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Cumulative lung dose for several motion management strategies as a function of pre-treatment patient parameters

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Abstract

Purpose—To evaluate patient parameters that may predict for relative differences in cumulative 4D lung dose among several motion management strategies.

Methods and Materials—Deformable image registration and dose accumulation were used to generate 4D treatment plans for eighteen patients with 4DCT scans. Three plans were generated to simulate breath hold at normal inspiration, target tracking with the beam aperture, and mid-ventilation aperture (control of the target at the mean daily position and application of an iteratively-computed margin to compensate for respiration). The relative reduction in mean lung dose (MLD) between breath hold and mid-ventilation aperture ($\Delta\text{MLD}_{\text{BH}}$) and between target tracking and mid-ventilation aperture ($\Delta\text{MLD}_{\text{TT}}$) was calculated. Associations between these two variables and parameters of the lesion (excursion, size, location, and deformation) and dose distribution (local dose gradient near the target) were calculated.

Results—The largest absolute and percentage differences in MLD were 1.0 Gy and 21.5% between breath hold and mid-ventilation aperture. $\Delta\text{MLD}_{\text{BH}}$ was significantly associated ($p < 0.05$) with tumor excursion. $\Delta\text{MLD}_{\text{TT}}$ was significantly associated with excursion, deformation, and local dose gradient. A linear model was constructed to represent ΔMLD versus excursion. For each 5mm of excursion, target tracking reduced the MLD by 4% compared to a mid-ventilation aperture plan. For breath hold, the reduction is 5% per 5mm of excursion.

Conclusions—The relative difference in MLD among different motion management strategies varied with patient and tumor characteristics for a given dosimetric target coverage. Tumor excursion is useful to aid in stratifying patients into an appropriate motion management strategy.

Keywords

Respiratory motion; lung cancer; 4D radiotherapy; 4DCT

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Conflict of Interest

William Beaumont Hospital holds a research agreement with Elekta Oncology Systems.

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Introduction

The progression towards higher precision in thoracic radiotherapy has motivated the development of methods to manage anatomical motion (1). A variety of techniques to specifically manage the detrimental effect of respiration on the delivered dose distribution have arisen in the recent past including internal margins (2), respiration gating (3), target tracking (4), active (5) or self (6) breath hold, 4D inverse planning (7,8), and asymmetric margins (9). These strategies range from the very simple to the technically complex. The ability to provide a precise knowledge of target location, and therefore to enable dose escalation or normal tissue dose reduction, varies among the strategies. An approach such as the internal target volume concept (2), which provides a relatively large safety margin to compensate for respiration, does not ideally allow for the same level of dose escalation as a more technically demanding approach such as respiration gating (10). It is apparent that the anticipated benefit of reducing the target volume by half (10) outweighs the costs (e.g., additional required equipment and increased treatment time) of implementing the more complex strategy of gating in this case.

However, the distinction in possible benefit between other strategies may be subtle. Assuming that each strategy is designed to achieve target coverage, it would be useful to know the relative difference in normal tissue dose provided by different strategies. For a given patient, we would like to determine the difference in lung dose among the strategies assuming the delivery with the motion management strategy in question is ideal and without error. A secondary aim of this study is to then use this ideal lung dose to stratify patients by different motion management strategies using some pre-treatment predictor for this minimum lung dose. To achieve these aims, we evaluated the cumulative lung dose for several approaches that covered a range of technical complexity: an approach using mid-position control and margin compensation for respiration, breath hold, and target tracking, and evaluated the strength of pre-treatment predictors for the relative difference between the cumulative lung dose among the strategies.

Methods and Materials

Eighteen patients were enrolled on a Human Investigation Committee approved study. A first subgroup of patients, treated with stereotactic body radiotherapy, had either T1N0 or T2N0 non-small cell lung cancer. A second subgroup had early stage to locoregionally advanced (T1N2 to T2N3) lung cancer, and were treated with conventional fractionation. This heterogeneous study population was formed so that the study population included lesions of various sizes and location. All patients underwent a respiration correlated CT scan (4DCT) during the simulation process. This scan was acquired using a slow helical method on a multidetector CT simulator (Brilliance Big Bore, Philips Medical Systems), and sorted by respiration phase using a bellows device. All patients were instructed to breath quietly and normally; scans were acquired during normal respiration.

All 4DCT scans were sorted into ten equally-spaced phase bins, with the first phase image corresponding to end of inhalation. This end of inhalation phase image was used as the reference image for the purposes of this study. For this study, only the primary tumor volume as delineated by the treating physician was considered as the gross tumor volume (GTV); nodal GTVs were removed. The bilateral lung volumes were delineated on the reference phase image by the treating physician, as well. A deformable image registration algorithm was used to generate a voxel-specific displacement vector field (DVF) for each phase image in relation to the reference phase image. The algorithmic details of this registration system have been reported previously (8,11). Briefly, the algorithm is based on a correlation coefficient similarity metric with a free-form model. The accuracy of the algorithm is dependent on image quality, so each registration was inspected visually by comparison to the reference image. However, the accuracy of this algorithm is estimated to be $1.1 \text{ mm} \pm 1.0 \text{ mm}$ based on a known-landmark

evaluation with 4DCT. In all, nine total DVFs were generated for each patient, mapping Phases 2 through 10 to the reference phase image. The DVFs were used to propagate the GTV and lung delineations to Phases 2 through 10. The propagated structures were compared visually to the physician-delineated manual structures for accuracy. After the individual GTVs were propagated, individual clinical target volumes (CTV) were formed by applying a 5 mm isotropic expansion of the GTV delineated from the corresponding phase image.

Three motion management strategies were evaluated: free-breathing target tracking, free-breathing mid-ventilation aperture, and breath hold at end of normal inspiration. Each strategy was simulated using a 4D planning technique, and the cumulative dose was computed. For each strategy a static plan was created using the reference phase image as the patient model. Dose was calculated and stored. Subsequently the static plan was mapped to all other phase images, the plan was adjusted as described below to simulate each motion management strategy, and dose was calculated for each different phase image. The dose matrices for Phases 2 through 10 were then mapped back to the reference phase dose grid by inverting the DVFs calculated for contour propagation, and the cumulative dose was accumulated using a method similar to that described by Rosu et al. (12).

All plans were designed to achieve a minimum dose of 63 Gy in 35 fractions to the CTV, which corresponded to a prescription isodose level of 90% of the dose at isocenter. Isocenter was placed at the centroid of the CTV on the reference phase image. All plans were generated with three to six beams in a coplanar arrangement using a commercial treatment planning system in research mode (Pinnacle v7.4f, Philips Medical Systems). Beam angulation and number of beams varied among patients. However, for a single patient, the same beam angulation and number of beams were used for all strategies to reduce bias among the strategies. The energy for all beams was 6 MV. A heterogeneity-corrected adaptive convolution dose calculation algorithm was used to plan the strategies conformally; intensity modulation was not allowed.

For free-breathing target tracking, the static plan for each phase image was generated by conforming the beam aperture to deliver a minimum dose to the CTV. For each phase, the CTV was formed from the corresponding phase GTV, so that the aperture tracked the target exactly throughout the respiration cycle. For each phase plan, the aperture was adjusted to preserve a minimum dose corresponding to the prescription isodose level to the phase CTV. This adjustment was necessary due to small variations in the dose distribution with phase (which were due to changes in target shape and volume, and density variations in and around the beam portals and target).

Free-breathing mid ventilation aperture (MVA) is a motion management strategy that achieves target dose coverage through a combination of controlling the mean tumor position (13–15) and applying a proper margin for the random blurring effect of respiration on the dose distribution (16–18). This strategy requires the GTV delineated at the mean position in the respiration cycle. To achieve this GTV_{mean} , the DVFs for all phases were averaged over time. This operation resulted in a single DVF, DVF_{mean} , that consisted of the average displacement of a voxel over the respiration cycle from the reference phase image. By propagating the GTV from the reference phase by DVF_{mean} , GTV_{mean} was generated. The CTV_{mean} was constructed by expanding the GTV_{mean} by 5 mm isotropically.

The required margin for respiration was generated through a patient-specific algorithm for MVA. First, a static conformal plan was constructed by setting the beam aperture equal to the CTV_{mean} . This static plan was mapped to all phase images, dose was calculated, and the cumulative dose was generated using the method described above. Coverage of the CTV on the reference phase with the cumulative dose was evaluated. The beam aperture for the static plan was adjusted, the plan remapped to each phase, and dose and cumulative dose recalculated.

until the CTV on the reference phase was covered by 90% of the isocenter dose (63 Gy) from the cumulative dose distribution. In other words, the CTV_{mean} is used to design the aperture for the 4D plan, but the cumulative dose is evaluated on the reference phase CTV. This iterative method produces an effective respiration-compensating margin similar to the recipe method described by van Herk (18). Although the iterative method is generally slower than margin generation through a recipe, the iterative method accounts for several parameters assumed invariant by the margin recipe (19) including intra- and inter-patient variation in the dose distribution and spatial invariance of the dose distribution with variation in the applied margin. Beam weights were allowed to vary slightly between phase plans in order to achieve similar target coverage between the MVA and tracking plans, but an attempt was made to keep the weights (and therefore total monitor units) as similar as possible. For simulation of the breath hold strategy, a static plan on the reference phase image was generated to simulate breath hold at end of normal inspiration.

For all three strategies, no safety margin was used. The addition of margin to compensate for errors would generally reduce the disparity between the strategies. We chose, therefore, to perform this simulation in a manner to provide the minimum lung dose theoretically possible with each strategy. Thus, variability or errors common to all and unique to each of the strategies were ignored.

The cumulative dose distributions from the three strategies were used to calculate several dose-volume metrics for the target volumes and lungs. D_{99} (minimum dose to 99% of the volume) and D_1 (maximum dose to 1% of the volume) to the CTV, mean lung dose (MLD) and percentage volume of lung receiving greater than 5, 10, and 20 Gy (V_5 , V_{10} , V_{20}) were calculated. Both lungs together minus the GTV were used to calculate all lung dose-volume metrics. The effect of the motion strategy on lung dose was assessed by calculating the difference in MLD, V_5 , V_{10} , and V_{20} between the different strategies for each patient. The MVA strategy was used the reference strategy. The difference in MLD between breath hold and MVA (ΔMLD_{BH}) and between target tracking and MVA (ΔMLD_{TT}) were calculated, both as a percent and an absolute difference. Similar difference metrics were calculated for lung V_5 , V_{10} , and V_{20} . These difference metrics can be thought of as ability of breath hold or target tracking to reduce the lung dose compared with MVA.

Four patient-specific parameters were evaluated for their ability to predict the difference in lung dose between the three strategies. Gross tumor volume, GTV deformation, GTV location, tumor excursion with respiration, and mean dose gradient near the target were calculated and both univariate and multivariate models used to measure the strength of the association between these variables and the difference in lung dose between the three strategies. For gross tumor volume, the volume (cc) at end of normal inspiration was used. GTV deformation was quantified as the percent volume change between inhale and exhale of the GTV (percentage difference between end of exhalation and end of inspiration gross tumor volume). While the GTV can deform without change of volume, volume difference was used as it is a simple parameter to calculate clinically. GTV location was quantified as distance (cm) from the edge of the GTV to chest wall, diaphragm, or mediastinum, whichever was closest. A more standard measure of tumor location in the lung, such as distance from apex, was not used for two reasons. First, location in relation to the apex has been demonstrated to correlate with excursion (20), and we have attempted to remove correlated independent variables from the analysis. Our GTV location metric correlated poorly ($r^2=0.03$) with excursion in the study population. Second, we thought that the dominant effect of location (ignoring the effect on excursion) would be a change in the shape of the dose distribution. Thus, tumors closer to the chest wall, diaphragm, or mediastinum may be more affected by variations in the dose distribution with respiration. Tumor excursion was measured as the magnitude of the maximum vector displacement (cm) between exhalation and inhalation center of mass of the tumor. Dose gradient was represented

by the ratio of the volume encompassed by the 90% to the 75% isodose surfaces. The closer this value was to unity, the higher the gradient. The 75% surface was used rather than a lower isodose level to insure that the surface was entirely contained within the dose grid.

Results

Table I lists the gross tumor volume, tumor motion characteristics, and patient characteristics. The average 3D extent of motion was 0.8 cm for all patients. One patient was excluded from the analysis due to extensive tumor involving the chest wall, which limited the accuracy of the image registration, and therefore, the dose accumulation. The data from this patient are not listed in Table 1.

For the mid-ventilation aperture approach, the target margin required to compensate for the random component of respiration is listed in Table II for all patients. The required aperture expansion, or margin, for respiration ranged from 0.0 cm to 0.6 cm. The largest expansion was required in the superior-inferior direction, which corresponded to the largest tumor excursion, on average. The margin was asymmetric in the superior-inferior direction due to asymmetry in the dose distributions and motion patterns. While this asymmetry was present in the left-right and anterior-posterior directions as well, the small magnitude of the required expansion masked it in the margin results. Either one or two iterations were required to achieve coverage with the prescription dose for the cumulative dose calculation. The majority of patients (72%) required a single iteration only to achieve adequate CTV coverage.

Figure 1 shows the static dose on several phases for target tracking and mid-ventilation aperture and the cumulative dose on the reference phase for both methods. Due to respiration-induced dose blurring, the isodose lines tend to spread apart for the cumulative dose when no active motion compensation is applied (for MVA). With active motion compensation (target tracking or breath hold), the isodose distribution tends to be preserved in comparison to the static dose.

To compare the three techniques by evaluating the effect on lung dose, the dose volume histogram of the target and lung for Patient 3 is shown in Figure 2. The minimum dose to the CTV was similar for all three techniques, as this was a planning objective. The maximum dose was largest for the breath hold plan, followed by the mid-ventilation aperture plan, with the target tracking plan having the lowest maximum dose. The MLD was lowest for the breath hold plan, followed by the target tracking, then the mid-ventilation aperture plan. The MLD for the mid-ventilation aperture plan was 7.2 Gy, 6.6 Gy for the target tracking plan, and 6.4 Gy for the breath hold plan. The V_{20} followed a similar pattern (11.2% for MVA, 10.0% for target tracking, 9.5% for breath hold). The slight improvement in MLD and V_{20} with breath hold over tracking is most likely due to the larger lung volume at end of normal inspiration.

To determine if the difference in MLD was due to the different strategies, or due to scaling of the dose (for example, if the target dose coverage was not matched between the strategies), we evaluated the minimum and maximum dose to the CTV using D_{99} and D_1 . For any single patient, the maximum difference in D_{99} between the strategies was 2.4 Gy (MVA to tracking) and 2.0 Gy (MVA to breath hold). The maximum difference in D_1 was 2.1 Gy (MVA to tracking) and 1.3 Gy (MVA to breath hold). The average differences over all patients were 0.6 Gy (D_{99}) and 0.4 Gy (D_1), for both strategies. We evaluated the association of D_{99} with MLD to determine if a strategy increased the D_{99} , would the MLD increase as well. Difference in D_{99} and MLD between the strategies were not significantly associated ($p>0.05$, $r^2<0.2$) for either target tracking or breath hold in relation to MVA. D_1 and MLD were also not significantly associated ($p>0.05$, $r^2<0.2$). Most likely, this result is due to the small spread (over all patients) in the difference in D_{99} and D_1 between the strategies, which was by design.

Figure 3 shows the MLD for all patients, all three strategies. The general trend was that the breath hold plan produced the lowest MLD, followed by the target tracking plan, and the mid-ventilation aperture plan. For one patient the target tracking MLD was the lowest. Figure 4 shows the V_{20} for all patients, which follows the same general trend as for the MLD. The largest difference between the mid-ventilation aperture MLD and the breath hold MLD was 1.0 Gy (a 7.6% decrease with breath hold from MVA) in Patient 12. This patient also had the largest difference in lung V_{20} , at 2.2%, between the mid-ventilation aperture and the breath hold plans. The largest percent change in MLD between the techniques was a 21.5% difference in MLD (MVA was 21.5% higher than the breath hold MLD).

The difference in MLD between the MVA and target tracking plans ($\Delta\text{MLD}_{\text{TT}}$) and between the MVA and breath hold plans ($\Delta\text{MLD}_{\text{BH}}$) were evaluated in a univariate linear model as a function of several independent variables (Table 3). Similar models were evaluated for the difference in V_{20} ($\Delta V_{20\text{TT}}$ and $\Delta V_{20\text{BH}}$), V_5 , and V_{10} . However, due to the strong correlation (Pearson product moment) between ΔMLD , ΔV_5 , ΔV_{10} , and ΔV_{20} , (r^2 ranged from 0.84 to 0.95), only the ΔMLD models are presented here. The absolute and percent difference in MLD were also correlated ($r^2=0.77$ for target tracking and $r^2=0.75$ for breath hold). Therefore, only the $\Delta\text{MLD}_{\text{TT}}$ and $\Delta\text{MLD}_{\text{BH}}$ calculated as percent differences are presented here.

The size of the gross tumor and the GTV location were not associated with either $\Delta\text{MLD}_{\text{TT}}$ or $\Delta\text{MLD}_{\text{BH}}$ on univariate analysis. GTV deformation was associated with $\Delta\text{MLD}_{\text{TT}}$ ($p=0.01$), but not with $\Delta\text{MLD}_{\text{BH}}$. As deformation increased, the difference between the MLD from the MVA plan and the tracking plan decreased. Deformation had no effect on the breath hold plan because this plan was generated on datasets only at end of inhalation. A sharper dose gradient was associated with an increase in $\Delta\text{MLD}_{\text{TT}}$ ($p=0.04$) but not with $\Delta\text{MLD}_{\text{BH}}$. A significant association was observed between increasing tumor excursion and increasing ΔMLD for both target tracking ($p=0.03$) and breath hold ($p=0.01$). Multivariate analysis was performed, but due to small sample size, only excursion was found to be significant ($p<0.05$).

The $\Delta\text{MLD}_{\text{TT}}$ as percentage difference from the MLD for the MVA plan is plotted in Figure 5a as a function of the three-dimensional magnitude of the tumor excursion per patient. The larger the value of $\Delta\text{MLD}_{\text{TT}}$, the larger the MLD was for the MVA plan in relation to the target tracking plan; $\Delta\text{MLD}_{\text{BH}}$ behaved similarly for the breath hold plan in relation to the MVA plan (Fig. 5b). Based on this analysis, a simple linear model was constructed to generate the predicted $\Delta\text{MLD}_{\text{TT}}$ and $\Delta\text{MLD}_{\text{BH}}$ based on an estimate of the magnitude of tumor excursion. For each 5mm of excursion, target tracking reduces the MLD by 4% compared to a MVA plan. For breath hold, the reduction is 5% per 5mm of excursion.

Discussion

In this study we performed a 4D dose calculation, the goal being to evaluate the relative difference in the cumulative lung dose between several ideal implementations of the strategies as a function of several patient parameters. Differences were found in the cumulative lung dose between breath hold, target tracking, and MVA as patient parameters varied. Based on the results, we can conclude that this difference was due to the strategies themselves, and not due to variations in the target dose between the strategies. As expected, the strongest factor in producing a relative difference in lung dose was the amplitude of tumor excursion with respiration. As this amplitude increased, the active motion compensation techniques of breath hold and target tracking tended to preserve the cumulative lung dose compared to the MVA approach. The respiration-compensating margin of the MVA approach is designed to provide CTV dosimetric coverage for a given respiration pattern, without consideration of the dose to normal tissue. While this approach selects the minimum margin required for this coverage, the dose to the surrounding normal tissue cannot be reduced beyond the minimum defined by

selection of this margin using standard planning techniques. Therefore, as the mean amplitude of respiration increases, the cumulative lung dose will increase. It may be feasible to reduce the cumulative lung dose by including positional variability and respiration in the inverse planning process (7,8), but this possibility was not evaluated in this study. Another option would be to combine the MVA approach detailed in this study with the margin recipe method. In this way, a patient-specific cumulative dose, which would include the effect of random variations on the dose distribution, could be generated. This would allow for compensation in the recipe for variations in the dose distribution among patients.

The difference in relative reduction in lung dose between breath hold and target tracking is most likely due to two effects. The breath hold technique was modeled at end of normal inspiration, while in target tracking dose is delivered throughout the breathing cycle. The larger volume of the lung at end of inspiration has been shown to reduce the dose to the lung for a given beam aperture (6). Additionally, calculation of the breath hold dose did not require a deformable registration and subsequent dose accumulation. This process contains error, which, if random in nature, may appear as a further blurring of the dose distribution, increasing the cumulative lung dose.

Deformation of the target was correlated with a relative reduction in MLD for target tracking compared to MVA. As deformation of the target increases, phase to phase tracking of the target requires adjustment of the beam aperture, which cannot follow the target shape exactly. This may introduce error into the process, which manifests as dose blurring if the error is random. As dose blurring increases for both the target tracking and MVA approaches simultaneously, the relative difference in lung dose between the two approaches will decrease.

The difference in cumulative lung dose among all three motion management strategies was generally small, the maximum difference being 1.0 Gy. However, the largest tumor excursion of any patient in this study was 1.3 cm. Patients with larger excursions will exhibit larger relative differences in lung dose among strategies. Still, relative differences in lung dose between the strategies were found to correlate with patient parameters. For large excursions, the relationship between relative lung dose difference and excursion may not be linear. However, we are unable to make a determination using only the data available here.

This model may be useful for clinics with multiple motion management solutions available. Based, on a pretreatment estimate of the tumor excursion, a patient could be stratified to MVA, or an active motion compensation strategy. The selection of a threshold for assignment into a management strategy will need to be based on a number of factors including anticipated non-managed lung dose, fractionation scheme, and therapeutic goal. Additionally, each of the evaluated strategies possesses unique advantages and disadvantages that must also be considered when selecting a strategy. MVA, as implemented in this study, relies on a stationary mean position during a single fraction and on the stability of the predicted respiration pattern over the treatment course. Patient compliance with breath hold strategies may be limited due to poor lung function. MLC-based tracking accuracy may be limited by response to non-periodic events (such as coughing) and quality of the tumor position surrogate.

Starkschall et al. observed a reduction in lung dose (both V20 and MLD) with respiration gating compared to an ITV approach (21). The reduction was associated with the size of the GTV, with the difference between the approaches being minimal for GTV sizes greater than 100 cc. Similar to the current study, the magnitude of the reduction was 22 similar regardless of which toxicity metric (V20 or MLD) was used. Starkschall et al. assessed target volume differences between the gating and ITV approaches, whereas here we assess cumulative lung dose for similarly sized target volumes. Thus the current study focuses on differences in lung dose due

to the motion management technique itself, not the ability of the technique to enable margin reduction.

Underberg and colleagues observed a large reduction in target size with gating compared to an ITV approach (10). However, the blurring effect of respiration was not modeled in the study. In our study, margins for the MVA approach were not based on an internal margin method as with the ITV method. Rather, with some knowledge of the blurring effect of respiration on the cumulative dose distribution, we were able to generate a patient specific margin to compensate for this respiration blurring, provided that the respiration pattern remained stable. Thus, the margins for the MVA approach are generally smaller than for the ITV approach, resulting in a less pronounced difference in lung dose between the strategies evaluated in this study and those evaluated by Underberg.

This study is not the first to evaluate cumulative lung dose as a function of delivery method. Rosu et al. determined the number of phase images required to represent cumulative dose-volume metrics for conformal radiotherapy planned with asymmetric margins (22). Both Rosu et al. and Flampouri et al. (23) determined that one to three phase images may be adequate to estimate cumulative dose-volume parameters. Ehler and Tome and Seco et al. evaluated cumulative dose for IMRT, with an ITV strategy. Ehler and Tome determined that the cumulative dose to the lung was not well-approximated by the dose calculated from a single phase image. Seco et al. evaluated the effect of interfraction variations in respiration on the cumulative dose to the target and found that generally the effect was small. However, the validity of applying the conclusions of these studies, which were conducted with an ITV or asymmetric margin strategy, to the current results is questionable, since the ITV is generally much larger than the respiration margin of the current study.

Several areas for possible future investigation exist. We did not consider errors unique to each strategy, but rather evaluated the theoretical best implementation of each method. Including a similar level of error and uncertainty through a safety margin for each strategy would reduce the relative difference in lung dose between the strategies. Relative differences in errors would mostly likely reduce the distinction in lung dose between the strategies as well, but of course this would largely depend on which strategy was dominated by the largest uncompensated uncertainties.

Additionally, here we considered only primary tumor as a target. A more important benefit of motion management may be evident for multiple targets in late stage disease, where target volumes are larger, although we observed no correlation between benefit (lung dose reduction) and target volume size. For multiple targets (e.g., primary and nodal regions) with independent motion distributions, active motion compensation with any of the three evaluated methods becomes complex. Limitations may exist in particular for large, independent variations such as baseline variation (24).

Conclusions

Clinical implementation of motion management requires selection of an appropriate technique based on an estimate of the intended benefit to the patient. Here we have evaluated the cumulative lung dose over the respiratory cycle for three motion management strategies. The dominating factor stratifying the techniques by lung dose was the mean tumor excursion. A linear model relating difference in lung dose between the strategies to magnitude of tumor excursion was constructed. This model can be used to stratify patients into a motion management strategy based on a pretreatment assessment of tumor excursion.

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Figure 1.

4D dose calculation for mid-ventilation aperture (a–d) and target tracking (e–h). For MVA, the static dose at end of normal expiration (a), mid-ventilation (b), and end of normal inspiration (c) are displayed. (d) displays the cumulative 4D dose. The CTV is displayed in colorwash. For target tracking, (e) through (g) are the corresponding static dose calculations and (h) is the cumulative 4D dose. The cumulative dose distribution is more heterogeneous and blurred (isodose lines are further apart) for MVA compared to target tracking.

Figure 2.

Cumulative 4D dose-volume histogram for Patient 3, for the three strategies. The prescription of 63 Gy minimum dose to the CTV was similar for the strategies, while the maximum dose in the CTV was highest for breath hold and lowest for target tracking. This was not a trend among the patient population. The lung dose-volume parameters (V_{20} and mean lung dose) were lowest for breath hold and highest for MVA. As explained in the text, this was a general trend among patients.

Figure 3. Mean lung dose (cGy) per patient for the three strategies. Generally, MLD was lowest for breath hold and highest for MVA.

Figure 4. Lung V₂₀ (%) per patient for the three strategies. Generally, V₂₀ was lowest for breath hold and highest for MVA.

Figure 5.
 (a) $\Delta\text{MLD}_{\text{TT}}$ and (b) $\Delta\text{MLD}_{\text{BH}}$ as a function of tumor excursion (cm), for all patients.

Table 1
Patient characteristics.

Patient	Stage (TN)	*GTV (cc)	ΔGTV (%)	GTV Location	GTV Distance (cm)	Tumor Excursion (cm)		
						LR	AP	SI
1	T1N2	5.4	6.2	RML	0.0	0.1	0.4	0.6
2	T2N0	24.0	3.8	LLL	0.5	0.2	0.0	1.1
3	T2N2	31.8	4.7	RLL	0.0	0.3	0.4	1.2
4	T1N0	9.2	2.6	RLL	0.0	0.2	0.1	1.1
5	T2N0	19.1	10.6	LLL	0.2	0.1	0.1	1.0
6	T1N0	3.0	5.9	RLL	0.5	0.4	0.1	0.9
7	T2N3	17.4	9.5	LLL	0.1	0.1	0.0	0.3
8	T1N0	3.6	21.8	RUL	2.4	0.1	0.2	0.6
9	T2N0	41.9	6.0	RUL	0.5	0.2	0.2	0.4
10	T2N1	25.1	4.6	RLL	0.0	0.2	0.2	0.7
11	T1N0	5.6	13.6	LLL	0.5	0.1	0.4	0.4
12	T2N2	60.0	2.4	LLL	0.0	0.1	0.2	1.1
13	T1N0	5.4	17.8	RUL	0.2	0.1	0.1	0.2
14	T2N0	46.4	0.3	LUL	0.0	0.1	0.3	0.2
15	T1N0	3.8	13.5	RUL	0.8	0.1	0.2	0.3
16	T1N0	8.0	0.3	RLL	0.0	0.1	0.1	0.9
17	T1N0	5.0	5.9	LLL	0.7	0.1	0.2	1.1
Mean		18.5	7.6		0.4	0.1	0.2	0.7

GTV – gross tumor volume size, ΔGTV – change in GTV size, exhale to inhale, GTV Distance (cm) – radial distance from edge of GTV to lung border (mediastinum, diaphragm, or chest wall), LR – left/right, AP –anterior/posterior, SI – superior/inferior, 3D – three-dimensional magnitude of excursion, RUL – right upper lobe, LUL – left upper lobe, RML – right middle lobe, RLL – right lower lobe, LLL – left lower lobe.

* All patients were M0.

Table 2
Required margin for random component of respiration, mid-ventilation aperture plan.

Patient	Required Respiration Margin, MVA (cm)				Iter
	LR	AP	Sup	Inf	
1	0.1	0.2	0.0	0.5	2
2	0.0	0.0	0.1	0.3	2
3	0.2	0.0	0.0	0.6	2
4	0.0	0.0	0.2	0.2	1
5	0.0	0.0	0.0	0.2	1
6	0.1	0.2	0.0	0.3	2
7	0.1	-0.1	0.2	0.0	1
8	0.1	0.0	0.0	0.1	1
9	0.1	0.0	0.0	0.0	1
10	0.0	0.1	0.0	0.0	1
11	0.1	-0.1	0.2	0.1	1
12	0.1	0.1	0.0	0.1	1
13	0.1	0.0	0.3	0.0	1
14	0.1	0.0	0.1	0.0	1
15	0.0	0.1	0.1	0.0	1
17	0.1	0.1	0.0	0.4	1
18	0.1	-0.3	0.0	0.2	2
Mean	0.1	0.0	0.1	0.2	

LR – mean margin in the left-right direction, AP – mean margin in the anterior-posterior direction, Sup – margin in the superior direction, Inf – margin in the inferior direction, Iter – required number of iterations to achieve minimum target coverage with the cumulative dose.

Table 3

p-values and significance testing from univariate and multivariate analyses.

Independent Variable	Univariate Dependent Variable		Multivariate Dependent Variable	
	$\Delta\text{MLD}_{\text{TT}}$ (%)	$\Delta\text{MLD}_{\text{BH}}$ (%)	$\Delta\text{MLD}_{\text{TT}}$ (%)	$\Delta\text{MLD}_{\text{BH}}$ (%)
Gross tumor volume (cc)	0.35	0.92	0.17	0.38
GTV deformation (%)	0.01	0.18	0.16	0.29
Dose gradient (unitless)	0.04	0.39	0.23	0.21
Tumor excursion (cm)	0.03	0.01	<0.01	<0.01
GTV location (cm)	0.28	0.92	0.36	0.17

Significant ($p < 0.05$) associations in bold. $\Delta\text{MLD}_{\text{TT}}$ – percent difference in mean lung dose, mean ventilation aperture to target tracking, $\Delta\text{MLD}_{\text{BH}}$ – percent difference in mean lung dose, mean ventilation aperture to breath hold, GTV – gross tumor volume.