reported that 20 Gy in two fractions following 44 Gy in 22 fraction regime was a tolerable dose (13) as no grade 3 or higher toxicities were reported whereas, Doyen *et al* reported that three fractions of 11 Gy were safe following 46 Gy in 23 fraction chemo-radiotherapy (27).

Several methods have been used for dose escalation, however, none of the studies has evaluated the possibility of multiple adaptive dose escalation to the adapted GTV during the course of radiotherapy for inoperable advanced-stage NSCLC patients. In this study, a personalised progressive dose escalation to adapted GTV was studied without increasing OAR doses compared to the original clinical (i.e., 'homogeneous' – no dose escalation plan). Furthermore, knowledge-based planning models were developed to predict dose to the initial dose escalation and the adapted (during treatment) dose escalation whilst maintaining OAR doses similar to the non-dose escalation plans.

Methods

Data collection

The data for twenty-five previously treated patients was curated from our Eclipse treatment planning system database; patient's demographics, histopathology, tumour staging, PTV volume in a cubic centimetre (cc), $GTV_{Clinical}$ volume, adapted GTV ($GTV_{Adaptive}$) volume and dose-volume histogram (DVH) for target structures were collected.

Treatment planning

The planning protocol used for this study mirrors that used in a previous study which we have previously (28) described. Where patients are able to comply, a four-dimensional computerised tomography scan (4DCT) (as well as a free-breathing (FB) scan, otherwise only the latter is used. To capture full tumour motion, the gross tumour volume (GTV) contoured on at least three (of the ten) binned phases on the 4DCT (e.g. max-inhale, max-exhale, and mid-phase). These are transcribed to the FB scan and their union defines the 4D-GTV. The FB scan is used to produce treatment plan. The 4D-GTV/ GTV were isotropically expanded, by 0. 6cm for squamous cell carcinomas and 0.8 cm for adenocarcinomas respectively, to create the ITV (4DCT) / CTV (3DCT). A 0.5 cm isotropic margin was applied to the ITV for 4D patients and a 0.9 cm circumferential and 1.2 cm superior and inferior margin was applied to the CTV (3DCT) to defined the PTV.

Plans with two partial arcs (6MV, flattened beams) were used for all patients, care was taken to minimise dose to the contralateral lung by not allowing direct beam entry to it. They were produced with the Eclipse™ treatment planning system (Version 13.7, Varian Medical Systems, Palo Alto, CA); using the Acuros® algorithm (dose to water), and a uniform dose grid of 0.25 cm. The patient plans were prescribed to 55 Gy in 20 fractions (the prescription dose was the same for both GTV and PTV in the clinical plans) and optimised to meet goals presented in Table 1. The normal tissue objective (NTO) function was used to reduce dose to the normal tissues (29),. with default (i.e., distance from target border 1.0 cm, start dose 105%, end dose 60% and fall-off 0.05) with a priority set similar to PTV.

Assessment for adaptive planning

Production of synthetic CT (sCT): each fraction's pre-treatment cone beam computerised tomography (CBCT) verification data sets and planning CT (pCT) data sets, were imported into the Velocity 'adaptive radiotherapy' software (Velocity 4.0, Varian Medical System, Palo Alto, CA). The CBCT images are reconstructed with a slice thickness 0.3cm to match the the planning CT images.

To facilitate the image processing within Velocity, the following process (see (28) for further detail) was followed:

1) to remove the impact of residual setup errors (30);

the pCT and CBCT images were rigidly registered, using the same transformation obtained during the respective treatment fraction

2) to produce the sCT; the CBCT images were deformed to match the pCT images

3) using the deformation matrix, obtained in step 2, a secondary structure data set was produced in the sCTs from the original structures (including GTV and OARs),

4) The registration and volumes for each sCT were reviewed.

Evaluation of dosimetric variations: The sCT datasets were imported into the treatment planning system. The associated GTV for each fraction was reviewed and edited where required by experienced clinical oncologists to account for tumour baseline shift and anatomical changes. Furthermore, clinical and planning target volumes were produced on each sCT by applying the same margin as the clinical plan. The GTV contoured on each fraction

was evaluated and the fractions where the GTV volume reduced compared to the $GTV_{Clinical}$ were noted and considered for dose escalation.

Table 1. 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%
		V_{5Gy}	≤ 60%
	Heart	Mean dose	≤ 26Gy
		V_{30Gy}	≤ 46%
Wish-list priority	PTV	$V_{95\%}$	≥ 99%
	Lungs-GTV	V_{5Gy}	< 60%
		V_{20Gy}	≤ 30%
	Heart	Mean Dose	≤ 20Gy
		V_{30Gy}	≤ 30%

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)

Dose escalation strategies

For this planning study, two dose-escalation strategies were considered for each patient:

1. Personalised Dose Escalation (PDE); where dose to the $GTV_{Clinical}$ was escalated, beyond the conventional prescription dose, as achievable given the individual patients delineated anatomy.
2. Adaptive Dose Escalation (ADE); where dose escalation was considered for individual 'fractions' when the $GTV_{Adaptive}$ volume seen on the sCT was reduced in comparison to the previous fractions.

For both PDE and ADE plans, the dose to GTV was allowed to be increased/ escalated whilst constraining the PTV dose to that intended in the clinical protocol (see Table 1) and the OAR doses were kept similar to those obtained in the original clinical plan. A mixture of traditional and bespoke prescriptions within PTV (depending on the patient's anatomy) were used, we characterise this prescription configuration as being heterogeneous.

Adapted dose-volume histogram: The dose to 99% (D_{99}) of $GTV_{Clinical}$, $GTV_{Adaptive}$ and PTV volumes were recorded from the PDE plan and for the ADE fractions and the total estimated dose was calculated for target structures and OARs by summation over all fractions. The distribution for an adapted fraction was used for subsequent fractions until a new adaption was made, to estimate the total dose the GTV, PTV and OAR volumes using this technique.

The OARs doses for each metric (see Table 1) were calculated and compared with the original clinical plan.

Biological equivalent dose (BED): BED was calculated for $GTV_{Clinical}$, $GTV_{Adaptive}$, and PTV_{DVH} volumes using $D_{99\%}$ statistics for the original clinical (no dose escalation) plans and for dose escalation plans (PDE: $GTV_{Clinical}$ and $PTV_{Clinical}$; ADE: $GTV_{Adaptive\_Total}$ and $PTV_{Adaptive\_Total}$). BED was calculated using equation 1 with an α/β value of 10 (this is referred as BED_{10} below). Finally, a total BED was calculated by summing BED over all fractions.

$$BED_{10} = nd\left(1 + \frac{d}{\alpha/\beta}\right) \quad \textbf{1}$$

Where, n is the number of fractions (n = 20) and d is dose per fraction.

Tumour control probability (TCP): TCPs for $GTV_{Clinical}$ and $GTV_{Adaptive}$ and $PTV_{Clinical}$ and $PTV_{Adaptive}$ structures were calculated using the Linear Quadratic (LQ: this is referred as TCP_{LQ} below) model within the Biosuite software (31) for clinical plans, fraction '0' plans and for total plans using the parameters identified by Nahum et al for non-small cell lung cancer. These are, an α/β = 10 Gy, α = 0·307 Gy^{-1}, a clonogen density of 10^7 and a clonogen doubling time of 3·7 days (32). Note: here we acknowledge, the use of the generic parameters for TCP_{LQ} calculations and that the TCP values are used for relative comparison only in this study.

Development of knowledge-based planning (KBP) Model

Knowledge-based planning models were developed to predict achievable D_{99} of $GTV_{Clinical}$ and $GTV_{Adaptive}$ without increasing OAR doses. Two KBP models were developed to predict achievable dose escalation, first to the $GTV_{Clinical}$ and the second for $GTV_{Adaptive}$. The process to develop the model consists of finding plan signatures (volumes) that show strong correlation to the achieved dose metrics of interest. The (best-fit) relationship describing the correlation is then used as the predictive function. A number of patient-specific volumes were considered including, $GTV_{Clinical}$, $GTV_{Adaptive}$ $PTV_{Clinical}$, $PTV_{Adaptive,}$ PTV-$GTV_{Clinical\ and\ Adaptive}$, Lungs-GTV and Heart to deveop the models. Dose to $GTV_{Clinical}$, $GTV_{Adaptive}$ $PTV_{Clinical}$, $PTV_{Adaptive}$ Lungs-GTV and Heart structures were recorded and compared with the doses achieved in clinical plans, ensuring tha the OAR doses and target coverage is not significantly affected in the dose escalation plans (see Figure 2 and Table 2). Doses achieved to the $GTV_{Clinical}$ and $GTV_{Adaptive}$ structures were correlated with the $GTV_{Clinical}$, $GTV_{Adaptive}$ volumes to develop the models.

PDE: The model was developed using fifteen patients plans and verified using the remaining ten patients' plans. For the verification, the test plans were optimised to achieve the predicted D_{99} to $GTV_{Clinial}$ whilst ensuring the OARs did not exceed the doses achieved in the original clinical plan and the $PTV_{Clinical}$ received the originally intended (prescribed) dose. Differences between predicted and the achieved doses were calculated.

ADE: A total of seven patients' (n = 20 plans) data were used to developed a model. The model was then verified using four independent patients's (n = 11 plans) data. Finally, differences between predicted and the achieved doses to $GTV_{Adaptive}$ were calculated.

Results

Personalised and Adaptive dose escalation: A total of twenty-five patients were initially included in this study; however, only eleven patients demonstrated a reduction in GTV volume 'during' their treatment and therefore considered for adaptive dose escalation.

Development of KBP models: A number of volumes and their combination were considered to develop the models. For PDE model, the $GTV_{clinical}$ size in cubic centimetre showed strongest correlation with the achieved D_{99} of $GTV_{Clinical}$ (see Figure 1A). Whereas, for ADE, percentage change in $GTV_{Adaptive}$ compared to the $GTV_{Clinical}$ had strongest correlation with the percentage increase in D_{99} of the $GTV_{Adaptive}$ (see Figure 1B).

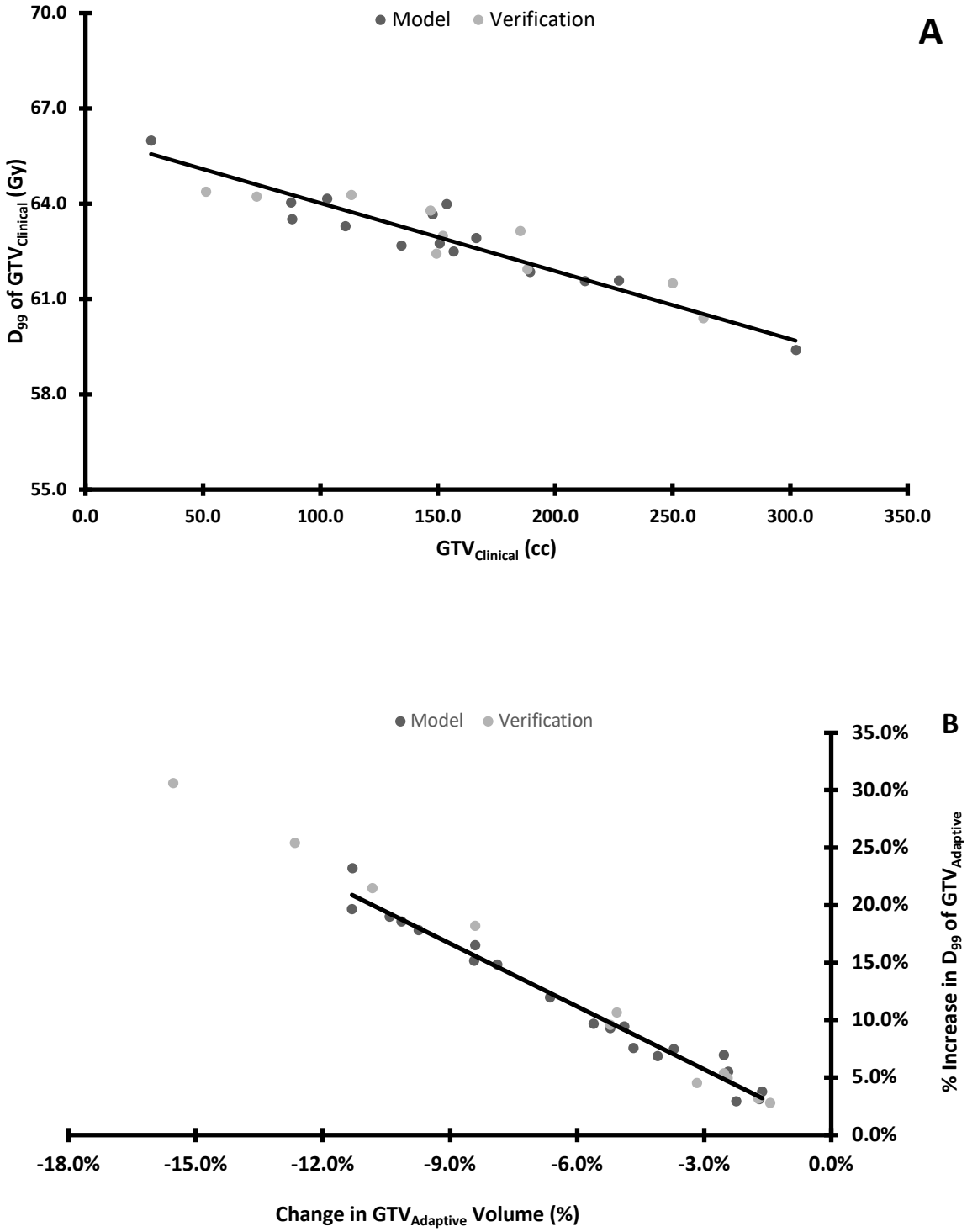

Figure 1: the plots showing models produced to predict the achievable D_{99} of $GTV_{Clinical}$ (A) and $GTV_{Adaptive}$ (B) without exceding OAR doses achived in the non-dose escelated plans. The models were verified using the independent data set and the results are shown in the plots. The variable, constant and the R^2 values for model A were -0.0214, 66.159 and 0.886 and for model B, -0.1.826, -0.003 and 0.974 respectively.

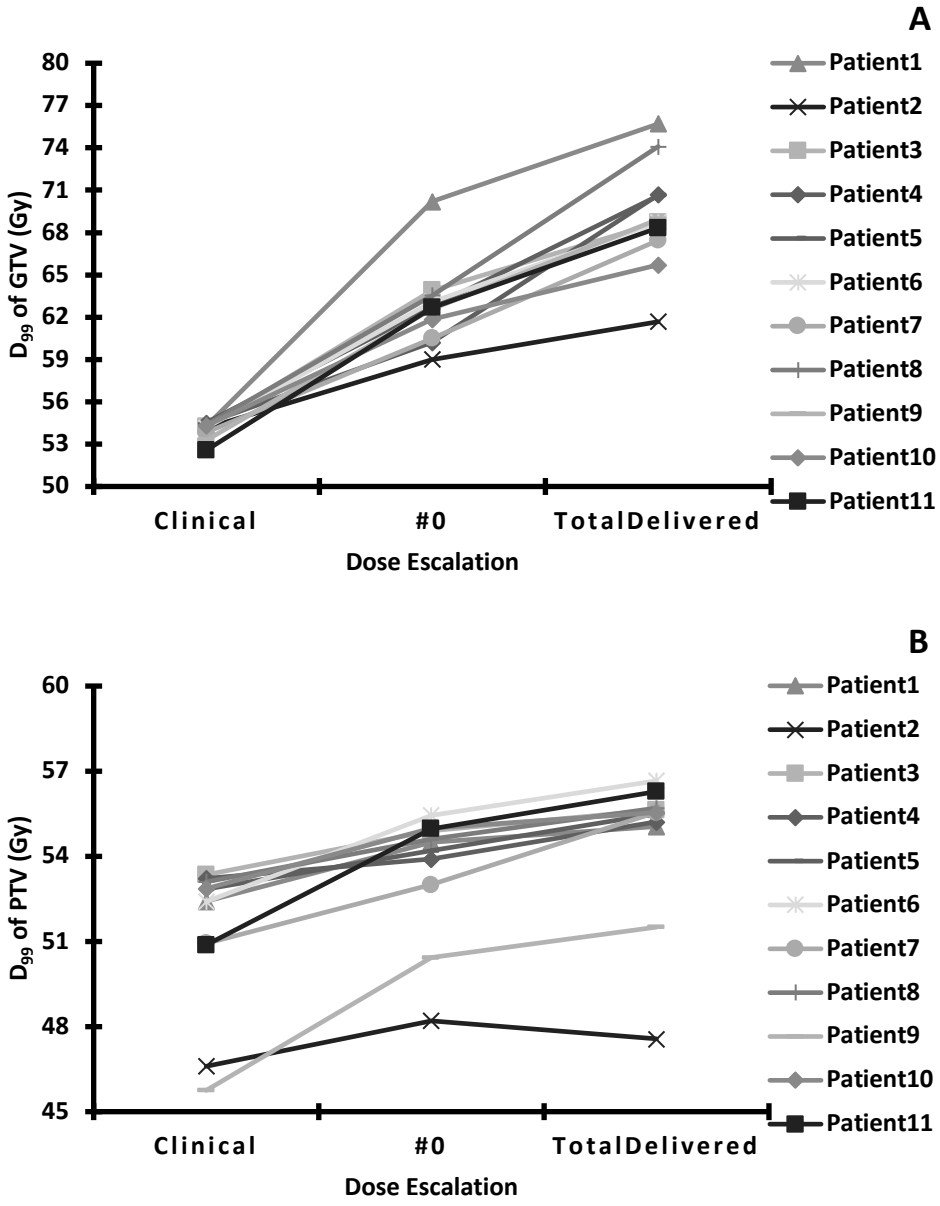

Figure 2: Adaptive dose-escalation comparison.

Plots depict doses escalated to GTV volume (A) and doses received by PTV_{DVH} volume (B) in fraction 0 and total plan compared to the original clinical plans (B). Doses reported here are to the 99.0 % of target volumes.

The average dose escalation results are given in Table 2 and Figure 2. The results show that, an average total dose to the composite GTV object through the treatment can be increased by 15.1 Gy (28.0%) with personalised and adapted dose escalation method (i.e, PDE and ADE) compared to the original plans (without dose escalation). Whereas, it was increased by 8.7 Gy (16.1%) with single personalised dose escalation (i.e., PDE). Neither statistical nor clinical

differences were seen in the OAR doses between dose-escalated and no dose escalated clinical plans (Table 2 and Figure 2).

BED and TCP: the BED_{10} and TCP_{LQ} were calculated and were seen to increase significantly for $GTV_{Clinical}$, $GTV_{adaptive}$, $PTV_{Clinical}$ and $PTV_{Adaptive}$ volumes, compared to those for the original clinical plans. BED_{10} for $GTV_{Clinical}$ and $PTV_{Clinical}$ increased by 20.3% and 5.3% for PDE plans and 35.7% and 7.7% respectively for adapted plans (i.e., PDE + ADE) based on a comparison of the accumulated doses against the original clinical plans. TCP_{LQ} values increased from 36.5% to 84.5% and 35.0% to 60.0% for PDE plans and 36.5% to 93.9% and 35.0% to 71.0% for accumulated plans for $GTV_{Adaptive}$ and $PTV_{Adaptive}$ volumes respectively (see Table 2).

Table 2: Mean dose-volume statistics for the original clinical plans and mean difference in target and OAR dose-volume compared to the original clinical plans. Total_DE shows the mean dose difference between original clinical plans and the total estimated escalation doses (PDE and ADE).

Parameters		**Original Clinical Plans**	**PDE - Clinical (average)**	**P**	**Total_DE (average)**	**P**
PTV	$D_{99\%}$ (Gy)	51.3	2.3	0.045	3.3	0.010
GTV	$D_{99\%}$ (Gy)	54.0	8.7	0.000	15.1	0.000
Lungs-GTV	V_{5Gy} (%)	46.0	-0.3	0.959	0.4	0.929
	V_{20Gy} (%)	17.8	-0.7	0.761	-0.6	0.785
	Mean Dose (Gy)	10.5	0.2	0.886	0.4	0.721
Heart	V_{30Gy} (%)	6.4	-0.5	0.848	0.1	0.969
	Mean Dose (Gy)	9.5	-0.2	0.924	0.2	0.950
Spinal Cord PRV	$D_{0.01cc}$ (Gy)	32.8	-2.7	0.509	-2.3	0.590
PTV	BED_{10} (Gy_{10})	64.5	3.4	0.044	5.0	0.009
GTV	BED_{10} (Gy_{10})	68.6	13.9	0.000	24.5	0.000
PTV	TCP_{LQ} (%)	35.0	25.0	0.000	36.0	0.000
GTV	TCP_{LQ} (%)	36.5	48.0	0.000	57.1	0.000

Validation of knowledge-based planning models: The prediction accuracy of the models was verified using independent data sets. PDE, the mean difference between predicted and the achieved D_{99} $GTV_{Clinical}$ was 0.4% (range = 1.3% to -0.7%) (Figure 3A) and for ADE, the average difference was 0.7% (range = 2.5% to – 1.6%) (Figure 3B). The OAR doses achieved in the adapted plans were not statistically significantly different compared to those in the original clinical plans and whereas $PTV_{Clinical}$ and $PTV_{Adaptive}$ coverage improved compared to the clinical plans (Figure 1, Figure 3 and Table 2).

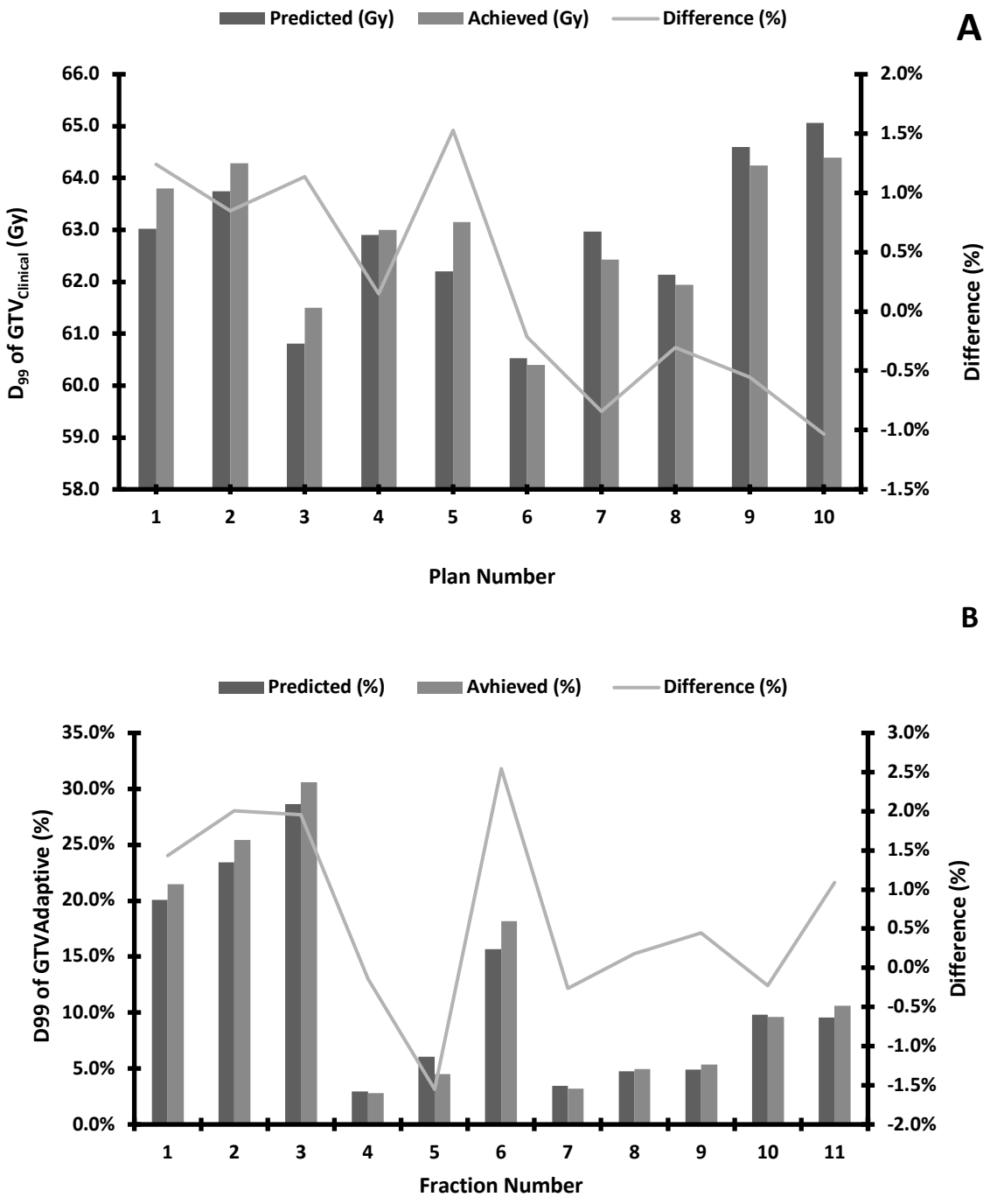

Figure 3: Verification of KBP models. Image A and B, showing predicted and achieved doses for $GTV_{Clinical}$ and $GTV_{Adaptive}$ and the percentage difference between achieved and predicted doses.

Discussion

Several studies have demonstrated that increasing prescribed doses can lead to an increase in the overall survival in NSCLC patients, including those with inoperable advanced stage disease (7, 10) (4-6, 8, 9, 11-14). However, an increase in organs at risk doses can adversely affect patients' quality of life and, potentially, survival. It is therefore important to investigate methods for dose escalation that increase the therapeutic ratio by increasing the probability of disease control and by reducing the probability of toxicity.

Single inhomogeneous 'personalised' dose escalation was studied by Nielsen et. al., (9), optimising prescription dose to the pre-treatment imaging. They reported an increase of 3.6 Gy (from 64.8 ± 0.9 Gy to 68.4 ± 2.9 Gy) dose to the $GTV_{98\%}$ whereas, in our study dose to GTV $D_{99\%}$ increased by 8.7 Gy (from 54.0 ± 0.6 Gy to 62.8 ± 2.9 Gy). However, the present study reports personalised progressive adaptive dose-escalation where, following personalisation, the opportunity to dose escalate was continually assessed prior to each fraction. In this method, OAR and PTV_{DVH} (see Figure 1B) dose coverage were kept very similar to the original (non-dose escalated) plans that had been used clinically. Doses were escalated whilst keeping the total number fractions the same, with the dose per fraction to the adapted GTV increased in each escalated plan.

A number of patients in this study had treatment volumes comprising of primary plus nodal volumes and some had volumes in close proximity to the spinal cord volume, nevertheless, adaptive dose escalation was achievable whilst keeping the OAR doses similar to the original clinical plans for all patients. We noted that patients with apical tumours were able to receive higher doses compared to the patients where tumour appears on the same slices as the heart and tumours near the spinal cord.

The application of our method to identify patients that would benefit from progressive dose escalation following the initial personalisation of prescription dose increased their mean GTV_{DE} dose and TCP_{LQ} by 10.2% and 10.8% respectively compared to those receiving personalised dose (escalated) prescription only, without increasing OAR doses or compromising PTV_{DVH} coverage. Thereby demonstrating that personalised progressive adaptive dose escalation is feasible and may lead to significantly increased tumour control probability compared to the standard or personalised prescription plans for inoperable advanced-stage NSCLC patients.

A knowledge-based planning model was successfully developed in this study to predict maximum achievable doses to adapted GTV using our approach. Accuracy of the models was assessed, the prediction accuracy for PDE (initial plan personalisation) plans and ADE plans (i.e., subsequent adaption) was similar and was deemed acceptable to use clinically. Could therefore be used as efficient tools to predict if spending time performing additional plans, either in the planning stage or at the Linac to consider 'on table adaption; would be worthwhile. From a pragmatic perspective, the benefit afforded by the use of the KBP planning prediction of which patients may benefit is the streamlining of the decision making process for on-table adaption. Without requiring a full dose calculation, appropriate patients can be quickly identified and in the case that a beneficial adaption is not predicted the planned treatment can continue without any further time-consuming interruption.

One of the objectives of this study was to assess if dose to GTV can be increased without increasing OAR doses compared to the original clinical plans (i.e., the homogeneous plan) so that tumour control probability can be increased without increasing toxicities or reducing the quality of life; our results showed this to be possible. Furthermore, potentially significant increases in TCP, over the standard or personalised prescription plans were demonstrated by the personalised progressive adaption strategy. Whilst such calculations may be considered subjective, we considered the results of the Biosuite software to at least indicate relative probabilities for the structures considered.

This objective was set to ascertain if we could achieve personalisation and progressive adaptive dose-escalation within (potential) treatment toxicities that we are clinically comfortable with. We consider this to be an experience-based isotoxicity regime, however, we acknowledge that further and potentially more beneficial dose escalation might be achievable if we extended our isotoxocity considerations to literature-based tolerance doses. However, although increased dose to target volume could improve local control, increases in OAR doses could significantly affect survival (33, 34) and so we considered such as approach outside the scope of our study.

In this study, we assumed that the adaptive GTV contoured sCT (produced using CBCT) represents the 'true' GTV (i.e., similar to the one contoured on 4DCT scans – including full extend of motion). As the CBCT image was acquired over a period of few breathing cycles, it is considered to capture or demonstrate full tumour motion as seen on the 4DCT images.

Furthermore, we did not investigate if the CBCT slice thickness used locally has any impact on quality of the sCT images and the target delineation. Whereas these might be considered as limitations of the study, however for prospective clinical implementation, 4DCT scan and/ or PET-CT scan will be used to accurately delineate target and OAR volumes thus removing the impact of these observations. However, the models developed here will help identifying patients for dose escalation based on evidence (GTV contoured on CBCT images) acquired during the delivery of the treatment.

Conclusion.

We demonstrated that a Personalised Progressive adaptive dose-escalation strategy could significantly increase the dose to adapted GTV and relative TCP_{LQ} without increasing OAR doses. This may improve local control and overall survival of the patients with inoperable advanced stage NSCLC without an increase in toxicities compared to the non-doses escalated plans. Limiting OAR dose will also help these patients maintaining the quality of life and we based our dose levels on our clinical experience. In this study, we present the first report of the development of a knowledge-based planning model for rapidly predicting D_{99} of the GTV, whilst maintaining OAR doses and PTV coverage similar to our current clinical protocol requirements, thus remaining within our experience bounds. The model can be used as predictive tools to assess the potential for adaption prior to performing the treatment planning itself and therefore to streamline the adaptive planning decision-making processes.

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