Original Article

The impact of different modalities of chemoradiation therapy and chemotherapy regimens on lymphopenia in patients with locally advanced non-small cell lung cancer

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Background: Chemotherapy and radiotherapy (RT) would induce lymphopenia, leading to a poor prognosis. This study investigated whether chemotherapy increased lymphopenia during RT and explored the impacts of different chemotherapy regimens on the lymphocyte counts of patients receiving RT.

Methods: Clinical parameters and lymphocyte data were collected from 215 patients with locally advanced non-small cell lung cancer (LA-NSCLC). Severe lymphopenia (SRL) was defined as an absolute lymphocyte count (ALC) of $\leq 0.2\times10^3$ cells/μL. Patient overall survival (OS) was analyzed using the Kaplan-Meier method. The predictors of SRL were extracted using univariate and multivariate regression analyses with backward likelihood ratio elimination.

Results: Compared with patients without SRL, patients with SRL with LA-NSCLC showed a poorer prognosis in terms of OS (P=0.003). Of the 215 patients, 130 underwent concurrent chemoradiotherapy (CCRT) and 85 underwent sequential chemoradiotherapy (SCRT). The OS was better in patients without SRL (in the CCRT group, P=0.01 and in the SCRT group, P=0.08). The mean ALCs for CCRT and SCRT did not differ significantly (P=0.27). The minimum ALC of CCRT was significantly lower than that of SCRT (P<0.0001). CCRT was a predictor of SRL (P=0.008). However, multivariate analysis showed that the different chemotherapy regimens were not predictors of SRL (all P>0.1).

Conclusions: In LA-NSCLC, the outcomes of patients with SRL were poorer than those without SRL. RT and chemotherapy were the main factors affecting SRL development, while different chemotherapy regimens were not significantly associated with lymphocyte counts in LA-NSCLC.

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Keywords: Locally advanced non-small cell lung cancer (LA-NSCLC); radiotherapy (RT); lymphopenia; chemotherapy regimen

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Introduction

Lung cancer remains the most common cancer, with the highest incidence and mortality rates worldwide (1). Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer, and many cases are already locally advanced when detected. A significant decrease in lymphocyte counts after irradiation in patients with locally advanced non-small cell lung cancer (LA-NSCLC) (2) was previously reported, consistent with other pan-cancers (3-5). Furthermore, radiation-induced lymphopenia (RIL) is associated with a poor prognosis (6-8).

The standard treatment for LA-NSCLC is concurrent chemoradiotherapy (CCRT) followed by maintenance immunotherapy. CCRT provides a better prognosis than sequential radiotherapy (RT) (9) and is widely used in LA-NSCLC. However, in real-world settings, some patients may not receive CCRT due to their willingness or physical condition. Sequential chemotherapy (SCRT) is another primary treatment option for LA-NSCLCs. However, whether CCRT and SCRT accelerate the decrease in lymphocyte counts or have significant effect during RT remains unknown. Tang *et al.* suggested that RT might play a more important role in the development of lymphopenia than CCRT (10). Previous studies have demonstrated that chemotherapy affects lymphocyte counts (11) even one year after chemotherapy (12). However, the effects of chemotherapy on lymphocyte counts during RT have rarely been investigated.

Chemotherapeutic drugs vary and their effects on lymphocytes have rarely been discussed in the literature. Nakamura *et al.* found no significant differences in lymphopenia severity among different regimens for NSCLC (13). Tang *et al.* reported no differences in hematological toxicities between cisplatin and carboplatin in patients receiving definitive platinum-based doublet chemoradiation for NSCLC (14). Furthermore, etoposide was associated with a higher frequency of grade 3 white blood cell (WBC), platelet, and neutrophil counts than paclitaxel or docetaxel; however, no difference was observed in lymphocyte count (14). Given the scarcity of relevant literature, this study focused on exploring the effects of RT, chemotherapy, and different chemotherapy regimens on lymphocytes.

This study included patients with LA-NACLC receiving intensity-modulated radiotherapy (IMRT) to determine the association between different chemoradiotherapy modalities (CCRT and SCRT) and lymphopenia during IMRT. We also assessed the impact of different chemotherapy regimens on the lymphocyte counts of patients receiving RT. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-60/rc).

Highlight box

Key findings

- Our study demonstrated that radiotherapy (RT) and chemotherapy were the main factors affecting severe lymphopenia development, while different chemotherapy regimens were not significantly associated with lymphocyte counts in locally advanced non-small cell lung cancer (LA-NSCLC).

What is known and what is new?

- The standard treatment for LA-NSCLC is concurrent chemoradiotherapy (CCRT) followed by maintenance immunotherapy. However, in real-world settings, some patients may not receive CCRT due to their willingness or physical condition. Whether CCRT and sequential chemoradiotherapy (SCRT) accelerate the decrease in lymphocyte counts or have significant effect during RT remains to be determined.
- This study determined the association between different chemotherapy modalities (CCRT and SCRT) and lymphopenia during intensity-modulated RT and assessed the impact of different chemotherapy regimens on the lymphocyte counts of patients receiving RT.

What is the implication, and what should change now?

- In clinical, both RT and chemotherapy should be considered, which could induce lymphopenia, leading to poorer survival in LA-NSCLC.

Methods

Patients

Lymphocyte counts were determined in patients with LA-NSCLC [American Joint Committee on Cancer (AJCC) version 8 Stage II–III] who received chemoradiotherapy from June 2014 to May 2019 at Fudan University Shanghai Cancer Center and Shanghai Proton and Heavy Ion Hospital.

The patient inclusion criteria were: patients (I) aged 18–75 years; (II) with Eastern Cooperative Oncology Group (ECOG) scores of 0–2; (III) who were receiving radical RT with a dose/fraction of 60 Gy/30 fx for about 6–7 weeks; (IV) with NSCLC pathological type; (V) who were receiving CCRT or SCRT.

The exclusion criteria were a pathological diagnosis of small-cell lung cancer, having a second primary tumor, having received RT, chronic or acute inflammation, and hematological diseases affecting lymphocytes.

Before receiving IMRT, the patients underwent physical, hematological, and computed tomography (CT) or positron emission tomography/CT (PET/CT) examinations at baseline. Brain magnetic resonance imaging (MRI) was used to exclude brain metastases, while abdominal CT or B-ultrasound was used to exclude distant metastases.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The procedures were approved by the Institutional Review Board of Fudan University Shanghai Cancer Center and Shanghai Proton and Heavy Ion Hospital (No. 220706EXP-01), which waived the requirement for informed consent owing to the retrospective nature of the study.

RT

The patients underwent CT-based treatment simulation in the supine position to obtain images of the neck, chest, and upper abdomen with a 5-mm slice thickness. The gross tumor volume (GTV) was contoured based on CT and (or) PET/CT, and the clinical target volume (CTV) was expanded from the GTV by margins of 0.5–0.7 cm. Planning target volume (PTV) was determined by adding a 0.7-cm margin to the CTV. IMRT treatment plans were designed using the Philips Pinnacle treatment planning system (TPS) (version 8.0, Philips, Fitchburg, WI, USA) with 6 MV photon coplanar beams based on a direct machine parameter optimization (DMPO) algorithm. Cone-beam CT was performed on the first day of RT to confirm tumor location. The dosimetric parameters were exported from the TPS for further analysis.

Chemotherapy

The patients were administered platinum-based doublet chemotherapy. The main CCRT regimens were paclitaxel (135 mg/m^2, d1), pemetrexed (500 mg/m^2, d1), and docetaxel (75 mg/m^2, d1) with cisplatin (25 mg/m^2, d1–d3) administered every 3 or 4 weeks. The main SCRT regimens were paclitaxel (135 mg/m^2, d1), pemetrexed (500 mg/m^2, d1), and docetaxel (75 mg/m^2, d1) with cisplatin (25 mg/m^2, d1–d3) every 3 or 4 weeks, and gemcitabine (1,250 mg/m^2, d1, d8) with cisplatin (25 mg/m^2, d1–d3) every 21 days. Carboplatin was replaced in patients who could not tolerate cisplatin.

Clinical data collection

Patient clinical information and blood test results were collected from the medical record system of our center. Data on patient sex, age, tumor laterality, tumor location, pathological type, ECOG score, TNM stage, and chemotherapy regimen were collected for analysis. The mode of chemoradiotherapy and absolute lymphocyte count (ALC) during IMRT were recorded. The weekly average and minimum ALC values were extracted for subsequent analyses. Lymphocyte reduction was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, with severe lymphopenia (SRL) defined as an ALC of $\leq 0.2\times10^3$/μL during RT. During RT, the number of weekly tests should be ≥1 time.

Statistical analyses

The clinical parameters analyzed in this study included sex, age, ECOG status, tumor laterality, tumor location, pathological type, TNM stage, and chemotherapy regimen. The independent sample *t*-test was used for continuous variables, the Wilcoxon rank-sum test was used for ordered categorical variables, and the chi-squared test was used for binary and unordered categorical variables. Overall survival (OS) was defined the time as from receiving RT to death, while PFS was as receiving RT to disease progression. The Kaplan-Meier method was used to draw survival curves, and the log-rank test was used to analyze the survival differences between the groups of patients with and without SRL as well as the OS and progression-free survival (PFS) for the groups of patients receiving CCRT and SCRT. Univariate

and multivariate logistic regression analyses were performed to identify independent factors associated with SRL. In the multivariate logistic regression, models were created with backward likelihood ratio elimination, using a P value of >0.1 for the removal of variables. All analyses were conducted using R 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as P<0.05.

Results

This study included a total of 215 patients with NSCLC who received 60 Gy/30 fractions of IMRT. The baseline characteristics of the enrolled patients are shown in *Table 1*. The patients included 34 women (15.8%) and 181 men (84.2%) with a median age of 58.9 years (range, 30–75 years). Seventeen patients (7.9%) had an ECOG score of 0, and 198 patients (92.1%) had an ECOG score of 1–2. The pathological types included adenocarcinoma (ADC) (83 patients, 38.6%) and non-ADC (132 patients, 61.4%). Seventeen (7.9%) and 198 (92.1%) patients had stage II and III disease, respectively.

In this study, 130 patients underwent CCRT and 85 underwent SCRT. Among the patients who received CCRT, 34 (26.2%) were administered docetaxel as a platinum-containing dual-drug chemotherapy regimen [docetaxel cisplatin/carboplatin (DP)], 57 (43.8%) received pemetrexed as a platinum-containing dual-drug chemotherapy regimen [pemetrexed cisplatin/carboplatin (PP)], and 39 (30.0%) received paclitaxel as a platinum-containing dual-drug chemotherapy regimen [paclitaxel cisplatin/carboplatin (TP)]. Among the patients who received SCRT, 16 (18.8%) received DP chemotherapy, 36 (42.4%) received PP chemotherapy, 18 (21.2%) received TP chemotherapy, and 15 (17.6%) received gemcitabine-based platinum-based dual-drug chemotherapy [gemcitabine cisplatin/carboplatin, (GP)].

Overall, the median PFS times in patients without and with SRL were 10.5 and 8.3 months (P=0.08), while the median OS was 27.8 and 16.9 months (P=0.003), respectively (*Figure 1*). The median OS for patients receiving CCRT and SCRT were 24.7 and 22.4 months respectively (P=0.89), while the PFS was 10.7 and 9.1 months respectively (P=0.07) (Figure S1). Among patients receiving CCRT, the median OS was 28.8 months for those without SRL and 17.5 months for those with SRL. Among patients receiving CCRT, those without SRL had a longer OS compared to patients with SRL (P=0.01) (*Figure 2A*). Among patients receiving SCRT, the median OS times for those without and with SRL were 27.8 and 16.3 months, respectively. While the OS of patients receiving SCRT without SRL was not statistically significant than that in patients with SRL (P=0.08) (*Figure 2B*). For PFS in CCRT group, the median PFS was 11.0 months for those without SRL and 8.3 months for those with SRL (P=0.06) (*Figure 2C*). For PFS in SCRT group, the median PFS was 9.8 months for those without SRL and 8.0 months for those with SRL. There was no difference between the two groups in PFS (P=0.24) (*Figure 2D*). The characteristics for all cases with and without SRL were shown in Table S1.

In all, the mean ALC of total patients was 0.78×10^3 cells/μL during RT, while the minimum ALC was 0.41×10^3 cells/μL. The dynamic changes in the weekly mean and minimum lymphocyte counts in patients receiving CCRT or SCRT are shown in *Figure 3*. The mean ALC for CCRT and SCRT did not differ significantly (P=0.27) (*Figure 3A*). However, the minimum ALC after CCRT was significantly lower than that after SCRT (P<0.0001) (*Figure 3C*). The changes in the corresponding lymphocyte counts between the two groups did not differ significantly (all P>0.05) (*Figure 3B*,*3D*). At weeks 3 and 4, the lymphocyte counts in the SCRT group were slightly higher than those in the CCRT group; however, the difference was not statistically significant. Moreover, the lowest value during RT was observed at week six in both groups. The decreasing percentages of lymphocytes in the CCRT and SCRT groups were 67.9% and 67.6%, respectively. Additionally, CCRT was a predictor of SRL (P=0.008) (*Table 2*).

The changes in lymphocyte counts caused by different chemotherapy regimens are shown in *Figure 4*. Lymphocyte counts in patients receiving CCRT did not differ among chemotherapy drugs. At baseline, the number of lymphocytes in patients treated with the PP regimen was higher than that in patients treated with other chemotherapy regimens; however, no significant differences were observed between the groups (P=0.06). Patients receiving SCRT demonstrated no significant differences in lymphocyte counts between chemotherapy regimens (all P>0.05, excluding that P=0.02 in the 4^{th} week in *Figure 4B*). Univariate and multivariate analysis showed that the different chemotherapy regimens were not predictors of SRL (all P>0.1) (*Table 2*). Univariate and multivariate regression analyses also showed that chemotherapy regimens were not factors for SRL after CCRT (Table S2) or SCRT (Table S3).

Our analysis of the dose volumes (Figure S2) showed that SCRT was higher than CCRT.

Table 1 Baseline characteristics of the patient cohort

Characteristics	All (N=215)	CCRT (N=130)	SCRT (N=85)	P
Sex, n (%)				>0.99
Female	34 (15.8)	21 (16.2)	13 (15.3)	
Male	181 (84.2)	109 (83.8)	72 (84.7)	
Age (years), median [range]	58.9 [30–75]	58.7 [30–75]	59.2 [37–75]	0.69
ECOG, n (%)				0.69
0	17 (7.9)	9 (6.9)	8 (9.4)	
1 or 2	198 (92.1)	121 (93.1)	77 (90.6)	
Tumor laterality, n (%)				0.02
Left	90 (41.9)	46 (35.4)	44 (51.8)	
Right	125 (58.1)	84 (64.6)	41 (48.2)	
Tumor location, n (%)				0.64
Lower lobe	40 (18.6)	26 (20.0)	14 (16.5)	
Upper and middle lobe	175 (81.4)	104 (80.0)	71 (83.5)	
Pathological type, n (%)				0.51
ADC	83 (38.6)	53 (40.8)	30 (35.3)	
Non-ADC	132 (61.4)	77 (59.2)	55 (64.7)	
TNM, n (%)				>0.99
II	17 (7.9)	10 (7.7)	7 (8.2)	
III	198 (92.1)	120 (92.3)	78 (91.8)	
Chemotherapy before RT, n (%)				<0.001
No	42 (19.5)	38 (29.2)	4 (4.7)	
Yes	173 (80.5)	92 (70.8)	81 (95.3)	
Concurrent chemotherapy cycles, n (%)				<0.001
0	85 (39.5)	0 (0.0)	85 (100.0)	
1–3	102 (47.4)	102 (78.5)	0 (0.0)	
5–6 (weekly)	28 (13.0)	28 (21.5)	0 (0.0)	
First-line chemotherapy cycles*, median [range]	3.79 [1–8]	3.62 [2–6]	3.89 [1–8]	0.24
Chemotherapy regimen, n (%)				<0.001
DP	50 (23.3)	34 (26.2)	16 (18.8)	
GP	15 (6.9)	0 (0.0)	15 (17.6)	
PP	93 (43.3)	57 (43.8)	36 (42.4)	
TP	57 (26.5)	39 (30.0)	18 (21.2)	
PTV (mm^3), median [SEM]	538 [281]	556 [289]	511 [268]	0.24

*, first-line chemo cycles: 5–6 (weekly) concurrent chemotherapy were replaced with 2 cycles in this analysis. ECOG, Eastern Cooperative Oncology Group; ADC, adenocarcinoma; RT, radiotherapy; DP, docetaxel cisplatin/carboplatin; GP, gemcitabine cisplatin/carboplatin; PP, pemetrexed cisplatin/carboplatin; TP, paclitaxel cisplatin/carboplatin; PTV, planning target volume; SEM, standard error of measurement; CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy.

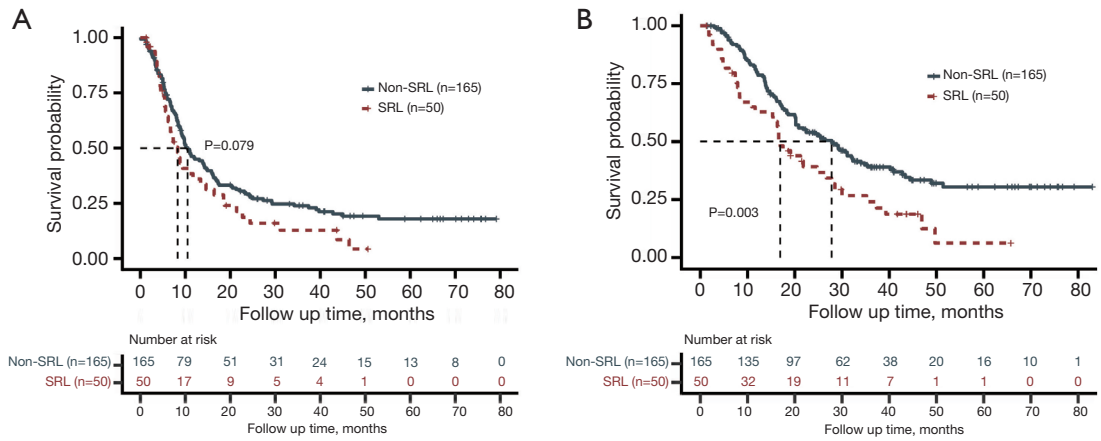

Figure 1 The survival analysis of non-SRL and SRL in LA-NSCLC. (A) PFS; (B) OS. SRL, severe lymphopenia; LA-NSCLC, locally advanced non-small cell lung cancer; PFS, progression-free survival; OS, overall survival.

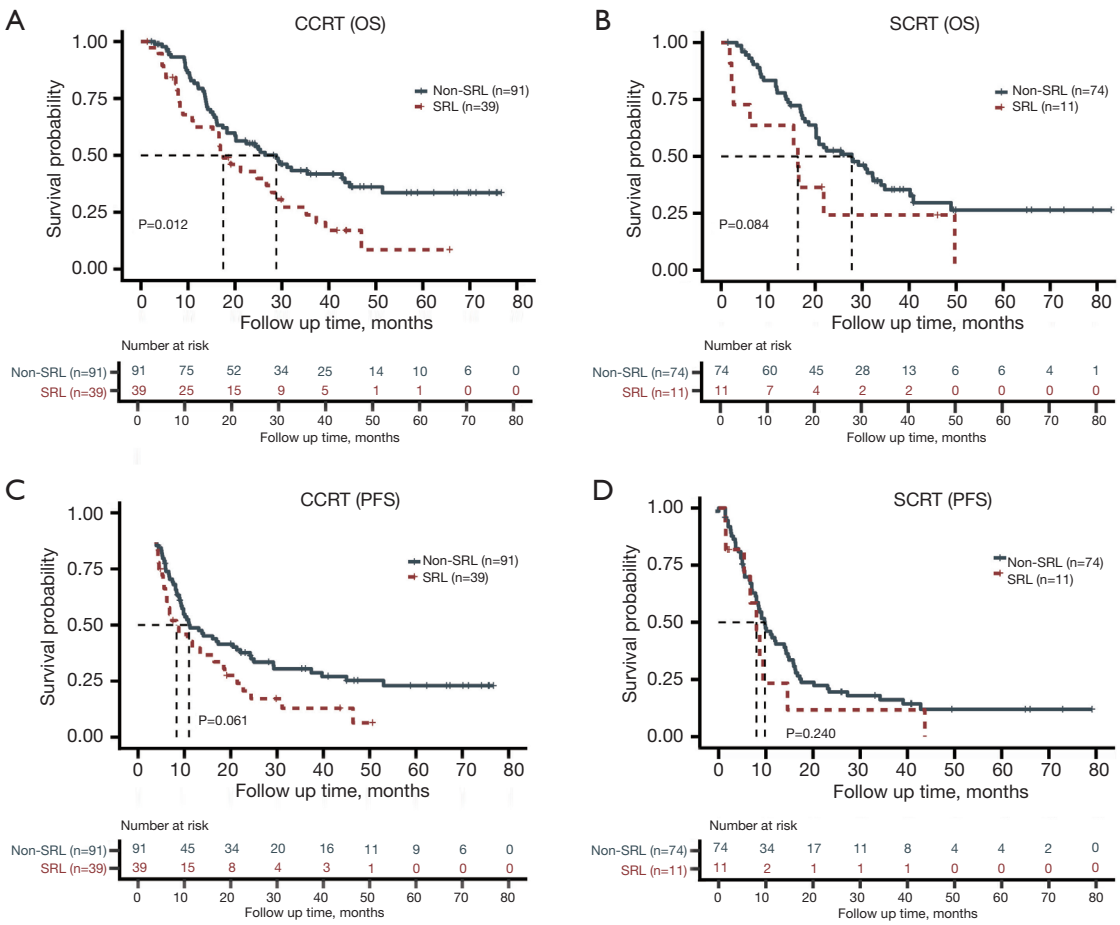

Figure 2 OS and PFS for different chemoradiotherapy modalities according to SRL status. (A) Comparison of OS between non-SRL and SRL in CCRT; (B) comparison of OS between non-SRL and SRL in SCRT; (C) comparison of PFS between non-SRL and SRL in CCRT; (D) comparison of PFS between non-SRL and SRL in SCRT. CCRT, concurrent chemoradiotherapy; OS, overall survival; SRL, severe lymphopenia; SCRT, sequential chemoradiotherapy; PFS, progression-free survival.

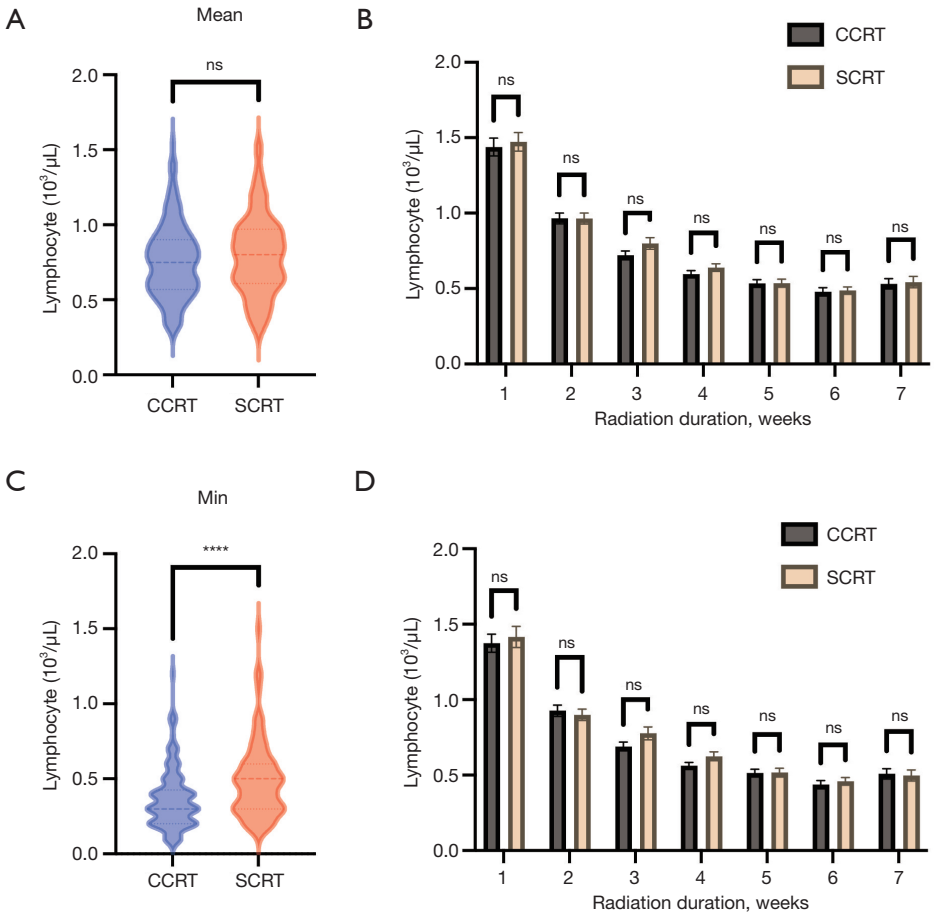

Figure 3 Comparisons of lymphocyte counts between CCRT and SCRT and dynamic changes in weekly lymphocyte counts during RT. (A) Mean value; (B) weekly mean; (C) minimum value; (D) weekly minimum. ****, P<0.0001. CCRT, concurrent chemoradiotherapy; SCRT, sequential chemoradiotherapy; ns, no significant statistical difference.

Discussion

The results of our present study showed that CCRT may lead to a more significant decrease in lymphocyte count compared to SCRT. However, different chemotherapy regimens had no significant effect on lymphocyte counts during RT.

Previous studies have investigated the impact of lymphocytes in predicting tumor responses and patient prognosis. In breast cancer (15), lung cancer (10,16-18) and esophageal cancer (19), RIL predicts a worse prognosis, which is consistent with our results. Our study results suggest that SRL during RT is correlated with poorer OS and PFS after comprehensive therapy.

Prior chemotherapy was the most significant risk factor for decreased peripheral lymphocyte count. It might cause lymphopenia at the start of adjuvant RT, which could negatively affect long-term patient outcomes (20). Chen *et al.* reported that RT was the only significant factor associated with lymphocyte depletion (21). A previous study also reported the influence of RT on lymphocyte count (2). Both chemotherapy and RT alone kill lymphocytes. However, the potential synergistic effect of the combination of these two therapies has rarely been investigated. In terms of baseline characteristics, we observed no significant differences between patients who received CCRT and those who received SCRT.

Moreover, the mean ALCs of lymphocytes did not differ significantly between the two groups during RT; however, the minimum ALC in the CCRT group was higher than that in the SCRT group. In addition, we observed no significant differences in the minimum and average lymphocyte counts per week between the two modalities.

Table 2 Univariate and multivariate regression analysis for SRL

Characteristics	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P	OR (95% CI)	P
Gender (female *vs.* male)	0.813 (0.352–1.880)	0.63	–	–
Age (continuous)	1.018 (0.982–1.056)	0.33	–	–
Tumor laterality (left *vs.* right)	1.376 (0.715–2.648)	0.34	–	–
Tumor location (upper + middle lobe *vs.* lower lobe)	0.417 (0.199–0.873)	0.02	0.373 (0.172–0.809)	0.01
Pathology (non-ADC *vs.* ADC)	0.747 (0.393–1.418)	0.37	–	–
ECOG (0 *vs.* 1–2)	1.453 (0.400–5.273)	0.57	–	–
TNM (II *vs.* III)	5.262 (0.680–40.706)	0.11	–	–
Chemotherapy regimen (ref. DP)				
GP	0.226 (0.027–1.903)	0.17	–	–
PP	1.040 (0.467–2.320)	0.92	–	–
TP	1.031 (0.425–2.501)	0.95	–	–
Chemoradiotherapy modality (SCRT *vs.* CCRT)	2.883 (1.381–6.019)	0.005	2.819 (1.311–6.059)	0.008
PTV (mm^3) (continuous)	1.002 (1.002–1.003)	0.002	1.002 (1.001–1.003)	0.002

SRL, severe lymphopenia; ADC, adenocarcinoma; ECOG, Eastern Cooperative Oncology Group; ref., reference group; DP, docetaxel cisplatin/carboplatin; GP, gemcitabine cisplatin/carboplatin; PP, pemetrexed cisplatin/carboplatin; TP, paclitaxel/carboplatin; SCRT, sequential chemoradiotherapy; CCRT, concurrent chemoradiotherapy; PTV, planning tumor volume; OR, odds ratio; CI, confidence interval.

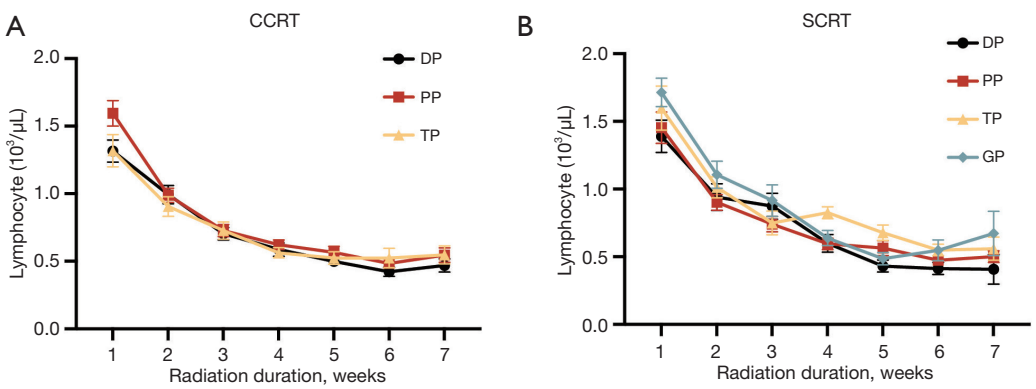

Figure 4 Weekly dynamic changes in lymphocyte counts in patients undergoing radiotherapy with different chemotherapy methods and protocols. (A) Lymphocyte of DP, PP, and TP regimens in CCRT; (B) lymphocyte of DP, PP, TP and GP regimens in SCRT. All P>0.05. CCRT, concurrent chemoradiotherapy; DP, docetaxel cisplatin/carboplatin; PP, pemetrexed cisplatin/carboplatin; TP, paclitaxel/carboplatin; SCRT, sequential chemoradiotherapy; GP, gemcitabine cisplatin/carboplatin.

In patients who received SCRT, the significant decrease in lymphocyte count indicated that radiation might be the main cause of lymphopenia. The decreasing percentage of lymphocytes in CCRT was higher than that in SCRT, indicating that CCRT affected lymphocyte counts and might increase the number of lesions for lymphocytes during RT, consistent with Tang *et al.*'s findings (10). Therefore, compared to CCRT, RT might play a more significant role in lymphopenia development. CCRT has side effects on lymphocyte counts (10). Campian *et al.* reported that total lymphocyte counts (TLCs) were normal before therapy and did not change in most patients (85%) following neoadjuvant chemotherapy. However, after radiation, TCLs decreased by 67%, verifying that radiation exposure plays a major role in lymphopenia development (22). The results of the present study suggested that RT may be the primary cause of lymphopenia, although CCRT also had a significant effect on lymphopenia during RT.

Few studies have reported the impact of different chemotherapeutic drugs on lymphocyte changes. Tang *et al.* observed no differences between platinum-based agents. In addition, compared to paclitaxel and docetaxel, etoposide was significantly associated with decreased WBC, platelet, and neutrophil counts but not lymphocyte count (14). Moreover, we did not observe a difference in lymphocyte changes between different chemotherapeutic drugs. For patients receiving chemoradiotherapy, lymphopenia might be mainly caused by RT and that CCRT also affects decreasing lymphocyte counts. However, we observed no differences in lymphopenia between chemotherapy regimens.

Besides the modalities of chemoradiotherapy, our results revealed that tumor location and PTV were also significant risk factors for SRL. The tumor in the upper and middle lobe might more easily be causing SRL than the lower lobe. It might be due to the location of the heart and heavy vessels. However, in esophageal cancer, Zhou *et al.* thought lower tumor location was an independent predictor of treatment-related lymphopenia (23), which is different from our result. We thought this was also related to the plan and treatment principles of RT for different cancers. For PTV, it had been confirmed in a large number of literature that it was associated with SRL (16,24,25), which is consistent with our result.

Our study has several limitations. In this retrospective study, bias caused by missing data was inevitable. Furthermore, due to the lack of data on lymphocyte counts after RT, we could not analyze the difference in lymphocyte recovery between CCRT and SCRT. Maintaining immunotherapy is the standard treatment after chemoradiotherapy, few patients used maintaining immunotherapy before the official market approval in our country. We are preparing to delve deeper into this issue with a new group of the population in future research. In addition, changes in lymphocyte subsets should be analyzed. Hakim *et al.* reported that chemotherapy can influence $CD4^+$ T cell recovery (26). Therefore, the effects of CCRT and RT on lymphocyte subsets and their recovery warrant further study.

Conclusions

In LA-NSCLC, the outcomes of patients with SRL were poorer than those without SRL. RT and chemotherapy are the main factors affecting lymphocytopenia in patients with LA-NSCLC undergoing radical RT and chemotherapy; however, chemotherapy regimens are not the main factors affecting lymphocyte counts. Finally, CCRT may increase the severity of treatment-related lymphopenia during RT.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-60/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-60/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-60/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-60/coif). 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 procedures were approved by the Institutional Review Board of Fudan University Shanghai Cancer Center and Shanghai Proton and Heavy Ion Hospital (No. 220706EXP-01), which waived the requirement for informed consent owing to the retrospective nature of the study.

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