ORIGINAL ARTICLE

High-Grade Pneumonitis Events in Patients With Unresectable, Locally Advanced NSCLC Treated With Definitive Chemoradiation Followed by Adjuvant Durvalumab

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ABSTRACT

Background: The standard of care for unresectable locally advanced NSCLC is concurrent chemotherapy and radiation (CRT) followed by adjuvant durvalumab, established by the PACIFIC trial, which revealed acceptable although higher rates of pneumonitis with durvaluamb than placebo. We retrospectively reviewed patients with locally advanced NSCLC from 2018 to 2022 treated with definitive CRT (≥60 Gy) followed by at least one dose of adjuvant durvalumab.

Objective: To review the incidence of pneumonitis and contributing factors, and also to review grade 5 pneumonitis (G5) events.

Methods: We identified 78 cases with a median age of 70.0 years and a median follow-up of 36 months. All patients received CRT of at least 60 Gy at 2 Gy per fraction. A total of 22 patients (28.2%) completed 12 months of durvalumab. The cumulative incidence of any-grade pneumonitis was 28.2%. Pneumonitis rate in grades 1, 2, 3, 4, and 5 was 1.3%, 10.3%, 7.7%, 0.0%, and 9.0%, respectively.

Results: Multivariate analysis did not reveal significant factors associated with G5 pneumonitis. There were 8 patients who received radiation therapy doses above standard limits and, of these, only two developed G5 pneumonitis. All patients with G5 pneumonitis had multiple comorbidities or previous malignancy treated with systemic therapy. The median overall survival was 31.1 months and the median progression-free survival was 12.7 months.

Conclusions: We report comparable overall rates of pneumonitis relative to published data with higher rates of G5 pneumonitis. Patients with high-dose radiation therapy (≥60 Gy) and Eastern Cooperative Oncology Group performance status greater than or equal to 2 may tolerate adjuvant durvalumab, though providers should exercise caution in patients with extensive comorbidities.

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Introduction

The standard of care for locally advanced NSCLC (LA-NSCLC) is concurrent chemotherapy and radiation followed by durvalumab on the basis of the phase 3 PACIFIC trial.[1] The first analysis of the PACIFIC trial, published in 2017, reported significantly improved progression-free survival (PFS) with the addition of up to 12 months of adjuvant durvalumab; 16.8 versus 5.6 months with placebo. A follow-up study confirmed improvement in the median overall survival (OS) in the durvalumab arm: 47.5 versus 29.1 months.[2] The toxicity profile was similar in both arms and established adjuvant durvalumab as the new standard of care in patients with unresectable LA-NSCLC.[1] However, the rate of pneumonitis was higher in the durvalumab group. In addition, the rates were lower than have been reported for radiation therapy (RT) and chemotherapy alone.[3–7] The trial included a favorable patient population with Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 1 after chemotherapy and excluded patients with radiation dose to the lung volume receiving at least 20 Gy (V20) of greater than or equal to 35% or a mean lung dose (MLD) of greater than or equal to 20 Gy. These criteria are not strictly adhered to when giving this regimen in standard practice.[8–12] Since the initial publication of the PACIFIC trial, several reviews have been published evaluating the real-world (RW) rates of pneumonitis with durvalumab after concurrent chemotherapy and radiation (CRT) and associated risk factors.[9,10,12–15] The overall rates of pneumonitis range from 19% to 90% with at least grade 3 from 1.6% to 14.3%, higher than what was reported in the PACIFIC trial (Table 1).[1]

We performed a retrospective review of all patients treated with chemoradiotherapy followed by durvalumab in a single academic system including the affiliated Veteran Affairs Medical Center. The primary objective was to evaluate the incidence of pneumonitis and contributing factors with a focus on grade 5 (G5) events.

Materials and Methods

Patients

Under institutional review board approval, records of all patients treated between 2018 and 2022 for LA-NSCLC with definitive-intent CRT followed by at least 1 dose of durvalumab were reviewed. Patients were excluded if they had received previous thoracic RT (TRT) other than stereotactic body RT or previous treatment with anti–programmed cell death protein 1 or anti–programmed death-ligand 1 (PD-L1) therapy. Informed consent of patients was not obtained nor required as this was a retrospective review and therapies had been completed at the time of data collection.

Data Collection and End Points

Clinical and treatment data were collected from electronic medical records and radiation treatment planning systems. Demographic data included patient sex, age, ECOG PS, current smoking status, tumor stage, and histology, PD-L1 expression, EGFR status, and concurrent chemotherapy agents. Durvalumab treatment details including start and end dates, number of cycles, and reasons for discontinuation of therapy if less than 24 cycles were given. RT plan data included dose-volume metrics including MLD, V5, V20, and V30 with V_x referring to the volume receiving greater than or equal to x Gy. Pneumonitis was graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, and the toxicity criteria from the European Organization for Research and Treatment of Cancer.[16] Detailed chart review was conducted for all cases of G5 pneumonitis with two separate independent reviews and a third collective review by both the first and senior author. OS was defined as the absence of death. Events for this outcome include deaths from any cause. PFS was defined as the state of being alive and free of progression of the primary malignancy. Events for this outcome include relapse or progression and deaths from any cause. Both OS and PFS were measured after the completion of TRT.

Statistical Analysis

Patient, disease, and treatment-related characteristics; pneumonitis events; and dosimetric variables were summarized using descriptive statistics. OS and PFS were estimated from the start of RT. The Kaplan-Meier estimator was used to describe OS and PFS in the study cohort. Patient loss to follow-up was assumed to occur independently of relapse or progression and death. Median survival times were estimated by inverting the Kaplan-Meier estimates.

The cumulative incidences of pneumonitis after RT completion were described using the Aalen-Johansen estimator for all grade events and grades 3 to 5 events. Fine-Gray subdistribution hazard models were used to estimate the relationship of dose volume histograms (DVH) variables with the cumulative incidence of any-grade and grades 3 to 5 pneumonitis; subsequently, the fitted models were used to estimate the incidence of pneumonitis at the recommended dose constraints for MLD, the radiation dose to the lung volume receiving at least 5 Gy (V5), V20, and radiation dose to the lung volume receiving at least 30 Gy (V30). The

proportionality assumption was checked for these models using Schoenfeld residuals; no evidence of a violation of this assumption was found for any model. The cumulative incidences of any-grade, grades 2 to 5, and grades 3 to 5 pneumonitis were described separately by subgroups determined by patient sex, age, ECOG performance score, current smoking status, tumor histology, PD-L1 expression, and DVH variables. These incidences were compared among levels of each factor using Gray's tests. All statistical analyses were performed using Statistical Analysis System version 9.4 and R software version 4.1.1.

Results

We identified 78 consecutive cases meeting the eligibility criteria. The median patient age was 70.0 years (interquartile range 51.7-88.7 years). Most patients were men (62.8%), White (74.4%), stage IIIA to IIIB (80.8 %), and squamous cell histology (57.7%). All patients received at least 60 Gy definitive RT at 2 Gy per fraction except for three patients treated with 46 to 56 Gy to meet normal tissue dose constraints. There were 9 (11.5%) who received greater than 60 Gy (62–72 Gy). All patients received concurrent carboplatin/paclitaxel or carboplatin/pemetrexed with TRT. Regarding PD-L1 expression, for the patients for whom this information was available, 31 patients had a PD-L1 expression of at least 1% and of those patients, 19 had a PD-L1 expression greater than or equal to 50%. ECOG PS was measured after completion of CRT and 30.8% of patients had PS greater than or equal to 2 (Table 2).

A total of 22 patients (28.2%) completed the entire 12-month course of durvalumab. Of the patients that did not complete 1 year of durvalumab, the mean number of cycles completed was 8.1 with a median of 6 (range 1–25). There were 63 (80.8%) patients who had their first cycle longer than 42 days from completion of CRT (Fig. 1). The most common reason for durvalumab discontinuation was disease progression (n = 24, 42.9%) followed by toxicity (n = 21, 37.5%). The most common toxicity resulting in the discontinuation of durvalumab was pneumonitis, which occurred in 14 of 21 patients.

In addition, three patients presented with stage IVB disease with 1 to 3 brain metastasis at diagnosis. All three patients received gamma knife stereotactic radiosurgery to existing lesions followed by CRT and adjuvant durvalumab. There was 1 patient who developed central nervous system progression after the initial gamma knife for which they then received hippocampal avoidant whole brain RT before treatment of thoracic disease. All three of these patients are alive at the time of review with no evidence of disease progression. The seven patients with stage IIA/IIB disease were treated with CRT

Table 1. Comparison of Published Pneumonitis Events

Study	Cases (n)	Median Age	ECOG	Any Grade Pneumonitis (%)	Grade 1-2 (%)	Grade 3-4 (%)	Grade 5 (%)	Radiation Dose Information	Radiation Dose Analysis	1-year OS, %
Current	78	70	0-4	28.2	11.6	7.7	9	10.2% did not meet PACIFIC criteria	No association between dose & pneumonitis	81
PACIFIC[1]	473	64	0-1	33.9	28.9	4.2	0.80	V20 ≤35% and/or MLD ≤10 Gy	NA	83.1
Saad[9]	71	67	0-2	49	43.40	5.6	0	NR	NA	83.1
Offin[13]	62	66	0-1	19.4	18 (G2)	1.6 (G3)	0	Per PACIFIC	NA	85
Tsukita[15]	107 (87 Durva)	70	0-1	89	81	7.5	0	Per PACIFIC	V5≥ 60 Gy associated with ≥ G2 pneumonitis	
Shintani[10]	146	70	0-2	35 (G1 not reported)	30 (G2)	4	1	Per PACIFIC	Higher V20 > 26% associated with ≥ G2 pneumonitis	NR
Saito[12]	302	70	0-2	85	79	6	1	3% of cases did not meet specific criteria	V20 ≥25% and MLD ≥10Gy were predictive for symptomatic pneumonitis	NR
Desilets[11]	147	67	0-2	30	24	4	2	NR	NA	92.5

ECOG, Eastern Cooperative Oncology Group; G1, grade 1; G2, grade 2; G3, grade 3; NA, not assessed; NR, not reached; OS, overall survival; PACIFIC, xxx, V20, radiation dose to the lung volume receiving at least 20 Gy.

Table 2. Demographics and Treatment Data Characteristics

Patient Characteristics	Number (%), or Median (Range)
Age (y)	70.0 (51.7-88.7)
Sex	
Male	49 (62.8%)
Female	29 (37.2%)
Race	
White	58 (74.4%)
African American	7 (9.0%)
Unknown	13 (16.7%)
AJCC stage at diagnosis	
IIA	4 (5.1%)
IIB	3 (3.8%)
IIIA	35 (44.9%)
IIIB	28 (35.9%)
IIIC	4 (5.1%)
*IVB	3 (3.8%)
Unknown	1 (1.3%)
Histology	
Poorly differentiated	1 (1.3%)
Adenocarcinoma	31 (39.7%)
Squamous cell	45 (57.7%)
Large cell	1 (1.3%)
ECOG PS	
0	15 (19.2%)
1	39 (50.0%)
2	16 (20.5%)
3	7 (9.0%)
4	1 (1.3%)
Smoking status	
Not current smoker	65 (83.3%)
Current smoker	13 (16.7%)
PD-L1 expression (%)	
$\geq$ 1%	31 (81.6%)
$\geq$ 50 %	19 (50.0%)
Unknown/not assessed	40
Completed 1 year of durvalumab	22 (28.2%)
Reasons for discontinuing durvalumab	
Disease progression	24
Toxicity	21
Systemic illness	7
Poor PS	4
Start of durvalumab $>$ 42 days after the end of CRT	63 (80.8%)
Radiation dose data	
Mean lung dose	16.3 (4.3-26.4)
V30 (%)	20.9 (5.7-32.7)
V20 (%)	28.9 (8.0-41.8)
V5 (%)	57.9 (12.0-97.7)
Mean RT dose $>$ 20 Gy and/or V20 $>$ 35%	8 (10.3%)

Note: All three patients had brain metastases only, treated with stereotactic radiosurgery followed by definitive chemoradiation and adjuvant durvalumab.

AJCC, American Joint Committee on Cancer; CRT, concurrent chemotherapy and radiation; ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1; PS, performance status; RT, RT; V5, radiation dose to the lung volume receiving at least 5 Gy; V20, radiation dose to the lung volume receiving at least 20 Gy; V30, radiation dose to the lung volume receiving at least 30 Gy.

and adjuvant durvalumab for a myriad of reasons including poor surgical candidates, concern for more extensive mediastinal adenopathy and high interventional risk, and protracted workup with slow progression of disease necessitating escalated therapy.

Pneumonitis

The median follow-up period was 36 months. The cumulative incidence of any-grade pneumonitis was 28.2%. Pneumonitis rates in grades 1, 2, 3, 4, and 5 were 1.3%, 10.3%, 7.7%, 0.0%, and 9.0%, respectively. All events occurred within 18 months after the completion of CRT. The median time from the start of durvalumab to any-grade of pneumonitis was 68.5 days. The risk of pneumonitis increased with increasing radiation dose although there was no specific dose parameter associated with grades 3 to 5 or G5 pneumonitis.

Regarding the clinical onset of pneumonitis after TRT, we defined this as occurring within 180 days of the last fraction of TRT in line with published data. Most patients with grades 2 to 5 pneumonitis developed reactions within 180 days of the last fraction of TRT (n = 17/22). Only five of the 22 pneumonitis events occurred longer than 180 days and were deemed unrelated to TRT. All events occurred within 18 months of completion of TRT. An additional analysis was conducted for the onset of pneumonitis in relation to immunotherapy and revealed that most patients developed reactions while receiving durvalumab.

Pneumonitis Events and DVH Information

The association of mean lung RT (RT) dose, V5, V20, and V30 with pneumonitis risk was evaluated. To align with published and historically acceptable dose constraints to produce a risk of pneumonitis of less than 20% after standard TRT, goal constraints should include MLD of less than or equal to 20 Gy, V5 of less than or equal to 65%, V20 of less than or equal to 35%, and V30 of less than or equal to 25%.[1,7] Overall, higher rates of pneumonitis were observed in patients exceeding published constraints for any-grade pneumonitis and specifically in the grades 3 to 5 pneumonitis group. Specifically, regarding the grades 3 to 5 pneumonitis events: an MLD of less than or equal to 20 Gy resulted in a 23.7% rate of pneumonitis, an MLD greater than 20 Gy resulted in a 33.3% rate of pneumonitis; V5 of less than or equal to 65% resulted in a 24.1% rate of pneumonitis and V5 greater than 65% resulted in 23.8% rate of pneumonitis; V20 of less than or equal to 35% resulted in 22.5% rate of pneumonitis and V20 greater than 35% resulted in 37.5% rate of pneumonitis; V30 of less than

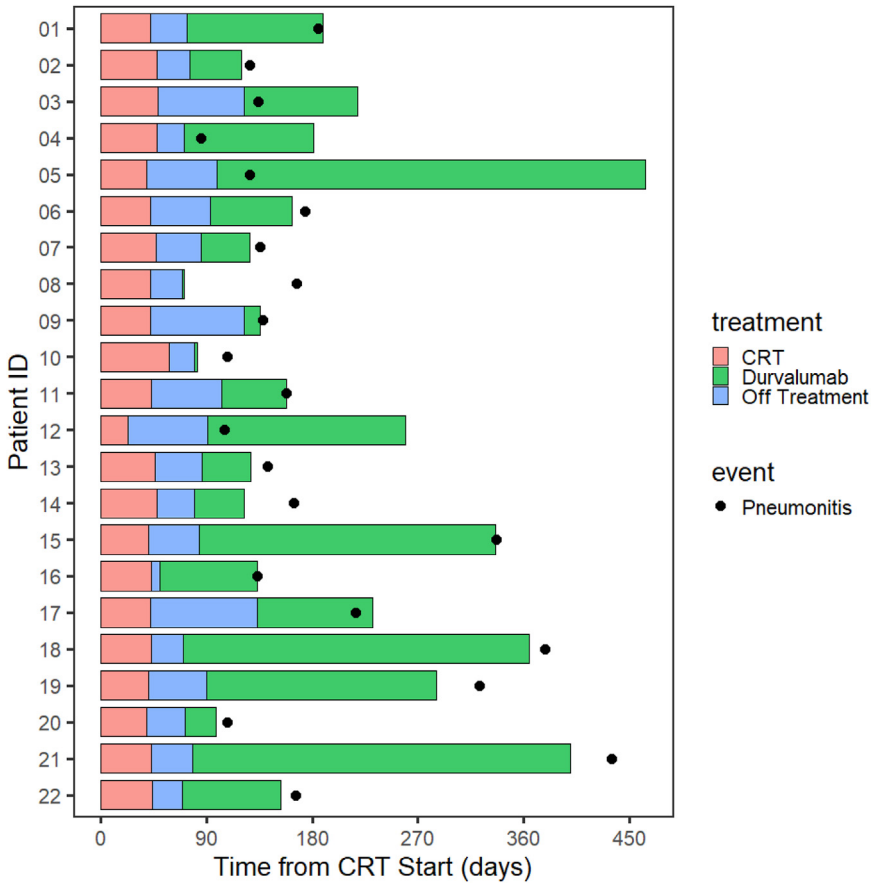

Figure 1. Timeline of therapies and pneumonitis events. CRT, concurrent chemotherapy and radiation; ID, identification.

or equal to 25% resulted in 21.9% rate of pneumonitis and V30 greater than 25% resulted in 33.3% rate of pneumonitis.

To formally evaluate the appropriateness of published TRT dose constraints with the addition of immunotherapy, we used univariate Fine-Gray regression models to estimate the cumulative incidence of pneumonitis (both any-grade and grades 3–5) onset as a function of these DVH values. These models were used to predict pneumonitis risk at any given values for MLD, V5, V20, and V30. These models were then used to predict the risk of pneumonitis at published TRT DVH constraints. We found that the rates of any-grade pneumonitis were statistically significant and exceeded 20% at MLD of 20 Gy, V5 of 65%, V20 of 35%, and V30 of 25% with rates of 38.3%, 32.6%, 41.2%, and 38.1% respectively.

A similar analysis was conducted to assess the risk of grades 3 to 5 pneumonitis with measured DVH information. Similar to the results observed for any-grade pneumonitis, the estimated grade 3 to 5 pneumonitis risk with published TRT dose constraints exceeded 20% for all variables but was not statistically significant.

Additional analyses were conducted on the cumulative incidence of grades 2 to 5 pneumonitis on the basis of patient demographic information and other patient-related factors. For grades 2 to 5 pneumonitis, patient sex, age, ECOG PS, current smoking status, tumor histology, and PD-L1 expression were not significant. However, when looking at PD-L1 expression, comparing expression less than 1% or greater than or equal to 1% did not significantly impact pneumonitis events, but there were seven pneumonitis events (38.7%) at 1 year with PD-L1 expression less than 50% versus 2 pneumonitis events (10.5%) at 1 year with PD-L1 expression greater than or equal to 50% with a p value of 0.053 that approached significance.

Detailed Assessment of Grade 5 Events

On multivariate analysis (MVA), patient sex, age, ECOG PS, current smoking status, tumor histology, and PD-L1 expression were not significantly associated with G5 pneumonitis. Three of the seven cases with G5 pneumonitis had adenocarcinomas (two EGFR-negative, one unknown) and four squamous cell carcinoma. PD-L1 status was available in three of the G5 cases and was 5%, 5%, and 50%. Demographic data for patients with G5 pneumonitis are presented in Table 3 and individual case details are in Table 4. All but one patient

Table 3. Patients Demographics With Grade 5 Pneumonitis

Demographics	Number (N=7)
Age (y)	
≥65	6
Sex	
Male	4
Female	3
Histology	
Adenocarcinoma	3
Squamous cell	4
ECOG performance status	
0	1
1	3
2	2
3	1
Smoking status	
Not current smoker	7
Current smoker	0
MLD dose >20 Gy and/or V20 >35%	2

ECOG, Eastern Cooperative Oncology Group; MLD, mean lung dose; V20, radiation dose to the lung volume receiving at least 20 Gy.

were older than 65 years and 5 were older than 70 years old at diagnosis. Five of the seven cases had chronic obstructive pulmonary disease (COPD) and of those, four used at least one inhaler or nebulizer treatment. All cases had multiple comorbidities. Of the two cases without COPD, one had severe neuropathy thought to be paraneoplastic and treated with intravenous immunoglobulin before definitive treatment and the other had a history of cholangiocarcinoma resected and treated with adjuvant gemcitabine 2 years before lung cancer diagnosis. Three patients with G5 events had ECOG PS of at least 2. Two of the three patients had pulmonary function tests available for review before receipt of durvalumab with one patient meeting the criteria for medical operability whereas the other with very poor pulmonary function with a diffusion capacity for carbon monoxide of 38% and a forced expiratory volume in 1 second of 0.75 L. Two of the cases had V20 greater than 35% and/or MLD greater than 20Gy and both had ECOG PS of at least 2 and high-dose RT (HDRT). Radiographic imaging revealed a significant progression of pulmonary inflammation consistent with pneumonitis primarily in the RT portals and also in the nontreated lung (Fig. 2).

RT Dose Above PACIFIC Trial Dose Criteria (HDRT)

There were 8 cases (8/78) in the cohort who had lung doses outside of acceptable ranges for the PACIFIC trial. The rate of pneumonitis was similar among the patients with doses that did and did not exceed standard RT dose constraints. A total of 50 patients eligible for the PACIFIC trial did not develop pneumonitis. Six of the eight patients treated with HDRT did not develop pneumonitis. However, pneumonitis after durvalumab in patients that received HDRT was fatal (Table 3, cases 1 and 4). All six cases with HDRT that did not have pneumonitis had ECOG greater than or equal to 1 including two with ECOG 2, and one with ECOG 3. One patient was 60 years old, and the remainder were older than 65 years old, including three who were older than 70 years. These patients' comorbidities were relatively limited and none of the patients had known pulmonary disease before lung cancer diagnosis (Table 5).

OS and PFS

The OS at 1, 2, and 3 years were 81.0%, 53.3%, and 45.7%. The median OS was 31.1 months and the median PFS was 12.7 months.

Discussion

Our analysis of pneumonitis in this retrospective review revealed overall pneumonitis rates to be similar to other RW reports and the PACIFIC trial; however, G5 toxicity was notably higher (Table 1).

We suspected that there may be a dose threshold that was exceeded with CRT resulting in G5 pneumonitis in our review. Although the TRT dose is likely a contributing factor, the risk of fatal pneumonitis with immunotherapy after CRT is multifactorial. There was no dose limit associated with G5 pneumonitis. In addition, there were no baseline factors on MVA that were statistically correlated with the risk of G5 pneumonitis.

Girard et al.[17] reported on the RW effectiveness of durvalumab from the observational PACIFIC-R study that revealed 16.5% of patients experienced adverse events leading to treatment discontinuation and 9.5% discontinued secondary to pneumonitis or interstitial lung disease. RW studies after PACIFIC reviews discussing higher-than-anticipated rates of pneumonitis with detailed analysis of radiation dose have been reported. A multicenter retrospective review by Shintani et al.[10] reported an overall incidence of at least grade 2 (G2) pneumonitis events of 34.4%, comparable to the 28.2% rate of any-grade pneumonitis in this cohort. Combined V20 was a significant risk factor for G2 pneumonitis events with significantly higher events found in those with V20 of at least 26%.[10] Tsukita et al.[15] reported a review of 107 patients treated with CRT with 81% receiving adjuvant durvalumab. Within that cohort, any-grade pneumonitis was found in 89% of the patients (53% grade 1, 28% G2, 6.5% grade 3 [G3], and 0.9% grade 4); in addition to V5 greater than or equal to 58.9%, age 70 years and older, and male sex were significantly associated with G2 and higher pneumonitis ($p = 0.0065$, 0.036, and 0.0013 respectively). Saito

Table 4. Case Reviews of Grade 5 Pneumonitis

Case	Age	ECOG	Durvalumab Cycles	Comorbidity	Histology	EGFR	V5 (%)	V20 (%)	V30 (%)	MLD (cGy)
1	79	3	1	Breast cancer >5 y COPD on inhalers HTN	SCCA	NA	77.88	41.82	27.77	2286
2	66	1	17	COPD (nebulizer) ARDS pneumonia 3 y before HLD Alcohol abuse Parkinson's	SCCA	NA	65.3	32.42	22.91	1847
3	64	1	8	Stage I lung cancer: SBRT 4 months before COPD HTN Hepatitis C HLD DM PVD Reactive airway disease ESRD on dialysis	SCCA	NA	49.18	29.07	20.75	1499
4	77	2	2	COPD on inhalers COPD exacerbation 1 month before starting Durvalumab PVD HLD	Adenocarcinoma	Negative	57.92	35.63	25.7	1771
5	83	2	4	CAD HLD HTN Paraneoplastic peripheral neuropathy with IVIG treatment 2 months before diagnosis Declining mental status	SCCA	NA	30.22	19.63	16.95	1151
6	73	1	4	Cardiomyopathy HF COPD on inhalers HLD Obesity HTN	Adenocarcinoma	NA	78.12	29.56	20.31	1799
7	71	0	4	Cholangiocarcinoma with adjuvant gemcitabine 2y before Hepatitis C HTN HLD Resected colon cancer 16 y before	Adenocarcinoma	Negative	70.74	29.92	23.27	1791

Note: Case example and radiographic review in Figure 1.

ARDS, acute respiratory distress syndrome; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; SCCA, squamous cell carcinoma; DM, diabetes mellitus; ECOG; Eastern Cooperative Oncology Group; ESRD, end-stage renal disease; HF, heart failure; HLD, hyperlipidemia; HTN, hypertension; IVIG, intravenous immunoglobulin; MLD; mean lung dose; NA, not assessed; PVD, peripheral vascular disease; SBRT, stereotactic body RT; V5, radiation dose to the lung volume receiving at least 5 Gy; V20, radiation dose to the lung volume receiving at least 20 Gy; V30, radiation dose to the lung volume receiving at least 30 Gy.

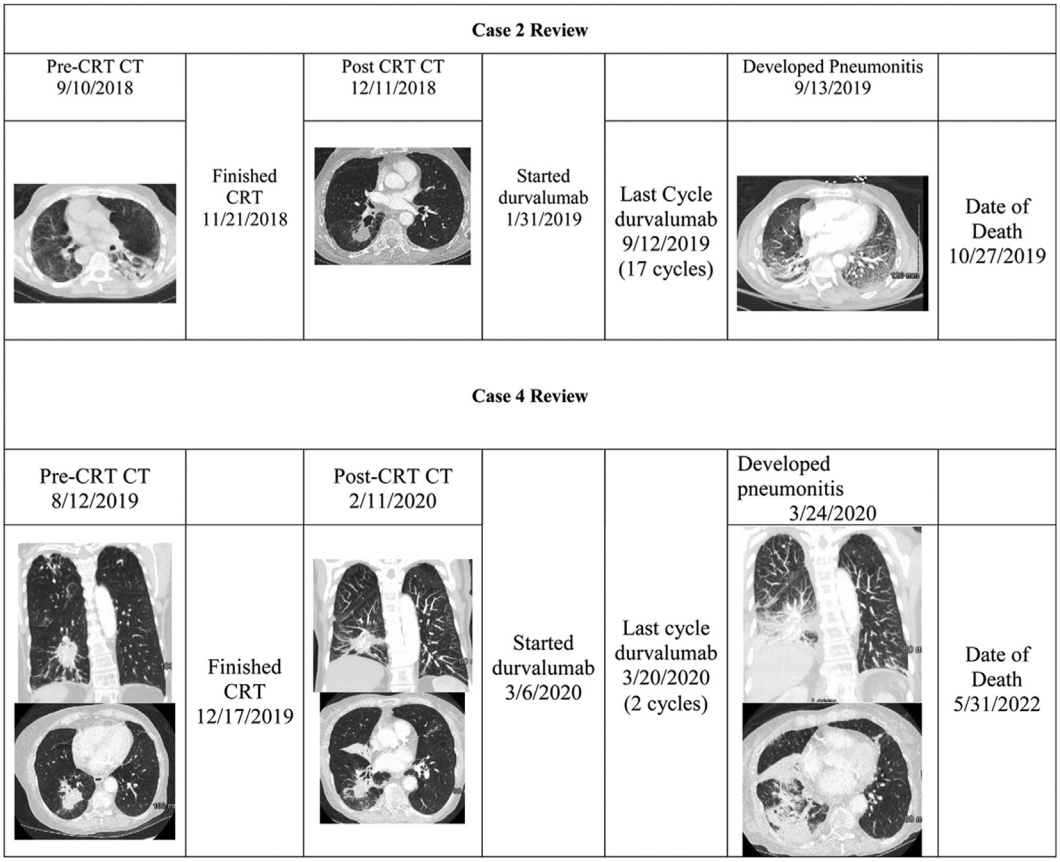

Figure 2. G5 pneumonitis radiographic review cases 2 and 4. CRT, concurrent chemotherapy and radiation; CT, computed tomography; G5, grade 5.

et al.[12] reported an extensive review regarding pneumonitis risk and radiation dose in 302 patients treated with CRT, 225 of whom received adjuvant durvalumab. Of the patients that received durvalumab, the overall rate of pneumonitis was 85% (51% grade 1, 28% G2, 4% G3, 2% grade 4, and 1% G5). There is no clear dose threshold from these reviews that defines the acceptable lung dose with CRT for the low rate of pneumonitis with adjuvant durvalumab.[12]

Risk factors for pneumonitis are multifactorial and not defined solely by radiation dose. Within our cohort, eight cases (10%) had lung doses exceeding PACIFIC criteria. However, only two of the eight cases had pneumonitis and both were G5 events (1 patient had an MLD of 22.86 Gy and V20 of 41.82 Gy and one patient had a V20 of 35.63). All seven of the G5 cases had complicated medical histories including five with COPD, one with previous treatment with gemcitabine, known to be a radiosensitizer with radiation recall, and one case with recent intravenous immunoglobulin therapy for neuropathy (case 5). Six patients that would have been ineligible for the PACIFIC trial on the basis of RT dose constraints did not develop pneumonitis and had limited medical comorbidities, no preexisting pulmonary disease, and no previous systemic chemotherapy. However, all six patients had ECOG of at least 1 including two with ECOG 2 and one with ECOG 3. Among patients with G5 pneumonitis, only one was younger than 65 years old and three were older than 70 years.

In our cohort, all pneumonitis events developed within 18 months of completion of TRT and developed after initiation of durvalumab. Of note, 63 (80.8%) patients within this cohort had their first cycle longer than 42 days from completion of CRT. Further investigation revealed that in general, patients were started on adjuvant durvalumab after their first visit with medical oncology after CRT, which typically occurred 4 to 10 weeks later. Some patients were delayed because of noncompliance, pulmonary infection at treatment completion, an additional pressing medical issue that required intervention, or concerns of resolving pulmonary ground glass opacities. Figure 1 illustrates a pictorial representation of the cohort's pneumonitis events for each case chronologically in reference to definitive CRT, time from completion of CRT to start of durvalumab, and adjuvant durvalumab therapy. We did not find a significant association among the timing of TRT, durvalumab, and the development of pneumonitis.

Table 5. Patients Exceeding PACIFIC Constraints Without Pneumonitis

Age	ECOG	Durvalumab Cycles	Comorbidity	Histology	EGFR	V5(%)	V20(%)	MLD (cGy)
71	1	24	DVT	Adenocarcinoma	negative	88.05	35	1693
66	1	16	CVA HLD Previous alcohol abuse	Adenocarcinoma	negative	53.47	35	1934
72	1	24	DM HTN PVD	SCCA	NA	97.67	39.36	2636
68	3	11	DM HTN Uterine Cancer	SCCA	NA	74.59	36.49	1855
87	2	6	PVD HTN HLD	SCCA	NA	58.87	35.42	1818
60	2	3	None	Adenocarcinoma	negative	57.19	34.9	2047

CVA, cerebrovascular accident; DVT, deep vein thrombosis; ECOG; Eastern Cooperative Oncology Group; HLD, hyperlipidemia; HTN, hypertension; MLD; mean lung dose; NA, not assessed; PVD, peripheral vascular disease; SCCA, squamous cell carcinoma; SBRT, Stereotactic body RT; V5, radiation dose to the lung volume receiving at least 5 Gy; V20, radiation dose to the lung volume receiving at least 20 Gy.

Similarly, several other studies evaluated the timing of radiation in relation to immunotherapy and did not find an association with increased toxicity.[9,10,18]

The PACIFIC trial, as do most prospective randomized trials (PRT), included a relatively favorable patient population. In that trial, patients had a median age of 64 years, ECOG 0 to 1, V20 less than or equal to 35%, and/or MLD less than or equal to 20 Gy, and all patients had stage III disease. RW reviews frequently exhibit less rigorous adherence criteria for treatment used in PRT; therefore, the same magnitude of benefit may not be observed in RW studies as compared with PRT and there may be unanticipated toxicity and outcomes. Furthermore, nuances of TRT delivery parameters are not widely disseminated in practice. Medical oncologists, responsible for administering durvalumab, are unlikely to be familiar with specific patient DVH information and may not be familiar with DVH parameters for PACIFIC trial eligibility. These RW results suggest that awareness of high-grade pneumonitis risk and both multidisciplinary discussions and management is needed for patient selection and treatment delivery.

Wang et al.[19] reported the results of a meta-analysis of toxicity and outcomes of 13 studies involving 1885 stage III lung cancer cases treated with CRT and adjuvant durvalumab. Common differences in patient characteristics in the RW studies relative to PACIFIC data were median age older than 65 years (9 studies), time from CRT to durvalumab of longer than 42 days (8 studies), and ECOG of at least 2 (5 studies). Only one study reported lung dose data with V20 at least 35%. The pooled incidence of pneumonitis was 35% and G3 or higher pneumonitis was 6%. Despite variation in adherence to the PACIFIC trial eligibility, RW studies continue to report improved favorable outcomes with durvalumab.[19]

In this review, the median OS and PFS were lower than in the durvalumab arm of the PACIFIC trial, as anticipated because of a relatively unfavorable patient population, including higher median age, PS greater than 1, and more advanced disease (Table 6). An RW review of veterans treated definitively with adjuvant durvalumab reported improved OS and PFS as compared with those without adjuvant durvalumab. This RW review also reported inferior results in their Veteran Affairs cohort as compared with the PACIFIC trial population.[20] There are no direct comparisons for standard treatment for this unfavorable cohort to draw conclusions regarding the benefit of adjuvant durvalumab. However, the median OS and PFS in this cohort are favorable

Table 6. Demographics Relative to PACIFIC Trial

	PACIFIC		
	Durva	Placebo	Current Cohort
Median age (y)	64	64	70
Stage (%)			
IA-IIB	1.7	2.1	0
IIIA	52.9	52.7	44.9
IIIB	44.5	45.1	35.9
IIIC	0	0	5.1
IV	0.8	-	3.8
PS (%)			
0	49.2	48.1	19.2
1	50.4	51.5	50
2	0	0	20.5
3	0	0	9
4	0	0	1.3

PS, performance status.

relative to the placebo arm of the PACIFIC trial, suggesting improved outcomes with adjuvant durvalumab.[1]

To conclude, in this single academic institution cohort, we found comparable overall rates of pneumonitis relative to published data with higher rates of G5 pneumonitis. Although we did not identify significant factors correlated with pneumonitis on MVA, our individual review of G5 pneumonitis events highlights the importance of comorbidity assessment for patient selection. Carefully selected patients treated with RT doses exceeding PACIFIC constraints, advanced disease, and unfavorable PS may tolerate and benefit from adjuvant durvalumab. Durvalumab after CRT for LA-NSCLC should be used with caution in patients with poor PS, multiple comorbidities, particularly cardiopulmonary disease, and those who previously received oncologic therapies. The risk of high-grade pneumonitis is multifactorial and multidisciplinary discussions regarding patient selection and management are imperative.

CRediT Authorship Contribution Statement

Ciani Ellison: Conceptualization, Data curation, Investigation, Project administration, Writing-original draft, Writing - review & editing

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Samantha Benz: Writing-review & editing.

Adam Currey: Conceptualization, Investigation, Writing-review & editing, Validation.

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Slade Klawikowski: Software, Resources, Data curation.

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Jonathan Thompson: Project administration, Validation, Conceptualization, Writing- review & editing.

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