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Dosimetric Comparison of Peripheral NSCLC SBRT using Acuros XB and AAA Calculation Algorithms

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***Manuscript**

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Abstract:

There is a concern for dose calculation in highly heterogenous environments such as the thorax region. This study compares the quality of treatment plans of peripheral non-small cell lung cancer (NSCLC) stereotactic body radiation therapy (SBRT) using 2 calculation algorithms, namely, Eclipse Anisotropic Analytical Algorithm (AAA) and Acuros External Beam (AXB) for 3-dimensional conformal radiation therapy (3DCRT) and volumetric-modulated arc therapy (VMAT). Four-dimensional computed tomography **(**4DCT) data from 20 anonymized patients were studied using Varian Eclipse planning system, AXB, and AAA version 10.0.28. A 3DCRT plan and a VMAT plan were generated using AAA and AXB with constant plan parameters for each patient. The prescription and dose constraints were benchmarked against Radiation Therapy Oncology Group (RTOG) 0915 protocol. Planning parameters of the plan were compared statistically using Mann-Whitney U tests. Results showed that 3DCRT and VMAT plans have a lower target coverage up to 8% when calculated using AXB as compared with AAA. The conformity index (CI) for AXB plans was 4.7% lower than AAA plans, but was closer to unity, which indicated better target conformity. AXB produced plans with global maximum doses which were, on average, 2% hotter than AAA plans. Both 3DCRT and VMAT plans were able to achieve D95%. VMAT plans were shown to be more conformal (CI = 1.01) and were at least 3.2% and 1.5% lower in terms of PTV maximum and mean dose respectively. There was no statistical significant difference for doses received by organs at risk (OARs) regardless of calculation algorithms and treatment techniques. In general, the difference in tissue modeling for AXB and AAA algorithm is responsible for the dose distribution between the AXB and the AAA algorithms. The AXB VMAT plans could be used to benefit patients receiving peripheral NSCLC SBRT.

Dosimetric Comparison of Peripheral NSCLC SBRT using Acuros XB and AAA Calculation Algorithms

Introduction

Lung cancer is one of the most common cancers in Singapore [1]. Non-small cell lung cancer (NSCLC) is the commonest type of lung cancer [2]. The preferred treatment for NSCLC is surgery. However, this is often limited by the patients' conditions, deeming them as medically inoperable.

Stereotactic body radiation therapy (SBRT) is a technique that delivers a high dose (10 to 30 Gy per fraction), providing treatment results comparable with surgery for medically inoperable patients [3]. SBRT can be planned and delivered using both 3-dimensional conformal radiation therapy (3DCRT) and volumetric-modulated arc therapy (VMAT) techniques.

Dose calculation in radiation therapy planning remains a challenge in the thorax region given the presence of large tissue inhomogeneities including bone, air and soft tissue [4]. The small field sizes in SBRT add to the challenging dose calculation, where electronic disequilibrium increases with decreasing field sizes. Different types of calculation algorithms have been developed to improve the accuracy of dose calculation. With advances in radiation transport modeling, improvements in the accuracy of dose calculations will be one of the ultimate goals in radiation therapy.

The Acuros External Beam (AXB) calculation algorithm has been implemented in the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA). The algorithm has been found to show greater calculation accuracy than its existing algorithm – the Analytical Anisotropic Algorithm (AAA). AXB uses a grid-based Linear Boltzmann Transport Equation solver to account for inhomogeneous materials in dose calculation. It solves the Linear Boltzmann Transport Equation using numerical methods and is expected to have solutions that converge with the Monte Carlo benchmark [5]. The AAA has been routinely used in treatment planning and consists of a photon beam source model, using the superposition-convolution method to approximate changes in lateral electron transport. Electron transport modeling is approximated by scaling the energy of primary electrons and scattered photons rectilinearly with the electron density of the medium [6]. A dosimetric validation in homogeneous medium showed that AAA and AXB are in agreement with homogeneous media to within 1.9%, but differences in calculated doses of up to 17.5% within heterogeneous medium were reported especially at tissue interfaces in low-density lung [7]. In reality, the

electron and photon scatter do not follow the rectilinear paths assumed in AAA. The electronic disequilibrium on the field central axis in low-density material becomes larger as the field size decreases. For small field sizes, there are more electrons traveling away from the corresponding volume element on the central axis than toward it. This is caused by missing scatter from the material outside the geometrical field boundaries, where part of the electrons from the central axis is transported [6].

AXB has a better spatial resolution than AAA, increasing resolution in high dose and high dose gradient areas, and reducing it outside the fields where there are fewer interactions [8]. This is owing to the improvements in how AXB models radiation transport, interaction and scatter. AAA uses radiological scaling to account for heterogeneity, where electron density is used to approximate electron dose deposition, whereas AXB uses mass density to calculate dose using macroscopic cross sections.

Fogliata *et al.* [9] created treatment plans for 10 patients with advanced NSCLC and compared the dose calculations between AXB and AAA calculation algorithms. They reported that AXB calculations were more accurate than AAA. The results of this study were also supported by other authors [10-12]. The accuracy of AXB dose calculation was also found to be comparable with Monte Carlo calculation algorithm, which is deemed to be the gold standard in dose calculation in radiation therapy.

Although some dosimetric studies have been reported, most comparisons were performed in subject groups with large data deviation. In some studies, the subject groups contained both patients with peripheral tumors and patients with central tumors, whereas in others, the tumor locations were not reported. In addition, the staging of the subjects varied from stage 1 to stage 3. These variables can introduce results which is not a good indicator if the dose distribution is purely due to differences in calculation algorithms.

Therefore, the primary aim of this study was to investigate whether there was a significant difference between the dose distributions calculated by the 2 algorithms, AAA and AXB for peripheral lobe lung SBRT. Comparisons would be by the dosimetric evaluation of the dose received by 95% of the planning target coverage (PTV), conformity index (CI), gradient index (GI), and doses to the organs at risk (OARs) defined in Radiation Therapy Oncology Group (RTOG) 0915 [13]. A secondary aim was to determine whether there was a difference in the quality of 3DCRT and VMAT treatment plans for lung patients receiving SBRT.

These results will provide clinicians with evidence of the 2 dose calculation algorithms and the preferred treatment technique for lung patients undergoing SBRT, assisting them in the possible implementation of SBRT using 3DCRT or VMAT.

Methods and Materials

Patient data

A total of 20 patients with NSCLC, who had undergone SBRT treatment between 2010 and 2014, were selected for this retrospective study. The subjects selected had fulfilled the following criteria:

- undergone 4-dimensional (4D) computed tomography (CT) acquisition;
- treatment intent is radical and for SBRT;
- patient's histology is NSCLC;
- size of tumor is less than or equal to 5 cm in the widest diameter;
- peripherally located tumor.

Each patient was setup in the supine position, with their arms above the head, immobilized using a blue vac-bag. During CT simulation, 2 scans were performed – 1 helical scan with contrast and another 4-dimensional CT scan. CT slice thickness for both scans was 2.5 mm in accordance with the departmental protocol. Before the commencement of this study, all the image datasets had been anonymized. Contouring of the target volumes and OARs was performed on the average intensity projection (AIP) image datasets, by the respective radiation oncologists according to RTOG 0915. Ethics approval was obtained from SingHealth Centralised Institutional Review Board.

Treatment planning

Two treatment techniques, namely 9-field coplanar conformal radiation therapy and VMAT, were used in this study. Nine equally spaced fields, over an arc of 160 degrees, were used for the planning of the conformal technique. Wedges were used to improve the dose homogeneity and conformity of the isodose distribution. For the VMAT treatment technique, 3 non-coplanar partial arcs were used for all the patients to achieve the planning requirements and ensure clinical delivery feasibility. Couch and collimator rotation were combined to provide a better dose homogeneity while reducing intra-leaf leakage and improving conformity to target volumes. Figure 1 shows a typical example of the beam arrangements for both the 3DCRT plan and the VMAT plan. All plans were generated for a Varian Clinac IX linear accelerator using 6 MV photons.

Both 3DCRT and VMAT plans were calculated using the AAA calculation algorithm. On completion of the 2 treatment plans, they were recalculated using the AXB (version 10.0.28 Varian Medical Systems, Palo Alto, CA) calculation algorithm, keeping all beam parameters the same. Thus, each patient had a total of 4 treatment plans – a 3DCRT plan for both AAA and AXB and a VMAT plan for both AAA and AXB. All the AAA plans were created with a prescription of 48 Gy in 4 fractions to encompass 95% of the PTV. To enable comparison of the impact of the algorithm on the distributions, the monitor units derived from AAA plans were used for the corresponding AXB plans. The plans were not adjusted if the recalculated plans did not meet the RTOG 0915 recommendations.

Dosimetric parameters evaluation

The prescription dose constraints for treatment planning, which were used by the department and study, were referenced from the RTOG 0915 protocol. Similarly, the limits for critical OARs were taken with reference to RTOG 0915.

In this study, the target coverage, CI, GI, mean (D_{mean}) and maximum (D_{max}) dose to the PTV, dose spillage and volume of lung receiving 5% and 20% of prescribed dose were recorded for comparison. The PTV coverage was defined by D95%, the dose received by 95% of the PTV.

The CI was defined as the ratio of the total volume receiving at least the prescription dose to the target volume receiving at least the prescription dose.

$$CI = \frac{\text{Total volume of tissue receiving the prescribed dose}}{\text{Volume of PTV receiving the prescribed dose}}$$

The GI was defined as the ratio of the volume of 50% of the prescription isodose to the PTV volume.

$$GI = \frac{\text{Volume of tissue receiving 50\% isodose}}{\text{PTV volume}}$$

A CI closer to 1 indicates better target conformity in the treatment plan, whereas a small value in GI represents steeper dose fall-off in the treatment plan, which may imply lower doses to the surrounding normal tissues. The dose spillage is determined using the D2cm, which is defined as the maximum dose, as a percentage of the prescribed dose, at 2 cm from the PTV in any direction. The volumes of lung receiving 20% of the prescribed dose (V_{20}) and receiving 5% of the prescribed dose (V_5) were also used as a supplement to determine dose fall-off in the treatment plans.

Statistical analysis

Normality tests were carried out on the data collected to determine the appropriateness of the statistical tests for analysis of D95%, CI, GI, D2cm and OAR doses. Statistical analysis was then performed using SPSS Statistics 20.0 software. The threshold for statistical significance was $p < 0.05$. Statistical analysis between the 2 algorithms and 5 treatment techniques was performed using Mann-Whitney U tests.

Results

In total, 80 plans were produced for 20 patients, with 4 treatment plans for each patient. The average PTV volume was 40.1 cm^3, with the largest being 105.0 cm^3 and the smallest being 15.1 cm^3. Fifty percent of the cohort had a lower D95% for the 3DCRT plans after recalculating it with the AXB algorithm, whereas 25% of the cohort achieved the D95% for the VMAT plans after recalculation. The statistical comparisons between the plans are shown in Tables 1 and 2.

The dosimetric parameters for all the AAA plans met all the criteria as specified by the RTOG 0915 protocol with 1 exception – the 3DCRT plan of 1 patient - in which the border of the heart tissue received a maximum dose of 100% as a result of its proximity to the PTV.

AAA vs AXB calculation algorithms

When comparing the distributions from the 2 calculation algorithms, the results showed statistically significant differences for D95%, CI and D_{max}. The median D95% for AXB plans, which fell below the prescribed dose by less than 1%, was approximately 1.2% lower than the median D95% for AAA plans. The D95% for AXB plans ranged from 44.11 Gy to 49.19 Gy, with 1 PTV receiving a dose that was 8.1% lower than the prescribed dose. The median CI and median GI for AXB plans were observed to be lower than AAA plans, the difference in CI between the 2 algorithms being statistically significant ($p=0.035$).

The maximum PTV doses from AXB were statistically significantly higher than those from AAA ($p=0.021$), AXB typically producing values up to 2% higher. Despite the differences observed between the D95% and the CI, the p-value of both the median GI and the median D2cm was close to 1 ($p>0.90$), which indicated that dose gradient and spillage between the 2 algorithms were similar, as detailed in Table 1.

3D vs VMAT treatment plans

With reference to Table 2, the results showed statistically significant differences for D95%, CI, GI, D_{max}, D_{mean} and D2cm. The D95%, D_{max}, and D_{mean} for VMAT plans were lower than 3D CRT plans.

For 3DCRT, the median D_{max} for all 20 patients to the PTV was 57.47 Gy, whereas in VMAT plans, the median D_{max} received by the PTV was 53.03 Gy. Although the median difference in D95% was statistically significant, the clinical significance of the magnitude of this difference (less than 0.3 Gy) is uncertain. By contrast, the recorded D2cm was close to 5% higher for VMAT plans than for 3DCRT. The median CI for VMAT plans was 1.01, whereas the median CI for 3DCRT plans was 1.1, indicating that VMAT was able to produce more conformal plans. The GI was 4.19 and 3.36 for the VMAT and 3DCRT plans respectively, which indicated that the 50% isodose volume in the VMAT plans was larger than in the 3DCRT plans.

Organs at risk (OARs)

The OARs being considered are shown in Tables 1 and 2. From the statistical analysis, there was no statistical difference ($p>0.05$ for all OARs) between the doses received by the OARs across calculation algorithms and treatment techniques.

Discussion

The aim of this study was to investigate the differences between the dose distributions for peripheral lobe lung SBRT calculated by 2 algorithms – AAA and AXB, by performing a dosimetric evaluation of the dose received by 95% of the planning target coverage (PTV), conformity index (CI), GI and doses to the OARs, defined in RTOG 0915 [13].

There is limitation in current CT technology and image resolution, which can be challenging for the algorithms to define the exact boundaries of interfaces around the tumor edge. The results from this study served as a good introduction to the understanding of beam modeling at interfaces. The idea was well demonstrated in a report published by Failla *et al*. [5], where differences in algorithm modeling, showed an improvement in modeling dose at tissue interfaces. However, the study was done in a controlled, simulated environment with no true representation of the patients' anatomy in the clinical setting. It is known that malignant tumors tend to be irregularly shaped, with ill-defined borders. This uncertainty is further worsened by the presence of motion artifacts, especially when using average intensity projection datasets, which makes measuring doses at air-tissue interfaces more challenging. To add to the challenge, the presence of scarred lung tissues and tissue distribution, at some point, adds to the uncertainty in determining air-tissue interfaces.

Both 3DCRT and VMAT can be used for treatment planning of lung SBRT. The advantages of VMAT over 3DCRT are faster delivery, which reduces intra-fractional motion, and better target conformity [14]. Statistically significant differences were observed between the dose distributions of 3DCRT and VMAT plans. This can be attributed to differences in field sizes between 3DCRT and VMAT, given that the beam energy and datasets used were consistent in this study, as explained by Fogliata *et al*. [15]. They reported that results of an algorithm's calculation are greatly dependent on energy, field size and density of materials, which supported the results observed in this study. In VMAT planning, small segments were created to allow fluence modulation for optimizing plan quality but in 3DCRT plans, the fields were created with a $\leq$0.3 cm margin around the PTV, and remained static throughout treatment delivery. It remains a challenge to correctly predict small field dosimetry behavior by AAA when compared with AXB.

This study also did not show any differences in the GI of the treatment plans regardless of the calculation algorithm used, which is in general agreement with the results published by Zhang *et al*. [14]. They generated various plans with different treatment techniques such as 3DCRT, coplanar and non-coplanar VMAT and plans using flattening filter free (FFF) beams, for 15 patients, reporting statistically

significant differences between the 3DCRT and the noncoplanar VMAT plans. Finer segregation of the subjects being studied by Zhang *et al*. may lead to different results.

It was also found that the D_{mean} of the PTV was not statistically significantly different when compared across the 2 calculation algorithms. This finding was supported by Liu *et al*. [10] when they performed a study on 77 patients who underwent SBRT to determine the relationship between tumor volume and location, and the number of beams used in SBRT calculated using both AXB and AAA calculation algorithms. The authors concluded that the mean target dose was the same for both algorithms. They found that there was a small difference in dose distribution in the target between the 2 algorithms, as evident in the difference in the conformity and heterogeneity index. The difference in conformity between the 2 dose algorithms was strongly correlated with pulmonary function, target location, and the number of beams used [10].

Overall, the VMAT plans were observed to be superior to 3DCRT plans, in terms of better dose conformity and lower D_{max} despite having achieved a similar D95%, attributed possibly to the fluence modulation characteristic of the VMAT technique. Although some reports [14, 16] found that the V_{20} doses to the lung were higher or comparable in all the VMAT plans and that VMAT significantly increases the volume of lung tissues receiving 5% of the prescribed dose (V_5) in most treatment plans for lung SBRT, this was not observed in this study. The numerical values for V_{20} and V_5 are higher in VMAT than in 3DCRT plans but they are not statistically significant.

In the AXB and AAA algorithms, materials are assigned according to the CT calibration curves in Eclipse™. The AXB CT calibration curve maps the Hounsfield unit (HU) value of each calculated voxel to the mass density of the material according to a specific HU range. AAA, on the other hand, assigns a reference material in each voxel according to the HU. As such, there is a difference in material assignment between these 2 algorithms. Although this is not reflected in the results in this study, Bush *et al*. [7] reported that calculated lung doses are patient-dependent and determined by the actual combination of field sizes, target location and lung density. Therefore, the type of calculation algorithm used may not be the only factor in determining underestimation or overestimation of doses to different types of tissues.

In this study, 3DCRT was planned using a coplanar beam arrangement, whereas VMAT was planned using 3 non-coplanar arcs for each patient. There are studies that show that non-coplanar beam arrangements for 3D and VMAT can improve PTV coverage and reduce doses to OARs at the same time [17-19]. This difference was not factored in when analyzing the data and could help to explain the superiority seen in the VMAT plans.

From the results, it was shown that there was no difference between the doses received by the organs across treatment techniques and calculation algorithms. With SBRT, the radiation planning margins accounting for set-up uncertainty are minimized. This allows for greater dose-volume sparing of the surrounding normal tissues, which enables the delivery of higher fractional doses of radiation (hypofractionation). The dose gradient is steeper than with conventional radiation, although the low dose region encompasses a larger volume and is irregularly shaped. A critical review on normal tissue toxicity after SBRT by Milano *et al.* further supported that hypofractionated SBRT to peripheral lobe lung tumors did not lead to severe radiation toxicity to other organs such as the lung, heart, and esophagus because of the distance relation between the tumor and the healthy organs [20]. Phantom comparisons between AAA and AXB by Fogliata *et al.* [15], have compared the doses calculated by the algorithms' after passing through materials with lung densities. They found that they were in good agreement in materials approximating soft tissue at distances greater than 1 to 2 cm beyond the lung for single incident beams.

The results from this study were also supported by Liu *et al*. [21], who showed that peripheral tumors are less dense than tumors near the mediastinum and hilum, thus producing less scatter. This may imply that lesser scatter will lead to lower dose deposition in the tissues around the targets. Although there were differences in how the 2 calculation algorithms model scatter radiation, there was no significant increase in the dose received by the OAR when recalculating using AXB because of the lower scatter from peripheral tumors. The findings are especially relevant to this study as the results generated were based only on patients with peripheral tumors. AAA simulates lateral density scaling of photon scatter kernels; these scatter kernels scale the energy at each location by the average density of the material assigned. AXB however, simulates scattering according to the macroscopic cross-section of the assigned materials in the voxel using their physical density[8].

Conclusion

In conclusion, this study showed that there was a statistically significant difference for PTV D95% across treatment techniques and calculation algorithms, with no statistical differences observed in OAR doses. The conformity index was statistically significantly different for VMAT plans between the 2 calculation algorithms. These differences observed were largely due to differences in beam modeling by AAA and AXB at interfaces. Based on this study, VMAT plans were shown to be superior to 3DCRT plans.

This study provided evidence to determine if there is a difference in the quality of plans for lung SBRT when different calculation algorithms are used. It also has the potential to assist clinicians in their choice of treatment technique to be used for patients undergoing lung SBRT.

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Figure 1 Typical 3DCRT and VMAT field arrangements used
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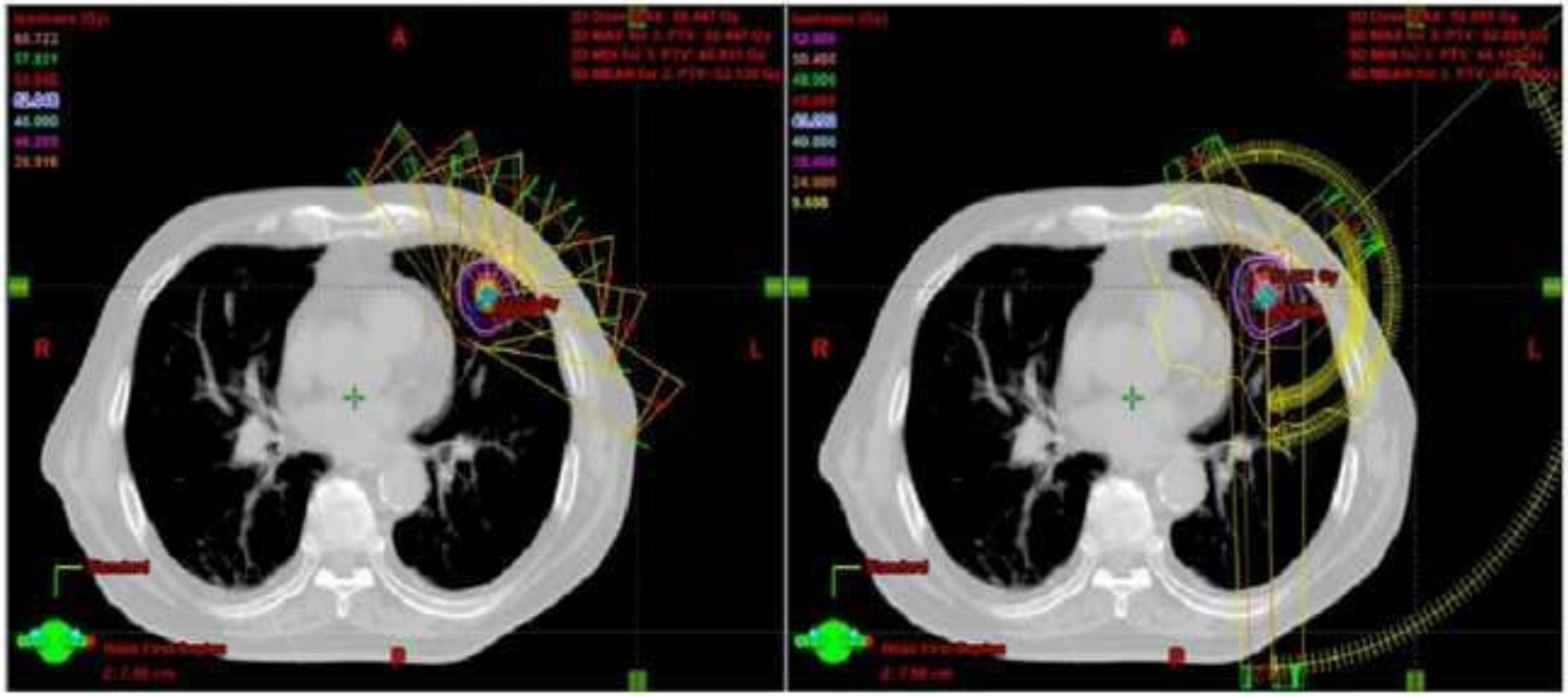
Figure 1. Typical 3DCRT and VMAT field arrangements used in the study. Left: 3DCRT field arrangement consisted of 9 beams, equally spaced, 20 degrees apart. Isodose distribution is optimized with the use of wedges. Right: VMAT field arrangement consisted of 3 non-coplanar partial arcs, with couch rotation of 0, 15 and 345 degrees respectively. Dose distribution is optimized using inverse planning.



Tables

Comparisons using Mann Whitney U Test

Table 1. Dosimetric parameter results comparisons between 2 algorithms

Parameter		AAA (median)	AXB (median)	p-Value
D95%	(Gy)	48.28 (48.02 - 49.21)	47.66 (44.11 - 49.19)	0.000
CI		1.07 (0.98 - 1.20)	1.02 (0.72 - 1.20)	0.035
GI		3.65 (3.01 - 4.94)	3.63 (2.90 - 5.00)	0.935
PTV max dose	(Gy)	54.61 (51.39 - 59.34)	55.52 (52.44 - 59.71)	0.021
PTV mean dose	(Gy)	51.18 (49.2 - 54.85)	50.69 (49.33 - 54.38)	0.322
D2cm	(%)	53.00 (45.5 - 65.5)	53.55 (43.2 - 64.8)	0.908
Lung V_{20}	(%)	4.25 (1.07 - 11.38)	4.23 (1.09 - 11.44)	0.923
Lung V_5	(%)	13.69 (2.07 - 42.05)	13.93 (2.03 - 42.19)	0.859
Cord max	(Gy)	10.34 (1.82 - 16.05)	9.93 (1.96 - 16.03)	0.690
Heart max	(Gy)	8.25 (0.15 - 57.00)	8.82 (0.11 - 57.47)	0.923
Skin max	(Gy)	19.91 (12.87 - 30.46)	20.82 (13.20 - 32.22)	0.795

Table 2. Dosimetric parameter results comparison across 2 treatment techniques

Parameter		3D (median)	VMAT (median)	p-Value
D95%	(Gy)	48.32 (44.11 - 49.21)	48.06 (44.65 - 48.64)	0.009
CI		1.1 (0.72 - 1.20)	1.01 (0.78 - 1.10)	0.000
GI		3.36 (2.90 - 3.92)	4.19 (3.47 - 5.00)	0.000
PTV max dose	(Gy)	57.47 (54.57 - 59.71)	53.03 (51.39 - 55.57)	0.000
PTV mean dose	(Gy)	52.49 (50.06 - 54.85)	49.9 (49.32 - 50.75)	0.000
D2cm	(%)	51.5 (43.2 - 63.2)	56 (46.3 - 65.5)	0.001
Lung V_{20}	(%)	4.19 (1.07 - 10.51)	4.31 (1.12 - 11.44)	0.836
Lung V_5	(%)	13.07 (2.03 - 27.29)	15.01 (3.46 - 42.19)	0.069
Cord max	(Gy)	10.14 (1.882 - 16.05)	10.17 (2.07 - 15.43)	0.482
Heart max	(Gy)	8.31 (0.11 - 57..47)	9.64 (0.11 - 52.63)	0.939
Skin max	(Gy)	20.48 (14.82 - 32.22)	19.84 (12.87 - 30.90)	0.529