



Thoracic Duct irradiation-induced lymphopenia Compromised Long-term Survival of Patients With pN2 Non-small Cell Lung Cancer Receiving Postoperative Radiotherapy

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BACKGROUND

Radiation-induced lymphopenia (RIL) is a well-recognized factor for tumor control and survival in solid tumors. This study aimed to explore the correlation between radiation dose–volume parameters of lymphocyte-related organs at risk [LROAR, including lung, heart, pericardium, great vessels and thoracic duct (TD)] and long-term absolute lymphocyte count (ALC), prognosis in the pN2 non-small cell lung cancer (NSCLC) patients with postoperative radiotherapy (PORT).

RESULTS

- Clinical and treatment characteristics are presented in **Table 1**, and survival endpoints are shown in **Table 2**.
- Higher 12-month post-RT ALC correlated with significantly favorable OS (Log-rank $P=0.0056$; HR 0.229, 95% CI 0.074–0.714, $P=0.0390$), disease-free survival (DFS) and locoregional recurrence-free survival (LRRFS) (all $P < 0.05$), with a protective trend for distant metastasis-free survival (DMFS) ($P=0.12$) (**Figure 1**).
- 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.

Table 1. Clinical and treatment characteristics of the 172 patients with NSCLC.

Characteristics	Mean (SD)	Statistics (N=172)
Age (years)	54.87 (7.62)	
Sex, n (%)	Male	102 (59.3%)
	Female	70 (40.7%)
Smoking History, n (%)	Never	85 (49.4%)
	Ever	87 (50.6%)
KPS Score, n (%)	80	72 (41.9%)
	90	87 (50.6%)
	100	13 (7.6%)
Tumor Location, n (%)	Left Lung	70 (40.7%)
	Right Lung	102 (59.3%)
Surgical Approach, n (%)	Thoracotomy	88 (51.2%)
	VATS	84 (48.8%)
Radiotherapy Tech, n (%)	IMRT	126 (73.3%)
	VMAT	46 (26.7%)
Pathological Type, n (%)	Adenocarcinoma	132 (76.7%)
	Squamous Cell	33 (19.2%)
	Others	7 (4.1%)
Differentiation, n (%)	Well	3 (1.8%)
	Moderate	109 (63.4%)
	Poor	58 (33.8%)
Max Tumor Diameter (cm)	Mean (SD)	3.39 (1.78)
T Classification, n (%)	T1	40 (23.3%)
	T2	112 (65.1%)
	T3	19 (11.0%)
	T4	1 (0.6%)
Chemotherapy Cycles, n (%)	4	166 (96.5%)
	Others	6 (3.5%)
Radiation Dose (Gy)	50	139 (80.8%)
	50.4–64	33 (19.2%)

Table 2. Survival outcomes of the cohort.

Endpoint	Median survival time (months)	5-year survival rate (95% CI)
OS	NR	75.8% (69.6%–82.6%)
DFS	28.47	41.7% (34.0%–51.0%)
DMFS	28.8	39.1% (31.4%–48.6%)
LRRFS	NR	80.4% (74.6%–86.6%)
LRFS	153.1	66.7% (59.0%–75.5%)
RRFS	Not reached (NR)	86.4% (81.4%–91.7%)

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. Dose–volume parameters of lung, heart, pericardium, great vessels and thoracic duct were collected. The optimal cut-offs were determined using the maxstat package in R. Univariate and multivariable linear regression analyses were performed to evaluate the effect of dose–volume parameters on long-term lymphocyte and overall survival (OS). Spearman rank correlation analysis was used to select the dose–volume parameters with the strongest correlation with long-term lymphocyte. Survival rates were estimated using the Kaplan-Meier method and compared with the log-rank test.

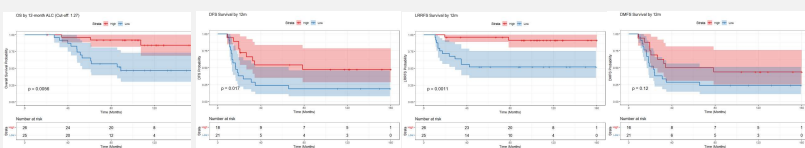


Figure 1 K-M curves of OS, LRRFS, DMFS and DFS in the patients grouped according to the optimal cut-off value (equal to median) of 12-month post-RT ALC

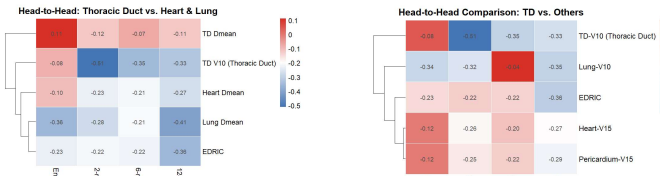
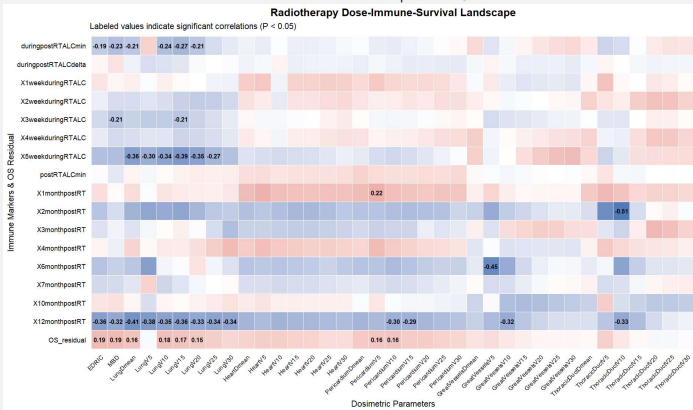


Figure 2 Pearson correlation analysis to evaluate the associations between 37 dosimetric parameters and ALC at various time points as well as OS residuals

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DISCLOSURES

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CONCLUSIONS

As a central hub for lymphocyte circulation, **TD exerts a more significant influence on long-term lymphocyte recovery and OS than other LROARs**. The impact of TD on OS is nearly entirely mediated by immune injury. **TD V10 remains an independent prognostic factor for OS and is also significantly associated with DMFS**.

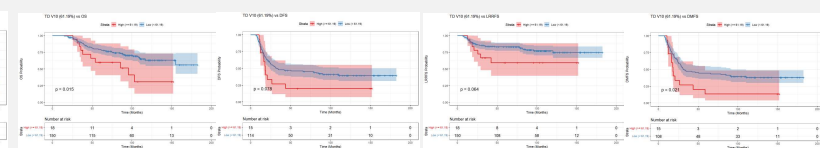


Figure 4 Kaplan-Meier curves of OS, DMFS, LRRFS and DFS in the patients grouped according to the optimal cut-off value of TD-V10

Mediation Pathway: Thoracic Duct - Immune - Survival Residuals

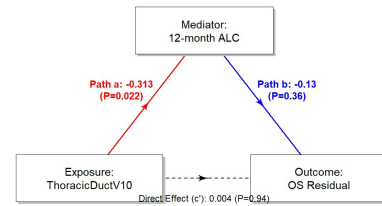


Figure 3 Mediation analysis: Elevated TD V10 impaired immune function and sustained low ALC at 12 months post-RT, mediating nearly 100% of its effect on OS residuals

Table 3. Multivariate Cox-regression analysis for overall survival adjusted for clinical covariates

Variable	Category	HR	95% CI	P-value
TD V10	Low-dose vs. High-dose (cut-off = 61.19)	2.11	1.04 – 4.29	0.039
Sex	Male vs. Female	1.52	0.86 – 2.70	0.148
Age	Continuous (per 1-year increment)	0.98	0.94 – 1.01	0.208
Histology	Adenocarcinoma	1.00 (reference)	—	—
	Squamous cell carcinoma	1.93	0.78 – 4.81	0.157
	Others	2.52	0.60 – 10.67	0.208
T stage	T1	1.00 (reference)	—	—
	T2	1.52	0.75 – 3.10	0.248
	T3-4	1.89	0.72 – 4.95	0.194

- Univariate analysis identified that the majority of dosimetric parameters for the lung, heart, pericardium, great vessels, and TD were significantly associated with OS. The most robust predictive windows were consistently within the low-to-moderate dose ranges (V10–V30).
- Pearson correlation analysis further revealed a close association between lung/TD dose parameters and post-PORT ALC. Notably, the 12-month post-RT ALC emerged as the most sensitive indicator. While multiple lung parameters and TD-V10 correlated with the 12-month post-RT ALC, only TD-V10 maintained a consistently high and stable correlation with ALC throughout the follow-up period from 2 to 12 months post-RT (**Figure 2**).
- Mediation analysis revealed that the thoracic duct exhibited the strongest immunosuppressive effect. TD-V10 showed a standardized coefficient of -0.313 for 12-month post-RT ALC, representing the strongest explanatory power among all dosimetric parameters. **Elevated TD-V10 impaired immune function and sustained low ALC at 12 months post-RT, mediating nearly 100% of its effect on OS residuals. The direct effect was nearly absent** ($P=0.943$) (**Figure 3**).
- Using an optimal threshold of TD-V10 = 61.19%, **patients in the low-dose group demonstrated a significantly reduced risk of death** (Log-rank $P=0.015$; HR = 2.291, 95% CI: 1.152–4.554, $P=0.0181$) compared to the high-dose group. Besides, **low TD-V10 was associated with significant improvements in DMFS** ($P < 0.05$), with positive trends observed for LRRFS ($P=0.064$) and DFS ($P=0.078$) (**Figure 4**).
- In a multivariate Cox regression model incorporating clinical factors, **TD-V10 remained an independent risk factor for OS** (HR=2.11, 95% CI: 1.04 - 4.29, $P=0.039$) (**Table 3**).

ABBREVIATIONS

NSCLC, non-small-cell lung cancer; TD, thoracic duct; 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;