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Scientific Article

Motion-Inclusive Treatment Planning to Assess Normal Tissue Dose for Central Lung Stereotactic Body Radiation Therapy

David Cooper, MD,[a,*] Laura Padilla, PhD,[b] Amy Watson, CMD,[c] Keith Neiderer, CMD,[c] Benjamin Smith, CMD,[c] and Elisabeth Weiss, MD[c]

[a]*Tennessee Oncology, Nashville, Tennessee;* [b]*Department of Radiation Medicine and Applied Sciences, University of California San Diego, San Diego, California; and* [c]*Department of Radiation Oncology, Virginia Commonwealth University Health System, Richmond, Virginia*

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Purpose: For lung stereotactic body radiation therapy, 4-dimensional computed tomography is often used to delineate target volumes, whereas organs at risk (OARs) are typically outlined on either average intensity projection (AIP) or midventilation (MidV = 30% phase) images. AIP has been widely adopted as it represents a true average, but image blurring often precludes accurate contouring of critical structures such as central airways. Here, we compare AIP versus MidV planning for centrally located tumors via respiratory motion-inclusive (RMI) plans to better evaluate dose delivered throughout the breathing cycle.

Methods and Materials: Independently contoured and optimized AIP and MidV plans were created for 16 treatments and rigidly copied to each of the 10 breathing phase-specific computed tomography image sets. Resulting dose distributions were deformably registered back to the MidV image set (used as reference because of clearer depiction of anatomy compared with motion-blurred AIP) and averaged to create RMI plans. Doses to central OARs were compared between plans.

Results: Mean absolute dose differences were low for all comparisons (range, 0.01-2.87 Gy); however, individual plans exhibited differences >20 Gy. Dose differences >5 Gy were observed most often for plan comparisons involving AIP-based plans (MidV vs AIP 23, AIP RMI vs AIP 12, MidV RMI vs AIP RMI 7, and MidV RMI vs MidV 8 times). Inclusion of respiratory motion reduced large dose differences. Standard OAR thresholds were exceeded up to 5 times for each plan comparison scenario and always involved proximal bronchial tree D4 cc tolerance dose. AIP-based contours were larger by, on average, 3% to 15%.

Conclusions: Large dose differences were observed when plans with AIP-based contours were compared with MidV-based contours, indicating that observed dose differences were likely due to contoured volume differences rather than the effect of motion. Because of blurring with AIP images, MidV RMI-based planning may offer a more accurate method to determine dose to critical OARs in the presence of respiratory motion.

Introduction

For early-stage lung cancer, stereotactic body radiation therapy (SBRT) has become a well-established treatment modality for medically inoperable patients, providing high local control and cure rates.[1-4] SBRT offers many advantages over conventionally fractionated radiation

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*Corresponding author: David Cooper, MD; Email: dcooper8941@gmail.com

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therapy, including an abbreviated treatment course, increased radiobiologically effective tumor dose, and the ability to better spare surrounding organs at risk (OARs). Because higher doses are delivered, image guidance, target definition, and OAR characterization become more important.[5] Moreover, an even higher level of caution must be used for tumors located near central structures. Outcomes from multiple prospective trials have demonstrated that high doses to central structures such as proximal bronchial tree (PBT) can confer increased toxicity and even a high risk for treatment-related death.[6,7]

SBRT planning, particularly for intrathoracic tumors, presents challenges, as the target and corresponding surrounding structures undergo positional change due to respiration. Commonly, 4-dimensional computed tomography (4D-CT) is used to create an internal gross tumor volume (iGTV), whereby the GTV on a given "phase" of the 4D-CT is propagated to all other phases to create an "envelope" that covers respiratory motion of the tumor.[8] In current clinical practice, OAR contours are typically not propagated, but generated on either a single CT phase at a "midpoint" in ventilation (midventilation [MidV], which is often the 30% breathing phase image set of the 4D-CT) or an average intensity projection (AIP) image set, in which the intensity of each pixel in the image is an average over all the 4D-CT phases. Dose calculation is usually performed on the same image set chosen for OAR contouring. AIP images often result in blurring and poorly defined anatomic boundaries of moving organs and frequently preclude accurate contouring of, particularly, the bronchial tree (Fig. 1). Given that the AIP image set is an average, it does account for respiratory motion. However, neither AIP- nor MidV-based structure sets will elicit the true dose delivered throughout the breathing cycle, as the contours themselves are static. Both approaches therefore do not reflect the "true" dose delivered for OARs, which limits the ability to establish dose-toxicity relationships.

We designed the current study to better understand the radiation dose differences between AIP- and MidV-based treatment planning and the effect of respiratory motion for OAR doses. Our analysis was focused on centrally located tumors, given the increasing body of evidence indicating potentially life-threatening toxicity for SBRT in this setting.

Methods and Materials

Patients and image acquisition

After obtaining institutional review board approval, we identified 14 patients (16 treatment plans) having previously received SBRT or hypofractionated radiation therapy delivered via SBRT technique to centrally located primary lung tumors at our institution. Central tumors were defined as those within a 2-cm distance to the PBT

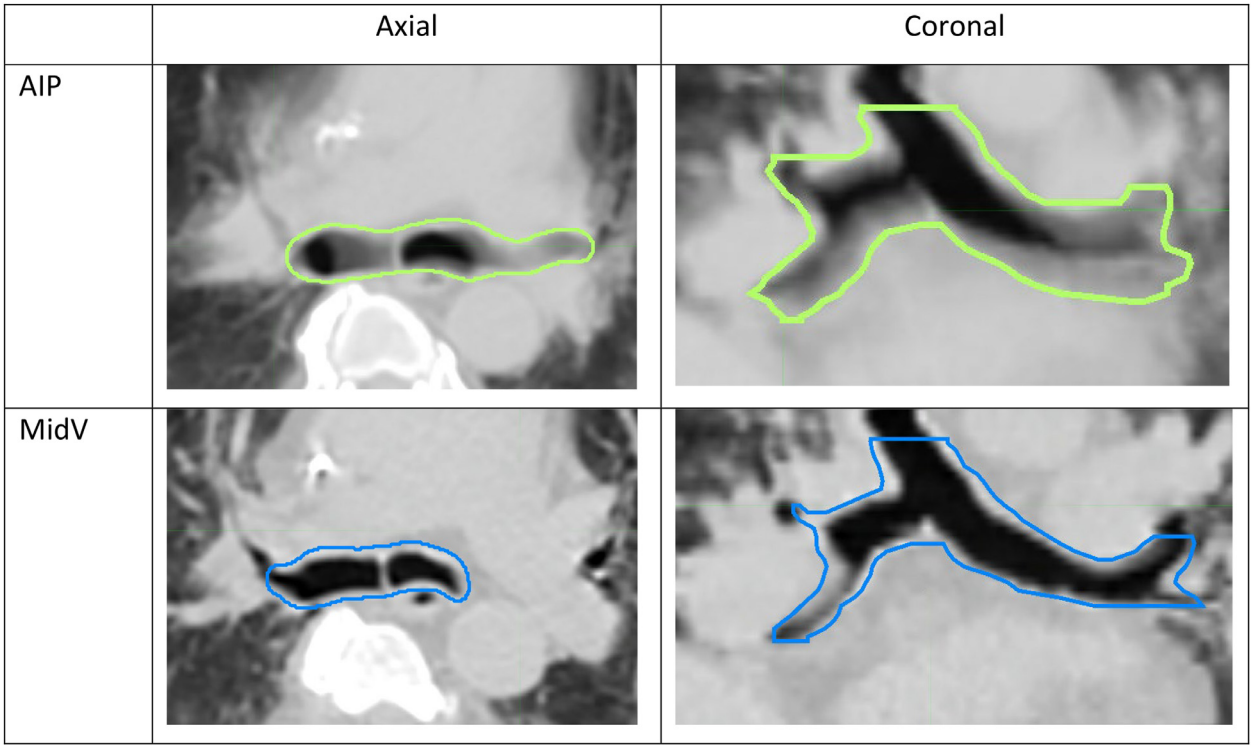

Figure 1 Example of proximal bronchial tree contours on average intensity projection and midventilation computed tomography image sets.

Table 1 Patient and treatment characteristics

Treatment	Histology	Location	Stage	Tumor size (cm)	Total dose (Gy)	Fractions	Carina motion Sup-Inf (cm)
1	NSCLC	LUL	IA2	1.6	50	5	0.48
2	NSCLC	RML	IA2	1.5	50	5	0.35
3	NSCLC	LUL	IA1	0.9	50	5	0.52
4	SCLC	RML	IIIA	1.8	48	4	0.36
5	SCLC	RLL	IIIA	1.4	48	4	0.36
6	NSCLC	RML	IVA	1.3	50	5	0.32
7	NSCLC	LUL	IVA	1.1	50	5	0.32
8	SCLC	LUL	IA2	1.8	60	8	0.65
9	NSCLC	RLL	IB	3.3	48	4	0.42
10	NSCLC	LLL	IIA	4.3	60	15	0.5
11	NSCLC	RUL	IIA	5.0	48	4	0.73
12	NSCLC	RUL	IA3	3.0	50	5	0.34
13	NSCLC	RUL	IA2	1.1	50	5	0.55
14	NSCLC	RML	IA1	1.0	50	5	0.53
15	NSCLC	RUL	IA2	1.7	60	15	0.65
16	NSCLC	LLL	IA2	1.5	40	5	0.57

Abbreviations: LLL = left lower lobe; LUL = left upper lobe; NSCLC = non-small cell lung cancer; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe; SCLC = small cell lung cancer; Sup-Inf = superior-inferior.

or mediastinal structures.[6] Each patient underwent a free breathing 4D-CT for treatment planning (Brilliance Big Bore; Philips Medical Systems), with the patient's images divided into 10 distinct equally time-spaced phase bins. A slice thickness of 3 mm was used, and a bellows belt was used to track breathing. This information was then used to create 10 unique 3D-CT data sets corresponding to individual phases of respiratory motion. For patient and treatment characteristics, see Table 1.

Treatment planning

For clinical treatment planning, tumor volumes were first outlined using the MidV respiratory phase, then propagated through all phases of respiratory motion via deformable propagation (MIM Software Inc, v7.0.6) to produce an iGTV. A planning target volume was generated with a 5-mm expansion from the iGTV. OARs were defined according to protocol Radiation Therapy Oncology Group 0813[6] and included heart, lungs, PBT, esophagus, great vessels, and spinal cord. These OARs were outlined on the CT data set, which was selected for treatment planning. All treatments were calculated using Varian Eclipse software (Varian Medical Systems Inc) and optimized using a goal of V100% prescription dose greater than 95% for the planning target volume, as well as a conformality index of less than 1.2. Acuros 16.1.0 was used for treatment planning using a grid size of 2 mm. Plans met current dose recommendations[8] and were delivered every other day. Before individual treatment fractions, surface imaging and cone beam CT were employed to ensure accurate patient and target alignment.

Dose reconstruction

For the purpose of this study, an AIP- and MidV-based plan was created for each patient. OARs were contoured on each image set. Consistency between the contour sets was ensured through peer review and by avoiding multi-observer delineation variations, as only 1 physician contoured all OARs. The target volume definition was the same for both plans. Treatment plans from the original clinical plan were copied to the corresponding MidV- or AIP-based image sets and optimized on each OAR contour set. Both plans were optimized in a similar fashion such that each plan would be deemed acceptable for patient delivery.

In Eclipse, both the AIP and MidV treatment plans were then applied to each respiratory phase CT and the dose was recalculated, with all treatment parameters unchanged. AIP-based plans were applied to each of the 10 respiratory phases, and MidV-based plans (which were planned and calculated on the 30% phase) were applied to the remaining 9 phases (Fig. 2). The dose distribution for each of the individual 10 phases was then imported into MIM to calculate an estimate of the dose delivered by each plan through respiratory motion. All phase-specific dose distributions for each plan were deformed to the

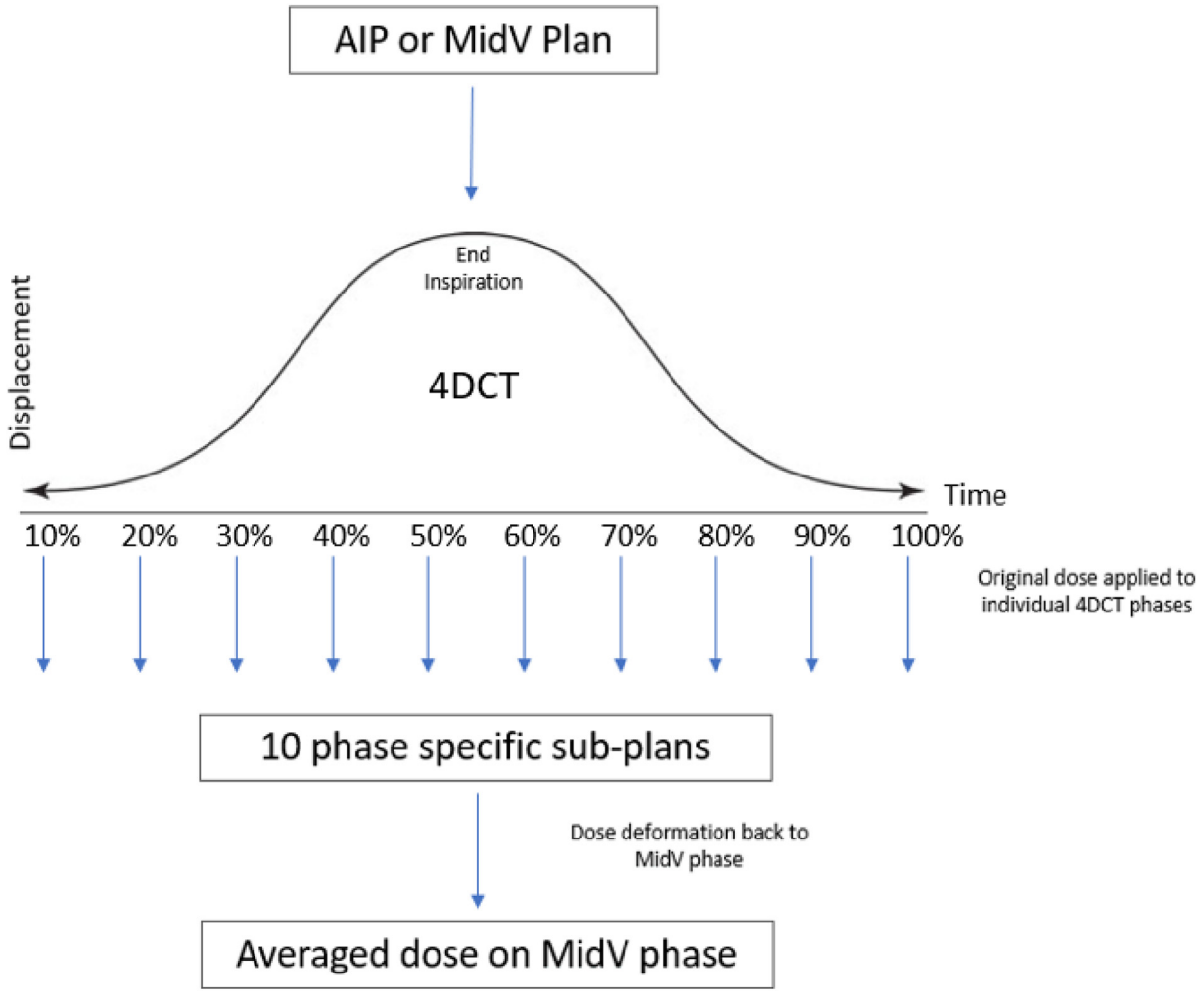

Figure 2 Deformable dose summation methodology for respiratory motion-inclusive based plans.

MidV scan. The dose deformation was accomplished via MIM VoxAlign deformable registration algorithm. We estimated the respiratory motion-inclusive dose delivery of each plan by summing over the dose from each phase, assuming that each phase contributed to 1/10th of the overall dose. All respiratory motion-inclusive summed doses were evaluated on the MidV phase using the MidV contours to ensure a fair comparison between the doses delivered during respiration by the AIP- and MidV-based plans. MidV phase was chosen as it represented a mid-breathing phase that displays anatomic organ boundaries clearly without blurring. This process ultimately resulted in respiratory motion inclusive (RMI) dose distributions of both the AIP- and MidV-based plans.

Comparison and analysis

Doses to OARs for the 2 original plans (MidV and AIP) and the 2 RMI plans (MidV RMI and AIP RMI) were recorded within MIM, and doses to the OARs were evaluated. Dose comparisons were performed for the following scenarios:

- AIP versus MidV: comparing clinical routine approaches on respective original AIP and MidV image sets
- MidV RMI versus AIP RMI: comparing the effect of respiratory motion-inclusive planning for original MidV and AIP contours propagated over 10 respiratory phases with dose evaluated on the reference 30% phase data set
- AIP RMI versus AIP: assessing the effect of respiratory motion inclusive-planning for AIP planning
- MidV RMI versus MidV: assessing the effect of respiratory motion-inclusive planning for MidV planning

Differences in maximum doses and selected volumetric parameters (reference 9 for $\leq$5 fractions, reference 10 for >5 fractions) were calculated. Differences were reported on a per patient/treatment scenario basis and as average differences for all patients/treatment scenario. In addition,

the number of instances where dose differences exceeded defined thresholds (2-5 Gy, >5 Gy) were reported. Instances where selection of 1 plan versus the corresponding comparison plan resulted in doses exceeding standard OAR thresholds were also recorded per planning scenario. To determine whether MidV versus AIP planning provides a more precise dose estimate of the respective motion-inclusive plans, Levene's test was performed to assess homogeneity of variances. Respiratory motion of the carina for each patient was assessed using 4D-CT data and correlated with the observed dose differences via linear regression. To document different visual appearance of OARs on MidV and AIP images, volume differences between the AIP and MidV data sets were investigated as well. Differences were assessed for statistical significance ($P < .05$) via paired t test.

Results

Treatments

Sixteen total treatment plans were evaluated from a cohort of 14 patients with primary lung tumors (Table 1). Six of these tumors were located within the left lung/hilum and 10 on the right. The median prescribed dose was 50 Gy (40-60 Gy in 5-15 fractions) with the most commonly prescribed regimen being 50 Gy in 5 fractions (8 treatments); only 2 plans consisted of 15 fraction treatments. A biologically effective dose of ≥100 Gy was delivered in 88% of cases and ranged from 72 to 105.6 Gy.

MidV versus AIP

Mean differences +/- SD between OAR maximum doses and volume-based dose thresholds for MidV- versus AIP-based plans ranged from 0.28 to 1.41 Gy (+/-1.38-5.98 Gy). Although mean dose differences were low, the ranges of differences seen were high depending on OAR (see Fig. 3). Notably, the maximum dose differences for PBT and esophagus were as high as 18.62 and 6.96 Gy, respectively. The largest volume-based dose differences for PBT D4 cc and esophagus D5 cc were 6.00 and 12.75 Gy, respectively. Dose differences 2 to 5 Gy/>5 Gy were observed in 22/23 instances (see Fig. 4).

MidV RMI versus AIP RMI

Mean differences +/- SD between OAR maximum doses and volume-based dose thresholds for MidV RMI versus AIP RMI plans ranged from 0.02 to 1.61 Gy (+/-1.02-3.84 Gy; see Fig. 3). Dose differences 2 to 5 Gy/>5 Gy were observed in 26/7 instances (see Fig. 4). The maximum dose differences for PBT and esophagus were 6.60 and 3.03 Gy, respectively. The largest volume-based dose differences for PBT D4 cc and esophagus D5 cc were 4.69 and 3.57 Gy, respectively. Compared with MidV versus AIP, the number of large dose differences between RMI plans was reduced.

AIP RMI versus AIP

Mean differences +/- SD between OAR maximum doses and volume-based dose thresholds for AIP RMI versus AIP plans ranged from 0.09 to 2.87 Gy (+/-0.48-6.39 Gy; see Fig. 3). The largest maximum dose differences for PBT and esophagus were 21.57 and 4.00 Gy, respectively. The largest volume-based dose differences for PBT D4 cc and esophagus D5 cc were 2.62 and 10.69 Gy, respectively. Dose differences 2 to 5 Gy/>5 Gy were observed in 14/12 instances (see Fig. 4).

MidV RMI versus MidV

Mean differences +/- SD between OAR maximum doses and volume-based dose thresholds for MidV RMI versus MidV plans ranged from 0.01 to 0.77 Gy (+/-0.16-1.43 Gy; see Fig. 3). The largest maximum dose differences for PBT and esophagus were 3.92 and 3.87 Gy, respectively. The largest volume-based dose differences for PBT D4 cc and esophagus D5 cc were 2.58 and 1.51 Gy, respectively. Dose differences 2 to 5 Gy/>5 Gy were observed in 8/0 instances (see Fig. 4). Large dose differences were significantly less frequent compared with all other plan comparisons. When comparing dose differences of MidV RMI - MidV to differences of AIP RMI - AIP, variances were smaller for MidV RMI − MidV comparisons for all analyzed OAR dose parameters except esophagus max and heart D15 cc. Variances were not statistically different for the majority of OAR parameters. MidV might be a more precise estimate of the motion-inclusive dose than AIP for esophagus D5 cc/mean, great vessels D10 cc/max, lung D1000 cc/1500 cc/mean, and trachea max where statistically significant differences between variances were observed ($P = .044 - P = .0003$).

Plans exceeding standard dose thresholds

Plan comparisons resulted in 3 to 5 instances for each scenario where plans that met dose constraints in 1 plan exceeded dose constraints in the corresponding comparison plan. Dose parameters exceeding standard constraints were observed for esophagus max dose (2 plan comparisons), great vessels max (3), heart D15 cc (2), heart max (2), PBT D4 cc (4), and PBT max (3).

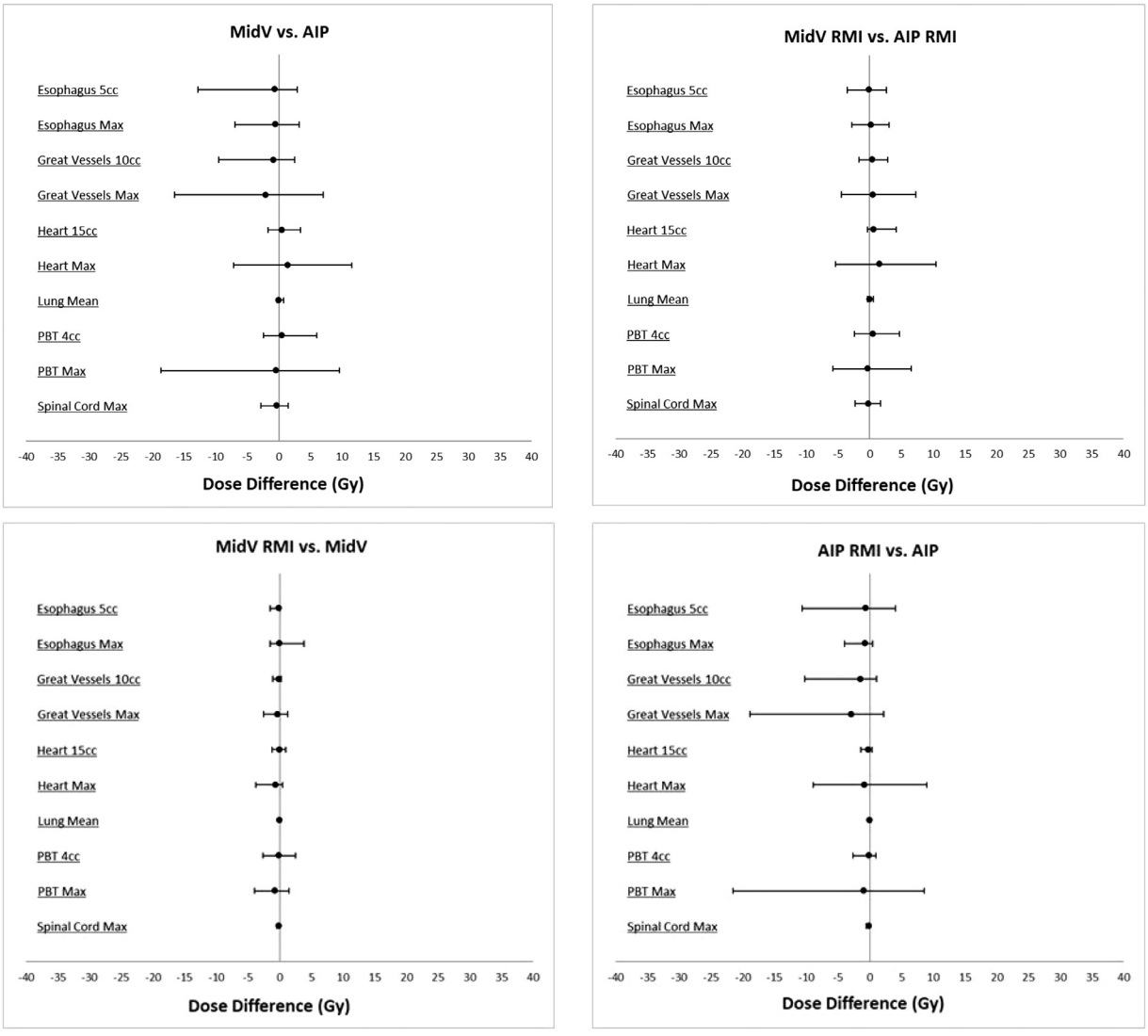

Figure 3 Plan comparisons for standard and motion-inclusive plans.

Volume and carina motion

The contoured volumes for each patient were recorded for AIP versus MidV plans. Except for esophagus, OAR volumes were on average larger on AIP than MidV image sets by 3% to 15% (n.s.). AIP-based PBT contours were larger than MidV-based contours for 6 treatments by an average of 23.58% (range, 16.59%-40.67%), likely because of blurred display of this structure resulting from breathing motion. In the 10 treatments where MidV-based PBT was larger than AIP-based contours, average differences were 5.52% (range, 0.16%-9.87%) which is likely within the range of typical contour variation (Fig. 5). Superior-inferior carina motion ranged from 0.32 to 0.73 cm. Linear regression analysis of carina motion versus maximum dose to each structure was performed. No significant relationship between carina motion and difference in contoured volumes was identified.

Discussion

Several published prospective trials have outlined concerning adverse events in the central and ultracentral settings. An early phase I trial from Timmerman et al[9] evaluated patients who received SBRT 60 to 66 Gy for both centrally and peripherally located tumors. In their analysis, tumor location did not affect disease control; however, grade 3 or higher toxicity occurred in 27% of patients with centrally located tumors. The Radiation Therapy Oncology Group 0813 trial was a dose escalation study that investigated SBRT to centrally located tumors.[6,10] Maximum tolerated dose was 12 Gy per fraction (60 Gy in 5 fractions); however, severe treatment complications were seen even in the 11.5 Gy per fraction group. Four patients (out of the 120 evaluated) had grade 5 events, 3 of which involved bronchopulmonary hemorrhage. In the Nordic-HILUS trial for

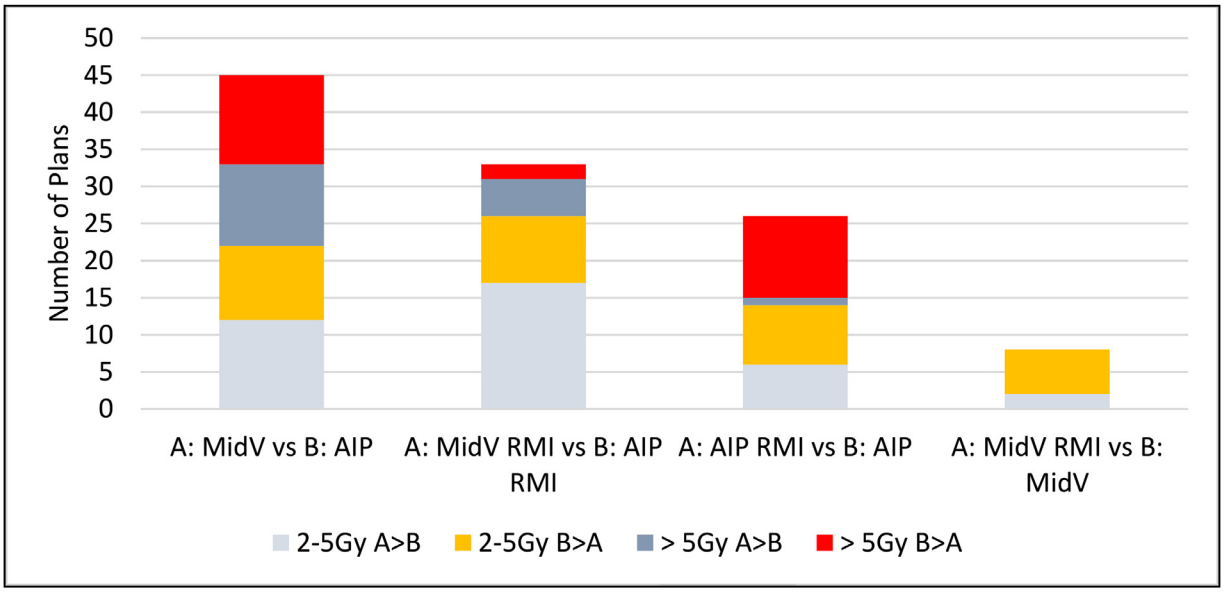

Figure 4 Dose differences 2 to 5 Gy and >5 Gy.

ultracentral lung tumors receiving an SBRT dose of 56 Gy in 8 fractions, 2-year local control was 83%; however, grade 3 to 5 toxicity was found in 22 patients, including 10 cases of treatment-related death.[7] Of these 10 cases, 8 were attributed to bronchopulmonary hemorrhage. Distance between tumor and bronchus and high dose volumes were identified as significant risk factors for fatal bleeding. A D0.2 cc of 100 Gy (equivalent dose in 2 Gy fractions) resulted in an estimated nearly 20% probability of fatal bleeding.

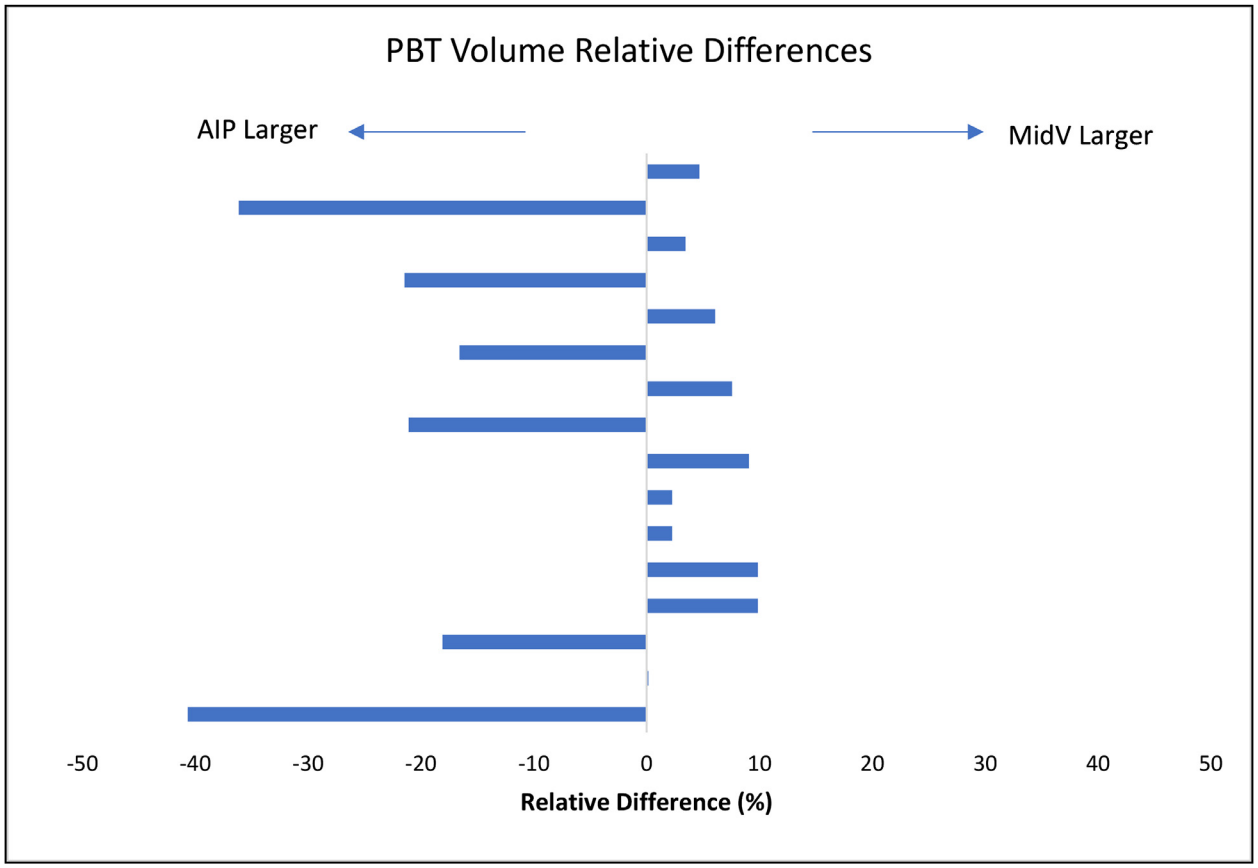

Figure 5 Volume differences for the proximal bronchial tree per plan.

As such, the methodology for planning these patients deserves more attention, including associated differences with MidV- versus AIP-based planning. AIP images often exhibit blurring, particularly at structural boundaries, which is not the case on single-phase respiratory images. Several groups have evaluated differences in target coverage between AIP-, MidV-, and also maximum intensity projection-based planning,[11–13] but only a few have extended this question to investigate how planning CT differences might affect OAR dosimetry. A recent study by Khamfongkhruea et al[14] examined dosimetric differences among MidV, AIP, and free breathing data sets using fractionated radiation therapy to doses of 50 to 66 Gy in 2 Gy fractions via intensity modulated radiation therapy or 3D-CRT. Another study looked specifically at SBRT treatments planned on free-breathing CTs versus 4D-CT AIP images.[12] Neither study found statistically significant differences in OAR dosimetry. The latter study, however, was limited to analysis of only lung doses, and tumor location varied.

In the present study, we included only centrally located lung tumors treated with SBRT. We also aimed to make a more thorough comparison by incorporating the dose received among 10 respiratory phases to better account for possible effects of breathing motion on dose delivery.

Motion-inclusive plans allow for a more direct comparison between MidV- and AIP-based plans, as they eliminate motion as a confounder for observed dose differences. As outlined in the results section, the ranges of max dose and volume-based dose differences between MidV- and AIP- based plans were high for individual plans with instances of >5 Gy dose difference observed in 23 plan comparisons. The comparison to motion-inclusive MidV RMI versus AIP RMI plans showed a reduction in high-dose differences, likely as a result of using the MidV contours as a reference for both plan evaluations. When comparing MidV versus AIP plans, their original contours created on the respective image sets were used. Using different contour sets for plan evaluation is likely also the reason for the observed large differences between AIP (on original AIP contours) and AIP RMI plans (on MidV contours). Larger dose differences for all plan comparisons involving AIP-based image sets are likely due to differences in contouring. As expected, on average, AIP contours were larger than MidV contours as AIP images make it difficult to confidently contour airways and other structures affected by physiological motion. As seen in Fig. 1, there is clearly a difference in the level of detail seen, with the MidV having cleaner demarcation of anatomic boundaries such as bronchial wall. The MidV RMI versus original MidV comparison highlights this well (Fig. 3), as both plans use the same set of contours and both were optimized with the same original MidV CT. The small differences for this comparison indicate that deformable registration accounted well for respiratory motion, with the observed remaining differences being likely due to real variations in organ position and volumes during respiration.

Most notably, PBT max dose is the structure with the widest range of differences and exhibits the most drastic variations when 2 different contour sets are used (ie, any comparison involving an AIP plan). In plan comparisons for all scenarios, PBT D4 cc threshold dose was exceeded in at least 1 individual plan comparison.

Although these results provide some understanding of potential issues affiliated with AIP-based planning, our study is limited to a relatively small cohort. Although some statistically significant differences were observed, most comparisons yielded high variability. In addition, although the goal of this study was to identify differences between AIP and MidV plans, contour variations cannot be excluded as the cause for some variability in our analysis, despite the measures taken to ensure consistent contouring. Also, respiratory motion was relatively small and was not significantly related to dose differences.

Although this investigation does not provide a definitive answer as to which CT data set might be more advantageous in a given clinical setting, it presents a method by which the dose to OARs can be more heavily scrutinized and insight into why differences between AIP and MidV planning might occur. In cases where tumors closely approximate central structures, a reasonable approach might be to use the MidV phase for treatment planning, particularly if the AIP reconstruction does not yield clear OAR visualization. In general, MidV appears to also give a more precise dose assessment of the motion inclusive plan compared with AIP. Furthermore, a motion-inclusive strategy, such as an RMI plan, combined with more accurate contouring via MidV-based planning, likely provides the highest level of certainty among the planning strategies outlined here. AIP-based planning is an efficient method to assess OAR dose for many clinical scenarios and when combined with cone beam CT during patient set-up is a reasonable approach to assess the approximate OAR position. As demonstrated here, AIP-based planning often over- and sometimes under-estimates OAR dose. We therefore feel that MidV RMI planning is a valuable tool to better evaluate deposited dose in cases at high risk for clinically significant toxicity, as is seen for centrally located SBRT, particularly when OAR doses are close to tolerance.

Conclusion

Observed dose differences appeared to originate primarily from contour differences rather than inclusion of respiratory motion. AIP-based plans frequently revealed larger contoured volumes, resulting in overestimation of actual OAR doses. For critical central structures such as PBT, motion-inclusive MidV-based planning may be considered for a more accurate dose assessment.

Disclosures

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