INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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CLINICAL INVESTIGATION

Assessment of the Effective Dose to Immune Cells as an Independent Predictor of Durvalumab Response in Patients With Non-Small Cell Lung Cancer After Chemoradiotherapy: A Multicenter Study

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Received Aug 13, 2025; Revised Oct 6, 2025; Accepted for publication Nov 4, 2025

Purpose: The effective dose to immune cells—radiotherapy course—adjusted (EDRIC) is a dosimetry-based metric that estimates radiation exposure to circulating immune cells during radiotherapy. Elevated EDRIC is linked to lymphopenia, immune dysfunction, and poor tumor control in unresectable non-small cell lung cancer (NSCLC) after chemoradiation. However, it is unclear if EDRIC directly correlates with clinical outcomes and particularly with durvalumab consolidation, or if confounding factors drive this association. This study examined whether EDRIC independently correlates with progression-free survival (PFS).

Methods and Materials: Data from 286 patients with unresectable stage III NSCLC treated with definitive-intent radiation therapy between 2017 and 2024 at 3 tertiary centers were collected. EDRIC was calculated using mean heart, lung, body doses, and the number of fractions. Maximally selected rank statistics identified the optimal EDRIC cutoff for PFS. Univariable and multivariable Cox regression models were used to assess the association between EDRIC and clinical outcomes.

Results: Following the exclusion of patients who did not meet the inclusion criteria, 251 patients remained in the final analysis dataset. Using a cutoff of 9.57 Gy, 53 patients were classified as having high EDRIC and 198 as low EDRIC. Patients with low EDRIC had significantly longer median PFS (23.7 vs 11.7 months; hazard ratios (HR) 0.56; 95% CI, 0.39-0.82; $P = .003$). In a multivariable analysis including EDRIC, PD-L1 (programmed death ligand-1) expression, N stage (N3 vs N0-2), and PTV (planning target volume), lower EDRIC remained directionally associated with longer PFS (low vs high HR = 0.67; 95% CI, 0.45-1.01; $P = .053$), PD-L1 positive status remained associated with longer PFS (vs PD-L1 negative: HR = 0.64; 95% CI, 0.44-0.94; $P = .021$), and N3 was directionally adverse (HR = 1.56; 95% CI, 0.99-2.46; $P = .054$).

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Disclosures: MM reports grants from AstraZeneca; consulting fees from Amgen, Bayer, MSD, and Takeda; honoraria from MSD, AstraZeneca, Roche, Takeda, and Pfizer; meeting support from Pfizer and Roche; and participation on a Data Safety Monitoring Board for MSD, all outside the submitted work. SA reports honoraria from MSD, outside the submitted work. All other authors declare no conflicts of interest.

Data Sharing Statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ijrobp.2025.11.004.

Int J Radiation Oncol Biol Phys, Vol. 125, No. 2, pp. 511–520, 2026

https://doi.org/10.1016/j.ijrobp.2025.11.004

Conclusions: In patients receiving durvalumab after chemoradiation for unresectable stage III NSCLC, lower EDRIC was associated with longer PFS. This effect was limited to patients with positive PD-L1 tumors.

Introduction

Stage III non-small cell lung cancer (NSCLC) presents a clinical and therapeutic challenge. Although treatment goals are typically curative, many cases are unresectable and are managed with definitive chemoradiotherapy as the primary curative modality. The PACIFIC trial established chemoradiation followed by anti-PD-L1 (programmed death ligand-1) therapy as the non-surgical standard of care for stage III NSCLC. In this study, durvalumab significantly improved both progression-free survival (PFS) and overall survival (OS) compared with placebo.[1] At 5 years of follow-up, the median OS increased from 29.1 to 47.5 months with durvalumab.[2] Despite these impressive survival gains, the majority of patients eventually experience disease progression, with a progression rate of 67% at 5 years.[2]

The interaction between irradiation and immune checkpoint blockade (ICB) represents a significant area of investigation in contemporary radiation oncology research.[3-5] Although the synergistic potential of combining these therapies has garnered substantial attention, concerns regarding their immunosuppressive effects highlight potential negative implications for long-term treatment efficacy. The sensitivity of lymphocytes to radiation therapy (RT) is well established and has been observed within the tumor,[6,7] the lymphatic drainage surrounding it,[8,9] and the broader systemic blood circulation.[9-11] This phenomenon underscores the necessity of considering immune modulation when evaluating combined therapeutic strategies. The recent PACIFIC-2 trial, evaluating concurrent durvalumab administration with chemoradiotherapy (CRT), illustrates this point.[12] In contrast to the original PACIFIC trial, in which durvalumab was administered as consolidation therapy after the completion of CRT and demonstrated notable PFS and OS benefits, PACIFIC-2 failed to achieve positive outcomes.[13] These findings suggest that CRT may compromise the immune system's capacity to respond effectively to immune checkpoint inhibitors such as durvalumab, warranting careful consideration in future research and clinical practice.

The effective dose of immune cells (EDIC) represents a summarized measure of RT dose received by immune cells within the systemic circulation. It integrates the mean radiation doses administered to the heart, lungs, and total body.[11] Studies in patients with NSCLC undergoing CRT have shown that elevated EDIC levels correlate with diminished survival rates[11] and heightened incidences of post-RT lymphopenia.[14,15] These observations are particularly concerning given that consolidation therapy with durvalumab has become the standard of care in this patient population, whereas available data on the impact of EDIC in those receiving ICB consolidation remain limited.[9,10] Furthermore, it remains unclear whether EDIC independently predicts clinical outcomes or merely reflects other contributing factors such as gross tumor volume or the extent of lymphatic involvement.

Before EDIC can be integrated into clinical practice, more robust evidence is required regarding its impact on outcomes, especially among patients treated with ICB. In this study, we aim to perform an analysis on a large cohort of patients who have undergone definitive CRT followed by durvalumab consolidation, with the goal of verifying the role of EDIC in treatment stratification and patient management.

Methods and Materials

Patients

Demographic, clinical, and pathological data were collected from the electronic medical records of all unresectable patients with stage III NSCLC treated with definitive-intent radiotherapy with concurrent chemotherapy between 2017 and 2024 at 3 university-affiliated tertiary medical centers. Inclusion criteria included treatment with intensity-modulated RT in conventional or hypofractionated regimens with concurrent chemotherapy (at least 1 cycle), patients who received at least 1 cycle of durvalumab consolidation and available radiotherapy metric data. Exclusion criteria included patients who received definitive radiotherapy with no concurrent chemotherapy, progressed before starting durvalumab, or had missing data. Patients with stage I-II who were treated with definitive radiotherapy followed by durvalumab were also excluded. Lymphocyte levels were assessed from routine blood counts taken within 1 week before or after the completion of CRT.

Calculation of EDRIC

The effective dose to immune cells−radiotherapy course −adjusted (EDRIC) is a revised, patient-specific metric derived from EDIC. It incorporates the number of radiation fractions to provide a more individualized estimate of immune cell exposure. EDRIC was calculated according to the model developed by Jin et al[11] and modified by Ladbury et al[14] using the mean heart dose (MHD), mean lung dose (MLD), mean body dose, and the number of fractions. The calculation formula is presented in Figure 1. All dosimetric data were extracted from treatment planning systems.

$$\text{EDRIC} = 0.12\text{xMLD}+0.08\text{xMHD}+[0.45+0.35\text{x}0.85\text{x}\left(\frac{\#\text{ of fractions}}{45}\right)^{0.5}]\text{xMBD}$$

Fig. 1. EDRIC formula. *Abbreviations*: EDRIC = effective dose to immune cells; MBD = mean body dose; MHD = mean heart dose; MLD = mean lung dose.

Statistical methods

The primary endpoint was PFS, defined as the time from durvalumab initiation to documented disease progression or death by any cause, whichever occurred first. Patients without an event were censored at the date of last follow-up. The secondary endpoint was OS, defined as the time from durvalumab initiation to death by any cause, with patients censored at the date of last follow-up. Maximally selected rank statistic was used to determine the optimal EDRIC cutoff. Using the identified cutoff, patients were categorized as having either high EDRIC or low EDRIC.

We performed 5-fold cross-validation to internally validate the cutoff identified. In each iteration, the EDRIC cutpoint was reselected in the 80% training data using the maximally selected log-rank statistic and then applied to the 20% test fold to estimate a Cox hazard ratios (HR) with Wald 95% CI and a log-rank *P*value. We summarized threshold stability (range, median, and proportion within ±0.5 Gy of identified cutoff) and effect robustness (fold-specific HR and % with HR < 1); test-fold group sizes were reported for context.

As an additional internal validation approach, we modeled EDRIC as a continuous variable using Cox proportional hazards regression with restricted cubic splines (4 knots) to assess linearity of the dose-response relationship. Nonlinearity was formally tested using the Wald test for the nonlinear spline terms.

Survival curves were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. HR and 95% CI were calculated using Cox proportional hazards regression models. Univariable Cox regression analyses were performed to identify factors associated with PFS and OS. Variables associated with PFS in the univariable

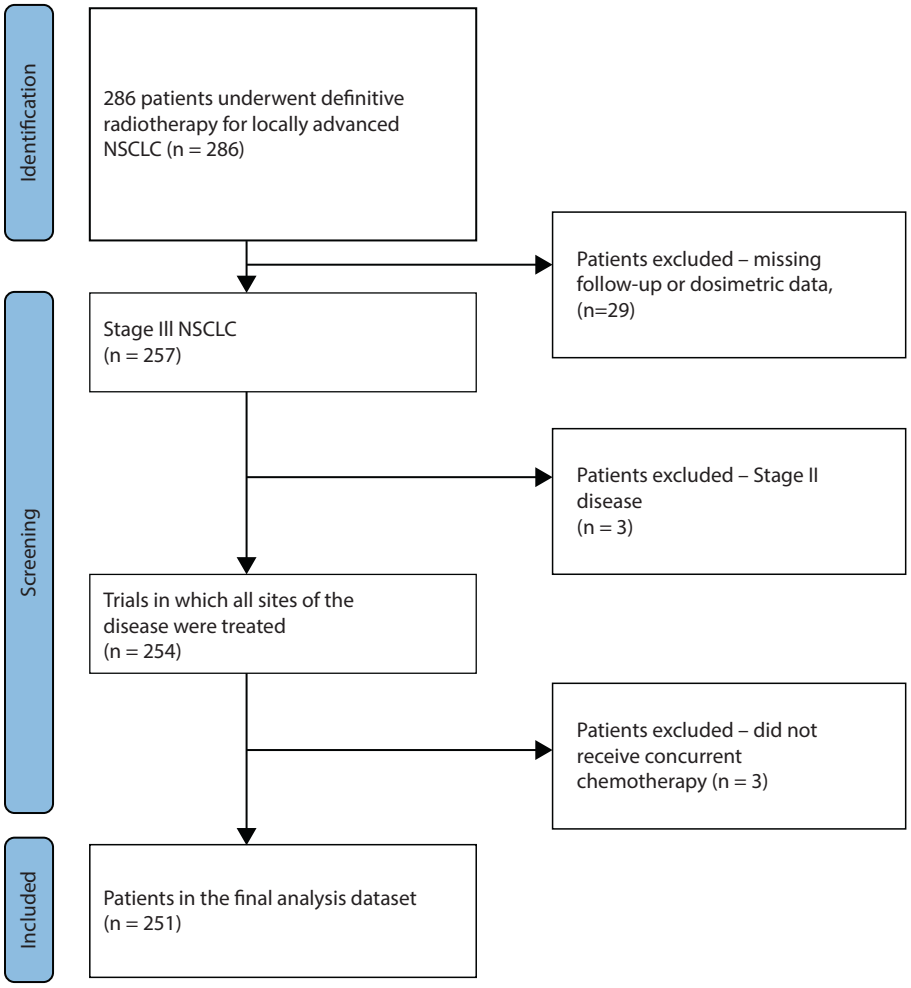

Fig. 2. Flowchart. *Abbreviation*: NSCLC = non-small cell lung cancer.

analysis, along with clinically relevant factors considered potential confounders were included in multivariable Cox regression models. Associations between categorical variables were assessed using the χ^2 test and Fisher's exact test. Linear regression analyses were conducted to evaluate the relationship between EDRIC and lymphocyte counts before and after CRT. A *P*value < .05 was considered statistically significant. Statistical analyses were performed using R version 4.4.3 software.

Results

Baseline characteristics and EDRIC

Between June 2017 and October 2024, a total of 286 patients with locally advanced NSCLC who underwent definitive radiotherapy were identified. All had received at least 1 dose of consolidation durvalumab. Thirty-five patients were excluded from the final analysis: 3 with stage II disease, 3 who did not receive concurrent chemotherapy, and 29 with missing follow-up or dosimetric data, leaving 251 patients in the final analysis dataset (Fig. 2). The median age was 74 years, and the majority were men (65%) and current or former smokers (87%). Stage IIIA disease was present in 55% of patients, and 45% had stage IIIB-IIIC disease. Squamous cell carcinoma histology was observed in 38% of cases, nonsquamous in 62% of cases. PD-L1 expression was negative in 27%, positive (Tumor propotion score >1%) in 44%, and unknown in 29%. The median EDRIC was 7.12, and the mean was 7.41. Using the maximally selected rank statistic, the optimal cutoff point for EDRIC based on PFS was 9.57 Gy. Based on this threshold, 53 patients were classified as having high EDRIC and 198 as low EDRIC. Baseline characteristics differed between the 2 groups. Compared with patients with high EDRIC, those with low EDRIC were younger, had a higher proportion of N0 disease and a lower proportion of N3 disease, and showed trends toward a higher percentage of PD-L1−negative tumors and more stage IIIA disease (Table 1).

Internal validation of the EDRIC cut-point

In 5-fold cross-validation with reselection of the threshold in each training fold, the training-derived EDRIC cut-points ranged from 8.54 to 10.01 Gy (median 9.53 Gy; IQR, 8.74-9.57 Gy). Three of fivefolds (60%) reselected a cut-point within ±0.5 Gy of the identified 9.57 Gy. In held-out test folds, the effect favored lower EDRIC in 4/5 folds (HR < 1), with a mean fold-specific HR of 0.78; none of the fold-specific tests was statistically significant (all $P \geq .161$), consistent with small test-fold high EDRIC groups (n_high 8-16 vs n_low 33-41). These results support a stable decision region in the 9 to 10 Gy range and a consistent risk gradient favoring lower EDRIC; we therefore retain 9.57 Gy for the primary analyses (see Supplementary material for details).

Table 1 Baseline characteristics

	Low EDRIC N = 198* (%)	High EDRIC N = 53* (%)	*P* value†
Age (y)	71 ± 7	75 ± 2	.003
Sex			
Male	130 (66)	34 (64)	.800
Female	68 (34)	19 (36)	
Smoking			
No	24 (12)	6 (11)	>.900
Yes	162 (82)	44 (83)	
Unknown	12 (6)	3 (6)	
PD-L1			
Negative	59 (30)	10 (19)	.051
Positive (>1%)	79 (40)	31 (58)	
Unknown	60 (30)	12 (23)	
Histology			
Nonsquamous	118 (60)	36 (68)	.600
Squamous	78 (39)	17 (32)	
Unknown	0	2 (1)	
Stage			
IIIa	114 (58)	23 (43)	.066
IIIb-c	84 (42)	30 (57)	
T stage			
1-2	78 (39)	22 (42)	.500
3-4	105 (53)	25 (47)	
Unknown	15 (8)	6 (11)	
N stage			
0	29 (15)	2 (4)	.029
1	4 (7)	4 (7)	
2	133 (67)	34 (64)	
3	24 (12)	13 (25)	
Dose			
High (>66 Gy)	21 (11)	5 (9)	.800
Standard (60-66 Gy)	177 (88.7)	48 (91)	

Abbreviations: EDRIC = effective dose to immune cells. PD-L1= programmed death-ligand 1
* n (%); Mean ± SD.
† Pearson's χ^2 test; Fisher's exact test; Wilcoxon rank sum test.

As an orthogonal internal validation, we modeled EDRIC continuously. Results showed a near-linear association (per 1 Gy HR = 1.05; 95% CI, 1.00-1.12; $P = .068$) with formal testing for nonlinearity yielding $P = .24$ (Wald $\chi^2 = 2.88$, df = 2). This indicates a stable risk gradient across the 9 to 10 Gy region and supports the prespecified 9.57-Gy threshold as a clinically convenient decision point rather than a data-mined optimum.

Clinical outcome by derived EDRIC grouping

Median follow-up time was 44.7 months. The median PFS for the entire cohort was 20.7 months (14.2-25.2), and the 3-year PFS rate was 40% (95% CI, 33%-47%). In a subgroup analysis based on the EDRIC level, the median PFS was 23.7 months (95% CI, 16.97-40.5) for patients with low EDRIC and 11.7 months (95% CI, 8.53-18.5) for patients with high EDRIC. This difference was statistically significant (HR = 0.57; CI, 0.39-0.83; P = .004) (Fig. 3). The median OS for the entire cohort was 48.4 months (95% CI, 39.1-NR), and the 3-year OS rate was 61% (95% CI, 55-69). In a subgroup analysis based on the EDRIC level, the median OS was not reached (NR) for patients with low EDRIC (95% CI, 42.06-NR), while it was 37.3 months (95% CI, 27-NR) for patients with high EDRIC. This difference was not statistically significant (HR 0.68; 95% CI, 0.43-1.06; P = .088) (Fig. 4).

PD-L1 expression and EDRIC

In the PD-L1 negative group, 59 (85.5%) had low EDRIC and 10 (14.5%) had high EDRIC, whereas in the PD-L1 positive group, 79 (71.8%) had low EDRIC and 31 (28.2%) had high EDRIC. In the PD-L1 positive subset, PFS was significantly longer for the low EDRIC group compared with the high EDRIC group (23.8 vs 11.7 months, respectively; HR, 0.54; 95% CI, 0.32-0.92; P = .024) (Fig. 5A). This difference was not statistically significant for patients with negative PD-L1 status (9.7 vs 13.3 months; HR, 1.07; 95% CI, 0.50-2.27; P = .9) (Fig. 5B).

Lymphocytes and EDRIC

A linear regression analysis was conducted to examine the relationship between EDRIC, pre- and post-CRT absolute lymphocyte count (ALC). The association between EDRIC and pre-CRT ALC was not statistically significant (estimate = 0.0684, P = .507) with R^2 = 0.00183. Analysis of the association between EDRIC and post-CRT ALC revealed a significant inverse relationship so that high EDRIC was associated with lower post-CRT lymphocytes values (estimate = −0.162, P < .001) with R^2 = 0. 0686.

Univariable and multivariable analysis

On univariable analysis for PFS, positive PD-L1 status (HR, 0.67; 95% CI, 0.46-0.97; P = .032) and low EDRIC (compared with high EDIRC; HR, 0.57; 95% CI, 0.39-0.83; P = .004) were associated with prolonged PFS. N3 disease, when compared with N0-2, was associated with shorter PFS (HR, 1.72; 95% CI, 1.10-2.67; P = .016). Pre-CRT ALC showed no association with PFS whether modeled continuously (HR = 1.02; 95% CI, 0.80-1.32; P = .90), by quartiles (Q2 HR = 1.21; Q3 HR = 1.14; Q4 HR = 0.96; all vs Q1), or using a threshold of <1000/μL (HR = 1.07; 95% CI, 0.49-2.35; P = .90). In the univariable analysis for OS, only N2 disease (vs N0; HR, 0.57; 95% CI, 0.34-0.97; P = .039) and younger age (HR, 1.05; 95% CI, 1.01-1.08; P = .011) were significantly associated with improved survival. A trend toward prolonged OS was observed in patients who received standard radiation doses of 60 to 66 Gy in 2 Gy daily fractions versus patients who received high

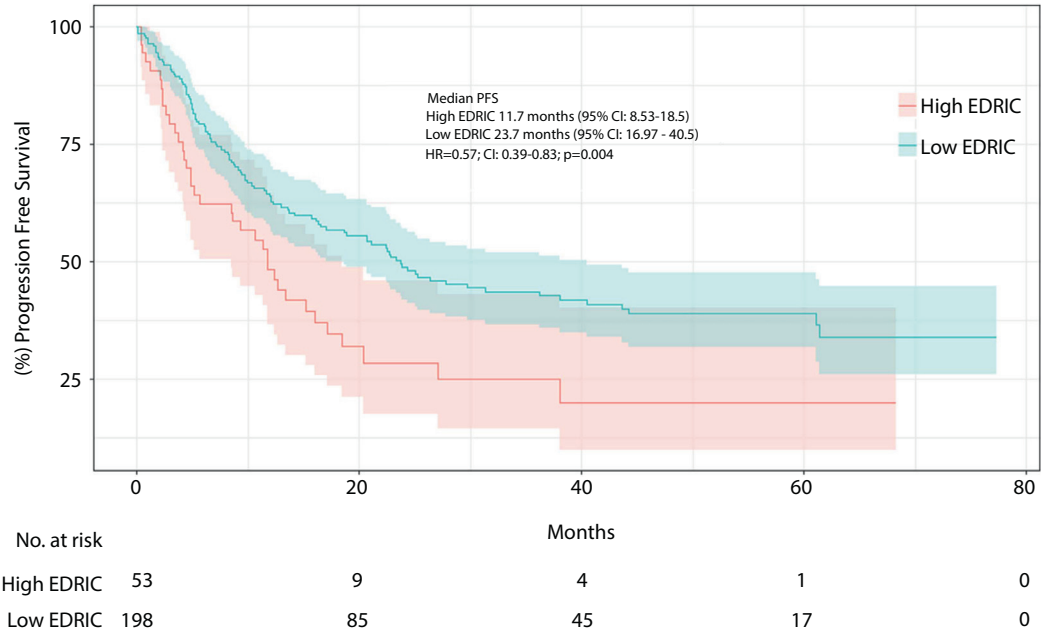

Fig. 3. Progression-free survival by EDRIC. *Abbreviations*: EDRIC = effective dose to immune cells; HR = hazard ratios; PFS = progression-free survival.

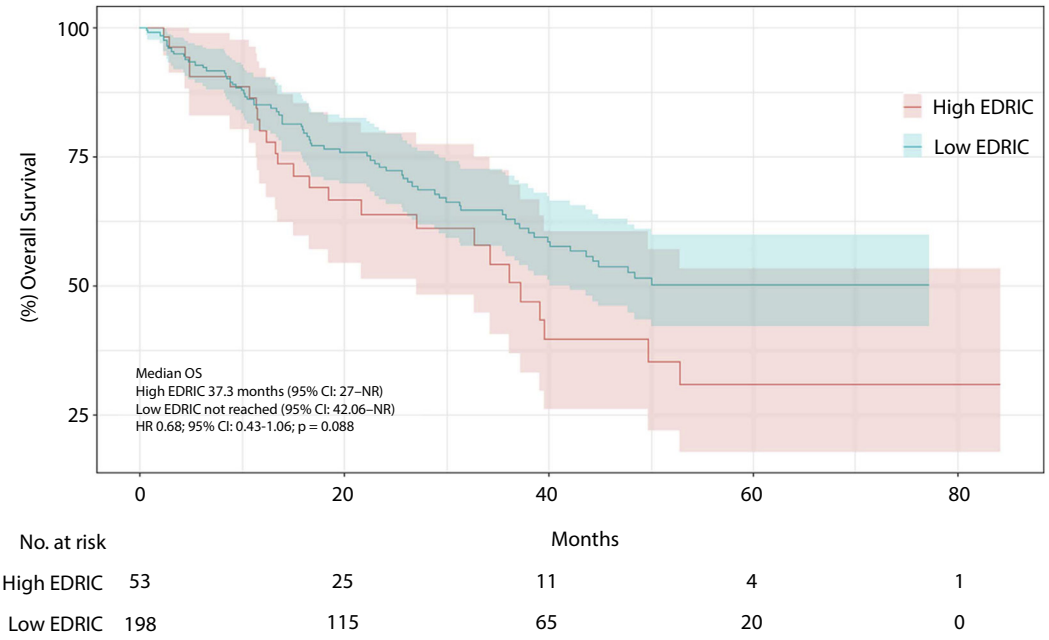

Fig. 4. Overall survival by EDRIC. *Abbreviations*: EDRIC = effective dose to immune cells; HR = hazard ratios; OS = overall survival; PFS = progression-free survival; NR= not reached.

radiation doses of 70 to 74 Gy in 2 Gy daily fractions (HR, 0.64; 95% CI, 0.37-1.09; P = .1), had low EDRIC (compared with high EDIRC; HR, 0.68; 95% CI, 0.43-1.06; P = .088), no mediastinal invasion compared with the presence of mediastinal invasion (HR, 1.53; 95% CI, 0.93-2.53; P = .093), and a trend toward shorter OS was observed for squamous histology compared with adenocarcinoma (HR, 1.45; 95% CI, 0.97-2.17; P = .068). Full details are provided in Tables 2 and 3.

We conducted a multivariable analysis including EDRIC, PD-L1 expression, N stage (N3 vs N0-2), and PTV (planning trarget volume). In this model, lower EDRIC remained directionally associated with longer PFS (low vs high HR = 0.67; 95% CI, 0.45-1.01; P = .053), PD-L1 positive status remained associated with longer PFS (vs PD-L1 negative: HR = 0.64; 95% CI, 0.44-0.94; P = .021), and N3 was directionally adverse (HR = 1.56; 95% CI, 0.99-2.46; P = .054).

Sensitivity analyses

Next-generation sequencing was not uniformly performed or available for all cases; 74 patients lacked molecular data. Among the remaining cases, 8 harbored confirmed EGFR driver mutations (3 in the high EDRIC group, 5 in the low EDRIC group), and no ALK, ROS1, or RET rearrangements were detected.

In a sensitivity analysis excluding patients with known EGFR mutations, the association between EDRIC and outcomes remained consistent. Specifically, EDRIC retained a significant effect on PFS (HR = 0.56; 95% CI, 0.38-0.83; P = .004) and showed a similar trend for OS (HR = 0.66; 95% CI, 0.42-1.05; P = .082).

We conducted a sensitivity analysis restricted to patients with known PD-L1 status. In univariable analysis, lower EDRIC was associated with improved PFS in the direction

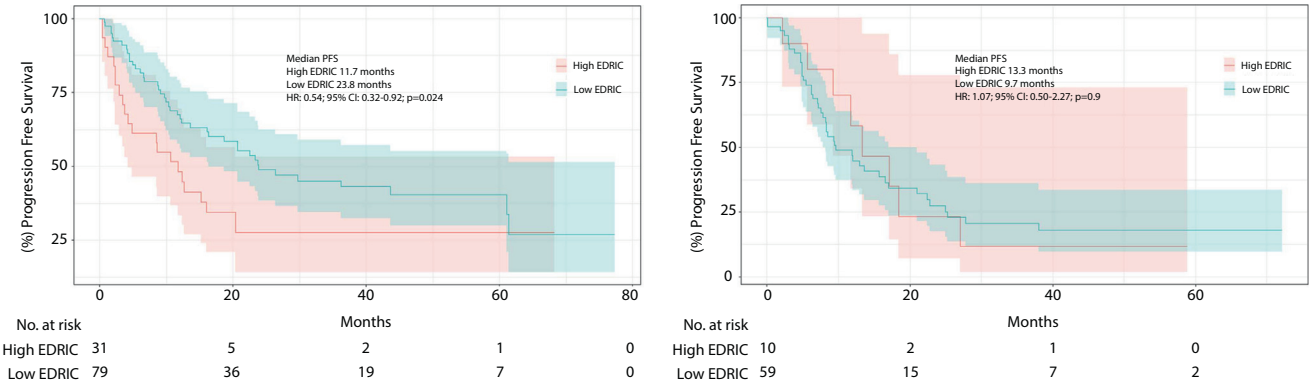

Fig. 5. Progression-free survival by EDRIC in patients with positive PD-L1 status (A) and negative PD-L1 status (B). *Abbreviations*: EDRIC = effective dose to immune cells; HR = hazard ratios; PFS = progression-free survival; PD-L1= programmed death ligand 1.

Table 2 Univariable analysis—progression-free survival

	HR	95% CI	*P* value
T stage			
T3-4	—	—	—
T1-2	0.99	0.70, 1.40	>.900
Unknown	1.15	0.61, 2.16	.700
N stage			
0	—	—	—
1	0.69	0.30, 1.59	.400
2	0.89	0.54, 1.46	.700
3	1.53	0.84, 2.80	.200
N stage			
0-2	—	—	—
3	1.72	1.10, 2.67	.016
Stage			
IIIA	—	—	—
IIIB-C	1.28	0.92, 1.78	.140
Histology			
Nonsquamous	—	—	—
Squamous	1.34	0.96, 1.87	.089
Unknown	0	0.00, Inf	>.900
Smoking			
Never smoker	—	—	—
Previous/current smoker	0.89	0.55, 1.43	.600
Unknown	0.89	0.33, 2.38	.800
PD-L1			
Negative	—	—	—
Positive	0.67	0.46, 0.97	.032
Unknown	0.41	0.26, 0.66	<.001
Sex			
Male	—	—	—
Female	1.19	0.85, 1.67	.300
Age	1.02	1.00, 1.05	.100
EDRIC group			
High	—	—	—
Low	0.57	0.39, 0.83	.004
GTV volume quartile			
1	—	—	—
2	1.06	0.52, 2.12	.900
3	1.27	0.64, 2.52	.500
4	1.47	0.75, 2.90	.300
PTV volume quartile			
1	—	—	—
2	0.85	0.53, 1.38	.500
3	1.53	0.97, 2.41	.070
4	1.18	0.74, 1.89	.500
Side			
Left	—	—	—
Right	0.98	0.69, 1.40	>.900
Radiation dose			
High	—	—	—
Standard	0.71	0.44, 1.16	.200
Pre-CRT lymphocytes			
≥1000	—	—	—
<1000	1.07	0.49, 2.35	.9

Abbreviations: CRT = chemoradiation; EDRIC = effective dose to immune cells; HR = hazard ratios. GTV= gross tumor volume. PTV= planning target volume. PD-L1 = programmed death ligand-1.

but did not reach statistical significance (HR = 0.71, 95% CI, 0.46-1.08, $P = .11$) (see Supplementary material for details). In the multivariable adjusted model, the association between lower EDRIC and improved PFS persisted but, as expected with the smaller sample, did not reach conventional significance (low EDRIC vs high EDRIC HR = 0.75; 95% CI, 0.48-1.18; $P = .20$). PD-L1 positivity remained independently associated with better PFS (HR = 0.64; 95% CI, 0.44-0.93; $P = .019$). N3 again trended toward worse outcomes (HR = 1.47; 95% CI, 0.88-2.45; $P = .14$). PTV volume (quartile 3 vs 1) showed an adverse association in this subset (HR = 1.72; 95% CI, 1.02-2.88; $P = .040$).

Discussion

In this study, we evaluated the independent association of EDRIC with clinical outcome in patients with unresectable NSCLC undergoing definitive CRT followed by durvalumab consolidation. Our analysis revealed a robust correlation between EDRIC and PFS: patients with lower EDRIC values experienced approximately double the median PFS compared with those with higher EDRIC when stratified using a data-adaptive EDRIC threshold., In multivariable Cox models, the adjusted association between lower EDRIC and longer PFS was similar in magnitude but did not reach conventional statistical significance ($P = .053$).

We used the maximally selected rank statistic to define an EDRIC cutoff point. By evaluating all potential cutoff values and selecting the point most strongly associated with outcomes, this method overcomes the limitations of traditional median-based dichotomization that is insensitive to outcome distribution. In our cohort, the maximally selected rank statistic identified 9.57 as the optimal cutoff. Although this threshold appears to stratify outcomes meaningfully, independent validation in external cohorts is essential.

Table 3 Univariable analysis—overall survival

	HR	95% CI	*P* value
T stage			
T3-4	—	—	—
T1-2	0.85	0.56, 1.29	.400
Unknown	0.99	0.45, 2.18	>.900
N stage			
0	—	—	—
1	0.73	0.30, 1.74	.500
2	0.58	0.34, 0.98	.043
3	0.82	0.41, 1.63	.600
N stage			
0-2	—	—	—
3	1.27	0.73, 2.20	.4
Stage			
IIIA	—	—	—
IIIB-C	1.06	0.71, 1.58	.800
Histology			
Nonsquamous	—	—	—
Squamous	1.45	0.97, 2.17	.068
Unknown	0	0.00, Inf	>.900
Smoking			
Never smoker	—	—	—
Previous/current smoker	1.58	0.82, 3.04	.200
Unknown	1.94	0.53, 7.14	.300
PD-L1			
Negative	—	—	—
Positive	0.76	0.48, 1.20	.200
Unknown	0.77	0.46, 1.29	.300
Sex			
Male	—	—	—
Female	1.09	0.72, 1.65	.700
Age	1.05	1.01, 1.08	.009
EDRIC group			
High	—	—	—
Low	0.68	0.43, 1.06	.088
GTV volume quartile			
1	—	—	—
2	0.49	0.17, 1.40	.2
3	1.63	0.72, 3.69	.2
4	1.87	0.82, 4.26	.14
PTV volume quartile			
1	—	—	—
2	0.72	0.39, 1.30	.3
3	1.34	0.78, 2.29	.3
4	1.22	0.71, 2.12	.5
Side			
Left	—	—	—
Right	0.83	0.54, 1.26	.4
Radiation dose			
High	—	—	—
Standard	0.64	0.37, 1.09	.1
Pre-CRT lymphocytes			
≥1000	—	—	—
<1000	2.77	0.83, 9.23	.10

Abbreviations: CRT = chemoradiation; EDRIC = effective dose to immune cells; HR = hazard ratios. GTV= gross tumor volume. PTV= planning target volume. PD-L1= programmed death ligand-1.

Our findings indicate that patients with low EDRIC experienced a median PFS nearly twice as long as those with high EDRIC (23.7 vs 11.7 months, respectively). We selected PFS as the primary endpoint over OS to more directly evaluate the therapeutic effect of durvalumab, independent of the broader poor prognosis typically associated with high EDRIC. This decision was based on the observation that high EDRIC correlates with other adverse disease characteristics—such as advanced stage, mediastinal involvement, and squamous histology—which could independently influence OS. Indeed, in our univariable analysis, factors associated with OS (eg, age, advanced disease, histology) reflected general prognostic indicators, whereas PFS was significantly associated only with PD-L1 expression, a known predictive biomarker of response to ICB. Notably, PD-L1 status was unavailable in approximately one-third of cases, which limits the granularity of subgroup interpretation. Additionally, a trend toward inferior OS was observed among patients who received higher radiation doses. Although dose escalation is not universally considered detrimental, findings from the RTOG 0617 trial in the pre-PACIFIC era suggest that higher radiation doses may, in some settings, worsen survival outcomes.[16]

In our study, we aimed to strengthen the hypothesis that high EDRIC is an independent predictor of poor outcomes of stage III unresectable patients with NSCLC treated with CRT followed by maintenance durvalumab, rather than a surrogate for other prognostic or predictive factors. To support this, we first conducted a multivariable analysis of potential confounders and then proposed a hypothetical biological mechanism.

For the multivariable analysis, we mapped all potential confounders and conducted a univariable analysis to identify those associated with PFS in our cohort. In the second stage, we performed a multivariable analysis including all factors associated with PFS in the univariable analysis and

additional factors that have a high likelihood of being confounders in this setting. For the multivariable analysis, we included N3 status, which we found to be associated with inferior PFS, PD-L1 status, and PTV as a surrogate for overall disease burden.[17] In this adjusted framework, lower EDRIC remained directionally associated with longer PFS but did not meet the $\alpha = 0.05$ threshold; the point estimate and CIs suggest a clinically relevant effect that merits external confirmation.

Current scientific data indicate that lymphocyte depletion impairs the efficacy of ICB by reducing the pool of functional T cells available for antitumor responses.[18-20] Therefore, we evaluated the influence of EDRIC on post-RT lymphocyte counts, as this may represent, at least in part, the mechanism underlying EDRIC's effect on durvalumab response. A linear regression analysis was conducted to evaluate the effect of EDRIC on lymphocyte count. A statistically significant, though modest, explanatory power was observed between high EDRIC and low lymphocyte count. Because lymphopenia is positively associated with high disease burden,[21,22] we evaluated whether the relationship between EDRIC and post-CRT lymphopenia was confounded by disease extent. The association between EDRIC and pre-CRT lymphocyte levels was minimal and not statistically significant, suggesting that high disease burden is unlikely to account for the observed effect. Because ICB relies on reactivating T cells within the tumor microenvironment, it is reasonable to assume that a reduction in the total number or specific subsets of systemic T cells before the start of ICB available for trafficking and activation at the tumor site may impair the ability of ICB to generate an effective antitumor response.[20,23,24]

Additional support for the notion that EDRIC is a predictor comes from a subgroup analysis based on PD-L1 status: the association between EDRIC and PFS was observed only among patients with positive PD-L1 expression. Notably, in a post hoc analysis of the PACIFIC trial, only patients with positive PD-L1 status derived OS benefit from durvalumab consolidation.[25] If EDRIC were merely a general marker of aggressive disease, we would expect it to be associated with worse PFS in both PD-L1 groups. With the limitation that only two-thirds of the patients had known PD-L1 status, this selective association suggests that EDRIC specifically impacts the effectiveness of durvalumab, rather than simply reflecting overall disease aggressiveness.

Although OS was not significantly longer in patients with low EDRIC, a strong trend toward longer OS was observed, suggesting that the lack of statistical significance likely reflects data immaturity rather than a true absence of effect. It should be noted that the median follow-up time in our study was 44.7 months. Similarly, in the initial publication of the PACIFIC trial, OS data were initially immature, with a statistically significant improvement observed only in a later paper release after 5 years of follow-up.[2]

The results of our study align with and expand upon prior findings regarding EDIC in locally advanced NSCLC. Earlier retrospective reports demonstrated that elevated EDIC is associated with increased rates of posttreatment lymphopenia and inferior survival outcomes in patients undergoing CRT, although these studies predated the routine use of durvalumab consolidation.[11,14] More recent data from McCall et al[10] and Pasquier et al[9] have suggested a potential interaction between EDIC and response to durvalumab consolidation. McCall et al[10] reported on a single-institution cohort of 100 patients and found that elevated EDIC (>6 Gy) was significantly associated with worse OS, PFS, and locoregional control. On multivariable analysis, high EDIC remained an independent predictor of adverse outcomes across all endpoints. Pasquier et al[9] reported on a cohort of 50 patients that an elevated EDRIC (>6.3 Gy) was associated with worse PFS. In multivariable analysis, high EDRIC showed a trend toward shorter PFS, though it did not reach statistical significance.

These results indicate that reducing EDRIC during radiotherapy planning may improve ICB outcomes. Whether EDRIC can be reduced without compromising target coverage or increasing dose to other organs at risk remains an open question. A promising strategy to facilitate such a reduction is the use of proton radiotherapy, which exploits the Bragg peak to deliver high tumor doses while sharply limiting exit dose.[26,27] Multiple dosimetric studies and clinical series have shown that proton therapy achieves lower MHD and MLD.[28-30] Given that MHD and MLD are key contributors to EDRIC, the ability of proton therapy to substantially reduce these parameters provides a strong rationale for its integration into future EDRIC-guided treatment strategies.

Limitations

Our study has several limitations. As an observational, retrospective analysis, it is subject to inherent biases. Second, molecular and PD-L1 data were incomplete, with PD-L1 status missing in roughly one-third of cases, raising the possibility of residual confounders. Third, although the cohort was relatively large and multi-institutional, the number of patients with high EDRIC was modest, potentially limiting statistical power for subgroup analyses. Furthermore, although our findings support the predictive value of EDRIC, causality cannot be definitively established. Finally, although the median follow-up was substantial, the OS data were not yet fully mature, and longer follow-up may be needed to confirm the observed OS trends.

Conclusion

In this multicenter study, we demonstrated that EDRIC independently correlated with outcomes following durvalumab consolidation in patients with unresectable stage III NSCLC treated with definitive CRT. Lower EDRIC values were significantly associated with longer PFS. These findings suggest that minimizing EDRIC during radiotherapy

planning may potentially enhance ICB outcomes. Strategies to minimize radiation exposure may include the use of proton therapy to reduce dose to immune-rich structures. Prospective validation in larger cohorts or in post hoc analyses of prospective trials—such as PACIFIC—is warranted, and incorporation of EDRIC constraints into treatment planning should be explored in future clinical trials.

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