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# Is clinical target volume necessary for locally advanced non-small cell lung cancer treated with 4D-CT intensity-modulated radiation therapy

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## Abstract

**Background** A dosimetric evaluation is still lacking in terms of clinical target volume (CTV) omission in stage III patients treated with 4D-CT Intensity-Modulated Radiation Therapy (IMRT).

**Methods** 49 stage III NSCLC patients received 4D-CT IMRT were reviewed. Target volumes and organs at risk (OARs) were re-delineated. Four IMRT plans were conducted retrospectively to deliver different prescribed dose (74 Gy–60 Gy), and with or without CTV implementation. Dose and volume histogram (DVH) parameters were collected and compared.

**Results** In the PTV-g 60 Gy plan (PTV-g refers to the PTV generated from the internal gross tumor volume), only 5 of 49 patients had the isodose ≥ 50 Gy line covering at least 95% of the PTV-c (PTV-c refers to the PTV generated from the internal CTV) volume. When the prescribed dose was elevated to 74 Gy to the PTV-g, 33 of 49 patients could have the isodose ≥ 50 Gy line covering at least 95% of the PTV-c volume. In terms of OARs protection, the SIB-IMRT plan showed the lowest value of V5, V20, and mean dose of lung, had the lowest V55 of esophagus, and the lowest estimated radiation doses to immune cells (EDIC). The V20, V30, and mean dose of heart was lower in the simultaneous integrated boost (SIB) IMRT (SIB-IMRT) plan than that of the PTV-c 60 Gy plan.

**Conclusions** CTV omission was not suitable for stage III patients when the prescribed dose to PTV-g was 60 Gy in the era of 4D-CT IMRT. CTV omission plus high dose to PTV-g (74 Gy for example) warranted further exploration. The SIB-IMRT plan had the best protection to normal tissue including lymphocytes, and might be the optimal choice.

**Keywords** CTV omission, 4D-CT, IMRT, EDIC, NSCLC

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## Introduction

Definitive radiotherapy is pivotal for unresectable, locally advanced non-small cell lung cancer (NSCLC) patients. Concurrent or sequential chemo-radiotherapy (CRT), followed by immunotherapy consolidation, has been the standard therapeutic strategies for these patients [1, 2]. There were also trials explored the efficacy and toxicity of concurrent immunotherapy and definitive chemo-radiotherapy in stage III NSCLC patients [3–5]. Although the addition of immune checkpoint inhibitors (ICIs) improved the survival outcome of these patients, the lung toxicity, induced by either immunotherapy or radiotherapy, was a remained unresolved problem. The PACIFIC-R study showed that 17.9% of stage III NSCLC patients received durvalumab after CRT experienced pneumonitis or interstitial lung disease (ILD), and 9.5% patients discontinued ICI treatment due to the lung toxic events [6]. In the KEYNOTE-799 trial, grade 3 or higher pneumonitis, including RP, occurred in 16 of 214 patients (7.48%), and 5 of them died from pneumonitis [4].

In the pre-immunotherapy era, elective node irradiation (ENI) strategy was questioned and discarded due to the increasement of radiation target volume and higher incidence of adverse events [7, 8]. The phase III PACIFIC-2 trial also found that smaller PTV volume ($<450$ $cm^3$) was associated with improved PFS in stage III NSCLC patients received concurrent durvalumab and definitive CRT [9].

To balance the benefit and toxicity of radiotherapy and immunotherapy in stage III NSCLC patients, one proposed strategy was the omission of clinical target volume (CTV). This strategy confine high dose to gross tumor volume (GTV), but spare the subclinical microscopic malignant lesions. In an early clinical trial conducted by J. M. Kilburn et al., a failure pattern analysis of 110 lung patients received 4-D imaging and image-guided radiotherapy (IGRT) suggested that CTV omission might be feasible [10]. In this trial, the prescribed dose was generally high (median radiation dose was 70 Gy). However, the phase III trial RTOG0617 showed that a higher radiation therapy dose of 74 Gy fail to improve survival outcomes and might even been potentially harmful [11, 12]. Thus, 60 Gy to 66 Gy is currently the standard radiation dose to stage III NSCLC patients. In addition to lung cancer, the omission of CTV is being considered for the radiation treatment of other tumors to reduce toxic side effects. For instance, in a study by Pranshu Mohindra and colleagues, IMRT plans and clinical outcomes were analyzed for 112 patients with oropharyngeal cancer (nodal classification N0-N2b), focusing on the coverage of ipsilateral and contralateral nodal level V. They found that there were no failures detected in nodal level V, regardless of whether it was included or omitted. The dosimetric evaluation revealed a significant reduction in integral dose as well as in V10 Gy, V20 Gy, V30 Gy, V40 Gy, and V50 Gy by excluding both unilateral and bilateral level V from the CTV.

Although a previous study reported that IMRT planning with CTV omission provided sufficient dose coverage of subclinical disease while reducing the dose to normal tissues [13]. However, only 13 patients were analyzed in this trial and 4D-CT technique was not applied [13]. Taken together, whether CTV omission is feasible in the modern era combining 4D-CT imaging and intensity-modulated radiation therapy (IMRT) still requires evidence from the dosimetric perspective when the prescribed dose is 60 Gy to 66 Gy. In this work, the 4D-CT images of 49 stage III NSCLC patients were included for analyses. The dosimetric parameters of four treatment plans, with different prescribed dose (74 Gy–60 Gy), and with or without CTV implementation, were compared. We found that CTV omission was not feasible when the prescribed dose was 60 Gy to PTV-g (PTV-g refers to the PTV generated from the internal gross tumor volume), and simultaneous integrated boost (SIB) IMRT (SIB-IMRT) might be optimal for patients received both thoracic radiation and immunotherapy.

## Method

### Ethics approval and consent to participate

The Institutional Review Board (IRB) of the Xiangxi Autonomous Prefecture People's Hospital had waived the requirement for written approval of this study and the need for consent to participate since this was a retrospective study on radiation dosimetry and individual patients was not affected.

### Patient enrollment

All patients diagnosed with stage III NSCLC and received definitive 4D-CT IMRT in the Xiangxi Autonomous Prefecture People's Hospital from Jan 1, 2023 to May 31, 2023 were enrolled. The clinical data of patients were extracted from the hospital Information system (HIS), including age, gender, smoking status, pathological information, and TNM stage (according to the 8th version of the American Joint Committee on Cancer classification).

### Computed Tomography (CT) simulation

Before CT scan, patients were generally taught to breathe peacefully by using the abdominal rather than the thoracic muscles. They were taught to lie with the most comfortable position and then immobilized with a thermoplastic mask, with their arms generally placed above their head. The Varian respiratory gating for scanners (RGSC) system (Varian Medical Systems, Palo Alto, CA, USA) was used to observe and record the respiratory motion of each patient. Namely, a reflector blocker would place on patients' epigastric abdomen area, and

during the CT scan, the visual coaching device on the couch would record the respiratory signal. Once the scan was completed, the scanner would synchronize the respiratory information with the acquired image data to generate the 4D image set. The G.E. Advantage 4D software (G.E. Healthcare, Waukesha, WI, USA) was used to sort the reconstructed 4D-CT images and ten respiratory phases and the maximum intensity projection (MIP) CT dataset was generated. These sorted 4D images were then imported into the Eclipse treatment planning system (TPS) (Eclipse 15.6, Varian Medical Systems, Palo-Alto, Santa Clara, CA, USA) for target and organs at risk (OAR) delineation.

#### Target and OARs delineation

The targets were defined based on International Commission on Radiation Units and Measurements (ICRU) reports 62 and 83 [14, 15]. The defition of GTV has been reported in previously studies [13]. Firstly, the GTV delineation was done on the MIP dataset and labeled as $IGTV_{MIP}$. Then, GTV delineation was done on CT images of all the 10 phases of respiratory cycle and labeled from GTV0 to GTV90. Finally, a composite structure, labeled as IGTV, was produced by using the MIP dataset as a reference image dataset and copying the GTV0 to GTV90 on the MIP CT dataset. The internal clinical target volume (ICTV) is defined to be the IGTV plus an appropriate margin based on the following criteria: ICTV margins were 0.6 cm for squamous cell cancer and 0.8 cm for adenocarcinoma for primary tumor [16], and ICTV margins were 0.3 cm positive lymph nodes with a short axis less than 2 cm, and 0.5 cm for those with a short axis greater than 2 cm [7]. In addition, ICTVs were manually modified as reported in previous studies [13]. The PTV was then generated by adding 0.5 cm to the ICTV. Namely, the PTV generated from the IGTV (with CTV omission) is referred to as the PTV-g, and the PTV generated from the ICTV as the PTV-c. The OARs included the lung, heart, esophagus and spinal cord, and they were delineated according to RTOG 1106 atlas on organs at risk [17].

#### Intensity-Modulated Radiotherapy (IMRT) treatment plan

Four IMRT plans were generated: PTV-g 60 Gy plan, PTV-g 74 Gy plan, PTV-c 60 Gy plan and SIB-IMRT plan. In the former three plans, a dose of 60–74 Gy was prescribed at 2 Gy per fraction to the PTV-g or PTV-c (30–37 fractions). In the SIB-IMRT plan, the PTV-c received 50 Gy (1.667 Gy per fraction) and the dose to the PTV-g was simultaneously elevated to 60 Gy in 30 fractions (2 Gy per fraction). All the plans were required to meet the criteria reported in previous studies [13].

#### Statistical analysis

The data analyses and visualization were performed by R software (Version 4.3). paired t test was used for comparison of continuous variables. A p value less than 0.05 was considered statistically significant.

## Results

#### Evaluation of dose coverage of PTV-c

A total of 49 stage III NSCLC patients received definitive radiotherapy in the Xiangxi Autonomous Prefecture People's Hospital from Jan 1, 2023 to May 31, 2024 were used for evaluation. All patients received 4D-CT IMRT and Fig. 1A was a representative example of target and OARs delineation. The average PTV-g and PTV-c were 190.93 $cm^3$ and 339.62 $cm^3$, respectively (Fig. 1B). While the prescribed dose was 60 Gy to the PTV-g and ≥95% of the PTV-g received the prescribed dose in all patients, only 5/49 patients had the isodose≥50 Gy line covering at least 95% of the PTV-c volume (Fig. 1C). 48.98% (24/49) of these patients achieved the isodose≥45 Gy line covering at least 95% of the PTV-c volume (Fig. 1C).

In addition, when the prescribed dose was elevated to 74 Gy to the PTV-g and the dose was delivered to at least 95% of the PTV-g volume in all patients, 33/49 patients had the isodose≥50 Gy line covering at least 95% of the PTV-c volume (Fig. 1D). 83.67% (41/49) of these patients achieved the isodose≥45 Gy line covering at least 95% of the PTV-c volume (Fig. 1D).

The treatment plans and DVH plots of 3 representative patients received prescribed dose at 60 Gy to the PTV-g conducted by two independent medical physicists were displayed in Fig. 2A and C.

#### Comparison of OAR parameters

In terms of lung toxicity, the SIB-IMRT plan had significant lower V5, V20, and mean dose of lung than that of the PTV-c 60 Gy plan ($p<0.001$, Fig. 3A and C). No significant difference was observed between the SIB-IMRT plan and the PTV-g 74 Gy plan from the perspective of V5 and V20 of lung (Fig. 3A and B), but mean lung dose of the SIB-IMRT plan was lower than that of the PTV-g 74 Gy plan ($p<0.001$, Fig. 3C). On the contrary, the mean lung dose was similar between the PTV-c 60 Gy and PTV-g 74 Gy plans (Fig. 3C), but V5 and V20 of lung were significantly lower in the PTV-g 74 Gy plan when compared with the PTV-c 60 Gy plan (Fig. 3A and B).

From the point of heart toxicity, the SIB-IMRT plan had significant lower V20, V30, and mean dose of heart when compared with those of the PTV-c 60 Gy plan (Fig. 3D and F). But no difference was observed between the SIB-IMRT and PTV-g 74 Gy plan (Fig. 3D and F). The V20 of heart and mean heart dose were significantly lower in the PTV-g 74 Gy plan when compared with the PTV-c 60 Gy plan (Fig. 3D and F, $p<0.05$). In addition, the V30 of heart

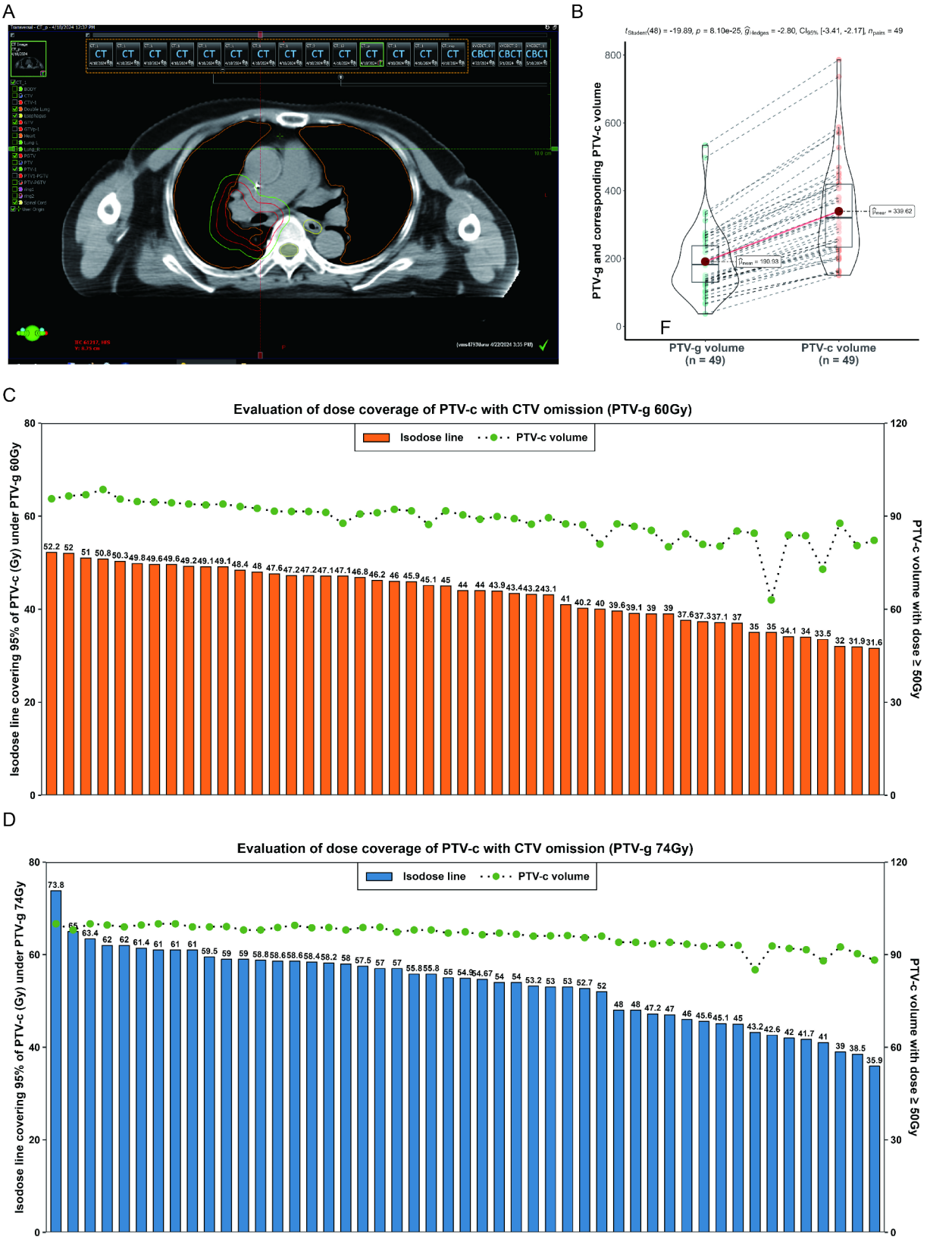


**Fig. 1** Evaluation of dose coverage of PTV-c with CTV omission. (**A**) A representative example of target and OARs delineation under 4D-CT IMRT. (**B**) PTV-g and corresponding PTV-c of 49 stage III NSCLC patients. (**C**) The isodose line (orange column) covering at least 95% of the PTV-c and the percentage of PTV-c received ≥ 50 Gy (green line) when the prescribed dose was 60 Gy to the PTV-g. (**D**) The isodose line (orange column) covering at least 95% of the PTV-c and the percentage of PTV-c received ≥ 50 Gy (green line) when the prescribed dose was elevated to 74 Gy to the PTV-g

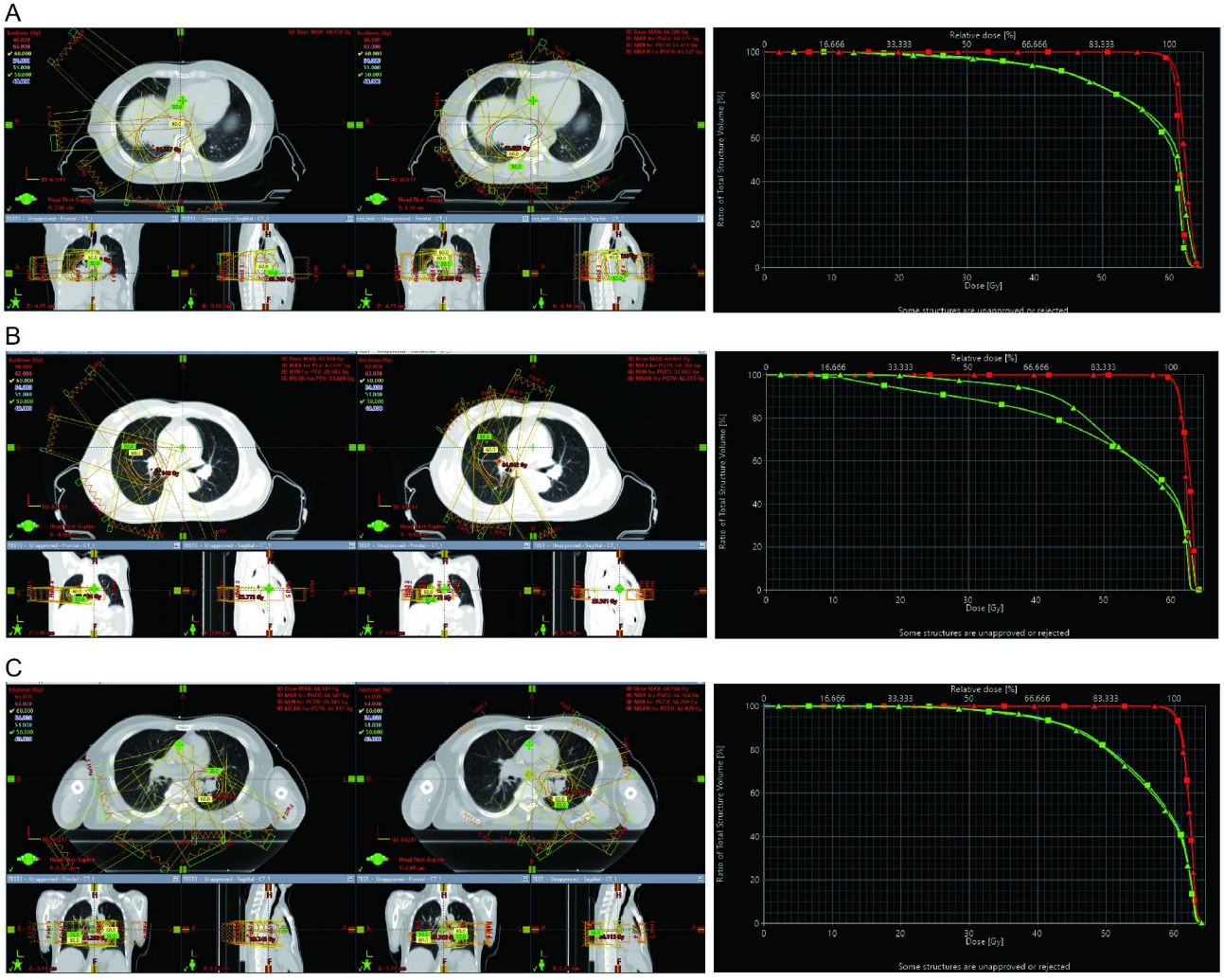


**Fig. 2** (**A-C**) Treatment plans and DVH plots of 3 representative patients received prescribed dose at 60 Gy to the PTV-g conducted by two independent medical physicists

exceeded its general limitation (V30>40%) in one patient when the PTV-g was elevated to 74 Gy, because the primary tumor was large (>5 cm) and located close to heart and spinal cord (Fig. 3E).

Besides, the SIB-IMRT plan had the lowest V55 of esophagus among the three plans ($p<0.001$, Fig. 3G). And all the three plans did not exceed the max tolerated dose of spinal cord (Dmax<45 Gy, Fig. 3H).

Previous studies revealed that estimated radiation doses to immune cells (EDIC) was an independent prognostic factor in stage III patients received chemo-radiotherapy with or without immunotherapy consolidation [11, 18]. Among the three plans, the EDIC was lowest in the SIB-IMRT plan ($p<0.001$, Fig. 3I), while no difference was observed between the PTV-c 60 Gy and PTV-g 74 Gy plan (Fig. 3I).

## Discussion

Optimization of radiation target volumes is essential to balance the benefit and toxicity of radiotherapy in the era of immunotherapy for stage III NSCLC patients [9, 18]. The aim of this work is to evaluate the feasibility of CTV omission from the perspective of dosimetry in patients received 4D-CT IMRT. We found that the majority of them (44/49) had an isodose 50 Gy line covering less than 95% of the PTV-c volume when the prescribed dose was 60 Gy to PTV-g (Fig. 1C). In this treatment plan, nearly half of them (48.98%) could achieve the isodose 45 Gy line covering at least 95% of the PTV-c volume (Fig. 1C). In patients treated with 3D-CT IMRT, Fan Xia et al. reported that the 50 Gy isodose line could cover at least 95% of the PTV-c volume in all patients [13]. However, the sample size in this work was small ($n=13$) and the tumor movement observed under fluoroscopy was not so accurate, thus, these results could not be extended to

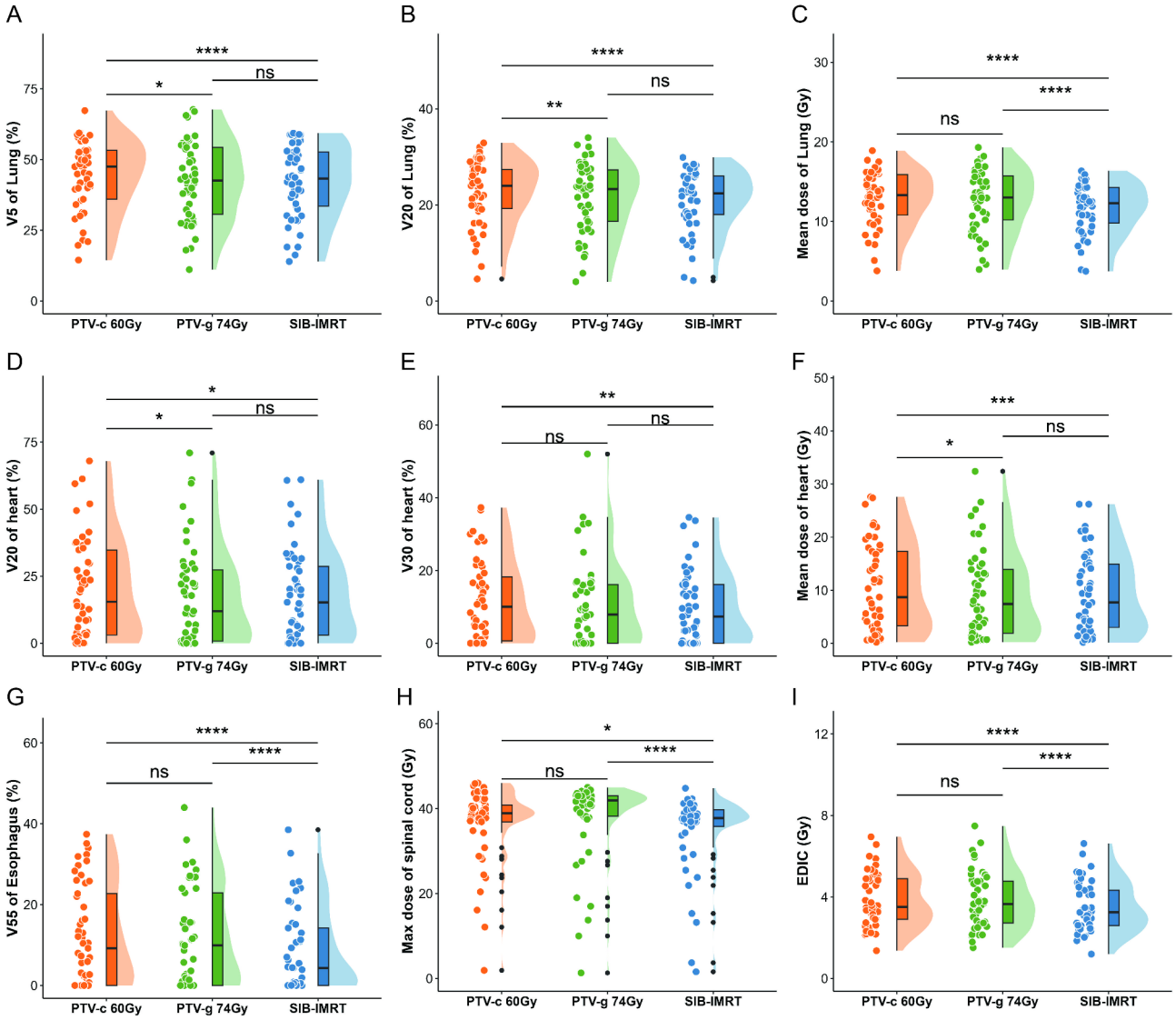


**Fig. 3** Comparison of OAR parameters. (**A-C**) Comparison of V5 (**A**), V20 (**B**), and mean dose of lung (**C**) across the PTV-g 74 Gy, PTV-c 60 Gy and SIB-IMRT plans. (**D-F**) Comparison of V20 (**D**), V30 (**E**), and mean dose of heart (**F**) across the PTV-g 74 Gy, PTV-c 60 Gy and SIB-IMRT plans. (**G**) Comparison of V55 of esophagus across the PTV-g 74 Gy, PTV-c 60 Gy and SIB-IMRT plans. (**H**) Comparison of maximum dose of spinal cord across the PTV-g 74 Gy, PTV-c 60 Gy and SIB-IMRT plans. (**I**) Comparison of estimated radiation doses to immune cells (EDIC) across the PTV-g 74 Gy, PTV-c 60 Gy and SIB-IMRT plans. The *p* values were shown as $*p<0.05$, $**p<0.01$, $***p<0.001$, and $****p<0.001$. ns represented no significance

the 4D-CT era. Previously, J. M. Kilburn et al. found that CTV omission appeared feasible since only two events failed in the retrospectively-derived CTV expansion in all 110 patients received 4D-CT and IGRT [10]. In their work, the prescribed radiation dose was relatively high (median dose 70 Gy). Indeed, when the radiation dose elevated to 74 Gy to the PTV-g volume, 83.67% patients had the 45 Gy isodose covering at least 95% of the PTV-c volume. Consequently, CTV omission is only feasible when high radiation dose (74 Gy for example) is given to the PTV-g volume. This treatment plan warranted further exploration since it might be able to improve local-regional control [19].

The protection of normal tissues, lung and heart in particular, is of equal importance for patients received ICIs treatment and thoracic radiation [20, 21]. V5, V20 and mean lung dose are all associated with the incidence of radiation pneumonitis [20, 22]. Among the three treatment plans (PTV-g 74 Gy plan, PTV-c 60 Gy plan and SIB-IMRT plan), the SIB-IMRT plan had the lowest lung toxicity in terms of V5, V20 and mean dose of lung (Fig. 3A and C). Besides, the SIB-IMRT plan also had the best protection of heart since the V20, V30 and mean dose of heart were the lowest (Fig. 3D and F). It was worth noting that for patients whose tumor was large and located near heart and/or spinal cord, the PTV-g 74 Gy

plan might be inappropriate since it would be difficult to confine the dose to the heart and/or spinal cord within the generally acceptable threshold (Fig. 3E).

In addition, 40–70% of patients treated with radiotherapy were found to experience lymphopenia, which might resulted from direct irradiation of lymph nodes and circulating lymphocytes (CLs) traversing through the radiation field [23]. Accumulative evidence indicated that lymphopenia was associated with worse survival and lower response rate to immunotherapy in NSCLC patients [24, 25]. The effective dose to immune cells (EDIC) was proved to correlate with severe lymphopenia, recurrence, and survival of lung patients treated with concurrent chemoradiotherapy followed by immunotherapy consolidation [18, 26, 27]. In stage III NSCLC patients treated with chemoradiation followed by durvalumab, EDIC > 6 Gy correlated with worse survival outcomes and locoregional control (LRC). When the EDIC was analyzed as a continuous variable, higher EDIC was associated with worse OS, PFS and LRC [18]. In this work, we noticed that the EDIC was the lowest in the SIB-IMRT plan (Fig. 3I), indicating this treatment plan might have better protection to the lymphocytes and be more suitable for patients receiving thoracic radiation combined immunotherapy.

The complex interaction between radiation dose, fractionation schedules, and biological responses greatly affects treatment outcomes. The biological effective dose (BED) is particularly important for understanding the therapeutic effectiveness of various radiation regimens [28]. While previous studies indicated that total and BED dose levels in thoracic radiotherapy (TRT) were not significantly related to patient survival receiving concurrent chemoradiotherapy (CRT) [29], the optimal BED for effectively controlling tumors during the immunotherapy era remains unclear. Moreover, whether BED is associated with the prognosis of patients with stage III NSCLC requires confirmation through prospective clinical studies. Addressing these issues is crucial, as it will provide clinicians with a reliable benchmark to explore the best radiation doses and techniques.

Additionally, it is important to highlight a limitation of this study regarding radiation therapy techniques. Beyond SIB-IMRT, there are several newer radiation therapy technologies and concepts aimed at enhancing tumor control while minimizing harm to healthy tissues, such as image-guided radiation therapy (IGRT) and adaptive radiotherapy (ART) [30, 31]. IGRT enables precise tumor localization and allows for real-time adjustments during treatment delivery, which is essential for maximizing dose conformity and reducing toxicity [30]. At the same time, ART represents a significant shift in practice, as it involves modifying treatment plans in response to anatomical and physiological changes throughout the treatment course, resulting in improved dosimetric outcomes and enhanced patient safety [31]. To better reduce damage to critical organs and decrease adverse effects associated with radiation therapy, the use of IGRT and ART may be more reliable than omitting CTV, as these advanced techniques greatly enhance treatment precision and adaptability to tumor motion and variations in patient anatomy.

## Conclusions

In summary, our work demonstrated that CTV omission was not suitable for stage III patients when the prescribed dose to PTV-g was 60 Gy in the era of 4D-CT IMRT. CTV omission plus high dose to PTV-g (74 Gy for example) warranted further exploration since this treatment plan might result in improved local-regional control. The SIB-IMRT plan offered the best protection for normal tissues, including lymphocytes. However, it is important to note that most treatment planning system (TPS) algorithms, including Monte Carlo methods, have limitations in accurately calculating doses in heterogeneous lung regions. Whether SIB-IMRT is the optimal choice for stage III patients undergoing thoracic radiotherapy and immunotherapy requires validation through future clinical studies.

### Author contributions

The study was designed by ZW S and GY L. WX D delineated target and OARs of patients. ZW S and JS Z checked all the delineation. TX and HX conducted treatment plans and collected data. WW L, JL, and NX collected DVH data. ZW S and GY L processed data analyses and drafted the manuscript. ZW S, WX D and GY L revised the final manuscript. All authors have read and approved the final manuscript.

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### Data availability

The data was available with proper request.

## Declarations

### Competing interests

The authors declare no competing interests.

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