Improving radiotherapy planning for large volume lung cancer: A dosimetric comparison between hybrid-IMRT and RapidArc

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To the Editor,

Concurrent chemoradiotherapy (CT-RT) is often used to treat locally advanced non-small cell lung cancer (LA-NSCLC) [1]. However, 60–66 Gy can be challenging to deliver to large target volumes due to the need to spare organs at risk (OARs). Toxicity following CT-RT is not insignificant. Meta-analysis indicates a symptomatic pneumonitis rate of 30% [2] and an incidence of grade 2 and 3 esophagitis of 32% and 17% [3].

Hybrid-IMRT (h-IMRT) is currently our standard technique in LA-NSCLC, with most of the dose

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Table I. Patient characteristics.

Patient	Stage	Location	Lungs-PTV (cm^3)	PTV (cm^3)	PTV CCL in lung (cm)	Lungs CCL (cm)
1	T3N2M0	Left upper lobe (I)	4992	1071	13.5	22.5
2	T3N2N0	Right middle lobe (I)	5926	1023	15.5	21
3	T2N2M0	Left lower lobe (II)	1935	942	16.0	15.5
4	T3N2M0	Left lower lobe (II)	2992	993	20.5	19.5
5	T2N2M0	Right lower lobe (II)	3847	862	17.5	22.5
6	T3N2M0	Right lower lobe (II)	2020	1159	14.5	15.5
7	TxN3M0	Mediastinal (III)	3902	1221	15	17
8	T4N2M0	Mediastinal (III)	4995	893	12	20
9	T4N2M0	Right upper lobe (III)	3886	794	14	18
10	T4N3M0	Left lower lobe (III)	3841	1221	19.5	20.5
11	T4N3M0	Left upper lobe (III)	4008	1126	16.5	22
12	T2N3M0	Right upper lobe (I)	3585	1404	16	17
13	T2N3M0	Left lower lobe (II)	3114	1258	16	17
14	T1N3M0	Right hilus (I)	4635	1371	18	22

CCL, craniocaudal length; Lungs-PTV, total lung volume minus PTV; PTV, planning target volume. I: peripheral tumor with most disease in upper thorax half and mediastinal nodes; II: peripheral tumor with most disease in lower thorax half and mediastinal nodes; III: disease bulk largely centrally located.

delivered in antero-posterior/postero-anterior (APPA) directions, and 10–15% delivered with three IMRT fields. It is a fast, standardized planning technique which can improve PTV coverage, lung V_{20} (volume receiving ≥ 20 Gy) and contralateral lung V_5 (CL-V_5) [4]. However, limitations include high dose outside the PTV and restricted opportunities to reduce dose to OARs like esophagus, heart and skin.

We previously reported that volumetric modulated arc therapy (VMAT) with two arcs (RapidArc^{TM}, Varian Medical Systems, Pao Alto, CA, USA) resulted in comparable V_{20} to h-IMRT but higher CL-V_5 [4]. In the present planning study, we add to this work by: 1) comparing h-IMRT and RapidArc in patients with larger target volumes; 2) comparing plans made with two and four simultaneously optimized arcs [5]; and 3) evaluating the effect of additional OAR sparing, including the esophagus and heart.

Material and methods

Fourteen patients previously treated for LA-NSCLC were identified (Table I). All had a PTV approximately 800 cm^3 or more (794–1404 cm^3, mean = 1096 cm^3, SD = 188 cm^3). For each patient we compared: 1) h-IMRT; 2) lung sparing RapidArc using two coplanar arcs (2RA); 3) lung-sparing RapidArc with four coplanar arcs (4RA); and 4) additional OAR-sparing RapidArc plans made with two arcs. All plans were generated with a high priority on sparing total lung V_{20}, V_5 and CL-V_5.

Treatment planning

The internal target volume (ITV) was delineated on the average intensity projection of a 10-phase four-dimensional CT scan, using information from individual phases. An isotropic PTV margin of 1 cm was added. For this study, OARs included lungs, spinal cord (spinal canal), skin, esophagus and heart. Total lung volume minus PTV (lungs-PTV) was used for analysis. For reporting purposes skin was a 3 mm structure inside the external body contour on PTV-containing axial planes. Esophagus was contoured from cricoid to GE-junction. Heart was contoured using guidelines [6].

The PTV objectives were to deliver 95% of prescribed dose (PD) to at least 95% of the PTV ($V_{95\%} > 95\%$) while limiting the $V_{107\%}$. Other objectives included lungs-PTV $V_{20} < 35\%$ and $V_5 < 60\%$ and a maximum spinal cord point dose of < 50 Gy. A maximum dose objective of 67 Gy was applied to the 'body outside PTV' structure to avoid hotspots outside the PTV. The optimization algorithm was the Progressive Resolution Optimizer version 10.0.28 in the Eclipse treatment planning system and heterogeneity corrected dose was calculated with the Anisotropic Analytic Algorithm (AAA) using 2.5mm grid resolution.

h-IMRT

H-IMRT plans were created as previously described with the conventional component typically delivering 85–90% of PD and IMRT 10–15% [4].

RapidArc

For 2RA, two full arcs were optimized simultaneously for delivery on a TrueBeam^{TM} (Varian Medical Systems). Avoidance sectors were used to prevent direct irradiation through most of the contralateral lung (typical avoidance arc 80–100° long). Optimal

collimator angles for the PTV shape (usually between 30° and 60°) were chosen and angled 5° to each other. 6 MV beams were used with maximum dose rate of 600 MU/min. The optimizer uses a simple dose calculation algorithm that does not model well lateral electron transport. Therefore, the dose in low density PTV appears lower in the final AAA calculation. To compensate for this PTV in lung tissue was defined as a separate structure and higher doses were assigned to it during optimization. Two optimization objectives per parameter were used for lungs-PTV V_{20}, V_5 and CL-V_5, all set below the dose volume histogram (DVH) line that is displayed during optimization. Initially, the 2RA lung-sparing plans were generated using interactive optimization. After this, the 4RA lung-sparing plans were created by copying both arcs of the corresponding 2RA plans into one plan and simultaneously optimizing all four arcs using objectives from the end of the corresponding 2RA optimization, without further interaction. Further 2RA plans were created to additionally spare skin, esophagus and heart. For optimization purposes the esophagus + 3 mm was used, the heart was defined as above, and a 3 mm skin structure located on the ventral and dorsal aspects of the body (representing the high dose regions in h-IMRT plans). Objectives were placed on $V_{66}/V_{60}/V_{50}/V_{40}$ (esophagus + 3 mm), $V_{66}/V_{55}/V_{40}$ (heart) and $V_{50}/V_{40}/V_{30}$ (skin).

For comparison, plans were normalized such that mean PTV dose was approximately 101–102% of PD and PTV $V_{95\%}$ was typically $\geq 95\%$.

Endpoints and statistical analysis

Primary endpoints were lung dose [V_{20}, V_5/CL-V_5, mean lung dose (MLD)] and PTV metrics [$V_{95\%}$, $V_{107\%}$, D_{max}, D_{mean}, conformity index (CI) and homogeneity index (HI)]. CI was defined as absolute PTV receiving 95% of PD divided by absolute total body volume receiving 95% of PD. HI was defined as minimum dose in 2% of the PTV (D_2) minus D_{98} divided by D_{50}. Secondary endpoints were dose to other OARs: spinal cord (point D_{max}), skin (V_{50},V_{30}),

Table II. Average dosimetric parameters and monitor units for four planning approaches (n = 14 patients).

	h-IMRT mean ± SD	2RA mean ± SD	4RA mean ± SD	2RA OAR-sparing mean ± SD
PTV				
$V_{95\%}$ (%)	97.8 ± 1.1	95.3 ± 1.4	95.7 ± 1.5	94.3 ± 1.3
$V_{107\%}$ (%)	2.1 ± 3.8	8.9 ± 5.8	4.5 ± 4.0	12.7 ± 5.6
D_{max} (Gy)	71.8 ± 2.2	76.0 ± 1.4	75.0 ± 1.4	77.0 ± 1.3
D_{mean} (%)	101.2 ± 0.8	102.1 ± 0.4	101.8 ± 0.2	102.4 ± 0.3
CI	0.49 ± 0.10	0.66 ± 0.08	0.67 ± 0.08	0.70 ± 0.09
HI	0.12 ± 0.04	0.17 ± 0.03	0.15 ± 0.03	0.19 ± 0.03
Lungs-PTV				
V_{20} (%)	29.2 ± 6.1	27.5 ± 5.8	27.5 ± 5.8	27.9 ± 5.9
V_5 (%)	51.2 ± 9.5	56.6 ± 10.9	56.1 ± 10.6	57.6 ± 11.3
D_{mean} (Gy)	18.2 ± 3.4	16.4 ± 3.1	16.3 ± 3.1	16.5 ± 3.1
Contralateral lung				
V_5 (%)	31.0 ± 13.3	40.3 ± 12.8	39.6 ± 12.4	42.1 ± 13.0
Spinal cord				
D_{max} (Gy)	49.2 ± 3.0	48.8 ± 1.4	48.4 ± 1.5	49.5 ± 2.0
Heart				
V_{60} (%)	26.3 ± 20.4	15.4 ± 11.5	15.8 ± 11.7	9.6 ± 6.7
V_{40} (%)	35.5 ± 25.1	28.3 ± 22.1	30.7 ± 21.8	24.8 ± 18.2
D_{mean} (Gy)	26.9 ± 16.0	23.6 ± 14.3	23.8 ± 14.6	21.8 ± 12.6
Esophagus				
V_{60} (%)	36.7 ± 18.7	34.6 ± 19.5	35.5 ± 19.8	22.5 ± 13.3
V_{40} (%)	51.4 ± 15.6	48.0 ± 17.7	48.2 ± 17.7	41.5 ± 16.0
D_{mean} (Gy)	35.9 ± 10.0	35.0 ± 9.9	34.9 ± 10.0	31.4 ± 8.6
Skin				
V_{50} (cm^3)	39.2 ± 23.9	22.7 ± 17.6	20.8 ± 17.5	14.7 ± 12.6
V_{30} (cm^3)	203.8 ± 78.4	155.9 ± 61.0	157.9 ± 61.7	137.3 ± 49.3
Body-PTV				
V_{60} (cm^3)	1489 ± 472	722 ± 236	721 ± 240	598 ± 212
$V_{70.6}$ (cm^3)	37.4 ± 71.5	11.9 ± 12.5	4.9 ± 5.4	20.6 ± 30.8
Monitor Units	420 ± 149	698 ± 46	712 ± 49	709 ± 54

Body-PTV, body minus PTV; h-IMRT, hybrid intensity modulated radiation therapy; Lungs-PTV, total lung volume minus PTV; PTV, planning target volume; RA, RapidArc; SD, standard deviation.

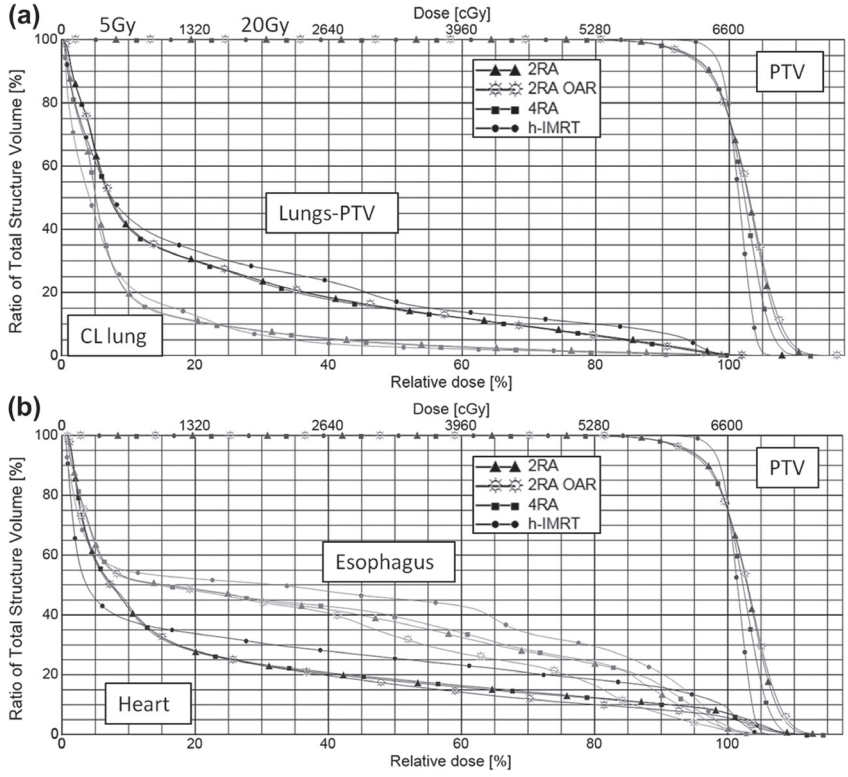

Figure 1. Dose volume histograms of planning target volume (PTV); (a) total lung volume minus PTV (Lungs-PTV) and contralateral lung (CL-Lung); (b) esophagus and heart.

esophagus, heart (V_{60}, V_{40}, D_{mean}) and body outside PTV (body-PTV; V_{60} and $V_{70.6}$, which is 107% of PD). Data were analyzed with summary descriptive statistics [mean ± standard deviation (SD)].

Three patients had their plans measured using the MatriXX ionization chamber array (IBA, Germany) and compared with dose calculations on the MatriXX. Gamma evaluations were made using 3% dose difference and 2 mm distance to agreement. Automated delivery times (including gantry rotation) were measured on the TrueBeam.

Results

Dosimetric parameters are summarized in Table II and illustrated in Figures 1 and 2. Compared to h-IMRT, RapidArc had lower V_{20} and MLD with higher V_5 and CL-V_5. On average, V_{20} was reduced from 29.2% with h-IMRT (16.4–40.4%) to 27.5% (15.5–37.4%) with 2RA and MLD from 18.2 Gy (11.2–24.4 Gy) to 16.4 Gy (10.2–22.1 Gy). V_5 and CL-V_5 increased from an average of 51.2% (33.2–66.4%) and 31.0% (10.5–53.9%) with h-IMRT to 56.6% (36.9–74.0%) and 40.3% (19.4%–60.9%) with 2RA. Using four instead of two arcs resulted in small differences in lung parameters.

RapidArc approaches resulted in more conformal plans with an increase in CI from 0.49 (0.34–0.71) with h-IMRT to 0.66 (0.48–0.80) and 0.67 (0.57–0.82) with 2RA and 4RA, respectively, at the expense of more PTV dose heterogeneity (Table II) and a reduction in $V_{95\%}$ from 97.8% to 95.7%. Using four arcs instead of two improved dose homogeneity in the PTV (HI 0.15 vs. 0.17) and reduced high-dose outside the PTV (Table II).

On average, when no attempt was made to spare additional OARs, RapidArc plans resulted in similar dose to esophagus, and less dose to heart (V_{60}) and skin (V_{50}), with similar results for two and four arcs. These are average data and in some individual cases, an increase of dose to spinal cord, heart and esophagus was observed in comparison with h-IMRT. Predictably, the addition of specific constraints to the esophagus, heart and skin led to dose reductions, especially in high dose (e.g. V_{50} and V_{60}). As an example, esophagus mean V_{60} was reduced from 34.6% to 22.5% and mean V_{40} from 48.2% to 41.5%. This was associated with an increase in PTV heterogeneity and more hot spots (>107% of PD) outside the PTV.

Dose measurements using the MatriXX agreed well with calculations for the 12 measured plans. Mean gamma averaged over the three patients was 0.24, 0.30, 0.25 and 0.37 for h-IMRT, 2RA, 4RA and 2RA OAR sparing, respectively. Averaged delivery times were 231 s, 140 s and 280 s for h-IMRT, 2RA and 4RA, respectively.

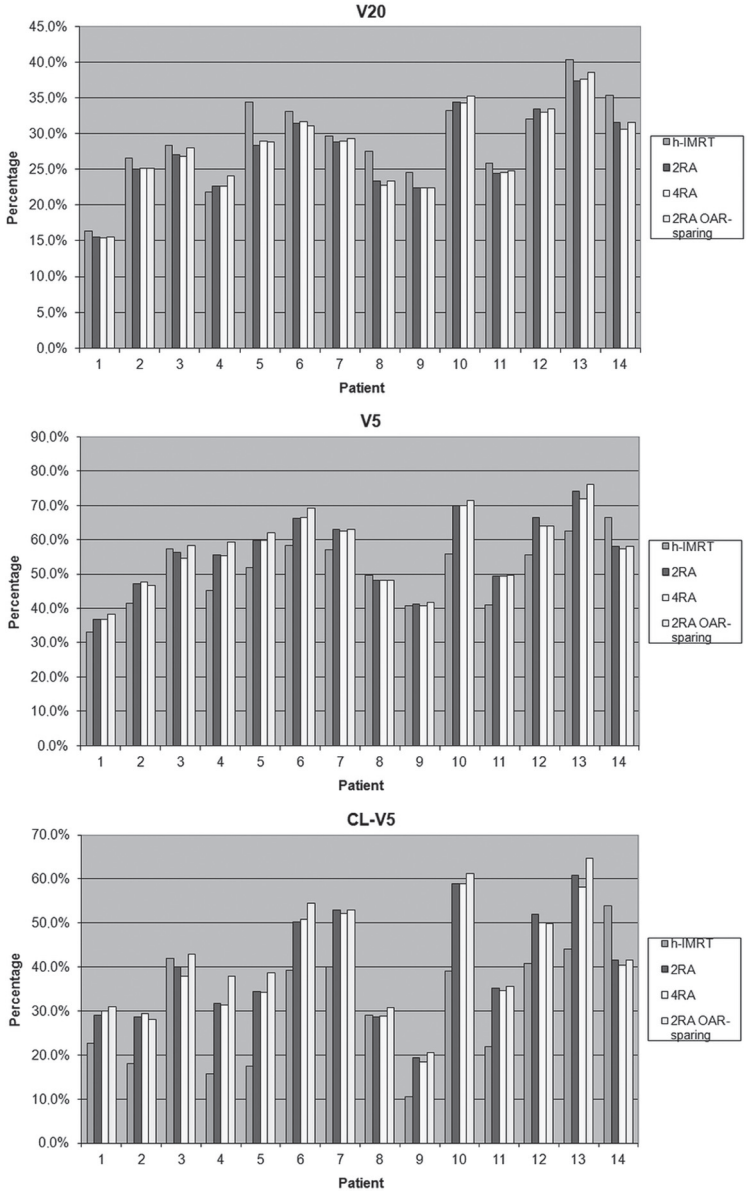

Figure 2. Bar chart demonstrating V_{20}, V_5 and contralateral lung V_5 (CL-V_5) for all individual patients.

Discussion

The main findings of this planning comparison between h-IMRT and RapidArc in large volume LA-NSCLC were: 1) reduction in average V_{20} and MLD with RapidArc at the expense of higher lung V_5, CL-V_5, and more PTV heterogeneity; 2) two extra arcs did not increase lung-sparing; and 3) additional OAR sparing was possible with RapidArc, with increased dose heterogeneity as a trade-off.

Lung V_{20} and MLD have been correlated with radiation pneumonitis [2,7]. While V_5 may also be important [8], it is less well defined and the significance of reducing V_{20} at the expense of more V_5 is unknown. Currently, we try where possible to keep $V_5 \leq 60\%$, which was not achieved with RapidArc and h-IMRT in five and two patients, respectively. If there are concerns about high V_5 and the trade-off with V_{20} and MLD is considered acceptable, h-IMRT merits consideration.

In this study we report lower V_{20} with Rapidarc than h-IMRT, which differs from previously [4]. We attribute this to greater emphasis on lung sparing in the current study. This is consistent with the reduction in PTV $V_{95\%}$ and increase in $V_{107\%}$ compared with h-IMRT, which was not the case in the previous study, and emphasizes the trade-offs between lung dose and PTV. This trade-off becomes more pronounced with additional constraints to other OARs and is consistent with our observations in head and neck planning [9].

RapidArc reduced the esophagus volume receiving 40–60 Gy, which could help to reduce esophagi-

tis [3]. Heart dose reduction may also be clinically relevant. High doses have been suggested to be a predictor for developing radiation pneumonitis [10] and in the RTOG 0617 LA-NSCLC dose escalation study excessive heart dose may have been a contributing factor to unexpected negative results [11].

There are some limitations. The study is relatively small, it is however consistent with other publications [4,12]. Some of the observed differences were small with an uncertain clinical significance. We tried to minimize bias during planning by using consistent objectives and fixed optimization priorities. We acknowledge that dose calculations were performed using AAA which can be suboptimal in low-density tissue, such as lung, where it may overestimate the dose when compared to Monte Carlo or newer algorithms like Acuros [13].

In conclusion, RapidArc lowered lung V_{20} and MLD at the expense of higher V_5 and CL-$V_{5,}$ and more PTV inhomogeneity. Four arcs did not improve lung sparing. Additional heart, esophagus and skin sparing was possible using RapidArc, but was associated with more PTV inhomogeneity.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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