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BACKGROUND

Radiation-induced lymphopenia (RIL) correlates with poor prognosis in solid tumors. This study aimed to investigate the dynamic changes in absolute lymphocyte count (ALC) and evaluate the prognostic value of longitudinal ALC in pN2 non-small cell lung cancer (NSCLC) patients with postoperative radiotherapy (PORT).

RESULTS

- The mean age of patients was 54.87 years. Adenocarcinoma was the predominant histological subtype. All patients received four cycles of adjuvant chemotherapy and a median radiation dose of 50 Gy (**Table 1**).
- With a median follow-up of 104.63 months, the median OS had not been reached, with a robust 5-year OS rate of 75.8% (**Table 2**).

METHODS

This retrospective study was conducted on data from 172 NSCLC patients receiving PORT after radical surgery and adjuvant chemotherapy. ALCs were obtained before, weekly during, and after PORT until the 18-month follow-up. The optimal cut-off ALC were determined using the maxstat package in R. Survival rates were estimated using the Kaplan-Meier method and compared with the log-rank test. Mean ALC at different time points was compared by the t-test. Univariate and multivariable linear regression analyses were performed to evaluate the effect of ALC on overall survival (OS).

- ALC peaked before PORT (mean: $1.8 \times 10^9/L$). During PORT, a rapid decline occurred as early as week 1 (mean: $1.38 \times 10^9/L$; $P < 0.05$), continuing through week 2–5 and reaching a nadir at week 5 (mean: $0.7 \times 10^9/L$; $P < 0.001$).
- ALC recovered gradually after PORT. Grade 3–4 lymphopenia was absent before PORT, its incidence peaked at 25% by week 5 during PORT and stabilized at 1%–2% from 1 to 12 months post-RT (**Table 3**).
- Recovery of ALC to $\geq 1.0 \times 10^9/L$ (median, 2 months) or to baseline (median, 4 months) was not associated with improved OS.
- Greater ALC decline, higher pre-PORT ALC and higher 12-month post-RT ALC correlated with significantly favorable OS (all $P < 0.05$) (**Figure 1**).
- By comparing ALC at different time points, we found that greater ALC decline was associated with higher baseline ALC and superior long-term recovery (**Table 4**).

Table 3. ALC at different time points.

Time points	Median (IQR) ($\times 10^9/L$)	P-value vs Pre-PORT
Pre-PORT	1.77 (1.47-2.18)	—
1 week duringRT	1.38 (1.08-1.65)	< 0.05
2 weeks duringRT	1.07 (0.89-1.32)	< 0.05
3 weeks duringRT	0.85 (0.72-1.08)	< 0.001
4 weeks duringRT	0.77 (0.64-0.94)	< 0.001
5 weeks duringRT	0.62 (0.51-0.8)	< 0.001
1 week postRT	0.72 (0.53-0.9)	< 0.001
2 weeks postRT	0.72 (0.72-0.8)	< 0.001
3 weeks postRT	0.78 (0.7-0.89)	< 0.001
1 month postRT	1.08 (0.86-1.26)	< 0.05
2 months postRT	1.23 (1.06-1.42)	< 0.05
3 months postRT	1.39 (1.11-1.55)	< 0.05
4 months postRT	1.19 (1.03-1.43)	< 0.05
6 months postRT	1.22 (1.09-1.44)	< 0.05
7 months postRT	1.25 (1.06-1.52)	< 0.05
10 months postRT	1.23 (1.01-1.53)	< 0.05
12 months postRT	1.27 (0.99-1.57)	< 0.05

Table 4. ALC compared between the lesser- or greater-decline group

Time points	lesser-decline-group	greater-decline-group	P-value
Pre-PORT baseline	1.665	2.480	< 0.001
1 week postRT	0.590	0.970	< 0.05
1 month postRT	0.970	1.290	< 0.05
3 months postRT	1.450	1.650	0.2297
4 months postRT	1.160	1.480	< 0.05
6 months postRT	1.175	1.675	< 0.05
7 months postRT	1.195	1.570	< 0.001
10 months postRT	1.175	1.345	0.2962
12 months postRT	1.155	1.750	< 0.05

ABBREVIATIONS

NSCLC, non-small-cell lung cancer; ALC, absolute lymphocyte count; RT, radiotherapy; PORT, postoperative radiation; KPS, Karnofsky performance status; VATS, video-assisted thoracoscopic surgery; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; OS, overall survival; DFS, disease-free survival; DMFS, distant metastasis-free survival; LRRFS, locoregional recurrence-free survival; LRFS, local recurrence-free survival; RRFS, regional recurrence-free survival; NR, not reached; KM, Kaplan-Meier; SD, standard deviation; HR, hazard ratio; CI, confidence interval;

CONCLUSIONS

Peri-PORT ALC exhibited a trend of initial decrease followed by gradual recovery. Both pre-PORT ALC and 12-month post-RT ALC were predictive of OS, with 12-month post-RT ALC serving as an independent prognostic factor for OS, showing significant associations with DFS and LRRFS. These findings suggest that long-term recovery of lymphocyte and immune function following PORT is a key prognostic factor.

- Though pre-PORT ALC was not associated with disease-free survival (DFS), locoregional recurrence-free survival (LRRFS), or distant metastasis-free survival (DMFS) (**Figure 2**), **12-month post-RT ALC was significantly associated with DFS and LRRFS (all $P < 0.05$), with a protective trend for DMFS ($P=0.12$) (Figure 3).**
- In multivariable analysis, **12-month post-RT ALC remained an independent prognostic factor for OS (HR=0.255, 95% CI 0.068–0.958, $P=0.0429$)** after adjustment for sex, age, smoking status, histology, and T stage.

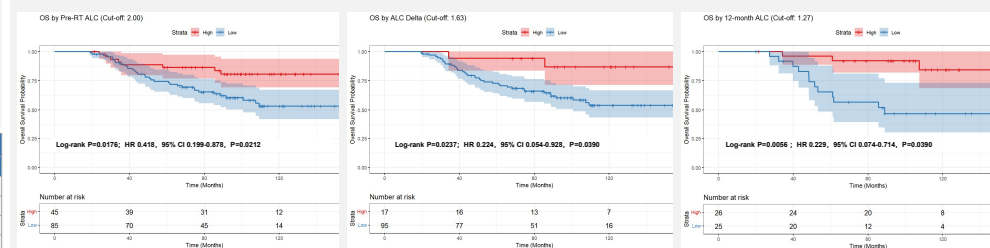


Figure 1 KM curves of OS in the patients grouped according to the optimal cut-off values of pre-RT ALC, ALC decline and 12-month post-RT ALC

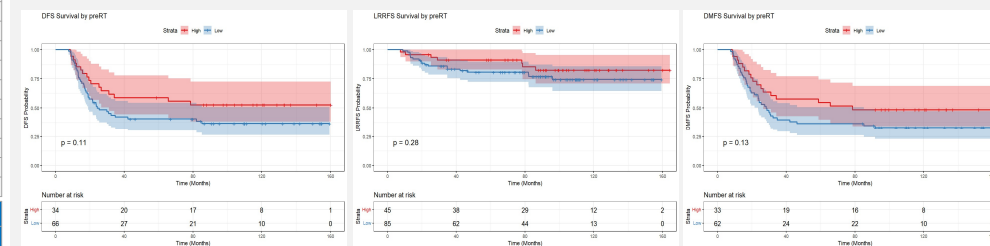


Figure 2 KM curves of LRRFS, DMFS and DFS in the patients grouped according to the optimal cut-off value of pre-RT ALC

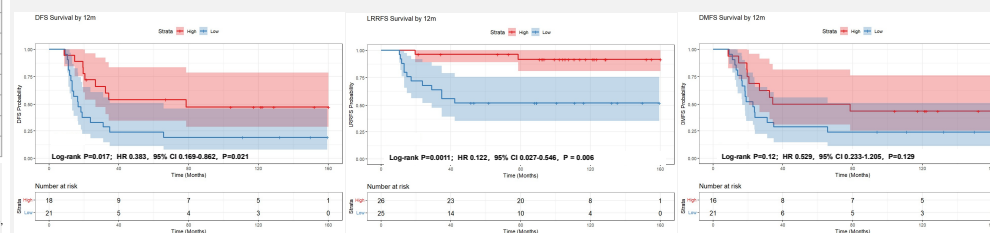


Figure 3 KM curves of LRRFS, DMFS and DFS in the patients grouped according to the optimal cut-off value (equal to median) of 12-month post-RT ALC

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