Organ at risks sparing with simultaneous integrated boost volumetric modulated arc therapy for locally advanced non-small lung cancer: an automated treatment planning study

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Abstract

Background : The technique of simultaneous integrated boost volumetric modulated arc therapy (SIB-VMAT) have been widely used in locally advanced non-small cell lung cancer, however, its dosimetric advantages are seldom reported. This study aimed to investigate the dosimetric benefit of SIB-VMAT compared to conventional VMAT plans (C-VMAT).

Methods : Forty patients with stage III non-small cell lung cancer in our hospital were randomly selected for the two type prescriptions. SIB-VMAT and C-VMAT plans were generated for each patient with the same optimization parameter by the automatic treatment planning system (TPS). The prescribed dose was 50.4 Gy in 28 fractions to PTV and 59.92 Gy in 28 fractions to PGTV in SIB-VMAT plans, with 60 Gy in 30 fractions to PTV in C-VMAT plans. Dose-volume metrics for the planning target volume, lung, heart, esophagus and spinal cord were recorded. The quality score (S D) was used to evaluate organ at risks (OARs) protection for two type prescription plans.

Results : Conformal coverage of the PGTV/PTV by the 95% of the prescription dose was well achieved in automated plans. SIB-VMAT plans achieved significantly lower S D values than C-VMAT plans (Mean: 0.064±0.106 vs. 0.145±0.181, P=0.001). Obvious reductions in mean dose, V 30 , V 40 and V 50 of total lung were observed in SIB-VMAT plans compared to C-VMAT plans, with median decreased proportions of 6.5%、8.7%、19.6% and 32.1%. Statistically significant decrease in heart V 30 and V 40 were also achieved in SIB-VMAT plans, with median decreased proportions of 26.1% and 38.8%. SIB-VMAT plans achieved significant reductions in the maximum doses to both esophagus and spinal cord.

Conclusions : SIB-VMAT technique could lead to a substantial sparing of normal organs, including lung, heart, esophagus and cord, mainly through reducing high and inter-median dose exposure.

Background

Definitive radiotherapy is the standard care for locally advanced non-small cell lung cancer (LA-NSCLC) but the outcome following treatment remains poor[1, 2]. Several retrospective studies indicated that increasing dose could improve local control and overall survival, which made dose-escalation become a promising strategy[3, 4]. However, the phase III trial of RTOG 0617 indicated that a higher dose of 74 Gy to planning target volume (PTV) did not improve overall survival but resulted in an increased death risk by 38% compared with standard dose of 60Gy[5], which might be due to excessive radiation-induced toxicity. Therefore, current efforts focus on better strategy for dose-escalation with limited toxicities.

Based on intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT), simultaneous integrated boost (SIB) was applied in cancer treatment. This approach could simultaneously confer an intense dose to the gross tumor at meantime a reduced dose to the subclinical area, resulting in improved normal-tissue sparing and treatment tolerance. The clinical efficacy and safety of SIB-IMRT/VMAT have been proved in LA-NSCLC[6–9], but there are few studies clarifying its possible dosimetric advantages.

In recent years, based on the method of deep machine learning, automated treatment planning has been applied in the generation of radiation plans. The mdaccAutoPlan system was developed based on our clinical protocol, with authorization from developer Zhang's team[10], and the technique improved the consistency and quality of plans and reduces treatment planning time. It has been proved that the volumetric modulated arc radiotherapy (VMAT) plans with high quality can be automatically generated for most stage III/IV NSCLC patients treated with curative radiotherapy[11, 12].

In this study, we implemented automated planning method to generate VMAT plans and aimed to quantify the dose-sparing benefits of SIB-VMAT compared to C-VMAT plans.

Methods

Patients

Forty patients with stage III NSCLC and received thoracic radiotherapy in our hospital between 2014 and 2016 were randomly selected, including 21 (52.5%) cases located in left lung and 19 (47.5%) cases in right lung. 8 (20%) patients had stage IIIA and 32 (80%) had stage IIIB. The patient characteristics were summarized in Table 1. Each patient was retrospectively optimized using automated VMAT planning methods. This study was approved by Ethics Committee of our hospital (Approval No. 19–048/1833).

Table 1
The characteristics of patients

Characteristics	n(%)
Median age(years)	62
Gender	
male	33(82.5%)
female	7(17.5%)
Smoking	
No	10(25%)
Yes	30(75%)
Tumor location	
Left	21(52.5%)
Right	19(47.5%)
Pathology	
SCC	22(55%)
ADE	16(40%)
NOS	2(5%)
TNM stage	
IIIA	8(20%)
IIIB	32(80%)
T stage	
T1	1(2.5%)
T2	26(65%)
T3	8(20%)
T4	5(12.5%)
N stage	
N1	1(2.5%)
N2	11(27.5%)

SCC squamous cell carcinoma, ADE adenocarcinoma, NOS not otherwise specified.

Characteristics	n(%)
N3	28(70%)
Total lung volume(cc)	2845 (1753–4958)
GTV volume(cc)	14.3 (1.9-247.6)
GTVnd volume(cc)	10.4 (0.9–64.8)
CTV volume(cc)	232 (109–674)
PTV volume(cc)	368 (200–898)
CTV/(GTV + GTVnd)	8.6 (2.2–34.8)
SCC squamous cell carcinoma, ADE adenocarcinoma, NOS not otherwise specified.	

Immobilization And Simulation

The patients were immobilized in the supine position with a thermoplastic custom-made mask (including head-neck-shoulder mask and chest mask). The computed tomographic (CT) scan at 5-mm intervals with contrast enhancement for each patient was obtained using an CT simulator. The scanned regions extended from the laryngeal prominence to the bottom of the L2 vertebral body. These CT images were transferred to Pinnacle 9.10 system (Version 9.10, Philips Radiation Oncology System, Fitchburg, WI, USA) for planning.

Target Volume And Organ At Risks Delineation

The Radiotherapy and Oncology Group (RTOG) guidelines served as reference for the delineation of target volumes and organs at risk (OARs). The gross tumor volume (GTV) involved the primary lesions and positive lymph nodes, which were defined as those with a short-axis diameter of at least 1 cm on CT images or less than 1 cm but had high fluorodeoxyglucose (FDG) uptake on Positron emission tomography (PET)-CT images. The clinical target volume (CTV) was generated by expanding GTV by 0.6–0.8 cm, covering the involved hilum and mediastinal nodal stations. The planning target volume (PTV) was created by a uniform expansion of 0.5 cm surrounding the CTV. The planning gross tumor volume (PGTV) was generated by expanding GTV by 0.5 cm. The lungs, heart, esophagus and cord were contoured as the dose constraint organ at risks (OARs).

Prescribed Dose And Dose Constraints

The prescribed dose was 50.4 Gy in 28 fractions to PTV and 59.92 Gy in 28 fractions to PGTV in SIB-VMAT plans, with 60 Gy in 30 fractions to PTV in C-VMAT plans. The dose should be prescribed to cover

≥ 95% of the PTV/PGTV volume. The maximum dose should be less than 110% of the prescribed dose. The dose constraints of OARs were referred to the values summarized in Table 2.

Table 2
C_j value of the objectives from the predefined structures

j	Cj	Value
1	Total lung V_5	≤65%
2	Total lung V_{20}	≤30%
3	Total lung V_{30}	≤20%
4	Total lung mean dose	≤18Gy
5	Heart V_{30}	≤40%
6	Heart V_{40}	≤30%
7	Esophagus Dmax	≤66Gy
8	Esophagus V_{50}	≤50%
9	Spinal cord Dmax	≤40Gy
10	Spinal cord PRV Dmax	≤45Gy

Automated Treatment Planning

Both SIB-VMAT and C-VMAT plans were designed with 160-leaf MLC VersaHD LINAC (Elekta, AB, Stockholm, Sweden). Each plan was designed with the same optimization parameter by the mdaccAutoPlan system and evaluated quantitatively for each patient. Plans can be generated by one button click in mdaccAutoPlan system which is as a plug-in to the Pinnacle^3 TPS. The mdaccAutoPlan system was developed based on our clinical protocol, with authorization from developer Zhang's team[10]. The quality of the planning outcome depends on the method followed by each planner[13], so the use of automated planning decreased inter-operator variability and guarantee high quality VMAT treatment plans in our study. VMAT plans were calculated using 6MV photons, with a maximum variable dose rate of 600MU/min. Double-arcs with coplanar arcs of 360° shared the same iso-center, using opposite rotation (clockwise and counter-clockwise). The collimator was always rotated to 10° and 350°, respectively, in two arcs, to avoid a tongue and groove effect. The gantry angle spacing was 4°. The calculation voxel size was isotropic and 4 mm.

Plan Comparison

Dose coverage of the PGTV/PTV by plans was evaluated using the endpoint of V_p (volume receiving at least prescribed dose). The following dosimetric parameters were recorded to evaluate tissue-spring: total lung; mean dose (MLD) and volume minus GTV receiving 5 Gy (V_5), 10 Gy (V_{10}), 20 Gy (V_{20}), 30 Gy (V_{30}), 40 Gy (V_{40}) and 50 Gy (V_{50}), esophagus; maximum dose (Dmax), mean dose and volume receiving 40G (V_{40}) and 50 Gy (V_{50}), heart; maximum dose, mean dose and volume receiving 5 Gy (V_5), 30 Gy (V_{30}) and 40 Gy (V_{40}), spinal cord; maximum dose, spinal cord PRV; maximum dose.

The quality score (S_D), which was introduced by QUASIMOD group[14], was used to evaluate OARs protection of plans. As there are more predefined structures in this analysis than in Ref 14, the dosimetric data were extracted from the collected data sets and were compared to the corresponding dose objectives which are listed in Table 2. The quality score S_D is defined as follows:

$$S_D=\sum_j \begin{cases} \left|\frac{M_j-C_j}{C_j}\right|, & \text{if objective is violated} \\ 0, & \text{else} \end{cases}$$

C_j is the objective j; M_j is the corresponding plan value. The C_j value is referred to the recommended dose constraints of OARs[15, 16]. Take objective C_1 as an example, which requires total lung V_5 65%, if M_1 = 70%, then S_1 = 0.077; if $M_1 \leq 65\%$, then S_1 = 0. The summation is overall 10 objectives that represent the different dosimetric indices. A plan with S_D being equal to zero means all objectives has been fulfilled.

Statistical analysis

The analysis was done using the SPSS software package (Version 22.0, SPSS, Inc.). Continuous variables were compared using the Mann-Whitney U test. All tests were two-sided, and p 0.05 was considered statistically significant.

Results

Dose coverage of PGTV and PTV

All of the automatically generated plans were able to achieve the prescribed dose to PGTV and PTV. For SIB-VMAT plans, the median V_p (volume receiving at least 59.92 Gy) of PGTV is 95.06% (94.8–95.5%), and the median V_p (Volume receiving at least 50.4 Gy) of PTV is 98.87% (95-99.92%). For C-VMAT plans, the median V_p (Volume receiving at least 60 Gy) of PTV is 95.03% (94.86–95.4%). Figure 1 showed the typical isodose distributions of the PTV/PGTV and the OARs from one patient. From Fig. 1, it can be seen that both SIB-VMAT and C-VMAT plans achieve good conformity to the prescription isodose line of the PGTV/PTV. A visible reduced volume of normal tissue was exposed to a 60 Gy dose in SIB-VMAT plan.

Quality Score (s)

All the S_D values of plans were smaller than 1. 75% of SIB-VMAT plans and 60% of C-VMAT plans got relatively low S_D values, which ranged from 0 to 0.1. SIB-VMAT plans achieved significantly lower S_D values than C-VMAT plans (Mean: 0.064 ± 0.106 vs. 0.145 ± 0.181, P = 0.001). 62.5% of SIB-VMAT plans got zero for S_D, which means that most SIB-VMAT plans satisfied the clinical requirement. However, only 17.5% of C-VMAT plans got the value of zero. The distribution of S_D values from both SIB-VMAT and C-VMAT plans were shown in Table 3.

Table 3
The comparison of S_D values between SIB-VMAT and C-VMAT plans

S_D	SIB-VMAT	C-VMAT	P value
Mean	0.064 ± 0.101	0.145 ± 0.181	0.001
Median	0 (0-0.405)	0.049 (0-0.684)	
0	25 (62.5%)	7 (17.5%)	
0-0.1	5 (12.5%)	17 (42.5%)	
0.1–0.2	5 (12.5%)	5 (12.5%)	
0.2–0.3	2 (5%)	0	
0.3–0.4	2 (5%)	6 (15%)	
0.4–0.5	1 (2.5%)	4 (10%)	
0.5–0.6	0	0	
0.6–0.7	0	1 (2.5%)	

Pulmonary Dose

The median total lung volume is 2845 cc (1753–4958 cc). As illustrated in Table 4, several dosimetric objectives in lung have exclusively reduced as following: 1) The total lung V_{30} decreased from 19.2% (12.4–26.2%) in C-VMAT plans to 17.08% (10.21–25.4%) in SIB-VMAT plans (P = 0.037), with median decreased proportion of 8.7% (0.2–24.6%); 2) The MLD is 14.7 Gy (11.32–19.44 Gy) in C-VMAT plans compared to13.8 Gy (10.6–18.1 Gy) in SIB-VMAT (P = 0.045) with median decreased proportion of 6.5% (3.7–14.5%); 3) The significant reductions in the total lung V_{40} (P = 0.002) were also achieved in the SIB-VMAT group, with median decreased proportion of 19.6% (1.6–31%); 4) In lung V_{50}, SIB-VMAT plans got a sharp reduction compared to C-VMAT plans (median, 4.79% vs. 7.16%, P□0.001), and the median decreased proportion is 32.1% (17.9–45.5%). Other dosimetric paranters, such as lung V_5 (P = 0.366), V_{10}

(P = 0.965) and V_{20} (P = 0.95) were comparable between SIB-VMAT and C-VMAT plans. The Dose volume histogram (DVH) taken from one patient was shown in Fig. 2. It can be seen that SIB-VMAT plan obtained lower V_{20-50} than C-VMAT plan.

Table 4

The comparison of dosimetric metrics between SIB-VMAT and C-VMAT plans

	SIB-VMAT	C- VMAT	Decreased proportions(%)	P value
Lung				
MLD (Gy)	13.8(10.6–18.1)	14.7(11.32–19.44)	6.5(3.7–14.5)	0.045*
V_5 (%)	54.65(40.5-70.86)	57.77(42.45–74.37)	/	0.366
V_{10} (%)	40.16(29.3-51.24)	40.1(29.82-52)	/	0.965
V_{20} (%)	27.18(19.9–36.4)	27.47(19.53–35.38)	/	0.95
V_{30} (%)	17.08(10.21-27)	19.2(12.4–26.2)	8.7(0.2–24.6)	0.037*
V_{40} (%)	8.83(4.39–19.2)	11.35(6.08–20.09)	19.6(1.6–31)	0.002*
V_{50} (%)	4.79(1.88–13.53)	7.16(3-16.5)	32.1(17.9–45.5)	0.001*
Esophagus				
Dmax (Gy)	62.82(51.73–65.28)	66.84(61.06–70.63)	7.2(1.6–19.9)	0.001*
MLD (Gy)	24.97(11.86–40.79)	28.08(13.81–47.04)	/	0.119
V_{40} (%)	37.34(4.79–68.86)	39.19(11.9-69.33)	/	0.613
V_{50} (%)	26.39(0.18–67.15)	32.4(3.21–67.5)	/	0.346
Heart				
Dmax (Gy)	61.47(7.02–65.1)	66.21(8.18-70)	8.6(2.2–20)	0.001*
MLD (Gy)	11.13(1.26–23.79)	12.31(1.3-27.04)	/	0.225
V_5 (%)	47.6(3.84–96.73)	49.27(3.04–99.11)	/	0.658
V_{30} (%)	10.34(0-35.96)	15.4(0-44.1)	26.1(0-53.7)	0.049*
V_{40} (%)	4.36(0-21.99)	6.93(0-24.69)	38.8(0-67.2)	0.005*

MLD mean lung dose, Dmax maximum dose, PRV planning organ at risk volume

*$p < 0.05$ was considered significant

Figure legends.

	SIB-VMAT	C- VMAT	Decreased proportions(%)	P value
Spinal cord				
Dmax (Gy)	32.55(30.1–39)	38.77(36.03–42.28)	15.7(0-21.3)	0.001*
Spinal cord PRV				
Dmax (Gy)	37.74(32.79–43.97)	44.78(38.48–58.38)	14.7(5.7–24.7)	0.001*
MLD mean lung dose, Dmax maximum dose, PRV planning organ at risk volume				
*p < 0.05 was considered significant				
Figure legends.				

Heart Dose

Compared with C-VMAT plans, statistically significant reductions in heart V_{30} (median, 10.34% vs. 15.4%, P = 0.049) and V_{40} (median, 4.36% vs 6.93%, P = 0.005) were observed in SIB-VMAT plans, with decreased proportions of 26.1% (0-53.7%) and 38.8% (0-67.2%). The maximum dose to heart is 66.21 Gy (8.18-70Gy) in C-VMAT plan, while 61.47 Gy (7.02–65.1 Gy) in SIB-VMAT with a significant reducation(P 0.001). Box-plots of dosimetric metrics for SIB-VMAT versus C-VMAT plans were shown in Fig. 3. The group of SIB-VMAT plans achieved lower heart Dmax, V_{30} and V_{40} than C-VMAT plans.

Esophagus Dose

A large decrease in the maximum dose of esophagus was observed with SIB-VMAT plans, from 66.84 Gy (61.06–70.63 Gy) to 62.82 Gy (51.73–65.28 Gy) (P0.001). The median decreased proportion is 7.2% (1.6–19.9%). No statically significant differences was observed in esophagus mean dose of SIB-VMAT plans (median, 24.97 Gy vs. 28.08 Gy, P = 0.119).

Spinal Cord Dose

The SIB-VMAT plans achieved statistically significant reductions in maximum dose of spinal cord (median, 32.55 Gy vs. 38.77 Gy, P0.001) compared to C-VMAT plans. The maximum dose of cord PRV was as well (median, 37.74 Gy vs. 44.78 Gy, P0.001). The plan achieved an acceptable maximum doses by SIB-VMAT approach, ranging 30.1-39Gy to spinal cord.

Discussion

The aim of this study was to clarify the dosimetric advantage of reducing CTV dose with SIB-VMAT for the LA-NSCLC VMAT radiotherapy. The automated planning method was applied to exclude the influence caused by subjective factors. And this approach could implemented straightforward in future clinical practice as saving human labor and guarantee the consistency and quality of VMAT plans. The results showed that SIB-VMAT plans yielded full protection for normal tissues compared to C-VMAT plans, with significant reductions in the doses to lung, heart, esophagus and spinal cord. SIB-VMAT plans got lower S_D values than C-VMAT plans, indicating a superior normal-tissue sparing for SIB-VMAT approach.

Radiation-induced pneumonitis (RP) is the most common dose-limiting complication of LA-NSCLC treated by thoracic radiotherapy. Numerous studies indicated that dosimetric parameters, such as mean lung dose (MLD), V_5, V_{10}, V_{20}, V_{30}, V_{40}, V_{50}, were associated with the occurrence of RP[17–20]. All metrics above were evaluated in our study. According to the study conducted by sheng et al.[20], total lung V_5, V_{20}, V_{30} and mean dose were all correlated with grade ≥ 2 RP, furthermore, lung V_{30} was the independent risk factor. Patients with high lung V_{30} (exceed 14.2%) suffered 2.92-fold increased risk of RP compared to those with low V_{30} (no more than 14.2%). Other two studies also considered lung V_{30} as an independent predictor for the occurrence of symptomatic RP[19, 21]. In our study, the SIB-VMAT plans achieved a sharp reduction in lung V_{30}, with median decreased proportion of 8.7%, which would benefit a lot in the reduction of lung toxicities. Xia et al.[22] compared the SIB-IMRT and conventional IMRT plans, and found that the SIB-IMRT plans got lower mean dose, V_5 and V_{20} of total lung. According to the study conducted by Xhaferllari et. al[23], VMAT is dosimetrically advantageous in treating early-stage NSCLC with SABR compared to fixed-beam IMRT, while providing significantly shorter treatment times. Moreover, they pointed out that no significant difference was observed in the two VMAT techniques (SmartArc (SA) and RapidArc (RA)). No studies dig into the SIB and conventional prescription VMAT plans. As it is widely known that VMAT is superior to IMRT in dosimetric aspect[23], our study focus on this two type prescription in VMAT plans. SIB-VMAT plans achieved significant reductions in mean dose, V_{30}, V_{40} and V_{50} of total lung compared to C-VMAT plans, while lung V_5 (P = 0.366), V_{10} (P = 0.965) and V_{20} (P = 0.95) were comparable between the two groups. The advantages of SIB-VMAT mainly rest on the reduction of high and inter-median dose exposure in the pulmonary, not significant in low dose exposure.

The cardiac doses have been proved correlated with the outcomes of LA-NSCLC, including both radiation-induced toxicities and overall survival. According to the systematic review conducted by Zhang et al [24], the heart dose-volume parameters of V_5 and V_{30} were independent predictors for both cardiac events and overall survival among patients with NSCLC. Similarly, Wang et al.[25] found that heart V_{30} were significantly correlated with cardiac toxicity, including pericardial, ischemic and arrhythmic events. The secondary analysis of RTOG 0617 also indicated that heart V_{40} was significantly associated with OS for LA-NSCLC (HR 1.012, P□0.001) [26]. Our study observed obvious dosimetric advantages in heart V_{30} and V_{40} in SIB-VMAT plans compared with C-VMAT plans, with decreased proportions of 26.1% and 38.8%. It

suggested that SIB-VMAT plan had better performances in heart protection, especially the volume reduction of high and inter-median dose irradiation.

Esophagus toxicity is also a common complication when radiotherapy is delivered to the thorax. Numerous studies has correlated esophagus toxicity with dose-volumetric data for lung cancer patients treated with radiotherapy, including the maximum dose, mean dose and the volume of esophagus receiving 20-70Gy[27]. But the best predictors remained unclear. According to the model made by the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) group, the rate of acute esophagitis was supposed to surpass 30% as V_{50} exceed 40%[28]. Other studies also reported that the maximum dose ≥ 58 or 60 Gy was significantly associated with the risk of grade 3–5 esophagus injury[29, 30]. The SIB-VMAT plans achieved significant reductions in maximum dose of esophagus, which will benefit a lot in the prevention of severe esophagitis.

The technique of automated planning was used in VMAT plan design in the present study, and conformal coverage of the PGTV/PTV by the 95% of the prescription dose was well achieved. All plans obtained low values for S_D (less than 1), and most ranged from 0 to 0.1. It represented that the plan quality by automated planning technique is promising. Several plans with large volume of PTV (600 cc) exceed the OARs constraints, therefore manual intervention in plan design should provide for particular patients with large target volume. At this point, automated plan served as a benchmark for planner (dosimetrists or medical physicists) and radiation oncologists making clinical decision, for example, by sacrificing the conformity or homogeneity of targets, the dose OARs could protect better.

There are several limitations in the present study. Firstly, as a single center and small example size study, the results may be affected by potential confounding factors. Secondly, the plans were generated retrospectively, which were not used in clinical practice. The comparison of the toxicity based on these two prescription type plans is not provided currently. Therefore, further studies are still needed to present the reduced toxicity of SIB-VMAT technique in clinic practice.

Conclusions

In summary, we demonstrated that SIB technique could lead to substantial sparing of OARs, including lung, heart, esophagus and cord, mainly through reducing high and inter-median dose exposure. The technique of automated planning method is first implemented in the VMAT plan design and comparison for LA-NSCLC. Future prospective studies are required to identify which patients will benefit most from SIB and whether the dosimetric advantage will translate into improved toxicity outcomes.

Abbreviations

SIB: Simultaneous integrated boost; VMAT: Volumetric modulated arc therapy; IMRT: Intensity modulated radiation therapy; NSCLC: Non-small cell lung cancer; GTV: Gross tumor volume; CTV: Clinical target volume; CT: Computed tomograph; PTV: Planning target volume; PGTV: Planning gross tumor volume;

OS: Overall survival; PFS: Progression-free survival; OARs: Organ at risks; MLD: Mean lung dose; Dmax; the maximum dose; PRV planning organ at risk volume

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committees of the institution (Approval No. 19-048/1833). Written informed consent for scientific usage of clinical data was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from

the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

NB was responsible for design of the project. DQW, JYC and XDZ participated in the generation of radiation plans. DQW, JYC and NB performed data acquisition, data analysis and the drafting of manuscript. TZ, LHW, QFF, ZMZ, JRD and NB critically reviewed the manuscript. All authors read and approved the final manuscript.

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References

1. Bezjak A, Temin S, Franklin G, et al. Definitive and Adjuvant Radiotherapy in Locally Advanced Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. J Clin Oncol. 2015;33:2100–5.

2. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103:1452–60.
3. Machtay M, Bae K, Movsas B, et al. Higher biologically effective dose of radiotherapy is associated with improved outcomes for locally advanced non-small cell lung carcinoma treated with chemoradiation: an analysis of the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys. 2012;82:425–34.
4. Brower JV, Amini A, Chen S, et al. Improved survival with dose-escalated radiotherapy in stage III non-small-cell lung cancer: analysis of the National Cancer Database. Ann Oncol. 2016;27:1887–94.
5. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol. 2015;16:187–99.
6. Wang D, Bi N, Zhang T, et al. Comparison of efficacy and safety between simultaneous integrated boost intensity-modulated radiotherapy and conventional intensity-modulated radiotherapy in locally advanced non-small-cell lung cancer: a retrospective study. Radiat Oncol. 2019;14:106.
7. Ji K, Zhao LJ, Liu WS, et al. Simultaneous integrated boost intensity-modulated radiotherapy for treatment of locally advanced non-small-cell lung cancer: a retrospective clinical study. Br J Radiol. 2014;87:20130562.
8. Fondevilla Soler A, Lopez-Guerra JL, Dzugashvili M, et al. Outcome and toxicity of intensity modulated radiotherapy with simultaneous integrated boost in locally advanced non-small cell lung cancer patients. Clin Transl Oncol. 2017;19:1469–77.
9. Peng J, Pond G, Donovan E, et al. A Comparison of Radiation Techniques in Patients Treated With Concurrent Chemoradiation for Stage III Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2020;106:985–92.
10. Zhang X, Li X, Quan EM, et al. A methodology for automatic intensity-modulated radiation treatment planning for lung cancer. Phys Med Biol. 2011;56:3873–93.
11. Della Gala G, Dirkx MLP, Hoekstra N, et al. Fully automated VMAT treatment planning for advanced-stage NSCLC patients. Strahlenther Onkol. 2017;193:402–9.
12. Quan EM, Chang JY, Liao Z, et al. Automated volumetric modulated Arc therapy treatment planning for stage III lung cancer: how does it compare with intensity-modulated radio therapy? Int J Radiat Oncol Biol Phys. 2012;84:e69–76.
13. Batumalai V, Jameson MG, Forstner DF, et al. How important is dosimetrist experience for intensity modulated radiation therapy? A comparative analysis of a head and neck case. Pract Radiat Oncol. 2013;3:e99–106.
14. Bohsung J, Gillis S, Arrans R, et al. IMRT treatment planning:- a comparative inter-system and inter-centre planning exercise of the ESTRO QUASIMODO group. Radiother Oncol. 2005;76:354–61.
15. Ettinger DS, Wood DE, Aggarwal C, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1.2020. J Natl Compr Canc Netw. 2019;17:1464–72.

16. Liang J, Bi N, Wu S, et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: a multicenter randomized phase III trial. Ann Oncol. 2017;28:777–83.
17. Ueyama T, Arimura T, Takumi K, et al. Risk factors for radiation pneumonitis after stereotactic radiation therapy for lung tumours: clinical usefulness of the planning target volume to total lung volume ratio. Br J Radiol. 2018;91:20170453.
18. Madani I, De Ruyck K, Goeminne H, et al. Predicting risk of radiation-induced lung injury. J Thorac Oncol. 2007;2:864–74.
19. Hernando ML, Marks LB, Bentel GC, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys. 2001;51:650–9.
20. Sheng L, Cui X, Cheng L, et al. Risk factors of grade >/= 2 radiation pneumonitis after gemcitabine induction chemotherapy for patients with non-small cell lung cancer. Radiat Oncol. 2019;14:229.
21. Zhao Y, Chen L, Zhang S, et al. Predictive factors for acute radiation pneumonitis in postoperative intensity modulated radiation therapy and volumetric modulated arc therapy of esophageal cancer. Thorac Cancer. 2015;6:49–57.
22. Xia F, Zhou L, Yang X, et al. Is a clinical target volume (CTV) necessary for locally advanced non-small cell lung cancer treated with intensity-modulated radiotherapy? -a dosimetric evaluation of three different treatment plans. J Thorac Dis. 2017;9:5194–202.
23. Xhaferllari I, El-Sherif O, Gaede S. Comprehensive dosimetric planning comparison for early-stage, non-small cell lung cancer with SABR: fixed-beam IMRT versus VMAT versus TomoTherapy. J Appl Clin Med Phys. 2016;17:329–40.
24. Zhang TW, Snir J, Boldt RG, et al. Is the Importance of Heart Dose Overstated in the Treatment of Non-Small Cell Lung Cancer? A Systematic Review of the Literature. Int J Radiat Oncol Biol Phys. 2019;104:582–9.
25. Wang K, Pearlstein KA, Patchett ND, et al. Heart dosimetric analysis of three types of cardiac toxicity in patients treated on dose-escalation trials for Stage III non-small-cell lung cancer. Radiother Oncol. 2017;125:293–300.
26. Chun SG, Hu C, Choy H, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. J Clin Oncol. 2017;35:56–62.
27. Bar-Ad V, Ohri N, Werner-Wasik M. Esophagitis, treatment-related toxicity in non-small cell lung cancer. Rev Recent Clin Trials. 2012;7:31–5.
28. Werner-Wasik M, Yorke E, Deasy J, et al. Radiation dose-volume effects in the esophagus. Int J Radiat Oncol Biol Phys. 2010;76:86–93.
29. Qiao WB, Zhao YH, Zhao YB, Wang RZ. Clinical and dosimetric factors of radiation-induced esophageal injury: radiation-induced esophageal toxicity. World J Gastroenterol. 2005;11:2626–9.
30. Ahn SJ, Kahn D, Zhou S, et al. Dosimetric and clinical predictors for radiation-induced esophageal injury. Int J Radiat Oncol Biol Phys. 2005;61:335–47.

Figures

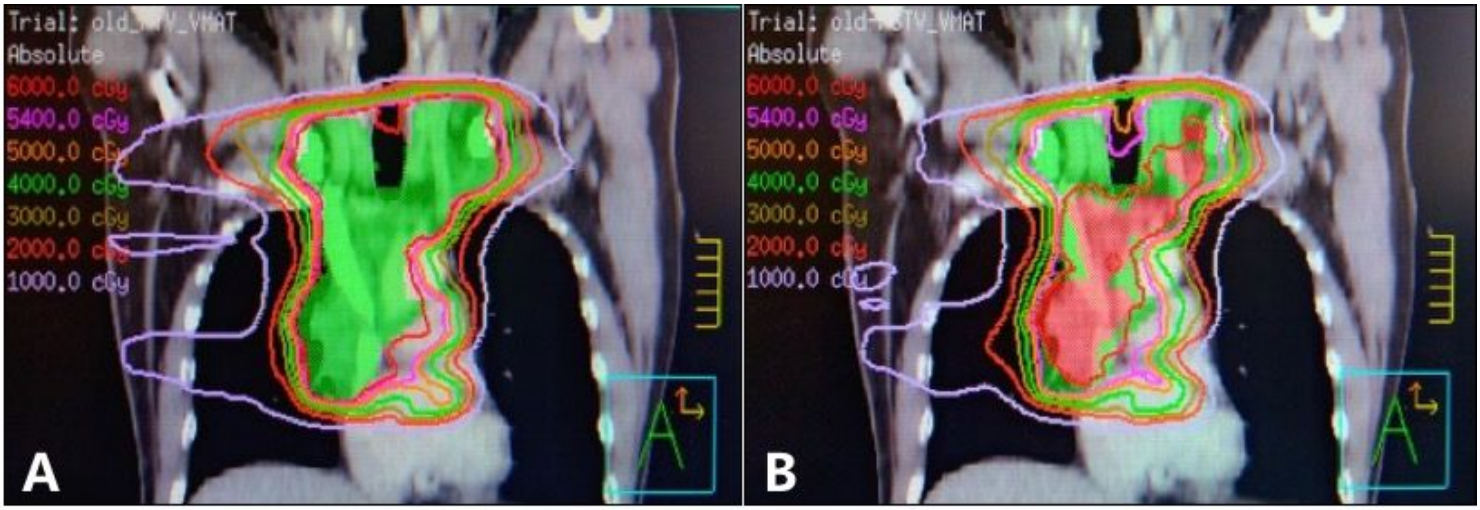

Figure 2

The comparison of isodose lines distribution about the PTV/PGTV and the OARs in the C-VMAT plan (A) and the SIB-VMAT plan (B) from 1 patient. The isodose lines are presented by various colors: 6000cGy (red), 5400cGy (pink), 5000cGy (orange), 4000cGy (green), 3000cGy (olive), 2000cGy (tomato) and 1000cGy (lavender)

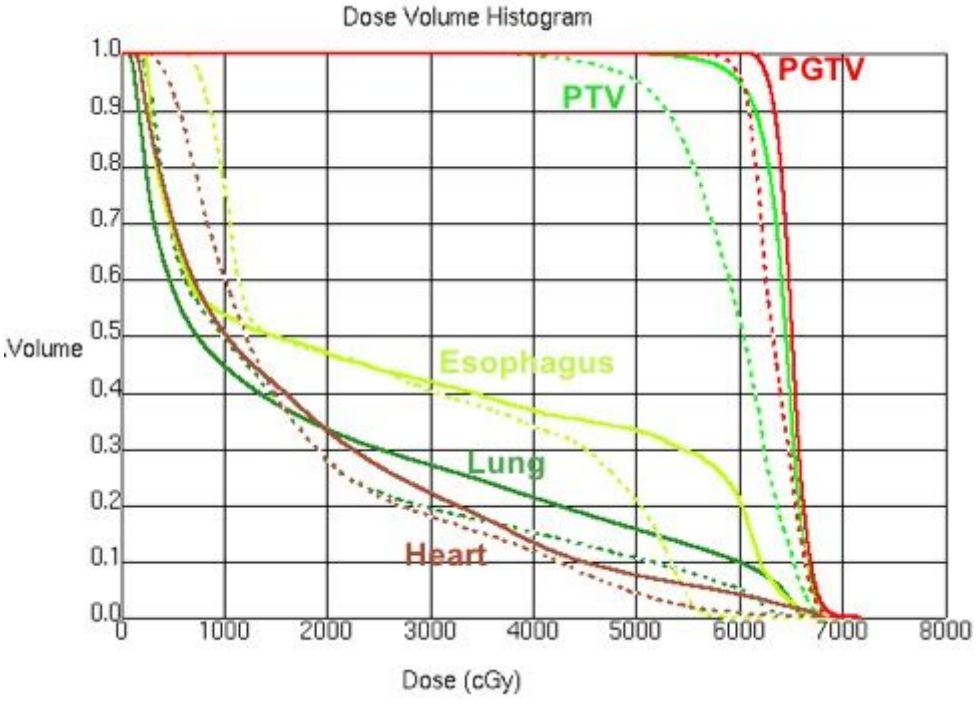

Figure 4

Representative DVH for OARs when comparing SIB-VMAT and C-VMAT plan. (solid line, SIB-VMAT; dashed line, C-VMAT) DVH taken from one patient.

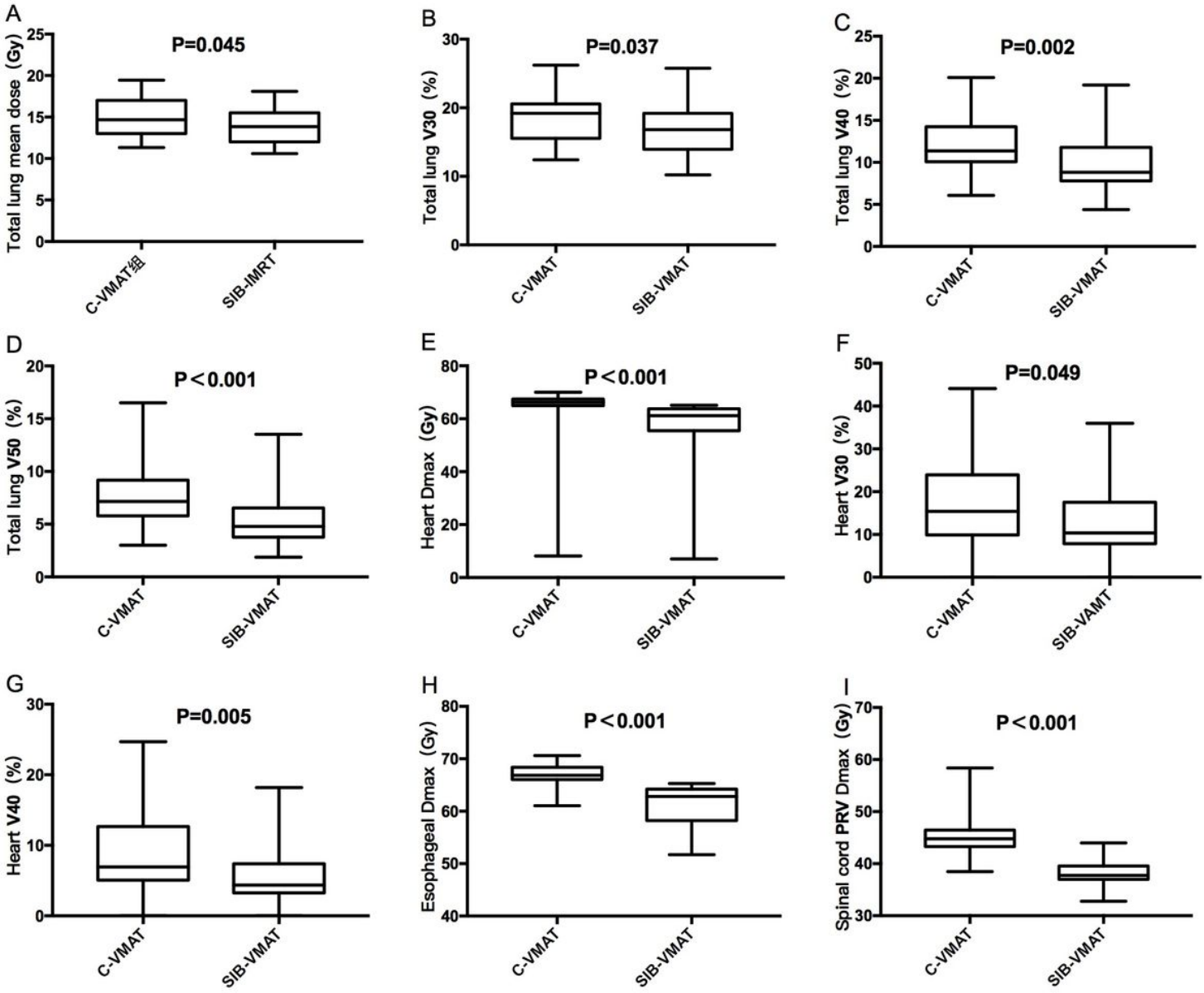

Figure 5

Box-plots of dosimetric metrics for SIB-VMAT versus C-VMAT plans. (A. total lung mean dose B.total lung V30 C. total lung V40 D.total lung V50 E. heart maximum dose F. heart V30 G. heart V40 H. esophagus maximum dose I. spinal cord PRV maximum dose)