Multiple anatomy optimization of accumulated dose

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Purpose: To investigate the potential advantages of multiple anatomy optimization (MAO) for lung cancer radiation therapy compared to the internal target volume (ITV) approach.

Methods: MAO aims to optimize a single fluence to be delivered under free-breathing conditions such that the accumulated dose meets the plan objectives, where accumulated dose is defined as the sum of deformably mapped doses computed on each phase of a single four dimensional computed tomography (4DCT) dataset. Phantom and patient simulation studies were carried out to investigate potential advantages of MAO compared to ITV planning. Through simulated delivery of the ITV- and MAO-plans, target dose variations were also investigated.

Results: By optimizing the accumulated dose, MAO shows the potential to ensure dose to the moving target meets plan objectives while simultaneously reducing dose to organs at risk (OARs) compared with ITV planning. While consistently superior to the ITV approach, MAO resulted in equivalent OAR dosimetry at planning objective dose levels to within 2% volume in 14/30 plans and to within 3% volume in 19/30 plans for each lung V20, esophagus V25, and heart V30. Despite large variations in per-fraction respiratory phase weights in simulated deliveries at high dose rates (e.g., treating 4/10 phases during single fraction beams) the cumulative clinical target volume (CTV) dose after 30 fractions and per-fraction dose were constant independent of planning technique. In one case considered, however, per-phase CTV dose varied from 74% to 117% of prescription implying the level of ITV-dose heterogeneity may not be appropriate with conventional, free-breathing delivery.

Conclusions: MAO incorporates 4DCT information in an optimized dose distribution and can achieve a superior plan in terms of accumulated dose to the moving target and OAR sparing compared to ITV-plans. An appropriate level of dose heterogeneity in MAO plans must be further investigated.

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1. INTRODUCTION

Probabilistic treatment planning (PTP) directly incorporates multiple anatomic instances in the dose optimization process. Statistical characteristics of the dose distribution evaluated on planning structures can be inferred from a known probability density function (PDF) of the variant anatomies. The concept of using predictable geometries to optimize dose expectation value was introduced by Li and Xing¹ based on organ specific, Gaussian PDFs. Birkner *et al.*² proposed a similar method to account for rigid motion based on measured random and systematic setup error. McShan *et al.*³ introduced a method termed a multiple instance geometry approximation (MIGA).

MIGA calculates dose on multiple anatomic instances and computes an expected dose. PTP has been investigated in research settings, but has not been clinically implemented due to factors including insufficient evidence that PTP provides dosimetric benefits compared to conventional approaches and concerns regarding robustness of PTP methods.

Methods of optimizing the accumulated dose using four dimensional computed tomography (4DCT) were described by Trofimov *et al.*⁴ who introduced two methods of dose estimation, a weighted sum of dose kernels (similar to MIGA) and a convolution approach, where the motion PDF is convolved with a planning image, 3D-dose.^{5,6} Plans generated via the motion kernel method were compared to margin-based

plans, gating plans, and idealized tracking plans for one lung and one liver case. Trofimov *et al.* show that motion kernel methods can produce plans comparable to idealized gating and tracking in terms of target dose coverage and sparing of organs at risk (OARs). Zhang *et al.*⁷ compared target tracking and 4D-inverse planning using a convolution dose calculation and demonstrated that 4D-optimization can achieve similar target dose coverage and OAR sparing to target tracking without necessitating delivery synchronization. Söhn *et al.*⁸ compared lung cancer plans optimized based on the internal target volume (ITV) method, idealized-tracking, and a weighted sum of dose kernels for one patient and also show potential to spare OARs using PTP. Roland *et al.*⁹ introduced the concept of a 4D-interpolated target volume in which the ITV was redefined to reduce dose to surrounding normal tissues. A “robust inspired” optimization was recently performed by McCann *et al.*¹⁰ who also show that reducing the ITV size spares surrounding lung. All of these studies include evidence that PTP provides dosimetric benefits compared to ITV. However, each of these studies only considered patients with relatively large tumor motion, i.e., ≥ 0.8 cm. Moreover, concerns about the robustness of the proposed methods were not addressed.

For a known PDF, Unkelbach and Oelfke introduced robust, accumulated dose optimization for assumed Gaussian distributions¹¹ and estimated data using Bayesian inference.¹² By simultaneously optimizing dose and minimizing dose variance, their method achieved robustness against uncertainty in the PDF. Heath *et al.*¹³ implemented these methods in simulation of lung cancer treatment and included uncertainty in patient breathing. Heath *et al.* compare robust-optimized solutions to worst-case optimization (see, e.g., Fredriksson *et al.*¹⁴) and to a margin-based approach and show target dose can be compromised if the dose variance is not considered during plan optimization. A similar result was shown by Sheng *et al.*¹⁵ in a simulation study for helical intensity modulated delivery.

Addressing concerns about dose variability, others optimized dose expectation value and included uncertainty in patient breathing using a robust counterpart approach¹⁶ in which the objective function is redefined in terms of robust parameters.^{17–20} For a given parameter variation, solutions below a threshold sensitivity are considered robust. The threshold should depend on the level of risk and the level of risk in the lung cancer RT optimization problem depends on the intent of treatment and clinical significance of the variation in the parameter under consideration. For PTP of lung radiation therapy, the variation in target dosimetry due to motion variability inherent to breathing variations and fractionated delivery is unknown, especially for patients with moderate tumor motion (e.g., <1 cm) despite a recent study of 250 lung cancer patients showing that approximately 90% of all lung tumors move <1 cm.²¹

Our study introduces multiple anatomy optimization (MAO) which aims to optimize a single fluence to be delivered under free-breathing conditions such that the accumulated dose meets the plan objectives, where accumulated dose is defined as the sum of deformably mapped doses computed on each phase of a single 4DCT dataset. The purpose of our study is to investigate potential advantages of MAO compared to the ITV

method for patients with <1 cm of tumor motion. Comparison metrics include target dose coverage, OAR dose avoidance, and plan robustness, which is estimated for ITV and MAO plans via simulated delivery with various sampled breathing patterns.

2. METHODS

In MAO, the objective function is a scalar weighted sum of least-square penalty functions. The scalarization process maps the multiobjective decision problem to a single value. For N objectives, the objective function is

$$\begin{aligned} O(\vec{b}) &= \sum_{n \in N} w_n f_n(\vec{b}) = \sum_{n \in N} w_n \sum_{i \in n} c_{i,n} (K_{ij} b_j - D_n^{Rx})^2 \\ &= \sum_{n \in N} w_n \sum_{i \in n} c_{i,n} (d_i - D_n^{Rx})^2, \end{aligned}$$

where each objective is labeled by the index n for region of interest (ROI) represented by a collection of i voxels in the planning image, with dose d_i computed as the product of the influence matrix $\hat{K}$ (with elements K_{ij} , also defined on the planning image) and the vector of beamlet weights $\vec{b}$. Each objective has a prescription or tolerance dose D_n^{Rx} , objective weight w_n , and constant $c_{i,n}$ which include relative volumes (for edge voxels) and Heaviside functions which penalize dose above or below D_n^{Rx} for OARs and targets, respectively.

Consistent with the Broyden–Fletcher–Goldfarb–Shanno (BFGS) method,²² each iteration includes an approximation of the inverse Hessian²³ using the gradient of the objective function with the respect to the vector of beamlet weights. MAO computes the objective function score using the accumulated dose computed on the inhale phase image, which is designated as the reference image (ref). It is computed as a weighted sum of per-phase doses D_p each weighted by w_p and interpolated at positions defined by a deformation vector fields (DVF), $v_{\text{ref} \rightarrow p}(r_i)$ at the parameterized positions r_i . The accumulated dose vector is

$$\vec{d}^{4D} = 4DD_{\text{ref}}(\vec{r}) = \sum_p w_p D_p(\vec{r} + v_{\text{ref} \leftarrow p}(\vec{r})), \quad (1)$$

and the MAO objective function is

$$O(\vec{b}) = \sum_{n \in N} w_n \sum_{i \in n} c_{i,n} (d_i^{4D} - D_n^{Rx})^2.$$

During each optimization iteration, for each beamlet update, the 4D-dose (4DD) is computed using the 10-phase, 4DCT image set. The dose computation and accumulation are performed in the PINNACLE³ treatment planning system (TPS), version 9.100. The beamlets are updated using compiled c++ code interfaced to the PINNACLE³ TPS via a research plugin. The basic algorithm flow is shown in Fig. 1 for a simple numeric phantom with three-phase images. This phantom is also used to investigate potential advantages of MAO compared to ITV-based plans.

FIG. 1. Flow diagram of MAO using a simple, three-phase phantom. The beamlet fluence is copied and computed on each phase image with monitor units adjusted to account for weighting. Following dose accumulation, the objectives are recomputed and the fluence is updated. This continues until the objectives are met, or tradeoff consistency is achieved.

2.A. Phantom simulations

The numeric phantom shown in Fig. 1 is used to demonstrate possible advantages in MAO planning compared to ITV planning. Three images were created including a target which moves rigidly and is defined in left, middle, and right phases and a stationary OAR (both are water-equivalent spheres of radius 1 cm). The surrounding cube has a density similar to lung (0.3 g/cm^3).

The target objective is to deliver 70 Gy to 95% of the ITV delivered using a single anterior–posterior (AP) beam. Two objectives conflict with the planning target volume (PTV)-objective: a max-dose objective of 45 Gy on the OAR and a dose–volume objective on the surrounding cube to reduce volume at 20 Gy less than 15% ($V_{20} < 0.15$). Two potential advantages of MAO compared to the ITV method are investigated using this phantom. MAO explicitly considers per-phase dose and therefore, we hypothesize that (1) MAO will take advantage of the time-dependent relationship between the target and OAR and (2) MAO will treat the target in spatial locations of high probability and avoid treating regions of low probability. In order to show the second effect, the phantom phase weights are shifted from equal weightings,

i.e., $w_p = (0.33, 0.33, 0.33)$ for left, middle, and right phases, to unequal weights $w_p = (0.2, 0.1, 0.7)$.

2.B. 4D-patient planning

4DCT image sets for ten locally advanced nonsmall cell lung cancer patients (P1–P10) collected on an internal review board-approved study of image-guided adaptive radiation therapy at Virginia Commonwealth University were included in this study. The 4DCT image sets were created via phase sorting. 4DCT's include images acquired over multiple breathing cycles and therefore are not snapshots of immobile anatomy but include some residual motion due to finite temporal resolution.

The patient images were imported into the PINNACLE³ TPS and an expert physician provided contours on each phase. Interphase registration was performed using the insight toolkit (ITK) implementation of the Demons fast-symmetric algorithm implemented in the treatment planning system. DVFs resulting from the registration were produced at an isotropic resolution of $0.3 \times 0.3 \times 0.3 \text{ cm}^3$. Propagated physician drawn contours (from the reference, maximum inhale phase to all other phases) were visually verified with the physician drawn per-phase contours to ensure consistency of deformations.

Dose voxels were designed at the same resolution as the DVF and the dose-voxel grid encompassed the lungs in all phase images (approximately 10^6 dose-voxels per image). Each plan consisted of 7–9 coplanar beams, placed nonuniformly around the patient to avoid both OARs and hot spots in normal tissues not explicitly considered in the optimization. Four different plan optimizations were retrospectively performed for each patient with identical beam arrangements, three ITV plans and an MAO plan. The three ITV-optimizations were performed using different planning images, the 30% midventilation phase, the average 4DCT density (aCT) with structures defined from the 30% phase, and the maximum inhale phase (0% phase, with 0% structures) using the PINNACLE³ TPS. The three different ITV plans per patient were used to ensure the advantages of MAO were not due to limitations in the planning technique, including selection of planning image. For example, plans optimized on inhale phase image may have a disadvantage because they over-estimate lung volume.

The ITV is a union of the clinical target volumes (CTVs) on all phase images, and each CTV was defined as a 0.5 cm isotropic expansion of the propagated GTV. Interfractional setup error is not considered in this study, so the PTV was set equal to the ITV. For the ITV plans, the target objective was 70 Gy to 95% of the PTV ($PTV-D_{95} = 70 \text{ Gy}$). The MAO plans consider the accumulated, 4DD on the reference anatomy, therefore the PTV objective is a (moving) CTV objective for 4DD ($CTV-4DD_{95} = 70 \text{ Gy}$, $CTV-4DD_{\max} < 80 \text{ Gy}$). The plans were not constrained to meet a PTV minimum dose. The planning objectives are shown in Table I.

For each of the patient cases, differences in the accumulated dose (as optimized in MAO or computed by accumulating the ITV-plan) are reported. Comparisons of accumulated dose based on delivering ITV and MAO plans were consistently performed on the 0%, maximum inhale phase structures. The

TABLE I. Planning objectives used in ITV and MAO plans. Dose and structure volume is evaluated on the planning image (00%, 30%, or aCT image) in ITV plans. In MAO plans accumulated dose is evaluated on the reference, 00% image.

Structure	Objective
PTV	$D_{95} \geq 70$ Gy
	$D_{\max} < 80$ Gy
ips. Lung	$V_{20} < 10\%$
con. Lung	$V_{20} < 10\%$
Esophagus	$V_{25} < 5\%$
Heart	$V_{30} < 5\%$
Spinal cord	$D_{\max} < 40$ Gy

differences in target and OAR dose-indices are used to estimate potential advantages of MAO.

An initial comparison considers the ITV- and MAO-plans at optimized monitor units (MUs) which results in variable target 4DD. In a second comparison, the ITV and MAO-plan MUs are adjusted to a fixed accumulated target dose, $4DD_{95} = 70$ Gy and the potential for OAR sparing is examined. The different plan normalization strategies were employed because ITV-based plans do not optimize the 4DD distribution. However, scaling an ITV solution based on target-4DD may be a valid approach to incorporate 4DD in 3D planning.

The centroid CTV motion is measured in the 3 principle directions and these data, combined with the CTV volume and CTV/ITV ratio are detailed in Table II for each of the patients considered. The patients are ordered according to the value of the Euclidean norm of the 3D-motion vector, ranging from 0.28 cm for patient P1 to 0.95 cm for patient P10. In order to investigate and potentially identify patients who may benefit from MAO, OAR sparing is correlated to several patient-specific characteristics including CTV-motion, the size of the CTV, and to the CTV/ITV ratio. Additionally, the overlap between the moving CTV and OARs averaged over ten breathing phases, and the standard deviation in this value is reported as CTV–OAR overlap in Table I. Consistent with the phantom study, we hypothesize that MAO will take advantage

TABLE II. Patient details. The CTV volume is defined in the reference, 00% inhale phase in computing the CTV/ITV ratio. The CTV–OAR overlap considers variations throughout the breathing cycle.

Patient	Tumor centroid motion (cm)				ITV (cm ³)	Ratio (CTV/ITV)	CTV–OAR overlap (%)
	AP	LAT	SI	3D			
P1	0.15	0.07	0.24	0.29	221.5	0.83	46.4 ± 1.2
P2	0.21	0.13	0.22	0.33	294.8	0.89	21.5 ± 0.4
P3	0.21	0.28	0.17	0.39	401.8	0.84	26.6 ± 0.6
P4	0.08	0.24	0.31	0.40	60.2	0.78	77.8 ± 1.6
P5	0.16	0.19	0.43	0.50	174.6	0.70	60.5 ± 1.7
P6	0.08	0.07	0.57	0.58	174.4	0.81	26.6 ± 0.6
P7	0.30	0.41	0.41	0.65	232.6	0.70	53.5 ± 0.8
P8	0.32	0.25	0.56	0.69	105.1	0.80	52.5 ± 2.1
P9	0.44	0.15	0.61	0.77	173.1	0.79	58.1 ± 1.7
P10	0.36	0.16	0.86	0.95	442.4	0.82	45.4 ± 0.5

of target/OAR variations in each phase, and that patients who exhibit a large phase-dependence in CTV/OAR overlap may benefit from MAO. The total OAR sparing, defined as the sum of the preserved OAR volumes at planning objective levels, was correlated to these patient-specific parameters.

2.C. Simulated delivery to estimate target dose variations

The sensitivity of target dose was examined based on simulated delivery of MAO and ITV plans for four patients in order to estimate robustness. For patients P3, P6, P7, and P10, ten simulated deliveries of the 30%-ITV plan and the MAO plan were carried out based on sampling patient-specific breathing patterns for 30 fractions. Per-phase, per-fraction, and 30-fraction cumulative CTV-4DD₉₅ doses were estimated. The per-phase dosimetry shows target dose variations throughout the breathing cycle. Simulated delivery shows target dose variations due to sampling per-beam, per-phase doses with variable weightings over the course of one or more fractions.

Simulated delivery to the planning 4DCT image set was carried out by varying 4DCT phase-weights according to patient breathing patterns sampled for each beam at 600 monitor units per minute (MU/min) and 2400 MU/min. For each dose rate, ten simulated deliveries, each with 30 fractions (300 fractions total), were carried out for each plan. Per-beam phase weights were determined from sampling patient-specific breathing patterns as recorded by the real-time position management (RPM, Varian Medical Systems, Palo Alto, CA) system at the time of 4DCT simulation. Accumulated dose was estimated as a sum of deformed per-beam b , per phase p doses (D_p^b), with sampled weightings w_p^b according to

$$d^{\text{4D}} = 4DD_{\text{ref}}(\vec{r}) = \sum_b \sum_p w_p^b D_p^b(\vec{r} + \nu_{\text{ref} \rightarrow p}(\vec{r})).$$

The beam-on RPM-data used for simulation imaging define the RPM signal for each of the equiweighted, 4DCT phase images. For a given per-fraction beam duration (computed as the ratio of the per-fraction beam MUs and dose rate) each beam dose is assumed to be delivered conformally, i.e., MLC interplay was not included in this study. The sampled phase weights were determined under the assumption that the RPM-assigned phase (labeled between 0 to π) is correctly labeled and corresponds with the reconstructed 4DCT phase images used for planning. Figure 2 shows the interface used to connect sampled breathing patterns and 4DCT phase weights based on beam-on data (top) and based on a random starting phase and beam-on time (bottom images). Per-fraction beam-on times were determined according to beam MUs, dose-rate, and number of fractions, and ranged from 1.3 to 12.4 s when delivered at 2400 MU/min.

In sampling the patient-specific breathing patterns, it was assumed that the assigned phases are independent of the sampled amplitude, i.e., that the RPM-assigned phases are labeled correctly with respect to reconstructed phase images.

FIG. 2. An interface to correlate patient-specific breathing and 4DCT-phase weights is shown. The beam-on data is used to establish the equal phase weightings. By sampling a portion of the breathing pattern based on dose-rate and beam-MUs, the 4DCT phase-weights are assigned as shown in the lower images.

3. RESULTS

3.A. Phantom simulations

The left column of Fig. 3 shows the ITV solution (top) and the MAO solution (bottom) on the reference phase computed based on equiweighted phases. The MAO solution achieves the OAR objective ($OAR-D_{max} < 45$ Gy) and avoids treating the target in the reference phase. The ITV-approach implies the OAR must be treated to >45 Gy in order to treat the entire ITV. This phantom shows a potential advantage of MAO compared to ITV planning, if target and normal structures have a time-dependent relationship MAO can use this information to avoid treating in phases which include beams-eye-view

overlap and increase dose in phases which avoid the OAR. This phantom case also shows that MAO plans, in order to avoid treatment in certain phases, must increase maximum dose to the target.

The MAO-optimized solution shown in Fig. 4 is based on the phantom-phase weights of (0.2, 0.1, 0.7) for the left, middle, and right phases, respectively. The ITV solution is unchanged, whereas the MAO solution preferentially treats the target in the region where it spends the most time. The accumulated dose (right side of Fig. 5) meets prescription and reduces V20 on the surrounding cube from 26% to 22% compared to the ITV plan.

3.B. 4D patient planning

Differences in CTV-3DD₉₅ and CTV-4DD₉₅ in ITV plans ranged from -1.9 to 5.9 Gy, exemplifying the fact that ITV planning does not optimize dose to the moving CTV. MAO increased CTV 4DD-V70 by an average of 3.5% ($\pm 4.3\%$, $p = 0.01$) compared to ITV plans at optimized MUs, as shown in Fig. 5. However, increased CTV-4DD₉₅ with MAO planning was not significant, on average 0.35 ± 1.27 Gy ($p = 0.8$), but is >1 Gy in 8 of 30 comparisons. Due to the sharp dose gradient in the PTV-dose volume histogram (DVH) near prescription, the V70 or D_{95} may vary while the other metric is approximately constant. For example, the aCT plan of P8 shown in Fig. 5 indicates CTV 4DD-V70 $< 70\%$, however, the CTV-4DD₉₅ is 68 Gy (to within 3% of the 70 Gy prescription dose).

At optimized MUs, MAO and ITV dose differed in ipsilateral lung-V20 ($1.2\% \pm 2.1\%$, $p = 0.004$) and ipsilateral mean lung dose (0.36 Gy ± 0.66 Gy, $p = 0.005$), but these are the only OAR dose differences which reject the null hypothesis at the 5% significance level. Dose differences in contralateral lung V20 ($0.3\% \pm 2.1\%$, $p = 0.3$), contralateral lung mean dose (-0.04 Gy ± 0.6 Gy, $p = 0.7$), esophagus V25 ($0.4\% \pm 5.1\%$, $p = 0.7$), esophagus mean dose (-0.04 Gy ± 0.7 Gy, $p = 0.8$), heart V30 ($1.0\% \pm 3.9\%$, $p = 0.2$), and heart mean dose

FIG. 3. Static (left) and accumulated (right) dose in the reference phase image optimized using the ITV method (top) and MAO (bottom) for a single beam directed from top-to-bottom of the images. The ITV (outlined in black) is treated to prescription dose in the ITV plan, whereas the MAO plan treats only the moving tumor and avoids treating the OAR by increasing maximum dose in peripheral phases.

FIG. 4. An example of an MAO dose distribution on the reference phase (left) and accumulated on the reference phase (right). The target spends 70% of the time in the right phase and 20% of its time in the left phase, and MAO delivers a higher dose to the right phase.

($-0.5 \text{ Gy} \pm 1.6 \text{ Gy}$, $p = 0.09$) were not significant. The OAR data are not shown visually for brevity.

At fixed $\text{CTV-4DD}_{95} = 70 \text{ Gy}$, ITV and MAO solutions result in equivalent OAR dosimetry at planning objective dose levels to within 2% in 14/30 plans and to within 3% volume in 19/30 plans for each lung V20, esophagus V25, and heart V30 while meeting the spinal cord D_{max} objective. Averaged across the ten-patients, MAO did not significantly reduce OAR volumes at objective levels when compared to 00%-ITV plans at fixed 4DD_{95} . Compared to the 30%-ITV plan, reduction in esophagus V25 ($1.5\% \pm 1.8\%$, $p = 0.03$) and ipsilateral lung V20 ($3.1\% \pm 3.0\%$, $p = 0.01$) rejects the null hypothesis at the 5% significance level. Similarly, MAO reduced ipsilateral lung V20 when compared to plans designed on aCT ($2.1\% \pm 2.8\%$, $p = 0.05$), but sparing in other OARs was not consistent across the patient cohort. Relative OAR volume at each objective dose level is graphically displayed in Fig. 6 for plans at fixed CTV 4DD_{95} .

For P3, despite 3D motion of just 0.39 cm, potential advantages in MAO planning were apparent when compared to the midventilation, 30%-ITV plan. At optimized monitor units, MAO meets the CTV-4DD_{95} prescription, whereas the 30%-ITV plan treats to $\text{CTV-4DD}_{95} = 71.5 \text{ Gy}$. After reducing the ITV-MUs to achieve fixed $\text{CTV-4DD}_{95} = 70 \text{ Gy}$, MAO reduces ipsilateral lung V20 from 48% to 41%, esophagus V25 from 12% to 7%, and heart V30 from 28% to 25% compared

to the 30%-ITV plan. In order to reduce dose to these OARs, the MAO plan results in increased hotspots inside the moving CTV, as shown in the DVH for the MAO- and ITV-plans in Fig. 7. However, when compared to plans on inhale and aCT for this patient, there is no advantage to using MAO in terms of OAR sparing. A similar result was found for patients P1, P2, P4, P9, and P10, plans on inhale and aCT both show potential advantages for MAO in at least one plan, but other plans were equivalent to within 1% OAR volume sparing.

Only patients P5, P6, and P7 show potential for MAO to reduce OAR dose at fixed CTV-4DD_{95} independent of ITV planning image primarily due to dose reductions in ipsilateral lung. In the case of patient P5, MAO reduced ipsilateral lung dose by 1.1%, 9.1%, and 8.9% relative volume compared to the inhale, midventilation, and aCT plans but this reduction is negated by increases in dose to heart and esophagus in the midventilation and aCT plans. For patient P6, MAO creates hot spots in regions of the ITV which are consistently occupied by voxels of the CTV. These hot spots allow dose-reduction in peripheral regions of the PTV which include either moving CTV or healthy lung, depending on the evaluated phase. P7 shows the potential to reduce ipsilateral lung V20 by at least 2.5% and heart V30 by 1.5% compared to all three ITV plans.

MAO did not consistently spare OARs independent of planning image. Of the dose-volume objectives, only sparing

FIG. 5. The CTV volume at 70 Gy accumulated dose for each of the plans at optimized MUs. In seven of ten patients considered, at least one ITV plan fails to deliver 70 Gy to 90% of the CTV, however the MAO solution can ensure accumulated dose meets prescription.

FIG. 6. Relative volume of OARs at fixed accumulated dose to 95% of the CTV (CTV-4DD₉₅) for all plans. Shapes correspond to different plan types considered and the colors differentiate the indicated DVH metric for a given OAR.

of heart V30 ($r^2=0.64$, $p=0.005$) and contralateral lung V20 ($r^2=0.45$, $p=0.04$) in midventilation and aCT plans showed weak correlations at fixed CTV-4DD₉₅. These weak correlations imply that the potential advantages of MAO are likely related to suboptimal ITV plans and not to patient-specific factors in the cases considered. Further evidence of this conclusion is revealed by the correlation coefficients between the total OAR sparing (sum of the preserved OAR volumes at planning objective levels) and patient-specific factors including 3D-CTV motion, ITV and CTV size, the CTV/ITV ratio, the relative overlap of the CTV with surrounding OARs, and the overlap variation expressed through the standard deviation in CTV overlap in each phase. These correlation coefficients are shown in Table III.

3.C. Simulated delivery to estimate target dose variations

Four MAO patient plans were selected for simulated delivery because of the potential to reduce OAR dose at fixed CTV-4DD₉₅ compared to the 30%-ITV plan. Ideally, these advantages remain valid when considering dose variations due to breathing variations and fractionated delivery. Maximum single fraction phase weight variations >20% were observed

at 600 MU/min (i.e., weights ranged from 0.08 to 0.12 for 10-phase images) for all plans and patients considered. At 2400 MU/min, the per-fraction delivery time for many beams was less than the patient breathing period resulting in phase-weights ranging from 0.0 to approximately 0.25 (i.e., fractionated delivery to 4/10 phase images). Despite the large weight variations, the cumulative CTV-4DD₉₅ based on simulated delivery of 30 fractions and average per-fraction CTV-4DD₉₅ were constant independent of planning technique with maximum standard deviation of 0.02 Gy. The negligible variation in per-fraction dose and cumulative dose reflects the fact that fractionation results in CTV-4DD₉₅ converging to the expectation value.

Single fraction CTV dose as a function of respiratory phase was not constant for all patients as shown in Fig. 8 for patients P3 (top) and P6 (bottom). The CTV dose on MAO plans result in higher CTV- $D_{\max}$ compared to ITV in all cases considered, but CTV- D_{95} is approximately constant across breathing phases for patients P3 and P10 independent of planning technique. Standard deviations in CTV- $D_{99} < 0.30$ Gy, and CTV- $D_{\max} < 0.16$ Gy in these cases imply that these plans are robust to fractionated sampling of patient breathing. However, the MAO plans for patients P6 and P7 include per-phase CTV- D_{95} variations up to 1.03 and 3.01 Gy, respectively. A coronal image of the MAO (left) and ITV (right) dose distributions for patient P6, as computed on a single phase image (the 0% inhale phase), is shown in Fig. 9. The MAO-plan reduces ipsilateral lung V20 by 6% and MLD by 2.12 Gy compared to the ITV-plan at fixed CTV-4DD₉₅, but the level of dose-heterogeneity displayed

FIG. 7. DVH for patient P3 based on the 30%-ITV plan and the MAO plan. At fixed accumulated dose to 95% of the target volume (CTV-4DD₉₅), MAO spares all OARs at objective dose levels.

TABLE III. Correlation of relative OAR volume spared using MAO with patient-specific factors including motion, target volumes, and target-OAR overlap.

Correlation of total OAR sparing at fixed CTV-4DD ₉₅	Pearson linear correlation (r)	Spearman rank correlation (ρ)
3D-motion	0.11	0.08
ITV volume	-0.3	-0.56
CTV volume	-0.24	-0.57
CTV/ITV ratio	0.25	-0.12
CTV/OAR overlap	0.13	0.24
CTV/OAR overlap variation	0.29	0.23

FIG. 8. CTV dose as a function of respiratory phase computed for a single phase for patient P3 (top) and patient P6 (bottom) including CTV- D_{99} , CTV- D_{95} , and CTV- D_{max} . MAO plans can result in CTV- D_{95} dose variations >1 Gy depending on the breathing phase.

in the ITV may not be appropriate with conventional, free-breathing delivery.

4. DISCUSSION

In 13/30 plans considered, MAO shows the ability to spare OARs by at least 3% volume at objective dose levels compared to ITV plans; for the other 17 plans, MAO showed negligible dosimetric advantages. These results imply that the current standard clinical technique, ITV planning using 3D-dose, is adequate to within clinical tolerances for many

patients though MAO may provide benefits for others. Clinical implementation may require identification of a population of patients which will benefit from the technique. For patients exhibiting large motion (e.g., >1 cm), other studies have shown motion management offers potential benefits in terms of OAR sparing. Based on the results of our work, MAO may benefit patients which display moderate CTV motion as well. MAO optimizes the accumulated dose distribution and can achieve a robust plan despite large per-fraction breathing variations. However, we also observed cases with large CTV dose variations as a function of respiratory phase.

Equivalence between MAO and ITV for some patients implies that a uniform prescription dose across the entire ITV is an ideal solution even when breathing motion is considered in plan optimization. As shown using a phantom, introducing cold-spots in regions of the ITV must be balanced by hotspots in other regions in order to achieve uniform 4DD to the moving CTV. Because both ITV and MAO plans penalized dose above 80 Gy, it is intuitive that both plans may reach equivalent solutions which evenly distribute dose over the duty cycle. However, relaxing maximum dose limitations in MAO plans may result in additional freedom to increase dose in regions of persistent disease and avoid regions of the ITV which may include normal tissue. The appropriate balance between acceptable hot/cold spots in the ITV must be further explored.

There are limitations in MAO, and there are many hurdles to overcome in order to realize clinical implementation. Chiefly among these obstacles is the accuracy and validity of the planning 4DCT image set over the course of treatment. Guckenberger *et al.*²⁴ used repeat 4DCT imaging and showed >5 mm drift in mean tumor position in 2/10 patients, but concluded that a single 4DCT is reliable for many patients. Britton *et al.*²⁵ evaluated repeat 4DCT image sets and observed tumor regression as well as motion variations but did not observe consistent trends in motion variation. Sonke *et al.*²⁶ showed trajectory shape was consistent interfractionally generally to within 0.1 cm. 4D cone-beam computed tomography (CBCT) for image-guided verification is a potential solution which can ensure the tumor moves consistently with the 4DCT image set²⁷ including direct tumor tracking,^{28,29} marker tracking,³⁰ or

FIG. 9. A coronal slice of the planned MAO (left) and the ITV (right) dose distributions calculated on a single anatomy (inhale), where the CTV is outlined in black. The MAO dose distribution (left), creates CTV-hot and cold spots in individual phase doses to achieve a conformal accumulated dose, but this plan is susceptible to >1 Gy target dose variations when the PDF is varied.

probabilistic techniques.³¹ If anatomy is observed to deviate from the anatomy used for planning then replanning may be necessary independent of planning technique.

Even if inaccuracies in 4DCT can be fully quantified, when combined with geometric uncertainty due to the effects of deformable image registration (DIR), delineation uncertainty, and setup error, the potential advantages of MAO may be negated. DIR errors must accompany calibration of a 4DD algorithm using a realistic deformable phantom (see, e.g., Kashani *et al.*³²). Registration error will propagate into MAO dosimetric errors if evaluated in high dose-gradient regions³³ and many studies have evaluated registration error for the Demons algorithm³⁴ and for DIR in general.³⁵ MAO has been integrated with methods to optimize margins to account for both random³⁶ and systematic³⁷ geometric errors which also must be considered prior to clinical implementation. Until geometric uncertainties and the corresponding effects on dose-mapping are quantified, the appropriate level of dose heterogeneity within the ITV is unknown.

Simulated delivery of MAO plans indicated that variations in CTV-4DD₉₅ > 1 Gy are possible solely due to finite delivery time and patient-specific breathing. However, this study suggests the standard deviation of CTV-4DD₉₅ based on 10 simulated deliveries of 30 fractions is negligible and did not depend on dose rate. The effects of MLC and tumor interplay will cause additional variations in target dose although this effect has also been shown to average out over the course of fractionated radiotherapy^{5,38} similar to what was observed based on sampling patient breathing. These results may need to be independently validated for hypofractionated delivery, which is commonly used for early-stage lung cancer. It is plausible that the MLC delivery of an MAO plan must be coupled to patient specific motion in cases of limited treatment time for each aperture, which is especially relevant to arc-based therapy (see, for example, Ma *et al.*³⁹ or Chin and Otto⁴⁰). Court *et al.*⁴¹ have investigated MLC sequencing to ensure the interplay effect results in dose distributions within a known tolerance, and such a method may be applicable to MAO dose distributions.

5. CONCLUSIONS

MAO explicitly includes accumulated dose as presented in 4DCT simulation images and can be implemented without new hardware. The method shows potential advantages compared to ITV planning, including advantages for patients who exhibit moderate tumor motion. In many cases, MAO is equivalent to ITV to within clinical tolerances, but MAO can ensure target dose is achieved without necessitating a homogeneous dose distribution within the entire ITV.

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- ¹J. G. Li and L. Xing, "Inverse planning incorporating organ motion," *Med. Phys.* **27**, 1573–1578 (2000).
 - ²M. Birkner, D. Yan, M. Alber, J. Liang, and F. Nüsslin, "Adapting inverse planning to patient and organ geometrical variation: Algorithm and implementation," *Med. Phys.* **30**, 2822–2831 (2003).
 - ³D. L. McShan, M. L. Kessler, K. Vineberg, and B. A. Fraass, "Inverse plan optimization accounting for random geometric uncertainties with a multiple instance geometry approximation (MIGA)," *Med. Phys.* **33**, 1510–1521 (2006).
 - ⁴A. Trofimov *et al.*, "Temporo-spatial IMRT optimization: Concepts, implementation and initial results," *Phys. Med. Biol.* **50**, 2779–2798 (2005).
 - ⁵T. Bortfeld, K. Jokivarsi, M. Goitein, J. Kung, and S. B. Jiang, "Effects of intra-fraction motion on IMRT dose delivery: Statistical analysis and simulation," *Phys. Med. Biol.* **47**, 2203–2220 (2002).
 - ⁶A. E. Lujan, J. M. Balter, and R. K. Ten Haken, "A method for incorporating organ motion due to breathing into 3D dose calculations in the liver: Sensitivity to variations in motion," *Med. Phys.* **30**, 2643–2649 (2003).
 - ⁷P. Zhang, G. D. Hugo, and D. Yan, "Planning study comparison of real-time target tracking and four-dimensional inverse planning for managing patient respiratory motion," *Int. J. Radiat. Oncol.* **72**, 1221–1227 (2008).
 - ⁸M. Söhn, M. Weinmann, and M. Alber, "Intensity-modulated radiotherapy optimization in a quasi-periodically deforming patient model," *Int. J. Radiat. Oncol., Biol., Phys.* **75**, 906–914 (2009).
 - ⁹T. Roland, R. Hales, T. McNutt, J. Wong, P. Simari, and E. Tryggstad, "A method for deriving a 4D-interpolated balanced planning target for mobile tumor radiotherapy," *Med. Phys.* **39**, 195–205 (2012).
 - ¹⁰C. McCann, T. Purdie, A. Hope, A. Bezjak, and J.-P. Bissonnette, "Lung sparing and dose escalation in a robust-inspired IMRT planning method for lung radiotherapy that accounts for intrafraction motion," *Med. Phys.* **40**, 061705 (10pp.) (2013).
 - ¹¹J. Unkelbach and U. Oelfke, "Inclusion of organ movements in IMRT treatment planning via inverse planning based on probability distributions," *Phys. Med. Biol.* **49**, 4005–4029 (2004).
 - ¹²J. Unkelbach and U. Oelfke, "Incorporating organ movements in inverse planning: Assessing dose uncertainties by Bayesian inference," *Phys. Med. Biol.* **50**, 121–139 (2005).
 - ¹³E. Heath, J. Unkelbach, and U. Oelfke, "Incorporating uncertainties in respiratory motion into 4D treatment plan optimization," *Med. Phys.* **36**, 3059–3071 (2009).
 - ¹⁴A. Fredriksson, A. Forsgren, and B. Hardemark, "Minimax optimization for handling range and setup uncertainties in proton therapy," *Med. Phys.* **38**, 1672–1684 (2011).
 - ¹⁵K. Sheng, J. Cai, J. Brookeman, J. Molloy, J. Christopher, and P. Read, "A computer simulated phantom study of tomotherapy dose optimization based on probability density functions (PDF) and potential errors caused by low reproducibility of PDF," *Med. Phys.* **33**, 3321–3326 (2006).
 - ¹⁶A. Ben-Tal and A. Nemirovski, "Robust convex optimization," *Math. Oper. Res.* **23**, 769–805 (1998).
 - ¹⁷T. C. Y. Chan, T. Bortfeld, and J. N. Tsitsiklis, "A robust approach to IMRT optimization," *Phys. Med. Biol.* **51**, 2567–2583 (2006).
 - ¹⁸T. Bortfeld, T. C. Y. Chan, A. Trofimov, and J. N. Tsitsiklis, "Robust management of motion uncertainty in intensity-modulated radiation therapy," *Oper. Res.* **56**, 1461–1473 (2008).
 - ¹⁹O. Nohadani, J. Seco, and T. Bortfeld, "Motion management with phase-adapted 4D-optimization," *Phys. Med. Biol.* **55**, 5189–5202 (2010).
 - ²⁰J. M. Mulvey, R. J. Vanderbei, and S. A. Zenios, "Robust optimization of large-scale systems," *Oper. Res.* **43**, 264–281 (1995).
 - ²¹H. H. Liu *et al.*, "Assessing respiration-induced tumor motion and internal target volume using four-dimensional computed tomography for radiotherapy of lung cancer," *Int. J. Radiat. Oncol., Biol., Phys.* **68**, 531–540 (2007).
 - ²²J. Nocedal and S. J. Wright, *Numerical Optimization* (Springer, New York, NY, 1999).
 - ²³J. Lof, B. K. Lind, and A. Brahme, "Optimal radiation beam profiles considering the stochastic process of patient positioning in fractionated radiation therapy," *Inverse Probl.* **11**, 1189–1209 (1995).
 - ²⁴M. Guckenberger, J. Wilbert, J. Meyer, K. Baier, A. Richter, and M. Flentje, "Is a single respiratory correlated 4D-CT study sufficient for evaluation of breathing motion?," *Int. J. Radiat. Oncol., Biol., Phys.* **67**, 1352–1359 (2007).
 - ²⁵K. R. Britton *et al.*, "Assessment of gross tumor volume regression and motion changes during radiotherapy for non-small-cell lung cancer as measured

- by four-dimensional computed tomography," *Int. J. Radiat. Oncol., Biol., Phys.* **68**, 1036–1046 (2007).
- ²⁶J.-J. Sonke, J. Lebesque, and M. van Herk, "Variability of four-dimensional computed tomography patient models," *Int. J. Radiat. Oncol., Biol., Phys.* **70**, 590–598 (2008).
- ²⁷J.-J. Sonke, L. Zijp, P. Remeijer, and M. van Herk, "Respiratory correlated cone beam CT," *Med. Phys.* **32**, 1176–1186 (2005).
- ²⁸G. D. Hugo, J. Liang, and D. Yan, "Marker-free lung tumor trajectory estimation from a cone beam CT sinogram," *Phys. Med. Biol.* **55**, 2637–2650 (2010).
- ²⁹J. H. Lewis *et al.*, "Markerless lung tumor tracking and trajectory reconstruction using rotational cone-beam projections: A feasibility study," *Phys. Med. Biol.* **55**, 2505–2522 (2010).
- ³⁰J. C. Park *et al.*, "Four-dimensional cone-beam computed tomography and digital tomosynthesis reconstructions using respiratory signals extracted from transcutaneously inserted metal markers for liver SBRT," *Med. Phys.* **38**, 1028–1036 (2011).
- ³¹J. H. Lewis *et al.*, "Mitigation of motion artifacts in CBCT of lung tumors based on tracked tumor motion during CBCT acquisition," *Phys. Med. Biol.* **56**, 5485–5502 (2011).
- ³²R. Kashani, M. Hub, M. L. Kessler, and J. M. Balter, "Technical note: A physical phantom for assessment of accuracy of deformable alignment algorithms," *Med. Phys.* **34**, 2785–2788 (2007).
- ³³N. K. Saleh-Sayah, E. Weiss, F. J. Salguero, and J. V. Siebers, "A distance to dose difference tool for estimating the required spatial accuracy of a displacement vector field," *Med. Phys.* **38**, 2318–2323 (2011).
- ³⁴X. Gu *et al.*, "Implementation and evaluation of various demons deformable image registration algorithms on a GPU," *Phys. Med. Biol.* **55**, 207–219 (2010).
- ³⁵K. K. Brock and Deformable Registration Accuracy Consortium, "Results of a multi-institution deformable registration accuracy study (MIDRAS)," *Int. J. Radiat. Oncol., Biol., Phys.* **76**, 583–596 (2010).
- ³⁶J. A. Moore, J. J. Gordon, M. S. Anscher, and J. V. Siebers, "Comparisons of treatment optimization directly incorporating random patient setup uncertainty with a margin-based approach," *Med. Phys.* **36**, 3880–3890 (2009).
- ³⁷J. A. Moore, J. J. Gordon, M. Anscher, J. Silva, and J. V. Siebers, "Comparisons of treatment optimization directly incorporating systematic patient setup uncertainty with a margin-based approach," *Med. Phys.* **39**, 1102–1111 (2012).
- ³⁸S. B. Jiang, C. Pope, K. M. A. Jarrah, J. H. Kung, T. Bortfeld, and G. T. Y. Chen, "An experimental investigation on intra-fractional organ motion effects in lung IMRT treatments," *Phys. Med. Biol.* **48**, 1773–1784 (2003).
- ³⁹Y. Ma *et al.*, "Inverse planning for four-dimensional (4D) volumetric modulated arc therapy," *Med. Phys.* **37**, 5627–5633 (2010).
- ⁴⁰E. Chin and K. Otto, "Investigation of a novel algorithm for true 4D-VMAT planning with comparison to tracked, gated and static delivery," *Med. Phys.* **38**, 2698–2707 (2011).
- ⁴¹L. Court *et al.*, "Evaluation of the interplay effect when using RapidArc to treat targets moving in the craniocaudal or right-left direction," *Med. Phys.* **37**, 4–11 (2010).