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Severe Radiation-Induced Lymphopenia Attenuates the Benefit of Durvalumab After Concurrent Chemoradiotherapy for NSCLC

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ABSTRACT

Introduction: Durvalumab after concurrent chemoradiation (CCRT) for NSCLC improves survival, but only in a subset of patients. We investigated the effect of severe radiation-induced lymphopenia (sRIL) on survival in these patients.

Methods: Outcomes after CCRT (2010–2019) or CCRT followed by durvalumab (2018–2019) were reviewed. RIL was defined by absolute lymphocyte count (ALC) nadir in samples collected at end of CCRT; sRIL was defined as nadir ALC less than 0.23×10^9/L (the lowest tertile). Progression-free survival (PFS) and overall survival (OS) were calculated by the Kaplan-Meier method. Cox proportional hazard modeling evaluated associations between clinical variables and survival.

Results: Of 309 patients, 192 (62%) received CCRT only and 117 (38%) CCRT plus durvalumab. Multivariable logistic regression analysis indicated that sRIL was associated with planning target volume (OR = 1.002, $p = 0.001$), stage IIIB disease (OR = 2.77, $p = 0.04$), and baseline ALC (OR = 0.36, $p < 0.01$). Durvalumab extended median PFS (23.3 versus 14.1 mo, $p = 0.003$) and OS (not reached versus 30.8 mo, $p < 0.01$). sRIL predicted poorer PFS and OS in both treatment groups. Among patients with sRIL, durvalumab did not improve survival (median = 24.6 mo versus 18.1 mo CCRT only, $p = 0.079$). On multivariable analyses, sRIL (OR = 1.81, $p < 0.01$) independently predicted poor survival.

Conclusions: Severe RIL compromises survival benefits from durvalumab after CCRT for NSCLC. Measures to mitigate RIL after CCRT may be warranted to enhance the benefit of consolidation durvalumab.

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Introduction

Decades of research in the treatment of unresectable locally advanced NSCLC have led to a diverse set of combination therapies that have extended survival for patients with this otherwise lethal disease. The addition of concurrent chemotherapy to radiotherapy (CCRT) was found to greatly improve overall survival (OS) relative to radiotherapy (RT) alone; in a recent example, RTOG 0617 revealed that the addition of chemotherapy conferred a 5-year OS rate of 32% and a median OS time of 28.7 months.[1,2] This standard was quickly surpassed with the incorporation of the anti–programmed death-ligand 1 antibody durvalumab in the CCRT regimen, an advance on the basis of findings from the paradigm-changing randomized phase 3 PACIFIC trial.[3] In that trial, durvalumab significantly prolonged median progression-free survival (PFS) time (17.2 mo versus 5.6 mo for placebo, hazard ratio [HR] = 0.51) and OS time compared with placebo (HR = 0.68, p = 0.0025). Nevertheless, only a subset of patients experienced benefit. We propose that understanding the factors that may compromise the benefit from durvalumab may help in the development of strategies to augment the benefit from this agent.

Having an intact adaptive immune system is crucial for deriving benefit from immunotherapies, such as durvalumab and other checkpoint inhibitors.[4,5] Nevertheless, lymphocyte depletion after RT or chemoradiotherapy, with the corresponding suppression in immune function, is nearly universal after RT.[6,7] Indeed, rates of high-grade lymphopenia after chemoradiation have exceeded 80%.[8,9] Decreased numbers of lymphocytes have been linked with poor prognosis in a variety of tumors, including NSCLC,[10–13] and the effectiveness of checkpoint inhibitors could also be undermined by a drop in lymphocyte levels.[5,14,15] The host immune system can be considered an organ at risk during RT, and thus the number of lymphocytes in the peripheral blood is one marker of the host immune function.[16] In one retrospective study, receipt of high radiation doses to the immune system was associated with lower absolute lymphocyte count (ALC) and poor survival in patients with stage III NSCLC.[17] Until now, only one study from Johns Hopkins has investigated how severe lymphopenia influenced disease progression in locally advanced NSCLC after definitive treatment with chemoradiation and immunotherapy.[18] In that study of 78 patients, the PFS time for patients with severe radiation-induced lymphopenia (sRIL) who initiated consolidative immunotherapy was worse than that for patients who did not have sRIL (median PFS time = 217 d versus 570 d, $p <$ 0.001). What is unknown is whether sRIL could compromise the benefit of durvalumab over CCRT alone.

We sought to evaluate PFS and OS outcomes for locally advanced NSCLC treated with CCRT with or without durvalumab, in the context of the severity of RIL.

Materials and Methods

Patients

This retrospective record-based analysis was approved by the appropriate institutional review board, and the requirement for informed consent was waived. Patients with histopathologic and imaging confirmation of locally advanced NSCLC treated at a single institution from 2010 to 2019 were identified, and patients aged 18 years or more who received CCRT and had complete medical records available were selected. Patients who received CCRT followed by durvalumab consolidation had been treated from 2018 to 2019. All patients had performance status with Eastern Cooperative Oncology Group score less than or equal to 2. Disease stage ranged from II to III as defined in the seventh edition of the American Joint Committee on Cancer staging manual. Sequential chemoradiotherapy was not allowed, but induction chemotherapy followed by CCRT was acceptable, as was CCRT followed by adjuvant chemotherapy. Patients with a history of autoimmune disease or receipt of other checkpoint inhibitors were excluded.

Lymphopenia

Lymphocytes were isolated from peripheral blood samples obtained before CCRT (i.e., at baseline) and during CCRT. Lymphopenia was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which defines grade 3 (G3) lymphopenia as an ALC of less than 0.5×10^9 cells/L and G4 as an ALC of less than 0.2×10^9 cells/L. Patients were then stratified as having G3 to G4 lymphopenia (G3+ RIL) or having G0 to G2 lymphopenia (non-G3+ RIL). We also evaluated ALC thresholds by tertile seeking cutoff points to define sRIL. The lower tertile value of lymphocytes for the entire population was 0.23×10^9 cells/L, and thus sRIL was defined as an ALC of less than 0.23×10^9 cells/L (i.e., nearly equivalent to G4).

Treatment

Treatment consisted mostly of CCRT with or without durvalumab consolidation. Concurrent chemotherapy was delivered every 3 (Q3) weeks or once a week starting 1 week before or after the first day of RT. Chemotherapy

consisted of carboplatin/cisplatin plus paclitaxel or pemetrexed. Induction or adjuvant chemotherapy, if used, consisted of the same drugs. Generally, the procedure of platinum-based chemo-drugs in our cancer center was used as follows: carboplatin area under the curve 5 used for induction given Q3 weeks, but area under the curve 2 when given weekly with CCRT; paclitaxel 150 to 200 mg/m^2 given for induction Q3 weeks, but 50 mg/m^2 when given weekly with CCRT; cisplatin 75 mg/m^2, pemetrexed 800 mg/m^2, etoposide 100 mg/m^2, or gemcitabine 1250 mg/m^2 (day 1, day 8), given Q3 weeks. RT was delivered as either photon (x-ray) or proton therapy. Photon therapy was given as three-dimensional conformal RT, intensity modulated radiation therapy, or volumetric-modulated arc therapy. Proton therapy was delivered with intensity modulated or passive scattering techniques. Radiation (to a total dose of at least 60 Gy) was delivered five times per week in fractions of 1.2 to 2.0 Gy each. Planning target volume (PTV) was defined as clinical target volume (CTV) plus 5 mm margin. Generally, involved field irradiation was administered in our center. Hence, clinical target volume included gross target tumor and involved lymphocytic drainage regions. Durvalumab was administered intravenously at 10 mg/kg after CCRT was completed and was given every 2 weeks for up to 1 year or until the occurrence of intolerable toxicity, disease progression, or death, whichever comes first.

Statistical Analyses

Clinicopathologic and treatment characteristics were compared between patients given CCRT only and CCRT plus durvalumab. Categorical variables were summarized by frequencies and percentages and compared with chi-square tests or Fisher's exact tests, and continuous variables were summarized as means plus or minus SDs and evaluated with two-sample t tests or Wilcoxon ranked sum tests. Logistic regression was used to identify predictors of sRIL in the entire group. PFS was measured from the date the RT began to the date of disease progression or death; OS was measured from the date RT began to the date of death or last follow-up. The Kaplan-Meier method was used to evaluate PFS and OS for the two treatment groups, and comparisons were made with the log-rank test. Cox proportional hazards regression was used to estimate the effect of covariates on survival. All p values were two tailed, and p values less than 0.05 were considered to be statistically significant. All statistical analyses were performed with SPSS 23.0 (SPSS, IBM Corp., Armonk, NY).

Results

Patients

A total of 309 patients were identified as having been treated from July 2010 to September 2019 at a single institution, 117 (38%) of whom received CCRT followed by durvalumab and 192 (62%) CCRT only. Baseline clinicopathologic features are found in Table 1. The median age of the entire cohort was 67 (interquartile range [IQR]: 61–73) years. Most patients (79% [244 of 309]) were greater than or equal to 60 years old; male (54% [167 of 309]), White (88% [272 of 309]), and current or previous smokers (67% [206 of 309]); most had adenocarcinoma (55% [169 of 309]), stage IIIA disease (55% [170 of 309]), and N2 or N3 disease (75% [233 of 309]). Furthermore, most patients received photon therapy (75% [233 of 309]). Demographic and clinical characteristics at baseline were generally well balanced between groups, but those receiving CCRT plus durvalumab received a lower RT dose (60.4 ± 2.0 Gy versus 65.4 ± 5.6 Gy, $p < 0.01$) and fewer RT fractions (30.2 ± 1.0 versus 32.9 ± 3.3, $p < 0.01$). For the entire cohort, the median RT dose delivered was 60 Gy (IQR: 60–68.8) and the median number of RT fractions was 30 (IQR: 30–35); these features did not differ between the treatment groups.

A total of 52 patients (17%) were given induction chemotherapy, 21 patients in the CCRT plus durvalumab group and 31 patients in the CCRT-only group. The median number of induction chemotherapy cycle was 2 (range: 1–4). A total of 58 patients received adjuvant chemotherapy, with a median of 2 cycles (range: 1–4). At the date of this analysis (cutoff date: October 15, 2021), the median number of consolidative durvalumab cycles was 15 (range: 1–30), and at least 40 patients were continuing durvalumab (some with their local oncologist). The reason for interrupting or discontinuing durvalumab was mainly pneumonitis. The median interval from induction chemotherapy to concurrent CCRT was 1.1 (IQR: 0.8–1.8) months and from the end of CCRT to the start of durvalumab was 1.1 (IQR: 0.7–1.6) months.

Incidence and Predictors of sRIL

A total of 99 (32%) experienced sRIL (lower tertile with ALC $< 0.23 \times 10^9$ cells/L). Clinical features were well balanced between patients with sRIL versus those without sRIL (Supplementary Table 1), but the sRIL group had proportionately more stage IIIB disease (50% versus 24%, $p < 0.01$), larger PTVs (638.7 ± 376.7 cm^3 versus 458.0 ± 244.9 cm^3, $p < 0.01$), and lower baseline ALC levels (1.5 ± 0.6 versus 1.8 ± 0.7, $p < 0.01$) than the non-sRIL group (Table 2).

Possible predictors of sRIL identified through logistic regression were stage IIIB disease (OR = 2.77, 95% confidence interval [CI]: 1.06–7.25, $p = 0.04$), PTV (OR = 1.002, 95% CI: 1.001–1.003, $p = 0.001$), and baseline ALC (OR = 0.36, 95% CI: 0.21–0.60, $p < 0.01$) (Supplementary Table 2). No other clinical or radiation-related variables were associated with the development of sRIL.

Table 1. Baseline Characteristics of Patients With Locally Advanced NSCLC Receiving CCRT or CCRT + Durvalumab

Characteristics	CCRT Only, Mean SD or n (%) (n = 192)	CCRT + Durvalumab, Mean SD or n (%) (n = 117)	p Value
Sex			
Male	98 (51)	69 (59)	0.20
Female	94 (49)	48 (41)	
Race			
White	174 (91)	98 (84)	0.05
Non-White	18 (9)	19 (16)	
Age, y	66.3 ± 9.0	67.7 ± 9.0	0.17
$\geq$60	146 (76)	98 (84)	0.11
<60	46 (24)	19 (16)	
Smoking status			
Previous/current	128 (67)	78 (67)	1.00
Never	64 (33)	39 (33)	
Tumor location			
Right lung	121 (63)	65 (56)	0.23
Left lung	71 (37)	52 (44)	
Pathologic type			
Adenocarcinoma	105 (55)	64 (55)	0.22
Squamous cell carcinoma	69 (36)	48 (41)	
Other	18 (9)	5 (4)	
cT status			
T1-2	113 (59)	65 (56)	0.63
T3-4	79 (41)	52 (44)	
cN status			
N0-1	53 (28)	23 (20)	0.13
N2-3	139 (72)	94 (80)	
cDisease stage			0.74
II	27 (14)	13 (11)	
IIIA	105 (55)	65 (56)	
IIIB	60 (31)	39 (33)	
Lymphopenia			
sRIL (ALC $< 0.23 \times 10^9$ cells/L)	71 (37)	28 (24)	0.02
Non-sRIL (ALC $> 0.23 \times 10^9$ cells/L)	121 (63)	89 (76)	
RT modality			
Photon	140 (73)	101 (86)	0.01
Proton	52 (27)	16 (14)	
Photon technique			
3DCRT	1 (1)	2 (2)	<0.01
IMRT	75 (53)	7 (7)	
VMAT	64 (46)	92 (93)	
PTV	548.9 ± 334.4	458.3 ± 258.9	0.03
Radiation dose delivered, Gy	65.4 ± 5.6	60.4 ± 2.0	<0.01
No. of radiation fractions	32.9 ± 3.3	30.2 ± 1.0	<0.01
Baseline ALC, $\times 10^9$ cells/L	1.7 ± 0.7	1.6 ± 0.6	0.12

3DCRT, three-dimensional chemoradiotherapy; ALC, absolute lymphocyte count; CCRT, concurrent chemoradiation therapy; IMRT, intensity modulated radiation therapy; PTV, planning target volume; RT, radiotherapy; VMAT, volumetric-modulated arc therapy.

Evaluating the Overall Benefit of Durvalumab

The median duration of follow-up was 32.3 months for the CCRT plus durvalumab group and 71.6 months for the CCRT-only group. At the time of the data lock on October 15, 2021, 170 patients (55%) had died, 35 (21%) in the CCRT plus durvalumab group and 135 (79%) in the CCRT-only group. The median PFS times were 14.1 months for the CCRT-only group and 23.3 months for the CCRT plus durvalumab group ($p = 0.0034$; Fig. 1A). The median OS times were not reached for the CCRT plus durvalumab group and 30.8 months for the CCRT-only group (OR = 0.53, 95% CI: 0.38–0.75, $p < 0.01$) (Fig. 1B). OS rates at 1 year and 2 years were 89.6% and 75.3% in the CCRT plus durvalumab group versus 74.3% and 57.8% in the CCRT-only group.

Table 2. Clinical Characteristics of Patients Who Experienced sRIL Versus Those Who Did Not

Characteristics	No sRIL, n (%) (n = 210)	sRIL, n (%) (n = 99)	p Value
Sex			
Male	117 (56)	50 (51)	0.39
Female	93 (44)	49 (49)	
Race			
White	183 (87)	89 (90)	0.57
Non-White	27 (13)	10 (10)	
Age, y			
≥60	161 (77)	83 (84)	0.18
<60	49 (23)	16 (16)	
Smoking status			
Previous/current	137 (65)	69 (70)	0.52
Never	73 (35)	30 (30)	
Primary tumor location			
Right lung	120 (57)	66 (67)	0.13
Left lung	90 (43)	33 (33)	
Pathologic type			
Adenocarcinoma	111 (53)	58 (59)	0.60
Squamous cell carcinoma	82 (39)	35 (35)	
Other	17 (8)	6 (6)	
cT status			
T1-2	121 (58)	57 (58)	0.99
T3-4	89 (42)	42 (42)	
cN status			
N0-1	58 (28)	18 (18)	0.09
N2-3	152 (72)	81 (82)	
cDisease stage			
II	30 (14)	10 (10)	<0.01
IIIA	130 (62)	40 (40)	
IIIB	50 (24)	49 (50)	
Treatment			
CCRT only	121 (58)	71 (72)	0.02
CCRT + durva	89 (42)	28 (28)	
RT modality			
Photon	157 (75)	76 (77)	0.70
Proton	53 (25)	23 (23)	
PTV, cm^3, mean ± SD	458.0 ± 244.9	638.7 ± 376.7	<0.01
Radiation dose delivered, Gy	63.4 ± 5.2	63.8 ± 5.0	0.49
Number of radiation fractions	31.8 ± 3.1	32.1 ± 2.6	0.45
Baseline ALC, $\times 10^9$ cells/L	1.8 ± 0.7	1.5 ± 0.6	<0.01

Note: Defined as $<0.23 \times 10^9$ lymphocytes/L.
ALC, absolute lymphocyte count; CCRT, concurrent chemoradiation; durva, durvalumab; PTV, planning target volume; RT, radiotherapy; sRIL, severe radiation-induced lymphopenia.

Impact of sRIL on PFS

Among patients treated with CCRT only, the median PFS interval was significantly shorter for those who experienced sRIL (11.5 mo versus 19.7 mo no sRIL, $p = 0.0004$) (Fig. 2A), and this was also true of patients in the CCRT plus durvalumab group (17.1 mo sRIL versus 37.7 mo no sRIL, $p = 0.02$) (Fig. 2B). For patients with no sRIL, the addition of durvalumab marginally prolonged the PFS time (37.7 mo versus 19.7 mo, $p = 0.08$) (Fig. 2C), which was attenuated for patients with sRIL (17.1 mo versus 11.5 mo, $p = 0.12$) (Fig. 2D). Multivariate analysis reveals that sRIL is an independent predictor of poorer PFS, whereas receipt of durvalumab and higher baseline ALC were predictors of better PFS (Supplementary Table 3).

Impact of sRIL on OS

As was true for PFS, the occurrence of sRIL was associated with significantly shorter median OS time regardless of treatment (for CCRT only: 18.1 mo with sRIL versus 45.8 mo without sRIL, $p < 0.01$, Fig. 3A; for CCRT + durvalumab: 24.6 mo with sRIL versus not reached without sRIL, $p = 0.0038$; Fig. 3B). Among patients without sRIL, the addition of durvalumab
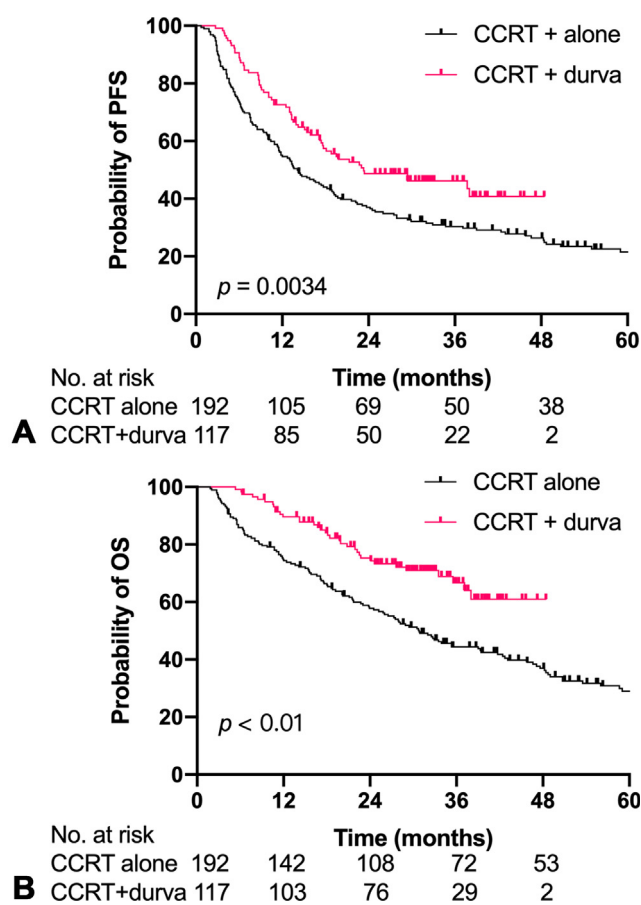
Figure 1. Kaplan-Meier plots of (*A*) PFS and (*B*) OS among patients receiving concurrent with or without durva. CCRT, chemoradiation therapy; durva, durvalumab; OS, overall survival; PFS, progression-free survival.

significantly prolonged median OS time (not reached for durvalumab versus 45.8 mo for CCRT only, $p = 0.014$; Fig. 3*C*); however, this was no longer true for patients with sRIL (24.6 mo durvalumab versus 18.1 mo CCRT only, $p = 0.079$; Fig. 3*D*).

Univariate and Multivariate Analyses of Factors Associated With OS

Findings from univariate and multivariate analyses of factors associated with OS for the entire group are found in Table 3. Univariate analysis indicated that receipt of durvalumab, severity of lymphopenia (sRIL versus no sRIL), and baseline ALC correlated with OS. These associations held in multivariate analyses, that is, sRIL (OR = 1.81, 95% CI: 1.31–2.50, $p < 0.01$), receipt of durvalumab (OR = 0.55, 95% CI: 0.37–0.81, $p = 0.003$), and baseline ALC (OR = 0.70, 95% CI: 0.55–0.89, $p = 0.004$) independently predicted OS. In the subset of patients in the CCRT-only group, univariate analyses indicated that primary tumor location, sRIL, and baseline ALC were associated with OS, associations that also held

in multivariate analyses (left tumor: OR = 1.43, 95% CI: 1.00–2.05; sRIL: OR = 1.72, 95% CI: 1.19–2.47, $p = 0.004$; baseline ALC: OR = 0.69, 95% CI: 0.53–0.90, $p = 0.007$) (Supplementary Table 4).

Discussion

The key finding of this study was that the addition of durvalumab to CCRT did not improve PFS or OS for patients with sRIL versus those without sRIL. Nevertheless, both PFS and OS were significantly worse for patients with sRIL, regardless of treatment (consolidative durvalumab or not), than in patients without sRIL. Therefore, sRIL was not only prognostic of poorer outcomes for all patients but also predictive of the benefit of durvalumab.

The reported incidence of RIL after treatment of locally advanced NSCLC varies among institutions, perhaps because of differences in the definition of lymphopenia or differences in patient populations. Two large reviews of patients treated with definitive chemoradiation for locally advanced NSCLC revealed rates of G3+ (i.e., G3 + G4) lymphopenia (defined per CTCAE version 4.0) of 92% (330 of 362)[19] and 88% (532 of 604).[20] Two smaller studies of G3+ RIL (defined per CTCAE version 5.0) reported rates of 91% (162 of 178 patients)[21] and 23% (18 of 78 patients).[18] A meta-analysis of 14 studies of risk factors associated with RIL in lung cancer indicated an overall mean incidence of G3+ lymphopenia (defined as ALC $< 0.5 \times 10^9$ cells/L) of 64.24%.[22] By comparison, the incidence of G3+ RIL (i.e., G3 + G4 lymphopenia) in our study was 79.1% and that of sRIL (i.e., ALC $< 0.23 \times 10^9$ cells/L or roughly equivalent to G4) was 32.9%. Two possible reasons for these lower rates may be our use of highly conformal RT techniques or lower RT doses. In our study, 22% of patients received proton therapy compared with 14% in the large study reported by Tang et al.[20] Although no clear evidence has been found to date that proton therapy can spare lymphocytes in the treatment of lung cancer, it has reduced the risk of severe lymphopenia in esophageal cancer.[23,24] With regard to radiation dose, the median RT dose in our study was 60 Gy (range: 60–74 Gy) but that in the study reported by Xie et al.[21] was 74 Gy (range: 60–78 Gy). Higher radiation doses are likely to cause more serious lymphopenia.[12] Although comparing RT target volumes across studies is quite difficult, the target volume does affect the incidence of lymphopenia. A series of studies calculated the estimated dose of radiation to immune cells (EDRICs) in terms of mean heart/lung dose, mean body dose, and number of RT fractions; those studies found that PTV was associated with EDRIC ($p = 0.0004$) and that higher EDRIC was associated with higher incidence of G3+
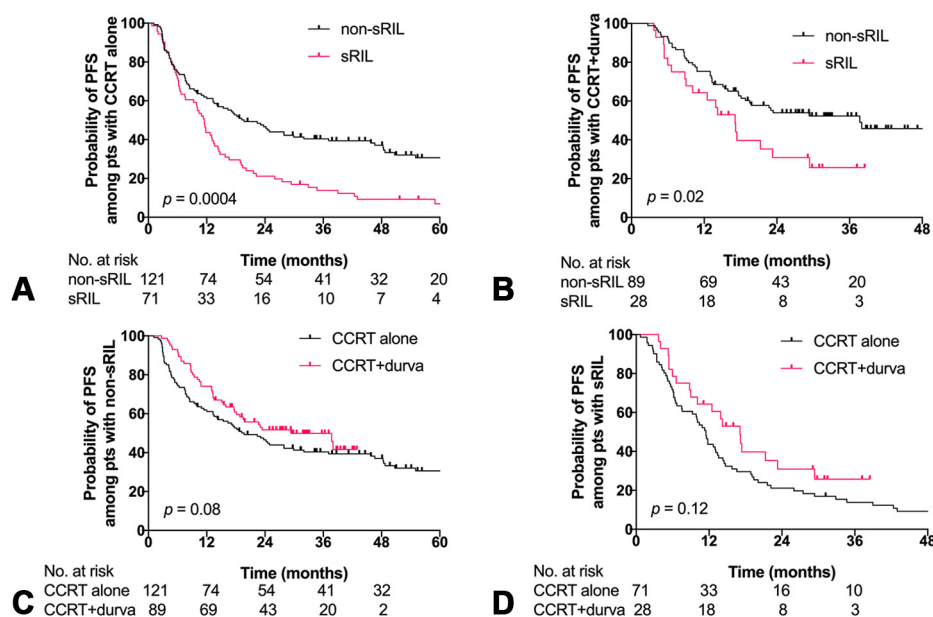
Figure 2. Kaplan-Meier plots of PFS stratified by treatment and lymphopenia status for the entire population. (*A*) PFS among patients treated with concurrent CCRT alone by the presence of sRIL (defined as ALC < 0.23×10^9 cells/L) or non-sRIL. (*B*) PFS among patients treated with CCRT followed by consolidative durvalumab (CCRT + durva) by having sRIL versus non-sRIL. (*C*) PFS among patients with non-sRIL comparing treatments (CCRT alone or CCRT + durva). (*D*) PFS among patients with sRIL comparing treatments (CCRT alone or CCRT + durva). ALC, absolute lymphocyte count; CCRT, chemoradiation therapy; durva, durvalumab; PFS, progression-free survival; sRIL, severe radiation-induced lymphopenia.
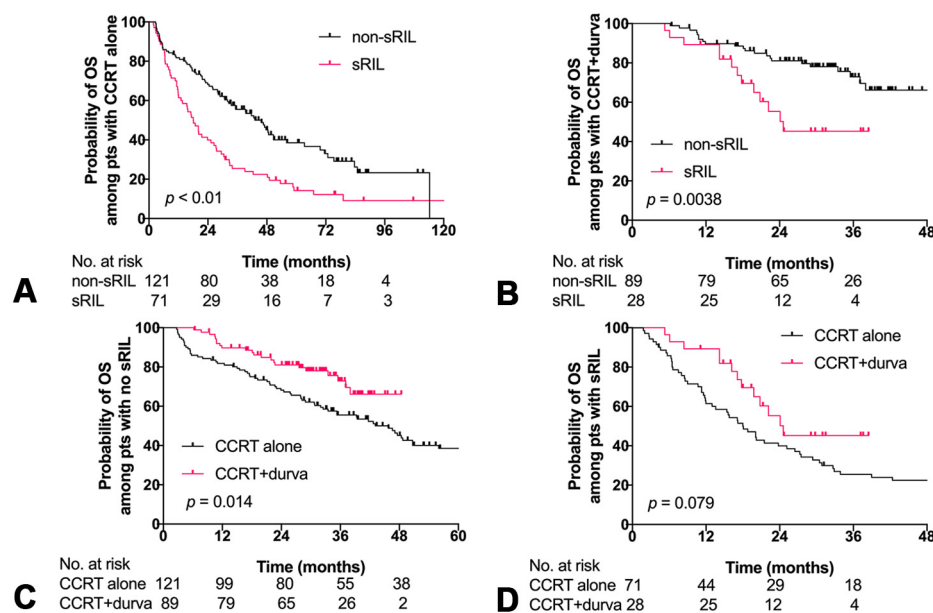

Figure 3. Kaplan-Meier plots of OS stratified by treatment and lymphopenia status for the entire population. (*A*) OS among patients treated with concurrent chemoradiation only (CCRT alone), by the presence of severe radiation-induced lymphopenia (sRIL; defined as absolute lymphocyte count [ALC] < 0.23×10^9 cells/L) or non-sRIL. (*B*) OS among patients with treated with CCRT followed by durvalumab (CRRT + durva), by having sRIL or non-sRIL. (*C*) OS among patients with non-sRIL comparing treatments (CCRT alone or CCRT + durva). (*D*) OS among patients with sRIL comparing treatments (CCRT alone or CCRT + durva). ALC, absolute lymphocyte count; CCRT, chemoradiation therapy; durva, durvalumab; OS, overall survival; sRIL, severe radiation-induced lymphopenia.

Table 3. Univariate and Multivariate Analyses of Factors Influencing Overall Survival Among All Patients

	Univariate		Multivariate	
Characteristics	OR (95% CI)	p Value	OR (95% CI)	p Value
Sex (male vs. female)	1.27 (0.94-1.72)	0.12		
Race (White vs. non-White)	1.08 (0.65-1.79)	0.75		
Age ($\geq$60 vs. <60 y)	1.00 (0.70-1.44)	0.99		
Smoking status[a]	1.15 (0.83-1.60)	0.39		
Tumor location				
Right vs. left	0.87 (0.64-1.19)	0.38		
Pathologic type				
Other	Ref			
Adenocarcinoma	0.70 (0.40-1.24)	0.22		
Squamous cell carcinoma	1.02 (0.57-1.82)	0.94		
Treatment				
CCRT + durvalumab vs. CCRT only	0.50 (0.34-0.73)	<0.01	0.55 (0.37-0.81)	0.003
cT status				
T3-4 vs. T1-2	1.04 (0.77-1.41)	0.78		
cN status				
N2-3 vs. N0-1	1.29 (0.89-1.86)	0.18		
cDisease stage				
II	Ref			
IIIA	1.08 (0.66-1.77)	0.77		
IIIB	1.48 (0.88-2.48)	0.13		
Lymphopenia				
sRIL[b] vs. no sRIL	2.22 (1.64-3.01)	<0.01	1.81 (1.31-2.50)	<0.01
Baseline ALC	0.63 (0.50-0.81)	<0.01	0.70 (0.55-0.89)	0.004

ALC, absolute lymphocyte count; CCRT, concurrent chemoradiation therapy; CI, confidence interval; Ref, referent; sRIL, severe radiation-induced lymphopenia.
[a]Previous or current vs. never.
[b]sRIL defined as ALC < 0.23 $\times$ 10^9cells/L.

lymphopenia (HR = 3.30, p = 0.004).[17,25,26] In the current study, 50% of the patients in the sRIL group had stage IIIB disease, but only 32% of those in the non-sRIL group did (p < 0.01). Higher disease stage tends to mean larger PTVs, which would promote the development of sRIL. In the current study, the PTV was significantly larger in the sRIL group, and PTV was also linked with lymphopenia in multivariate logistic regression analysis (OR = 1.005, p = 0.003). The influence of baseline ALC on lymphopenia should also be considered, as baseline ALC has been found to correlate with severe treatment-related lymphopenia in patients receiving CCRT followed by immunotherapy for locally advanced NSCLC.[18] Moreover, ALC (particularly during treatment) is influenced by RT technique and duration.[27,28] The existing evidence warrants exploration of how changes in aspects of RT, such as dose, fields, and technique, might be used to mitigate lymphopenia.

Lymphopenia is now known to reduce survival in patients with NSCLC treated with radiation; survival for patients with sRIL was significantly worse than that for patients without sRIL.[8,20,21] In one retrospective study of 604 patients with stage III NSCLC given CCRT, a decrease in lymphocyte numbers equivalent to G3+ (i.e., 0.5 $\times$ 10^9 cells/L) was associated with poor OS (HR = 1.5, p =

0.01) and poor event-free survival (HR = 1.4, p = 0.02).[20] Nevertheless, results from a smaller retrospective study of 47 patients receiving CCRT revealed similar median survival times for patients with G3+ RIL and those with less than G3 RIL (21.8 mo versus 27.3 mo, p = 0.38).[29] A previous study by our group indicated that sRIL was associated with poor survival in patients with NSCLC receiving postoperative RT.[30] Nevertheless, the optimal threshold for defining sRIL with regard to predicting outcomes is not known, although the CTCAE provides a somewhat arbitrary system by setting G3 lymphopenia as less than 0.5 to 0.2 $\times$ 10^9 cells/L and G4 as less than 0.2 $\times$ 10^9 cells/L. Thus, we also compared G3+ with G4 RIL for their potential predictive value. Among patients with G4 RIL given CCRT plus durvalumab, survival was similar to that in patients without G4 RIL (i.e., G0–G3), but prolonged to that in patients with G4 RIL given CCRT only. In addition, survival was significantly shorter for patients with G3+ RIL than for patients with non-G3+ RIL (i.e., G0–G2). The weakened predictive value of G4 may be due to the less cases in the G4 group. These findings suggest that a lymphocyte value between G3 RIL and G4 RIL may be more appropriate for predicting survival. In our study, the lowest tertile for all patients was 0.23 $\times$ 10^9 cells/L, which was

slightly larger than the value defining G4 RIL in the CTCAE. Hence, we investigated survival differences using this threshold as a cutoff tertile (i.e., sRIL) and found it to have predictive value as revealed in this study. Therefore, using this lower tertile value to define sRIL seems to be a reliable biomarker of survival for patients receiving CCRT with or without consolidative durvalumab.

Nevertheless, the relationship between lymphopenia and the effectiveness of immunotherapy remains unclear, particularly in locally advanced NSCLC. The lymphocytes are the target cell for the checkpoint inhibitors; therefore, the presence of fewer lymphocytes may reduce the probability that any individual lymphocyte would develop checkpoint inhibitor-induced antitumor immune response. Some emerging findings suggest that treatment-related lymphopenia hampers the effectiveness of immunotherapy and is associated with poor outcomes.[5,14,15,31] In one such study of patients with stage III or advanced NSCLC treated with nivolumab, the ALC at 6 weeks after the first dose of nivolumab correlated positively with OS ($p = 0.047$).[15] Another study of immunologic characteristics before and during nivolumab for advanced NSCLC indicated that having higher levels of almost all the effector T cell types at baseline was correlated with longer OS and PFS; furthermore, the proportion of exhausted T cells ($CD8^+PD1^+Eomes^+$) during treatment was significantly higher in patients with progressive disease than in patients with controlled disease.[31] As alluded to earlier, another study revealed that having G3+ RIL at the onset of immunotherapy (versus having G0–G2 RIL) was associated with significant decreases in median survival times for patients with advanced NSCLC (100 d versus 250 d, $p = 0.008$).[5] In another study, the median PFS times (2.2 versus 5.9 mo, $p < 0.001$) and median OS times (5.7 versus 12.1 mo, $p < 0.001$) were both poorer for patients with NSCLC and peri-immunotherapy lymphopenia, even when lymphopenia was defined as an ALC of less than 1.0×10^9 cells/L.[14] According to the latest study from Johns Hopkins, patients with G3+ RIL receiving consolidative immunotherapy after CCRT for locally advanced NSCLC had worse PFS than those who did not have G3+ RIL (median 217 d versus 570 d, $p < 0.001$); moreover, having G3+ RIL at the start of consolidative immunotherapy was an independent predictor of worse PFS (HR = 4.9, $p < 0.001$).[18] Possible reasons for the discrepancies between these studies and our own are as follows. Other studies included patients treated with several types of immunotherapy agents after CCRT, but our study considered only durvalumab. Furthermore, our study included patients with stages IIA to IIIB disease (versus stages IIB–IIIC in the Hopkins study), which may have contributed to the prolonged survival, despite our study

having a longer follow-up time (median 32.6 mo versus 10.7 mo in the Hopkins study). Furthermore, ALC was measured within 2 weeks of starting immunotherapy in the Hopkins study but was measured weekly during CCRT in our study. As a consequence, we cannot rule out the possibility of ALC recovery after CCRT but before immunotherapy, which may explain why the incidence of G3+ RIL was only 23% in the Hopkins study versus 79.1% in our own. The influence of lymphocyte recovery on survival in lung cancer is still unclear, but survival is known to be poorer in patients with esophageal cancer who did not recover from treatment-related lymphopenia.[32] Finally, we also stratified OS data by lymphopenic status and found that for patients who received durvalumab, OS significantly decreased in patients with sRIL. We further found that survival among patients with sRIL or G4 was similar in the CCRT-only and CCRT + durvalumab groups, suggesting the potential survival benefit of consolidative durvalumab was not found when there was severe reduction in lymphocyte numbers.

One strength of this study was the evaluation of the predictive value of RIL in two treatment conditions—CCRT or CCRT plus durvalumab—for locally advanced NSCLC. Furthermore, to our knowledge, this study is the first to report the predictive value of RIL for OS in patients given CCRT followed by consolidative durvalumab for locally advanced NSCLC. Nevertheless, we also acknowledge several limitations, among them the relatively short follow-up time (and correspondingly immature data on OS and PFS) for patients given CCRT plus durvalumab; however, we did find that survival was significantly shorter among patients with sRIL after CCRT plus durvalumab. Second, we did not evaluate other types of toxicity or patterns of progression associated with lymphopenia in either treatment group. Finally, we were not able to evaluate how lymphocyte recovery after CCRT may have influenced the effects of durvalumab consolidation on survival, given the fact that diagnostic laboratory studies during durvalumab consolidation were not readily available because patients often resorted to receiving durvalumab infusion locally. We cannot rule out the possibility that the degree of lymphocyte recovery would also influence the prognosis of patients.

In conclusion, we found that severe RIL, whether defined as the lower tertile of patients on the basis of lymphocyte counts or by CTCAE G4 RIL, significantly compromised the OS benefit of consolidation durvalumab after CCRT. This is consistent with the importance of an intact immune system in determining the effectiveness of immunotherapy. This supports the importance of future efforts for lymphocyte protection or RIL mitigation strategies after CCRT to enhance the outcomes of consolidation durvalumab.

CRediT Authorship Contribution Statement

Wang Jing: Methodology, Formal analysis, Data curation, Writing—original draft, Writing—review and editing, Visualization.

Ting Xu: Methodology, Formal analysis, Data curation, Writing—review and editing.

Lirong Wu: Formal analysis, Data curation.

Pablo B. Lopez: Data curation; Writing—review and editing.

Clemens Grassberger, Susannah G. Ellsworth, George R. Blumenschein, Janet Tu, Mehmet Altan, Percy Lee: Validation, Writing—review and editing.

Radhe Mohan: Investigation, Funding acquisition, Writing—review and editing.

Brian Hobbs: Methodology, Formal analysis, Writing—review and editing.

Zhongxing Liao: Conceptualization, Validation, Data curation, Supervision, Project administration, Writing—review and editing.

Steven H. Lin: Conceptualization, Methodology, Validation, Formal analysis, Resources, Data curation, Writing—original draft, Writing—review and editing, Supervision, Project administration, Funding acquisition.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the JTO Clinical and Research Reports at www.jtocrr.org and at 10.1016/j.jtocrr.2022.100391

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