Scientific Article

Predictors of Pneumonitis in Patients With Locally Advanced Non-Small Cell Lung Cancer Treated With Definitive Chemoradiation Followed by Consolidative Durvalumab

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Abstract

Purpose: In patients with locally advanced, unresectable non-small cell lung cancer (NSCLC), the standard of care is concurrent chemoradiation (CRT) followed by consolidative immunotherapy with durvalumab. Pneumonitis is a known adverse event of both radiation therapy and immune checkpoint inhibitors such as durvalumab. We sought to characterize pneumonitis rates and dosimetric predictors of pneumonitis in a real-world population of patients with NSCLC treated with definitive CRT followed by consolidative durvalumab.

Methods and Materials: Patients with NSCLC from a single institution who were treated with definitive CRT followed by consolidative durvalumab were identified. Outcomes of interest included pneumonitis incidence, type of pneumonitis, progression-free survival, and overall survival.

Results: Sixty-two patients were included in our data set treated from 2018 to 2021 with a median follow-up of 17 months. The rate of grade 2+ pneumonitis in our cohort was 32.3%, and the rate of grade 3+ pneumonitis was 9.7%. Lung dosimetry parameters including V20 ≥30% and mean lung dose (MLD) >18 Gy were found to be correlated with increased rates of grade 2+ and grade 3+ pneumonitis. Patients with a lung V20 ≥30% had a grade 2+ pneumonitis rate at 1 year of 49.8% compared with 17.8% in patients with a lung V20 <30% (*P* = .015). Similarly, patients with an MLD >18 Gy had a grade 2+ pneumonitis rate at 1 year of 52.4% compared with 25.8% in patients with an MLD ≤18 Gy (*P* = .01). Moreover, heart dosimetry parameters including mean heart dose ≥10 Gy were found to be correlated with increased rates of grade 2+ pneumonitis. The estimated 1-year overall survival and progression-free survival of our cohort were 86.8% and 64.1%, respectively.

Conclusions: The modern management of locally advanced, unresectable NSCLC involves definitive chemoradiation followed by consolidative durvalumab. Pneumonitis rates were higher than expected in this cohort, particularly for patients with a lung V20 ≥30%, MLD >18 Gy, and mean heart dose ≥10 Gy, suggesting that more stringent radiation planning dose constraints may be needed.

Introduction

Approximately one-third of patients with non-small cell lung cancer (NSCLC) present with locally advanced, stage III disease at diagnosis.[1] The standard of care for patients with unresectable stage III NSCLC is concurrent chemoradiotherapy (CRT) with platinum-based doublet chemotherapy.[2,3] The PACIFIC trial has demonstrated significantly improved progression-free survival (PFS) and overall survival (OS) with the addition of consolidative immunotherapy with durvalumab after definitive CRT.[4-8]

Pneumonitis is a known adverse event of both radiation therapy (RT) and immune checkpoint inhibitors such as durvalumab.[9-12] Radiation pneumonitis is a common, clinically significant toxicity that is associated with thoracic radiation.[10] In patients with locally advanced NSCLC treated with definitive chemoradiation, rates of symptomatic radiation pneumonitis range from 15% to 40%.[13-16] Pneumonitis is associated with significant morbidity, can be fatal, and has been suggested to limit the ability of patients to receive consolidative durvalumab.[9,12,17,18] The rate of grade 3+ pneumonitis in the PACIFIC trial was low at 3.4%; however, there are limited data regarding the dosimetry of patients enrolled in the PACIFIC trial.[4] It is unclear whether established constraints accurately predict pneumonitis rates in this particular patient population. We set out to explore predictors of pneumonitis risk in a real-world population of patients with locally advanced NSCLC treated with CRT followed by consolidative durvalumab to help determine optimal radiation dose constraints in this patient population.

Methods and Materials

This retrospective database study was approved by the institutional review board of Rhode Island Hospital. A total of 62 consecutive patients with locally advanced NSCLC treated nonsurgically with CRT followed by consolidative durvalumab were identified. Patients were excluded if they were <18 years old, did not have histologic confirmation of diagnosis, were enrolled in a clinical trial with alternative radiation therapy fractionation, or did not have full dosimetry data available for analysis.

Target delineation and radiation therapy dose

All patients were treated with intensity modulated radiation therapy using 4-dimensional computed tomography treatment planning and were treated with definitive intent. Dose prescription and fractionation were at the discretion of the treating radiation oncologist. PTV expansion was typically 0.5 cm. Treatment planning software was used to calculate doses to relevant organs at risk: the volume of lung receiving 20 Gy (V20), the mean lung dose (MLD), the volume of lung receiving 10 Gy (V10), lung V5, mean heart dose (MHD), the volume of heart receiving 5 Gy (V5), heart V10, heart V20, and heart V40.

Outcomes

Patient outcomes were analyzed retrospectively in a de-identified manner. National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0, was used for grading pneumonitis (grade 2 = new or worsening respiratory symptoms, grade 3 = severely symptomatic resulting in limits to self-care or requiring oxygen, grade 4 = life-threatening and required hospitalization, grade 5 = death).[19] Differentiation of radiation pneumonitis versus durvalumab pneumonitis was determined by a radiation oncologist using clinical, radiographic, and radiation dosimetry data to inform classification of pneumonitis type. OS was defined as time from completion of CRT to death, PFS was defined as time from completion of CRT to progression of disease or death, and time to pneumonitis was defined as time from completion of CRT to pneumonitis development.

Statistical analysis

Descriptive statistics were used to characterize the patient cohort. The Kaplan-Meier method was used to estimate OS, PFS, and pneumonitis incidence and the log-rank test was used to compare rates of pneumonitis among patient groups. Cox proportional hazards models were used to adjust for differences in age, sex, smoking status, baseline chronic obstructive pulmonary disorder (COPD), stage, histology, type of chemotherapy, cycles of durvalumab, and selected radiation dosimetric parameters. Receiver operating characteristic curve analysis was used to identify cut points to dichotomize dosimetric factors of interest and both clinical relevance and statistical significance was used to select cut points.[20] P values <.05 were considered statistically significant. Data analysis was performed using SPSS version 22 (IBM).

Results

Patient demographics and clinical variables

Baseline characteristics of patients treated with definitive CRT followed by consolidative durvalumab are summarized in Table 1. In total, 62 patients were identified with a median follow-up of 17 months. The median age was 67 years old (interquartile range [IQR], 62-73). All patients included had a smoking history with 85% of patients being former smokers, and 15% of patients were current smokers at the time of initiation of CRT. Among the total cohort, 42% of patients had a documented diagnosis of COPD. Ninety percent of patients included were stage III (39% stage IIIA, 45% stage IIIB, 6% stage IIIC). A minority, 10% of patients were stage IIB. All patients included had a diagnosis of NSCLC with 42% squamous histology, 37% adenocarcinoma histology, and 21% NSCLC unspecified histology.

Systemic therapy details

Systemic therapy including concurrent chemotherapy regimens as well as number of cycles of consolidative durvalumab are summarized in Table 2. The majority of patients (61%) received concurrent carboplatin/paclitaxel during CRT. The median number of cycles of durvalumab was 17 (IQR, 8-24).

Radiation details

Treatment planning technique, radiation dose, and dosimetry data are summarized in Table 2. All patients were planned using intensity modulated radiation therapy and 4-dimensional computed tomography. The median radiation therapy (RT) dose was 63 Gy (IQR, 60-64.8 Gy) and all patients were treated with conventional fractionation defined as a fraction size of ≤2 Gy. The median lung V20 was 27% (IQR, 23%-32%) with 35 patients with a V20 <30% and 27 patients with a V20 ≥30%. The median MLD was 15.5 Gy (IQR, 13-18) with 48 patients with an MLD ≤18 Gy and 14 patients with an MLD >18 Gy.

Patient outcomes and toxicity

Crude rates of grade 2+ and grade 3+ pneumonitis are summarized in Table E1. Based on National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, 32.3% (20 of 62) of patients experienced grade 2+ pneumonitis and 9.7% (6 of 62) of patients experienced grade 3+ pneumonitis. Of the 20 cases of grade 2+ pneumonitis, 75% (15 of 20) were attributed to radiation, 20% (4 of 20) were attributed to durvalumab, and 5% (1 of 20) were equivocal, only 11% (7 of 62) of patients discontinued durvalumab early due to pneumonitis. Of the 7 patients who discontinued durvalumab early due to pneumonitis, 2 were rechallenged with durvalumab after resolution of pneumonitis symptoms. One patient tolerated rechallenge with durvalumab and the other patient again developed pneumonitis requiring permanent discontinuation of durvalumab (Table E1). There was 1 case of grade 5 pneumonitis which was attributed to durvalumab. For the entire study population, the estimated 6- and 12-month incidence of grade 2+ pneumonitis were 27.8% and 31.7% (Fig. 1A). For the entire study population, the estimated 6- and 12-month incidence of grade 3+ pneumonitis were 8.4% and 11.8% (Fig. 1B).

Among the patient baseline and treatment characteristics including age, sex, smoking status, diagnosis of COPD, cancer stage, histology, type of chemotherapy, cycles of durvalumab, and lung and heart radiation parameters, only cycles of durvalumab and lung and heart radiation parameters were correlated with rates of pneumonitis on univariable analysis (Table 3). Number of durvalumab cycles was associated with a reduced incidence of pneumonitis on univariable analysis (hazard ratio [HR], 0.919; 95% confidence interval [CI], 0.872-0.968; $P = .002$) (Table 3).

We then examined lung dosimetric parameters including lung V5, V10, V20, and MLD and their association

Table 1　Baseline characteristics of patients with locally advanced NSCLC treated with definitive chemoradiotherapy followed by consolidative durvalumab

Median follow-up (mo)	17	
Age (median, IQR)	67	(62-73)
Male sex (n, %)	30	48%
Smoking (n, %)		
Former	53	85%
Current	9	15%
COPD (n, %)	26	42%
AJCC 8th edition stage (n, %)		
IIB	6	10%
IIIA	24	39%
IIIB	28	45%
IIIC	4	6%
Histology (n, %)		
Squamous	26	42%
Adenocarcinoma	23	37%
NSCLC unspecified	13	21%

Abbreviations: AJCC = american joint commission on cancer; COPD = chronic obstructive pulmonary disorder; IQR = interquartile range; NSCLC = non-small cell lung cancer.

Table 2   Radiation treatment planning technique, dose prescription, lung dosimetry, and systemic therapy details

RT dose (Gy) (median, IQR)	63	60-64.8
Lung V20 (median, IQR)	27%	23%-32%
V20<30% (n, %)	35	56%
V20≥30% (n, %)	27	44%
Mean lung dose (median, IQR)	15.5	13-18
MLD≤18 Gy (n, %)	48	77%
MLD>18 Gy (n, %)	14	23%
Mean heart dose (median, IQR)	9.50	6.25-14
MHD<10 Gy (n, %)	31	55%
MHD≥10 Gy (n,%)	32	45%
Type of chemotherapy (n, %)		
Carboplatin/paclitaxel	38	61%
Other	24	39%
Number of cycles of durvalumab (median, IQR)	17	(8-24)

Abbreviations: IQR = interquartile range; RT = radiation therapy. MLD = mean lung does, MHD = mean heart dose; V20 = volume receiving 20 Gy
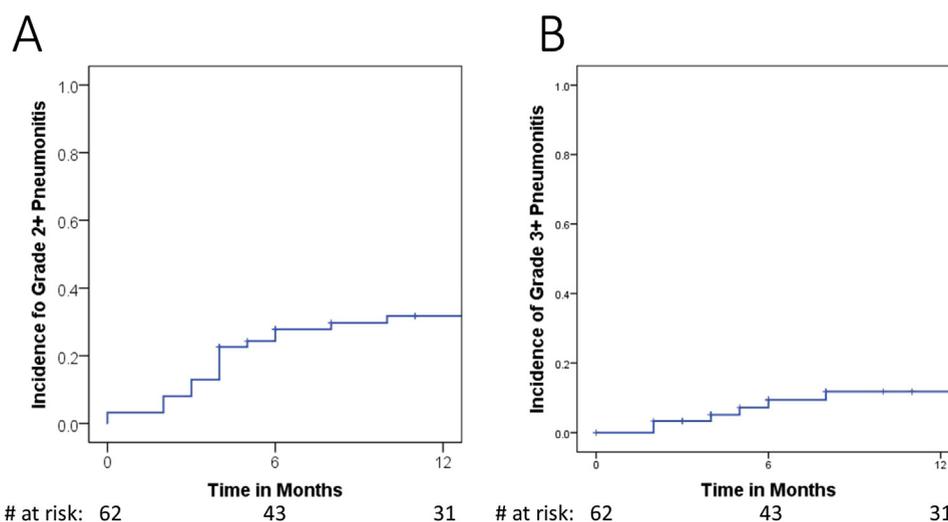
Figure 1   Kaplan-Meier curves for time to pneumonitis: (A) grade 2+ pneumonitis and (B) grade 3+ pneumonitis.

with grade 2+ pneumonitis on univariable analysis. Lung V20 (HR, 2.301; 95% CI, 1.045-5.068; P = .039) and MLD (HR, 7.5; 95% CI, 1.690-33.278; P = .008) were associated with increased pneumonitis risk whereas lung V5 (HR, 1.458; 95% CI, 0.948-2.240; P = .086) and V10 (HR, 1.204; 95% CI, 0.789-1.838; P = .389) were not (HR provided per 10 Gy or per 10%) (Table 3). Dosimetric cutoff levels found to confer a higher grade 2+ and grade 3+ pneumonitis risk, including V20 ≥30% and MLD >18 Gy, were selected for further analysis.

Patients with a lung V20 ≥30% were more likely to develop grade 2+ pneumonitis. The estimated 6- and 12-month rates of grade 2+ pneumonitis were 17.8% and 17.8% for the group with a lung V20 <30% compared with 41% and 49.8% for the group with a lung V20 ≥30% (P = .015) (Fig. 2A). Similarly, patients with a lung V20 ≥30% were more likely to develop grade 3+ pneumonitis. The estimated 6- and 12-month rates of grade 3+ pneumonitis were 3.6% and 3.6% for the group with a lung V20 <30% compared with 17.6% and 23.5% for the group with a lung V20 ≥30% (P = .024) (Fig. 2B). The National Comprehensive Cancer Network–recommended cutoff of V20 ≥35% was also analyzed.[21] Analysis of patients with lung V20 ≥35% was limited due to a very small number of patients with lung V20 ≥35% (n = 4). Rates of pneumonitis were not different between V20 ≥35% and V20 <35% with no difference between grade 2+ pneumonitis (P = .213) or grade 3+ pneumonitis (P = .102).

Table 3   Cox proportional hazard model of factors associated with rates of grade 2+ pneumonitis on univariable analysis

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age ≥60 y	0.527	0.202-1.375	.19			
Sex						
Female	1.171	0.485-2.827	.725			
Smoking						
Current smoker	1.003	0.294-3.426	.996			
COPD	1.315	0.547-3.159	.541			
Stage						
Stage IIB	-	-	-			
Stage IIIA	0.791	0.160-3.918	.774			
Stage IIIB	1.126	0.243-5.216	.879			
Stage IIIC	3.636	0.603-21.935	.159			
Histology						
Squamous	-	-	-			
Adenocarcinoma	0.747	0.259-2.157	.59			
NSCLC unspecified	1.826	0.632-5.276	.266			
Chemotherapy						
Carboplatin/paclitaxel	0.584	0.243-1.405	.23			
Durvalumab cycles	0.919	0.872-0.968	.002			
Lung V20 (%)	2.301	1.045-5.068	.039	1.132	0.289-4.426	.859
Lung V10 (%)	1.204	0.789-1.838	.389			
Lung V5 (%)	1.458	0.948-2.240	.086			
Mean lung dose (Gy)	7.5	1.690-33.278	.008	4.174	0.337-51.732	.266
Heart V40 (%)	2.073	1.249-3.439	.005	1.241	0.311-4.958	.76
Heart V20 (%)	1.467	1.152-1.869	.002	0.352	0.077-1.617	.179
Heart V10 (%)	1.328	1.095-1.609	.004	2.286	0.483-10.812	.297
Heart V5 (%)	1.274	1.070-1.516	.006	0.655	0.247-1.733	.394
Mean heart dose (Gy)	3.882	2.108-7.150	.001	9.064	3.187-25.775	.001
RT dose (Gy)	0.36	0.088-1.473	.155			
PTV volume (cc)	1.001	0.996-1.003	.112			

Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disorder; HR = hazard ratio; NSCLC = non-small cell lung cancer; PTV = planning target volume; RT = radiation therapy.
Variables that were significant on univariable analysis were included in multivariable analysis. Hazard ratios for dosimetric factors are reported per 10% for volumetric factors and per 10 Gy for mean dose factors.

Patients with an MLD >18 Gy were more likely to develop grade 2+ pneumonitis. The estimated 6- and 12-month rates of grade 2+ pneumonitis were 18.9% and 25.8% for the group with an MLD ≤18 Gy compared with 42.9% and 52.4% for the group with an MLD >18 Gy (P = .01) (Fig. 2C). Similarly, patients with an MLD >18 Gy were more likely to develop grade 3+ pneumonitis. The estimated 6- and 12-month rates of grade 3+ pneumonitis were 7.5% and 7.5% for the group with an MLD ≤18 Gy compared with 15.4% and 29.5% for the group with an MLD >18 Gy (P = .043) (Fig. 2D). The National Comprehensive Cancer Network−recommended MLD cutoff of 20 Gy was also analyzed.[21] Analysis of patient with an MLD >20 Gy was limited due to a small number of patients in our study population with an MLD >20 Gy (n = 8). Patients with an MLD >20 Gy were also more likely to develop grade 2+ pneumonitis compared with those with an MLD ≤20 Gy (P = .01). Patients with an MLD >20 Gy were not more likely to
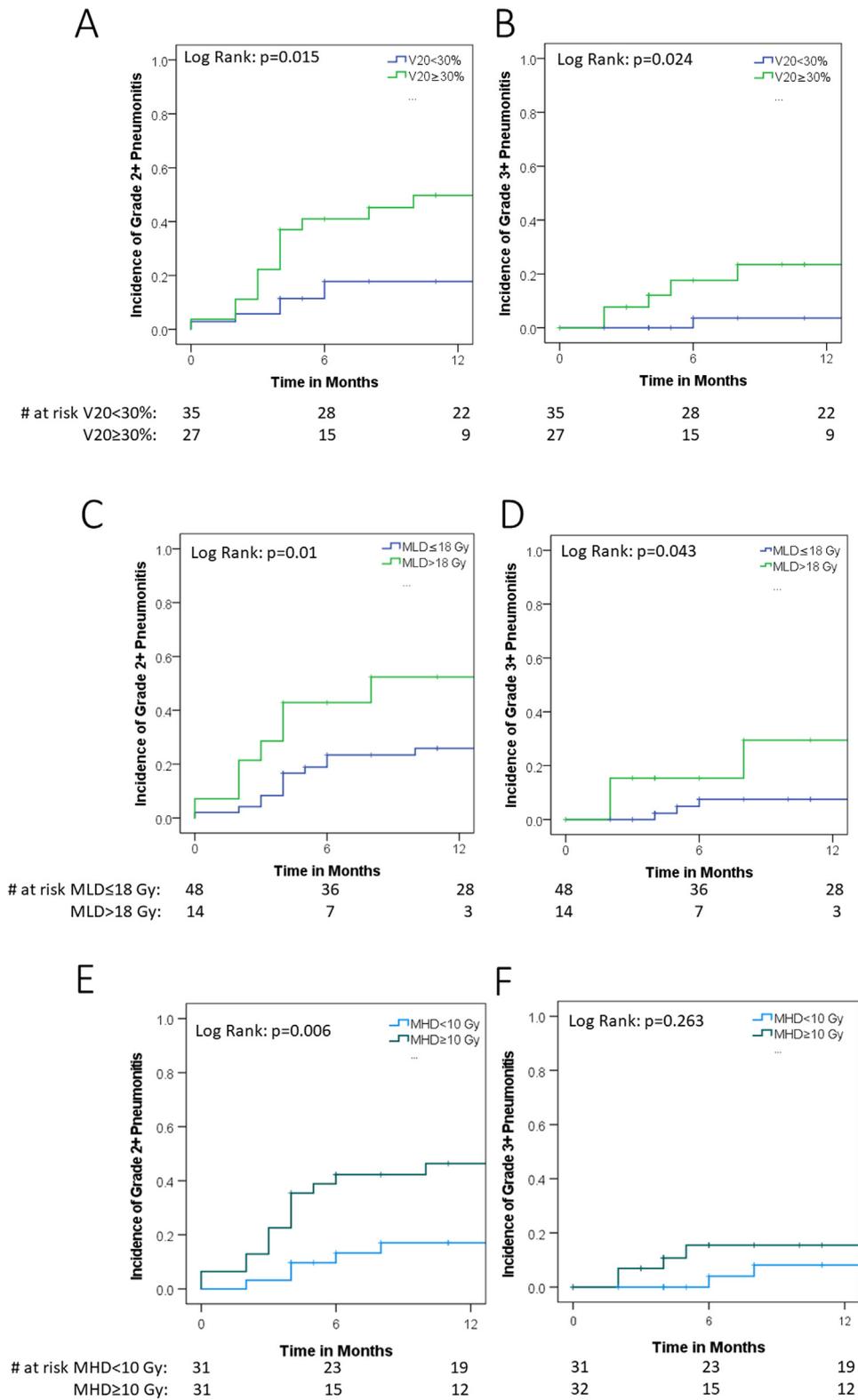
Figure 2 Kaplan-Meier curves for time to pneumonitis for patients with lung V20 <30% versus lung V20 ≥30%: (A) grade 2+ pneumonitis and (B) grade 3+ pneumonitis; mean lung dose (MLD) ≤18 Gy versus MLD >18 Gy: (C) grade 2+ pneumonitis and (D) grade 3+ pneumonitis; and mean heart dose (MHD) <10% versus MHD ≥10 Gy: (D) grade 2+ pneumonitis and (E) grade 3+ pneumonitis.

develop grade 3+ pneumonitis compared with patients with an MLD ≤20 Gy (P = .511).

We also examined heart dosimetric parameters including heart V5, V10, V20, V40, and MHD, and their association with grade 2+ pneumonitis on univariable analysis. Heart V5 (HR, 1.274; 95% CI, 1.070-1.516; P = .006), V10 (HR, 1.328; 95% CI, 1.095-1.609; P = .004), V20 (HR, 1.467; 95% CI, 1.152-1.869; P = .002), V40 (HR, 2.073; 95% CI, 1.249-3.439; P = .005), and MHD (HR, 3.882; 95% CI, 2.108-7.150; P = .001) were all associated with increased risk of grade 2+ pneumonitis (HR per 10 Gy or 10%) (Table 3). An MHD cutoff ≥10 Gy was selected and found to portend a higher rate of grade 2+ pneumonitis and was compared with a previously published MHD cutoff of ≥5 Gy.

Patients with an MHD ≥10 Gy were more likely to develop grade 2+ pneumonitis (P = .006). The estimated 6- and 12-month rates of grade 2+ pneumonitis were 13.3% and 17.1% for the group with an MHD <10 Gy compared with 42.3% and 46.4% for the group with an MHD ≥10 Gy. Similarly, patients with an MHD ≥5 Gy were more likely to develop grade 2+ pneumonitis (P = .038). The estimated 6- and 12-month rates of grade 2+ pneumonitis were 0% and 0% for the group with an MHD <5 Gy compared with 32.5% and 37.1% for the group with an MHD ≥5 Gy. Neither MHD ≥10 Gy (P = .260) or MHD ≥5 Gy (P = .263) were associated with an increased risk of grade 3+ pneumonitis.

Factors found to correlate with risk of grade 2+ pneumonitis including MLD, lung V20, MHD, heart V5, V10, V20, and V40 were selected for multivariable analysis. Cycles of durvalumab was not included on multivariable analysis because pneumonitis is a reason for durvalumab discontinuation. Only MHD was found to correlate with an increased risk of pneumonitis on multivariable analysis (HR, 9.064; 95% CI, 3.187-25.775; P = .001; HR per 10 Gy) (Table 3).

The estimated 6- and 12-month PFS for the entire cohort were 81.9% and 64.1% (Fig. 3A). Similarly, the estimated 6- and 12-month OS for the entire cohort were 96.7% and 86.8% (Fig. 3B). PFS was worse with the presence of pneumonitis with an estimated 6- and 12-month PFS of 65% and 50% in the group with grade 2+ pneumonitis compared with 90.2% and 71.2% in the group without pneumonitis (P = .02; Fig. E1A). Overall survival trended worse with the presence of pneumonitis with an estimated 6- and 12-month OS of 95% and 83.7% in the group with grade 2+ pneumonitis compared with 97.6% and 94.7% in the group without pneumonitis but were not statistically different (P = .062) (Fig. E1B). On univariable analysis number of cycles of durvalumab, RT dose, heart V40, heart V20, and MHD were correlated with survival. Number of durvalumab cycles was correlated with a reduced risk of death (HR, 0.927; 95% CI, 0.882-0.975; P = .003). Heart V40 (HR, 2.293; 95% CI, 1.393-3.777; P = .001), heart V20 (HR, 1.396; 95% CI, 1.042-1.869; P = .025), and MHD (HR, 2.346; 95% CI, 1.137-4.841; P = .021) were associated with increased risk of death. Lastly RT dose was correlated with a reduced risk of death (HR, 0.261; 95% CI, 0.068-0.994; P = .049). Factors found to correlate with risk of grade 2+ pneumonitis including heart V40, heart V20, MHD and RT dose were selected for multivariable analysis. Cycles of durvalumab was not included on multivariable analysis because death is a potential reason for durvalumab discontinuation. On multivariable analysis of variables which were significant on univariable analysis, only MHD was found to be correlated with an increased risk of death (HR, 7.633; HR, 2.754-21.151; P = .001; HRs provided per 10 Gy or per 10%) (Table E3).
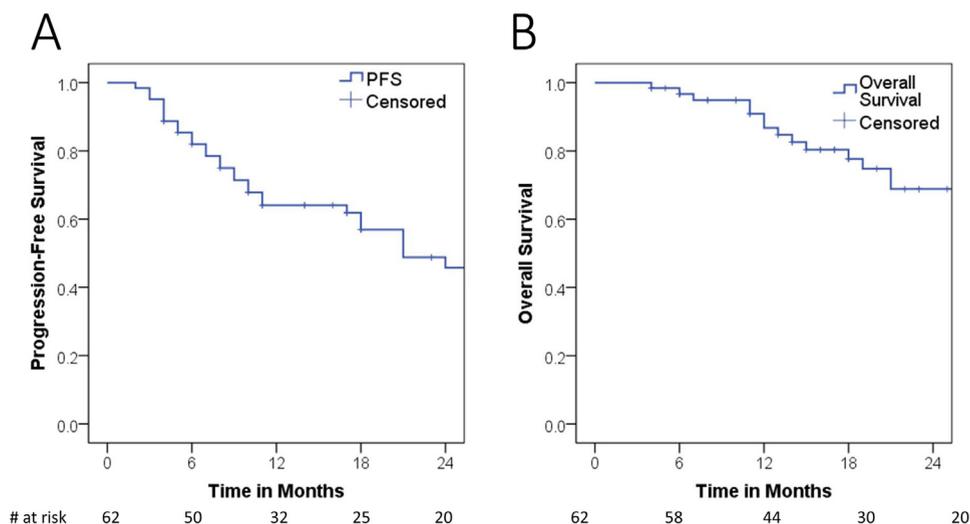

Figure 3   Kaplan-Meier curves for (A) progression-free survival and (B) overall survival for the entire patient cohort.

Discussion

In this single-institution study of real-world patients with locally advanced NSCLC treated with CRT followed by durvalumab, we found rates of grade 2+ pneumonitis at 32.3% and grade 3+ pneumonitis at 9.7% which are comparable with previously published modern case series which have shown rates of grade 2+ pneumonitis ranging from 15.7% to 46.7% and grade 3+ pneumonitis rates of 0% to 14.3%.[12,22-26] Similarly, our rate of grade 3+ pneumonitis of 9.7% was comparable but slightly higher than the 3.4% rate of grade 3+ pneumonitis in patients enrolled in the PACIFIC trial and 6% reported in a recent meta-analysis.[4,27] We also found that the development of pneumonitis led to discontinuation of durvalumab in 11.3% of patients which is in line with prior reports of 7.4% and 20.3%.[26,28] We found that number of cycles of durvalumab was correlated with development of pneumonitis and decreased risk of death as seen in a previous study.[26] In an analysis of the PACIFIC trial, the OS benefit of durvalumab was still maintained in patients who experienced pneumonitis.[29] However, other studies have shown that early discontinuation of durvalumab before completion of 4 months of therapy are associated with poorer overall survival highlighting the importance of optimizing definitive chemoradiation without compromising the ability to tolerate consolidative durvalumab.[28]

Limited dosimetry data are available from the PACIFIC trial.[4] Furthermore, patients were enrolled on the PACIFIC trial after completion of chemoradiation which may have generated selection bias and in turn enrolled patients with more favorable lung dosimetry. In our real-world study population, we identified potential lung dosimetry predictors of grade 2+ and grade 3+ pneumonitis including lung V20 ≥30% and MLD >18 Gy. Our low lung dose cohorts including V20 <30% and MLD ≤18 Gy had grade 2+ pneumonitis rates of 17.8% and 25.8% and grade 3+ pneumonitis rates of 3.6% and 7.5%, respectively, which are in line with rates of grade 2+ and grade 3+ pneumonitis in patients treated with chemoradiation alone in previous clinical trials, and in patients enrolled on the PACIFIC trial which reported a grade 3+ pneumonitis rate of 3.4%.[4,30,31] Conversely, our high lung dose cohorts including V20 ≥30% and MLD >18 Gy had grade 2+ pneumonitis rates of 49.8% and 52.4% and grade 3+ pneumonitis rates of 23.5% and 29.5%, respectively, which are higher than classically reported before immunotherapy and significantly higher than the overall rate of grade 3+ pneumonitis of patients treated on the PACIFIC trial and of real-world cohort of patients treated per the PACIFIC regimen.[4,12,30] A similar single-institution case series was recently published which also showed higher than expected rates of grade 2+ pneumonitis in patients based on their lung dosimetry parameters including lung V20 and MLD.[26] This Mayo Clinic study used lower cut points of MLD of 10 Gy and lung V20 of 15.8% compared with our cut points of MLD of 18 Gy and lung V20 of 30%. Their high lung dose cohorts of MLD ≥10 showed a 1-year rate of grade 2+ pneumonitis of 34%, and our even higher lung dose cohort of MLD >18 Gy showed a 1-year rate of grade 2+ pneumonitis of 52.4%.[26] Our data bolster these previous findings, suggesting that while the overall rates of pneumonitis are comparable to those of the PACIFIC trial, there exists a high-dose cohort with much higher-than-expected rates of pneumonitis compared with the preimmunotherapy era.

Additionally, dose to the heart was associated with development of grade 2+ pneumonitis with a heart mean of 10 Gy identified as a significant cutoff. Although heart dose may potentially be a surrogate for lung dose, previous studies have suggested a role for heart dose in the development of pneumonitis.[26,32-34] Our study detected a role for heart dosimetric parameters including MHD with a cut point of 10 Gy similar to a similar recently published case series which identified an MHD cut point of 5 Gy.[26] Similarly, we also found that increased cardiac dose metrics including MHD and V40 were correlated with increased risk of death corresponding to a Mayo Clinic case series, which showed worse OS with higher cardiac dose, as well as a secondary analysis of Radiation Therapy Oncology Group (RTOG) 0617, which showed certain cardiac dosimetry metrics corresponded with worse OS.[26,35]

Our study adds to previously published data demonstrating lung and heart radiation dose metrics specific to the development of pneumonitis in patients treated with CRT followed by consolidative durvalumab. Our rates of pneumonitis among patients with high lung doses are higher than reported in the preimmunotherapy era and suggest that new dose constraints may be needed in the immunotherapy era. This study is limited by the small sample size and retrospective design. Additional studies are needed to verify and validate these proposed new dose constraints. Given the clinical benefit of durvalumab, it is important to maximize patient outcomes by delivering safe and effective doses of radiation therapy that are curative but do not compromise patient tolerance of consolidative durvalumab.

Conclusion

Risk of pneumonitis in this single institution study of real-world patients with locally advanced NSCLC treated with definitive CRT followed by consolidative durvalumab was higher than reported in the PACIFIC trial. Pneumonitis risk was elevated in patients with lung V20 ≥30% or MLD >18 Gy, and MHD ≥10 Gy. Larger series are needed to determine the optimal dose constraints in this patient population in the era of durvalumab.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2022.101130.

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