Original Article

Is clinical target volume necessary?—a failure pattern analysis in patients with locally advanced non-small cell lung cancer treated with concurrent chemoradiotherapy using intensity-modulated radiotherapy technique

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Background: Our previous dosimetric study showed that for locally advanced non-small cell lung cancer (LA-NSCLC), radiotherapy with intensity-modulated radiotherapy (IMRT) technique could deliver sufficient dose coverage to subclinical regions and reduce the dose to normal tissues with the omission of clinical target volume (CTV). To further clinically validate this strategy, we conducted the current study to analyze the failure pattern for patients with LA-NSCLC treated with concurrent chemotherapy and CTV-omitted IMRT. We also investigated the effects of target volumes on lymphopenia during radiotherapy to further test the potential benefits of CTV omission in anti-tumor immunotherapy.

Methods: A total of 63 patients with LA-NSCLC treated with CTV-omitted IMRT with concurrent chemotherapy were enrolled in this study. Their planning target volume (PTV) (also PTV-g) was expanded directly from gross tumor volume (GTV). A virtual CTV was expanded from GTV, and the PTV generated from virtual CTV was named planning target volume with CTV expansion (PTV-c). Treatment failures were divided into local, regional, and distant failures, and local–regional recurrences were classified into inside PTV-g (IN-PTV-g), between PTV-g and PTV-c (PTV-g-c), and outside PTV-c (OUT-PTV-c). The relationship between lymphopenia during radiotherapy and the target volumes was also evaluated using Spearman's correlation analysis.

Results: Among the 60 patients with detailed follow-up data for recurrences, 46 (76.7%) experienced recurrences, with 18 (30.0%) being local recurrence, 5 (8.4%) being regional failure, and 33 (55.0%) being distant failure. For the 21 patients with local–regional recurrences, 16, 6, and 1 were IN-PTV-g, OUT-PTV-c, and PTV-g-c recurrences, respectively. Lymphopenia during radiotherapy was associated with both GTV and PTV, with larger volumes linked to severe lymphopenia.

Conclusions: CTV omission is feasible for LA-NSCLC treated with concurrent chemoradiotherapy and does not compromise failure inside the subclinical region. The radiation volumes were associated with lymphopenia during radiotherapy, with larger volumes related to severe lymphopenia. This finding supports the further exploration of CTV omission for immunotherapy.

Keywords: Non-small cell lung cancer (NSCLC); stage III; clinical target volume (CTV); intensity-modulated radiotherapy (IMRT); recurrence

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Introduction

For 20–30% of patients with locally advanced non-small cell lung cancer (LA-NSCLC) (AJCC TNM-8, stage III), tumors are unresectable and definitive concurrent chemoradiation is the standard care for unresectable LA-NSCLC (1,2). Radiotherapy is an important therapeutic strategy with radical cure potential for patients with LA-NSCLC, and intensity-modulated radiotherapy (IMRT) has been mainly recommended because it can achieve satisfying dose coverage of tumor while sparing normal tissue (3-7). For IMRT, radiation target contouring is crucial. The planning target volume (PTV) is generated by procedurally expanding gross tumor volume (GTV), clinical target volume (CTV), and internal target volume, and the radical radiation dose is then prescribed to PTV in the definitive radiotherapy for LA-NSCLC. However, CTV is the tissue volume that contains GTV and subclinical microscopic malignant lesions, and the required doses for subclinical disease eradication are lower than those used to control gross tumors in patients with common epithelial tumors (8,9). Given this finding, we hypothesized that the dosage prescribed to subclinical lesions in traditional target-contouring and a dose-prescription manner is higher than necessary. This hypothesis prompted us to explore the feasibility of omitting CTV in patients with LA-NSCLC. Our previous dosimetric study (10) showed that radiotherapy with IMRT technique can deliver sufficient dose coverage to subclinical diseases and reduce the dose to normal tissues even with CTV omission. To further validate the strategy in clinical practice, we conducted the current study to analyze the failure pattern for patients with LA-NSCLC treated with concurrent chemotherapy and CTV-omitted IMRT. We focused on the rate of recurrences in subclinical areas to directly test the feasibility of CTV omission.

At present, anti-tumor immunotherapy has become a necessity for LA-NSCLC treatment. Based on the results of the PACIFIC study (11,12) and the outcomes of consolidation treatment with the PD-L1 antibody, durvalumab after concurrent chemoradiotherapy has become the standard of care for patients with unresectable LA-NSCLC.

Immune system integrity is vital for stimulating effective anti-tumor immune effects during immunotherapy (13). However, lymphocytes, as part of systematic immune cells, are extremely sensitive to radiation (14) due to the direct irradiation of lymph nodes and to circulating lymphocytes (CLs) traversing through the radiation field (15). Radiation-induced lymphopenia (RIL) occurs in 40% to 70% of patients undergoing radiotherapy (16). The nadir of absolute lymphocyte counts (ALC) during radiotherapy is associated with poor survival in patients with NSCLC according to multiple studies (17-19), and a low ALC nadir during radiotherapy can also indicate a reduced response to immunotherapy for NSCLC (20,21). Thus, in addition to the routine toxicities caused by radiotherapy, RIL in immunotherapy must be further investigated. Accordingly, the present study evaluated the effects of target volumes on RIL during radiotherapy through several parameters reflecting lymphocyte counts with the aim of further testing the potential benefits of CTV omission in anti-tumor immunotherapy.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-523).

Methods

Patients and treatment

All patients with NSCLC treated with definitive chemoradiotherapy in our institution between 2013 and 2018 were reviewed, and patients were selected in accordance with the following criteria: pathologically confirmed stage III NSCLC according to the American Joint Committee on Cancer (8th edition); treated with concurrent chemoradiotherapy (at least 2 cycles of platinum-based chemotherapy delivered during radiotherapy, at least 4 cycles if weekly chemotherapy protocols were delivered); radiotherapy performed with IMRT technique at 60 Gy total dose in 30 fractionations at 2 Gy per fraction once per day for 5 fractions per week; and PTV generated directly from GTV without CTV expanding (PTV-g hereinafter), as previously described (10). Exclusion criteria was as follows: patients with other tumor at diagnosis of NSCLC; patients receiving neoadjuvant, adjuvant, and palliative radiotherapy; patients not treated with concurrent chemoradiotherapy; radiotherapy prescription was not IMRT with the dose of 60 Gy in 30

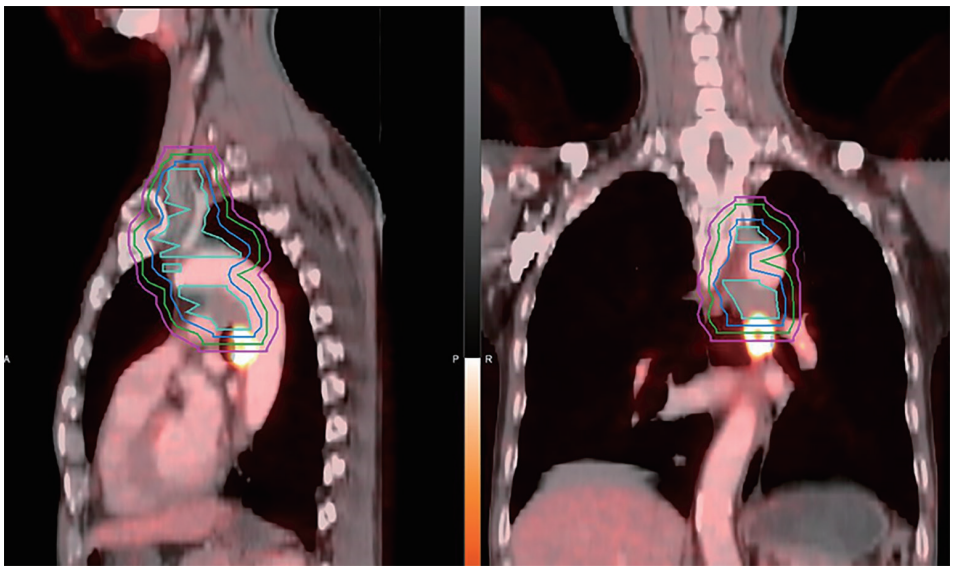

Figure 1 Failure location is based on the original treatment planning from coronal and sagittal CT) scans, with matched post-treatment PET scans demonstrating recurrence. The locations are visible as bright spots on the fusion PET/CT scans. The lines of different colors from inside to outside represent GTV, CTV, PTV-g, and PTV-c, respectively. The pictures are from a case of PTV-g-c recurrence in which the center of the recurrence lesion is located between PTV-g and PTV-c. CT, computed tomography; PET, positron emission tomography; GTV, gross tumor volume; CTV, clinical target volume; PTV-g, planning target volume without CTV expansion; PTV-c, planning target volume with CTV expansion.

fractions; and patients who didn't complete the prescribed dose of chemoradiotherapy were also excluded. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Fudan University Shanghai Cancer Center (No. IRB#090978-2). Patient consent was waived because this study was a retrospective study.

Radiotherapy and follow-up

Patients' immobilization, radiation target contour and generation, dose requirements for treatment planning, and radiation techniques are described elsewhere (10). In general, the patients were followed up every 3 months for 2 years, every 6 months for 2–5 years, and once per year thereafter. During follow-up, the medical history, physical examination, chest computed tomography (CT) scans, and abdominal ultrasound or CT of the patients were assessed. Other tests, such as brain magnetic resonance imaging, bone scanning, and positron emission tomography (PET) scans were performed at the discretion of the treating physicians. Follow-up through telephone interviews was also used as a supplementary measure.

Patterns of failure analysis

In this analysis, we focused on the patterns of first failure, which were first divided into local, regional, and distant failures. Local failure included the primary tumor and the originally metastatic regional lymph nodes (LNs); regional failure included the regional LN areas, including hilar, mediastinal, and supraclavicular LNs, but excluded the originally metastatic regional LNs; and everywhere else was considered distant failure. We then classified the local and regional (local-regional) failures into inside PTV-g (IN-PTV-g), between PTV-g and PTV-c (PTV-g-c), and outside PTV-c (OUT-PTV-c). PTV-c was generated as previously described (10): we first created a virtual CTV by expanding 6 and 8 mm from GTV for squamous cell carcinoma and adenocarcinoma, respectively; 3 and 5 mm for the nodes with a <2 and ≥2 cm short axis, respectively, with the vertebral bodies, trachea, proximal bronchial trees, heart, large vessels, and esophagus being manually modified for exclusion; and PTV-c was then created from virtual CTV by considering the set-up error factors and organ motion (the margin was the same as that from GTV to PTV-g expansion for each patient). A schematic of the target volumes is shown in *Figure 1*.

Local–regional failures were assessed on the basis of serial post-treatment chest CT. PET-CT and/or directed biopsy were performed for suspicious cases. Failure was scored from the first radiographic appearance of abnormality. Local-regional failure locations were further identified by fusing the current CT or PET-CT scans with the treatment plan CT scan (*Figure 1*).

Correlation between RIL and target volumes

Patients with medical records for weekly complete blood counts (CBC) during radiotherapy were retrospectively reviewed. All CBC has followed the CBC SOP (standard operating procedure) of the laboratory in our center. The nadirs of absolute lymphocyte count (ALC) during definitive radiotherapy were recorded, along with the nadir of white blood cell (WBC), neutrophil (NE), and monocyte (MO) counts. Three relative lymphocyte indexes during radiotherapy were also investigated: percentage of lymphocytes (LY%) nadir, ALC/NE baseline, and ALC/ALC baseline (within 3 weeks before the start of radiotherapy, $ALC_{RT}/ALC_{Baseline}$). GTV and PTV-g volumes were acquired from the Pinnacle treatment planning system version 8.0 (Philips Medical Systems, Fitchburg, WI, USA) to test the relationship between target volumes and these parameters.

Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 19.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were summarized by descriptive statistics, including means, standard deviations, medians, and ranges. Categorical variables were tabulated by frequency and percentage. Overall survival (OS) and recurrence-free survival (RFS) rates were analyzed by Kaplan–Meier analysis. OS was defined as the time from the start of radiotherapy to death due to any cause. RFS was documented as the time from the start of radiotherapy to first recurrence or death. Patients alive at the time of last follow-up were allocated that date. Spearman's correlation coefficients (r) were used to assess univariate associations between laboratory minimums with the log 10 of GTV and the log 10 of PTV-g being used to convert GTV and PTV-g into a normal distribution.

Results

Patient demographics and OS

A total of 63 patients were enrolled in our study. The characteristics of 63 patients are shown in *Table 1*. One patient was lost to follow-up for OS. For the remaining 62 patients, the median follow-up time was 20.2 months (range, 3.6–68.3 months), the median OS was 33.0 months [95% confidence interval (CI): 25.3–40.7 months], and the 1-, 2-, and 3-year survival rates were 82.3%, 60.4%, and 46.3%, respectively. The Kaplan-Meier estimate of OS is shown in *Figure 2A*.

Patterns of first failure

A total of 3 patients were lost to follow-up for recurrence status. The median RFS for the remaining 60 patients was 9.0 months (95% CI: 6.4–11.6 months), and the 1-, 2-, and 3-year RFS rates were 41.1%, 25.6%, and 25.6%, respectively. The Kaplan-Meier curve of RFS is shown in *Figure 2B*. Among these patients, 46 (76.7%) patients experienced recurrences, with 18 (30.0%), 5 (8.4%), and 33 (55.0%) experiencing local recurrence, regional failure, and distant failure, respectively. The numbers for each type of failures are shown in *Figure 3A*. The distribution of the local–regional failure is illustrated in *Figure 3B*. For the 21 patients who experienced local–regional recurrences at the first failure, 16, 6, and 1 patient encountered IN-PTV-g, OUT-PTV-c, and PTV-g-c failures, respectively. Representative scans illustrating the case with PTV-g-c failure are shown in *Figure 1*.

Association between lymphopenia during radiotherapy and radiation target volumes

A total of 56 patients with accessible continuous weekly blood test results during radiotherapy were included. The median volumes of GTV and PTV-g were 118.32 cm^3 (range, 14.48–393.96 cm^3) and 424.12 cm^3 (range, 74.18–1,033.58 cm^3), respectively. A significant inverse correlation was observed between ALC nadir during radiotherapy and log 10 (GTV) (r=–0.346, P=0.015) and log 10 (PTV-g) (r=–0.487, P<0.001) in these patients (*Figure 4*). However, no significant associations were found between GTV and PTV-g with the nadir of total WBC, NE, or MO counts during radiotherapy (all P>0.05, *Figure S1*). This finding suggests that lymphocytes were more sensitive to chemoradiotherapy than other peripheral blood cells, a result that is consistent with that of previous studies (8,14). For the other parameters that reflect lymphocyte counts during radiotherapy, the LY% nadir, ALC/NE nadir, and ALCRT/ALCB were all significantly correlated with log 10 (PTV-g), whereas LY% nadir and ALC/NE nadir were

Table 1 Patient baseline demographic data and treatment status

Patient characteristics	N=63, N (%)
Age (years)	
Median	62
Range	31–78
>70	10 (15.9)
Gender	
Male	50 (79.4)
Female	13 (20.6)
Clinical stage	
IIIA	25 (39.7)
IIIB	30 (47.6)
IIIC	8 (12.7)
T stage	
1	10 (15.9)
2	21 (33.3)
3	19 (30.2)
4	13 (20.6)
N stage	
1	5 (7.9)
2	39 (61.9)
3	20 (31.7)
Histological subtype	
Squamous cell	31 (49.2)
Adenocarcinoma	21 (33.3)
NSCLC NOS	11 (17.5)
Smoking status	
Non-smokers	22 (34.9)
Ever/current smokers	41 (65.1)
Chemotherapy protocol	
Docetaxel + platinum	30 (47.6)
Pemetrexed + platinum	21 (33.3)
Paclitaxel + platinum	12 (19.0)

NSCLC, non-small cell lung cancer; NOS, not otherwise specified. Data are presented as number of patients (N), with percentages in parentheses.

correlated with log 10 (GTV) (*Figure 5*).

Discussion

In the current analysis, we found that only 1 out of 60 (1.7%) patients experienced subclinical regional (PTV-g-c) recurrence after concurrent chemoradiotherapy at 60 Gy radical radiation dose for LA-NSCLC, even without the intended CTV implementation. This finding clinically supports our previous dosimetric study (10), which demonstrated the feasibility of omitting CTV in this scenario. We also found that RIL was associated with the target volumes, especially PTV-g, with larger volumes linked to severe RIL, indicating that the target volume reduction through CTV omission could maintain the integrity of the immune system that may potentially favor immunotherapy.

CTV omission did not compromise the control inside the subclinical region for several reasons. First, from the radiobiological perspective, the doses necessary to control the subclinical lesions of common epithelial tumors are lower than those used to eradicate gross tumors (8,9). Thus, the low peripheral doses around gross tumors may sufficiently control the subclinical foci, which has been proven by our dosimetric study (10). The second reason can be deduced from the present status of treatment failure patterns for LA-NSCLC treated with concurrent chemoradiotherapy. Consistent with many previous studies (22-24), we found that major failure occurred in the distant areas, which may shadow over the local–regional recurrences; most local–regional recurrences occurred with IN-PTV-g rather than subclinical regions, implying that the current standard radiation dose for LA-NSCLC (60 Gy per 30 fractions) may be insufficient in eliminating gross tumors. Thus, in such a state, using radical radiation doses to treat the invisible subclinical lesions even when the visible gross tumors cannot be well controlled is excessive. Third, the concurrently used chemotherapy may be more effective for the subclinical lesions than the gross tumors. This speculation is based on the evidence that shows adjuvant chemotherapy has long-term survival benefit in patients with NSCLC (25-28).

Combining radiotherapy and immunotherapy can revolutionize cancer treatment. The success of the

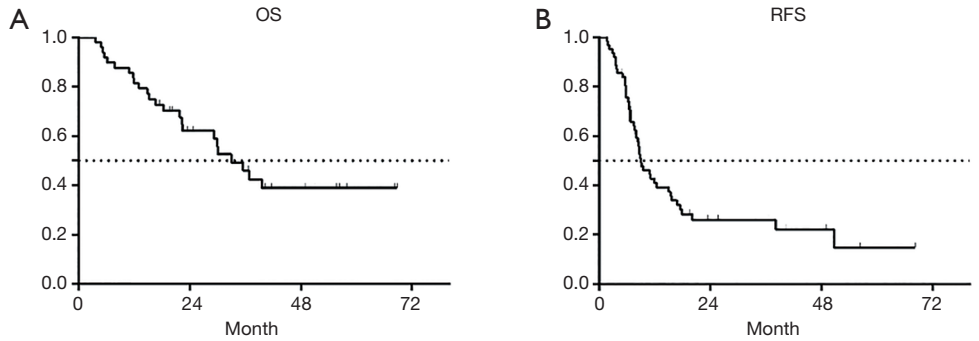

Figure 2 Kaplan-Meier curves for OS and RFS. (A) Kaplan-Meier plots for OS. (B) Kaplan-Meier plots for RFS. OS, overall survival; RFS, recurrence-free survival.

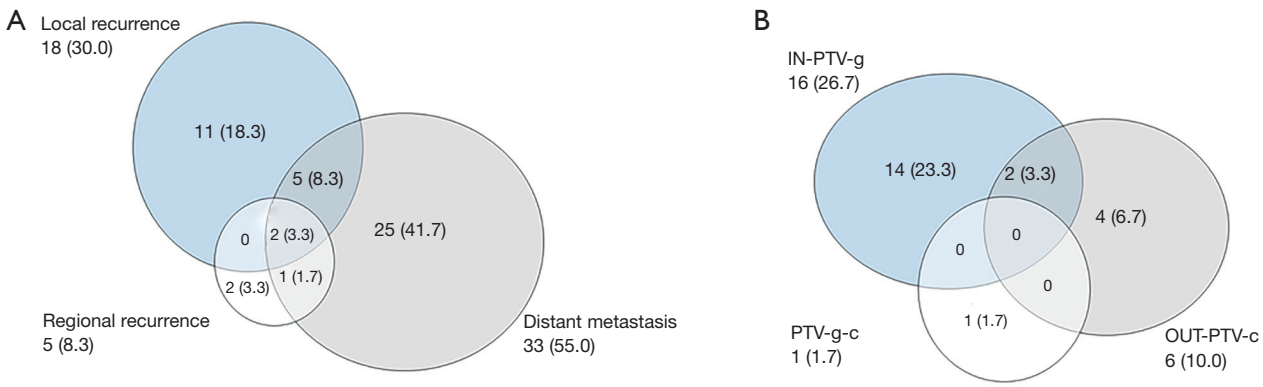

Figure 3 General and local-regional patterns of first failure are shown in A and B, respectively. Data are presented as the number of patients, with the percentages (shown in parentheses) relative to a total number of 60 patients (who had accessible follow-up data of local–regional recurrence).

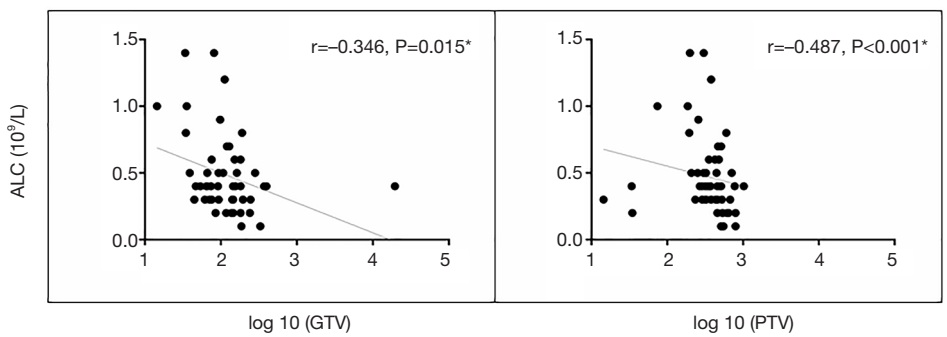

Figure 4 Correlations among ALC nadirs during radiotherapy and log 10 [GTV (cc)] and log 10 [PTV-g (cc)]. Spearman's correlation coefficients and corresponding P values are shown. A significant inverse correlation was observed between the ALC nadir during radiotherapy and log 10 (GTV) (r=–0.346, P=0.015), and log 10 (PTV-g) (r=–0.487, P<0.001). *, significantly correlated. ALC, absolute lymphocyte count; GTV, gross tumor volume; PTV-g, planning target volume without CTV expansion; r, correlation coefficient.

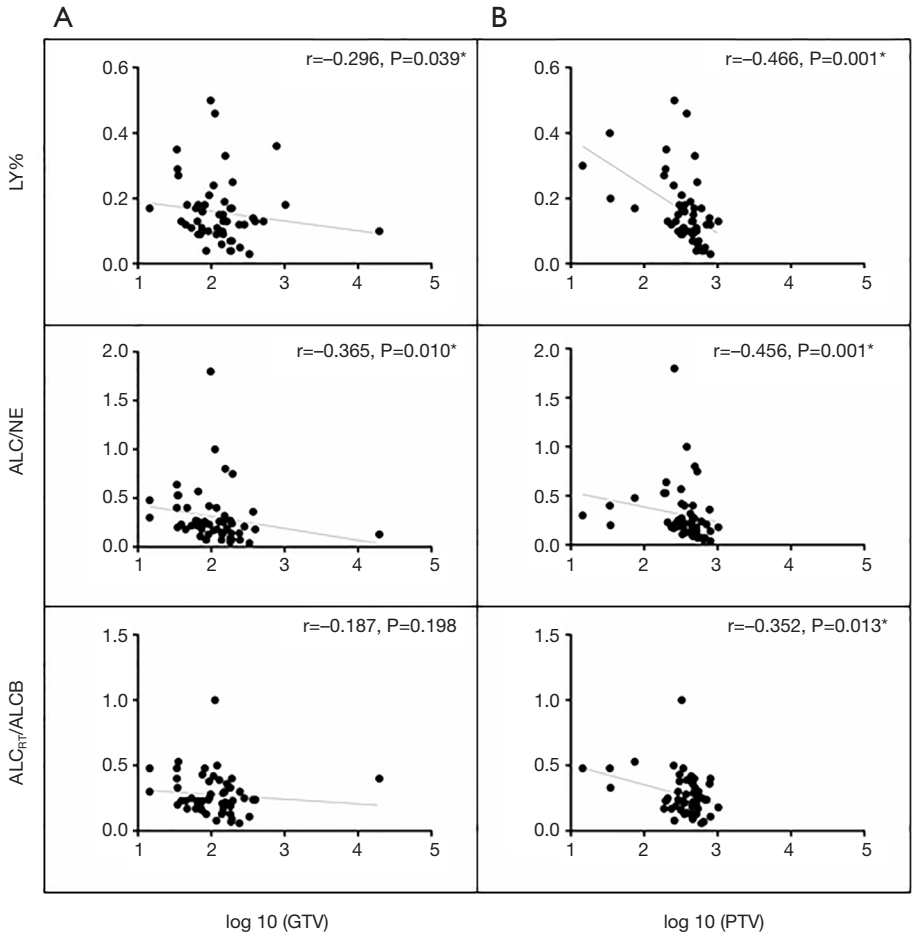

Figure 5 Correlations among the LY% nadir, ALC/NE nadir during radiotherapy, ALCRT/ALCB with log 10 [GTV (cc)] (A) and log 10 [PTV-g (cc)] (B). Spearman's correlation coefficients and corresponding P values are shown. *, significantly correlated. LY%, percentage of lymphocytes; NE, neutrophil; ALC, absolute lymphocyte count; GTV, gross tumor volume; r, correlation coefficient; PTV-g, planning target volume without CTV expansion.

PACIFIC trial (12) confirms the synergistic effects of radiotherapy and immunotherapy among patients with LA-NSCLC. However, radiotherapy is a double-edged sword for immunotherapy. In the PACIFIC trial (12), although severe side effects (≥ grade 3), such as pneumonitis, were not increased by the immunotherapy involved, the total toxicities (all grades) were higher in the combination treatment group. The synergistic interaction between immunotherapy and thoracic irradiation in increasing the risk of pulmonary and cardiac toxicities has also been proven in a series of preclinical models (29,30). As a result, routine toxicities must be continuously investigated in immunotherapy. The original intention of omitting the GTV-to-CTV expansion is to decrease the radiation volume and thus deliver less radiation dose to adjacent normal tissues. This goal has been achieved from the dosimetric perspective (10) and must be similarly applicable when immunotherapy is involved. Radiation exposure also suppresses the immune system, and RIL is especially evident in such conditions. Lymphocytes are important cellular components for immune response, and several studies have revealed that the tumor response to PD-1/PD-L1 blockade mainly results from recruiting the periphery effective lymphocytes to invade tumors (31). Therefore, we tested the peripheral blood lymphocyte counts during radiotherapy and their associations with target volumes with the aim to elucidate the influences of radiation target volumes to the immune system function. We found that both GTV and PTV were significantly related to lymphopenia during radiotherapy, with larger

volumes associated with severe lymphopenia. This finding is consistent with a previous report with a larger scale of patients (19). We also found that PTV was more sensitive than GTV to lymphopenia, a conclusion arrived at on the basis of the differences of Spearman's correlation coefficient (r) values between GTV and PTV (*Figures 4* and *5*). This result arose probably because the variability in PTV was greater than in GTV owing to the change in radius of GTV being cubed when generating PTV. In addition, most tissues between GTV and PTV were normal tissues, where many CLs and normal lymphoid tissues were irradiated during the period. Thus, omitting CTV to reduce PTV could better protect the immune function in radiotherapy, thereby favoring immunotherapy.

In our previous dosimetric study (10), we also tested the simultaneous integrated boost (SIB) technique that enables the intended simultaneous delivery of different doses to different areas of the treatment volume. We found that SIB could improve dose distribution compared with the CTV omission plan for the dose-sparing to the normal tissues while maintaining the adequate doses to the treatment targets. The SIB technique is also feasible in clinical settings for LA-NSCLC (32-36). However, the doses required to eradicate subclinical diseases were mainly derived empirically from preclinical research works (8,9,37) and only few retrospective studies with different dose deliveries (32-36) (the required doses may be lower or higher than 45–50 Gy). Thus, we cannot provide specific recommendations for the SIB technique on the basis of the aforementioned dosimetric study (10), and the present study suggests that further investigation is warranted.

Among the limitations of this study were its retrospective nature, with the associated biases, and its single-center single-arm study with a relatively small sample size. Furthermore, the immunotherapy involved after concurrent chemoradiotherapy is the current standard of care for unresectable LA-NSCLC. However, the treatment schedule of this study was completed before immunotherapy. Therefore, whether the results can be generalized to when immunotherapy is implemented is still questionable, while the beneficial effect of CTV omission for the immune system must be further evaluated in immunotherapy.

In conclusion, we found that CTV omission is feasible for LA-NSCLC treated with concurrent chemoradiotherapy by using the IMRT technique, and the failure inside the subclinical region was not compromised. The radiation volumes were associated with lymphopenia during radiotherapy, with larger volumes related to severe lymphopenia. This finding indicates that CTV omission IMRT should be considered in immunotherapy for further investigation.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-20-523). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Fudan University Shanghai Cancer Center (No. IRB#090978-2). Patient consent was waived because this study was a retrospective study.

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Supplementary

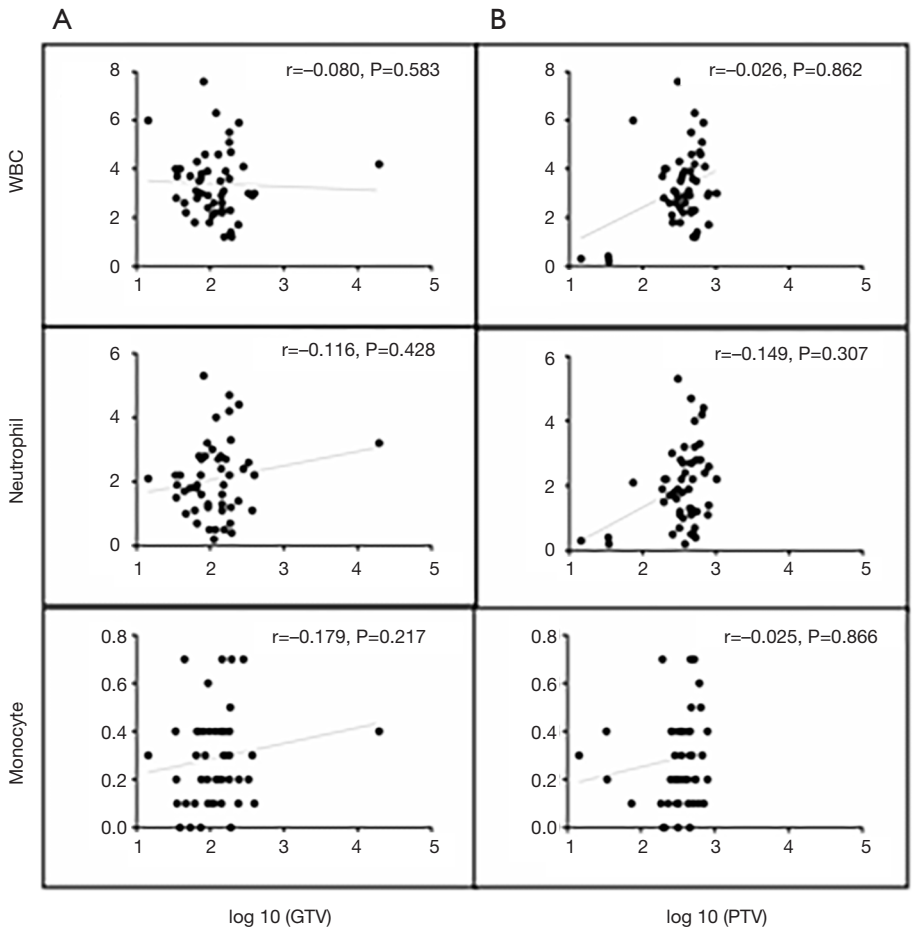

Figure S1 Correlations among nadirs of WBC, neutrophils, and monocytes during radiotherapy and log 10 [GTV (cc)] and log 10 [PTV-g (cc)]. Spearman's correlation coefficients and corresponding P values are shown. WBC, white blood cell; GTV, gross tumor volume; PTV-g, planning target volume without CTV expansion, r, correlation coefficient.