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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Daquan Wang
Chinese Academy of Medical Sciences and Peking Union Medical College

Jiayun Chen
Chinese Academy of Medical Sciences and Peking Union Medical College

Xiaodong Zhang
University of Texas MD Anderson Cancer Center

Tao Zhang
Chinese Academy of Medical Sciences and Peking Union Medical College

Luhua Wang
Chinese Academy of Medical Sciences and Peking Union Medical College

Qinfu Feng
Chinese Academy of Medical Sciences and Peking Union Medical College

Zongmei Zhou
Chinese Academy of Medical Sciences and Peking Union Medical College

Jianrong Dai
Chinese Academy of Medical Sciences and Peking Union Medical College

Nan Bi
Chinese Academy of Medical Sciences and Peking Union Medical College

✉️ binan_email@163.com Corresponding Author

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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%) |
| 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 \( \geq 95\% \) 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.

| \( j \) | 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:

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

$C_j$ 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 $V_5 \geq 65\%$,

- 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 $p \leq 0.05$ 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.

| $S_D$ | 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 to 13.8 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 V₅₀, 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 parameters, such as lung V₅ (P = 0.366), V₁₀ (P = 0.965) and V₂₀ (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 V₂₀−₅₀ 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*          |
| V₅ (%) | 54.65(40.5-70.86)              | 57.77(42.45–74.37)           | /                         | 0.366           |
| V₁₀ (%)| 40.16(29.3-51.24)             | 40.1(29.82-52)               | /                         | 0.965           |
| V₂₀ (%)| 27.18(19.9–36.4)              | 27.47(19.53–35.38)           | /                         | 0.95            |
| V₃₀ (%)| 17.08(10.21-27)               | 19.2(12.4–26.2)              | 8.7(0.2–24.6)             | 0.037*          |
| V₄₀ (%)| 8.83(4.39-19.2)               | 11.35(6.08–20.09)            | 19.6(1.6-31)              | 0.002*          |
| V₅₀ (%)| 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           |
| V₄₀ (%)| 37.34(4.79–68.86)             | 39.19(11.9–69.33)            | /                         | 0.613           |
| V₅₀ (%)| 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           |
| V₅ (%) | 47.6(3.84–96.73)              | 49.27(3.04–99.11)            | /                         | 0.658           |
| V₃₀ (%)| 10.34(0.35–96)                | 15.4(0.4–44.1)               | 26.1(0–53.7)              | 0.049*          |
| V₄₀ (%)| 4.36(0-21.99)                 | 6.93(0-24.69)                | 38.8(0-67.2)              | 0.005*          |
| **Spinal cord** | |                              |                           |                 |
| Dmax (Gy)| 32.55(30.1–39)               | 38.77(36.03–42.28)           | 15.7(0–21.3)              | <0.001*         |
| 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 V₃₀ (median, 10.34% vs. 15.4%, P = 0.049) and V₄₀ (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 reduction(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) (P < 0.001). 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, P < 0.001) compared to C-VMAT plans. The maximum dose of cord PRV was as well (median, 37.74 Gy vs. 44.78 Gy, P < 0.001). 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, P0.001) [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 $\geq$ 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.

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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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Figures

![Figure 1](image)

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 1

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Figure 2

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 2

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 3

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)
Figure 3
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.  
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