Clinical and Translational Radiation Oncology 41 (2023) 100643

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Exploring causes and consequences of early discontinuation of durvalumab after chemoradiotherapy for non-small cell lung cancer

Michael Pennock [a,*], Balazs Halmos [b], William Bodner [a], Haiying Cheng [b], Rasim Gucalp [b], Nitin Ohri [a]

[a] Albert Einstein College of Medicine and Montefiore Medical Center, Department of Radiation Oncology, 1625 Poplar Street, Suite 101, Bronx, NY 10461, United States
[b] Albert Einstein College of Medicine and Montefiore Medical Center, Department of Oncology, 1695 Eastchester Road, Bronx, NY 10461-2374, United States

ARTICLE INFO

Keywords:
Lung cancer
Immunotherapy
Radiotherapy
Durvalumab
Toxicity
Prognosis

ABSTRACT

Introduction: For most locally advanced non–small cell lung cancer (LA-NSCLC) patients who complete definitive chemoradiotherapy (CRT) and do not experience disease progression, one year of adjuvant durvalumab is recommended. Here, we explore causes and consequences of early durvalumab discontinuation.

Materials and Methods: We reviewed patients treated for LA-NSCLC with definitive CRT who began adjuvant durvalumab between 2017 and 2021. Duration of durvalumab receipt and causes for early discontinuation were tabulated. Logistic regression models were utilized to evaluate predictors of early durvalumab discontinuation. Landmark analyses were performed to explore associations between early durvalumab discontinuation and clinical outcomes (progression-free survival (PFS), overall survival (OS)).

Results: Fifty-nine patients were included. Forty-one patients (69%) discontinued durvalumab early, most commonly for disease progression (n = 14) or lung toxicity (n = 10). Multivariable analysis revealed mean heart radiotherapy dose (MHD) was associated with risk of durvalumab discontinuation from progression (HR = 2.34 per 10 Gy, p = 0.052), and there was a trend suggesting an association between MHD and risk of durvalumab discontinuation from lung toxicity (HR = 2.16 per 10 Gy, p = 0.126). Median PFS duration following durvalumab initiation was 14 months, and median OS duration was 32 months. Landmark analyses that excluded patients with progression or death within one year of durvalumab initiation demonstrated improved outcomes for patients who completed one year of durvalumab (2-year PFS 100% v. 40%, p < 0.001; 2-year OS 100% v. 67%, p = 0.862). Improved outcomes were observed for patients who received MHD below the cohort median (9.3 Gy) compared to patients with higher MHD (median PFS 32 months v. 8 months, p < 0.001; 2-year OS 69% v. 44%, p = 0.088).

Conclusion: For LA-NSCLC patients treated with CRT followed by immunotherapy, extent of cardiac irradiation may be a risk factor for immunotherapy discontinuation, disease recurrence, and death.

Introduction

Despite recent advances, lung cancer remains the leading cause of cancer mortality in the United States[1]. One key advancement in treating advanced non-small cell lung cancer (NSCLC) has been immune-checkpoint inhibitors targeting the programmed-death-1/programmed-death-ligand-1 (PD-1/PD-L1) axis. Based on the PACIFIC trial, adjuvant immunotherapy is recommended in the United States for most patients with locally advanced (LA-)NSCLC who complete curative-intent concurrent chemoradiotherapy (CRT) and lack evidence of disease progression on post-treatment imaging[2].

The PACIFIC trial showed that adjuvant durvalumab following definitive CRT for NSCLC improves rates of progression-free survival (PFS) and overall survival (OS)[2]. Updated analyses demonstrate sizeable improvements in 5-year PFS (33% v. 19%) and OS (43% v. 33%) [3] that seem to be driven by improvements in intrathoracic and distant disease control[3–5].

Interestingly, approximately half of PACIFIC subjects who were randomized to receive adjuvant durvalumab did not complete the planned 12-month treatment course. In the durvalumab arm, 31% of

* Corresponding author.
E-mail addresses: mpennock@montefiore.org (M. Pennock), bahalmos@montefiore.org (B. Halmos), wbodner@montefiore.org (W. Bodner), hcheng@montefiore.org (H. Cheng), rgucalp@montefiore.org (R. Gucalp), nitin.ohri@einsteinmed.org (N. Ohri).

https://doi.org/10.1016/j.ctro.2023.100643
Received 5 December 2022; Received in revised form 22 May 2023; Accepted 29 May 2023
Available online 1 June 2023

patients discontinued treatment because of progression, 31% experienced Grade 3+ toxicity, 4.4% experienced death, and 15% discontinued treatment because of adverse events, where the most frequent adverse events leading to discontinuation were pulmonary toxicities such as pneumonitis[2,3,6]. Interestingly, 10% of subjects receiving placebo discontinued infusions due to adverse events, demonstrating that delayed toxicities from CRT can interfere with the receipt of adjuvant immunotherapy.

It remains unclear how radiotherapy parameters influence the course and effects of subsequent durvalumab, if radiation oncologists should adjust planning for patients who will receive durvalumab after CRT, and how unique immunotherapy-mediated adverse events manifest in the setting of cancer and CRT[7–9]. Understanding risk factors for early durvalumab discontinuation could further improve outcomes for LA-NSCLC patients treated with definitive CRT, prevention and management of toxicity, and monitoring tolerance. Here, we review our institution's experience with adjuvant durvalumab following CRT for NSCLC to describe causes, predictors, and consequences of early immunotherapy discontinuation.

Materials and methods

Patients, treatment, follow-up

This is a retrospective review and analysis of consecutive patients treated with concurrent CRT with curative intent at our institution and were started on adjuvant durvalumab between November 2017 and April 2021. Our IRB approved this retrospective analysis. Based on institutional practice patterns, patients with American Joint Committee on Cancer (AJCC) version 8.0 stage III NSCLC, unresectable stage II NSCLC, or oligometastatic stage IV NSCLC with radical treatment of all distant metastases were considered eligible for concurrent CRT and adjuvant durvalumab. All patients underwent staging positron-emission tomography/computed tomography (PET/CT), brain MRI or head CT, and 4-dimensional CT simulation. We utilized standard techniques for GTV, CTV, and PTV delineation, and standard previously-described normal-tissue constraints[10]. The standard radiotherapy regimen was 60 Gy in 30 fractions. Some patients were enrolled on prospective trials testing dose-painted radiotherapy and received doses of 48–60 Gy in 20 or 25 fractions (2-Gy equivalent doses of 49.6–62.0 Gy, $\alpha/\beta = 10$ Gy). Weekly or daily cone-beam CT image-guidance was utilized. All patients received weekly carboplatin (area under the curve 2) and paclitaxel (45–50 mg/m^2) during radiotherapy.

Patients underwent chest CT two to four weeks after CRT completion and before initiating adjuvant durvalumab to rule out progression. Durvalumab was generally given at a dose of 10 mg/kg every 2 weeks. Some patients received durvalumab doses of 1500 mg every four weeks due to logistical considerations (e.g., minimizing visits during COVID). Durvalumab was continued until disease progression in any location, or unacceptable toxicity, for a maximum of one year.

Data collection

Clinical characteristics (gender, age, performance status), disease characteristics (stage, histology, PD-L1 tumor proportion score (TPS), mutational status), and treatment characteristics were tabulated. Mean radiotherapy dose received by the heart (MHD), lungs (excluding clinical target volumes), and esophagus was tabulated for each patient, as was lung volume receiving ≥20 Gy (V20) and ≥5 Gy (V5). As a measure of disease burden and gross tumor volume, pre-treatment total metabolic tumor volume (MTV) was calculated from each patient's staging PET/CT using a semiautomatic gradient-based contouring algorithm (MIMvista Corp, Cleveland, OH, U.S.A.), as in prior studies[11].

Duration of immunotherapy receipt was calculated in two ways: (1) number of infusions received, with each 10 mg/kg durvalumab dose counted as two weeks of immunotherapy and each 1500 mg durvalumab dose counted as four weeks of immunotherapy, and (2) time interval between first and last durvalumab infusion. Patients who received at least 48 weeks of immunotherapy using either definition were deemed to have completed the immunotherapy course. Reasons for early immunotherapy discontinuation were abstracted from patients' medical records and categorized as disease progression, death without progression, pulmonary toxicity, or other toxicity.

Statistical analyses

Descriptive statistics were used to report patient and treatment characteristics, durations of immunotherapy receipt, and causes for immunotherapy discontinuation. The most common reasons for immunotherapy discontinuation were identified, and treatment-related predictors of immunotherapy discontinuation for those reasons were tested using univariate logistic regression models. Variables with p-values below 0.20 in univariate models were included in a multivariable model.

Median follow-up duration was estimated using the Schemper method[11]. Kaplan-Meier curves and logrank testing were used to compare progression-free survival (PFS), which was not stratified into local or distant progression, and overall survival (OS) rates between patients who completed a course of adjuvant durvalumab and patients who discontinued durvalumab.

Cox proportional hazards models were utilized to test the prognostic value of durvalumab completion with respect to PFS and OS. To address immortal time bias, we utilized a landmark analysis technique, where patients with disease progression or death within one year after durvalumab initiation were excluded.

ANOVA analyses were used to assess differences in MHD between patients who discontinued durvalumab due to progression, lung toxicity, and other reasons. As MHD was implicated with early durvalumab discontinuation due to disease progression or lung toxicity, we generated violin plots to compare the distribution of MHDs in patients who discontinued durvalumab for those two reasons versus other patients. We tested MHD as a predictor of PFS and OS after durvalumab initiation among all patients using Kaplan-Meier curves and logrank testing.

Analyses were performed using Matlab (The Mathworks, Natick, MA, U.S.A.) and Stata (StataCorp, College Station, TX, U.S.A.).

Results

Patient characteristics and immunotherapy receipt

Fifty-nine patients were included. Patient characteristics are summarized in Table 1. Thirty-five patients (59%) could have been eligible for PACIFIC. Reasons for theoretical PACIFIC ineligibility were stage II or IV disease (n = 5), total radiation dose under 54 Gy (n = 7), or performance status 2–3 after radiotherapy completion (n = 15). The median time interval from completing CRT to beginning durvalumab was 35 days (IQR: 26 to 52 days). The median follow-up duration after durvalumab initiation was 29 months (IQR: 21 to 33 months).

The median number of durvalumab infusions received was 12 (IQR: 5 to 21). Twenty patients received at least one infusion of durvalumab using a fixed dose of 1500 mg every four weeks. Based on the number and doses of infusions received, the median duration of durvalumab therapy was 32 weeks (IQR: 12 to 48). Based on the interval from the first to last durvalumab infusion, the median duration of durvalumab therapy was 33 weeks (IQR: 15 to 49). Eighteen patients (31%) completed adjuvant durvalumab therapy. 41 patients (69%) discontinued durvalumab. The most common reasons for early durvalumab discontinuation were disease progression (n = 14), lung toxicity (n = 10), other toxicity (n = 7), or death without established disease progression (n = 4). Discontinuation for lung toxicity occurred after a median of 2 months from starting durvalumab therapy (range: 0 to 10 months), and durvalumab discontinuation for other toxicities occurred after a median of 5 months from starting durvalumab (range: 1 to 9

Table 1
Patient and treatment characteristics.

Gender, n (%)	
Female	30 (51%)
Male	29 (49%)
Age, mean (range)	68 (49 to 83)
T stage (AJCC 8th edition), n (%)	
T0/X	8 (14%)
T1	13 (22%)
T2	6 (10%)
T3	8 (14%)
T4	24 (41%)
N Stage (AJCC 8th edition), n (%)	
N0	9 (15%)
N1	45 (76%)
N2	3 (5%)
N3	2 (3%)
Clinical stage (AJCC 8th edition), n (%)	
II	3 (5%)
IIIA	30 (51%)
IIIB	15 (25%)
IIIC	8 (14%)
IV	3 (5%)
PS before RT, n (%)	
0	10 (17%)
1	33 (56%)
2	15 (25%)
3	1 (2%)
PS after RT, n (%)	
0	7 (12%)
1	37 (63%)
2	13 (22%)
3	2 (3%)
Histology, n (%)	
Adenocarcinoma	27 (46%)
Squamous cell carcinoma	25 (42%)
Other/not specified	7 (12%)
PD-L1 tumor proportion score, n (%)	
<1%	13 (22%)
1 to 49%	20 (34%)
50 to 100%	11 (19%)
Unknown	15 (25%)
Known EGFR mutation or ALK rearrangement, n (%)	
No	61 (98%)
Yes	1 (2%)
Metabolic tumor volume, median (range)	45 cc (2 to 261)
RT course length, n (%)	
30 fractions	40 (68%)
20-25 fractions	19 (32%)
Mean esophagus RT dose, median (range)	15.4 Gy (2.9 to 34.3)
Mean heart RT dose, median (range)	9.3 Gy (0.2 to 29.2)
Mean lung RT dose, median (range)	11.6 (2.1 to 20.2)
Lung V20, median (range)	22.3% (1.0% to 36%)
Lung V5, median (range)	40.6 (11.7% to 65.4%)

AJCC, American Joint Committee on Cancer; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PS, performance status; PD-L1, programmed death-ligand 1; RT, radiation therapy; Lung V20, volume of lung receiving ≥ 20 Gy; Lung V5, volume of lung receiving ≥ 5 Gy.

months).

Predictors and consequences of immunotherapy discontinuation

Univariate and multivariable logistic regression models examining predictors of early durvalumab discontinuation due to disease progression are displayed in Table 2. In a multivariable model, MHD was associated with increased risk of durvalumab discontinuation due to disease progression (HR = 2.34 per 10 Gy, p = 0.052). Logistic regression models did not reveal any statistically significant predictors of early durvalumab discontinuation due to lung toxicity, shown in Table 3. There was a trend suggesting an association between MHD and risk of durvalumab discontinuation due to lung toxicity (adjusted HR = 2.16 per 10 Gy, p = 0.126). Violin plots depicting MHD distributions for patients who discontinued durvalumab due to progression, patients who discontinued durvalumab due to lung toxicity, and other patients are shown in Fig. 1. One-way ANOVA testing revealed a significant between-group difference in MHD (p = 0.034).

Among the entire patient cohort, 27 patients (46%) developed disease progression, and 25 patients (42%) died. The median PFS duration following durvalumab initiation among all patients is 14 months, and the median OS duration following durvalumab initiation is 32 months.

Table 2
Predictors of durvalumab discontinuation due to disease progression. Univariate logistic regression models were utilized to identify potential predictors of durvalumab discontinuation due to disease progression. Variables with p-values below 0.200 in univariate models were included in a multivariable logistic regression model. Bold font denotes statistical significance using a p-value cutoff of 0.05.

Characteristic	Univariate Models		Multivariable Model	
	Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Metabolic tumor volume, per 10 cc	1.06 (0.98 to 1.16)	0.156	1.08 (0.98 to 1.18)	0.158
Stage Group				
II-IIIA	[reference]	–		
IIIB-IV	1.37 (0.41 to 4.56)	0.609		
ECOG PS after RT completion				
0-1	[reference]	–		
2-3	1.94 (0.53 to 7.13)	0.316		
PD-L1 TPS				
<1%	2.57 (0.68 to 9.75)	0.166	2.74 (0.64 to 11.74)	0.175
≥1% or unknown	[reference]	–		
RT Dose (EQD2)				
≥60 Gy	[reference]	–		
<60 Gy	0.89 (0.24 to 3.32)	0.857		
RT course length				
30 fractions	[reference]	–		
20–25 fractions	0.80 (0.21 to 2.98)	0.739		
Mean heart RT dose, per 10 Gy	**2.34 (1.03 to 5.31)**	**0.042**	2.34 (0.99 to 5.53)	0.052
Mean esophagus RT dose, per 10 Gy	1.36 (0.69 to 2.67)	0.378		
Mean lung RT dose, per 10 Gy	2.13 (0.42 to 10.84)	0.358		

RT, radiation therapy

Table 3
Predictors of durvalumab discontinuation due to lung toxicity. Univariate logistic regression models were utilized to identify potential predictors of durvalumab discontinuation due to lung toxicity. Variables with p-values below 0.200 in univariate models were included in a multivariable logistic regression model.

Characteristic	Univariate Models		Multivariable Model	
	Odds Ratio (95% CI)	p value	Adjusted Odds Ratio (95% CI)	p value
Metabolic tumor volume, per 10 cc	0.90 (0.78 to 1.03)	0.135	0.89 (0.76 to 1.03)	0.105
Stage Group				
II-IIIA	[reference]	–		
IIIB-IV	0.82 (0.20 to 3.27)	0.776		
ECOG PS after RT completion				
0-1	[reference]	–		
2-3	1.32 (0.72 to 5.93)	0.716		
RT course length				
30 fractions	[reference]	–	[reference]	–
20-25 fractions	2.50 (0.63 to 10.00)	0.195	2.99 (0.68 to 13.22)	0.149
Mean heart RT dose, per 10 Gy	1.95 (0.80 to 4.75)	0.141	2.16 (0.81 to 5.79)	0.126
Mean esophagus RT dose, per 10 Gy	0.97 (0.44 to 2.11)	0.934		
Mean lung RT dose, per 10 Gy	1.56 (0.26 to 9.43)	0.629		
Lung V20	1.04 (0.95 to 1.13)	0.446		
Lung V5	1.03 (0.98 to 1.09)	0.257		

RT, radiation therapy

Landmark analyses demonstrated that completing the adjuvant durvalumab course was associated with favorable PFS (2-year PFS 100% v. 40%, logrank $p < 0.001$, Fig. 2). Completing the adjuvant durvalumab course was also associated with numerically higher OS (2-year OS 100% v. 67%, logrank $p = 0.862$, Fig. 3).

Association between MHD and clinical outcomes

Kaplan Meier curves depicting PFS rate and OS rate, measured from initiation of durvalumab and evaluated after grouping patients by MHD, are shown in Fig. 4 and Fig. 5. The median PFS duration for patients who received MHDs below the cohort median (9.3 Gy) was 32 months, compared to 8 months for patients with higher MHDs (logrank $p < 0.001$, Fig. 4). Kaplan Meier analysis also revealed the 2-year OS rate for patients with MHD below the cohort median (9.3 Gy) was 69%, compared to 44% for patients with higher MHDs (logrank $p = 0.088$, Fig. 5).

Discussion

To our knowledge, this is the first study examining predictors and consequences of early durvalumab discontinuation following CRT for LA-NSCLC. As in the PACIFIC trial[2,4,5], we found that a minority of patients completed the planned one-year course of durvalumab, and the most common causes for durvalumab discontinuation were disease progression and toxicity. We found that early durvalumab discontinuation was associated with increased risk of disease relapse and death. In our cohort, extent of cardiac irradiation was significantly associated with early durvalumab discontinuation, disease progression, and death after durvalumab initiation. These findings, if validated in larger datasets, would add to a growing list of reasons why cardiac avoidance should be prioritized when planning CRT for LA-NSCLC.

Cardiac irradiation causes direct cardiac toxicity

Radiation-induced acute inflammation can cause a pathogenic

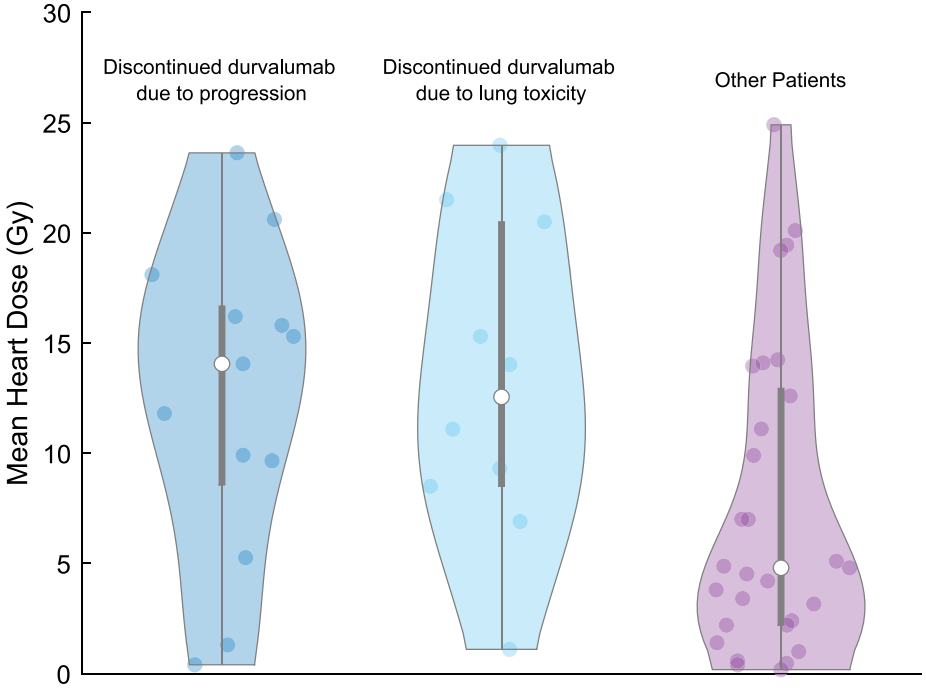

Fig. 1. Violin plots and one-way ANOVA analysis. Mean heart radiotherapy doses for patients who discontinued durvalumab due to disease progression (n = 14), patients who discontinued durvalumab due to lung toxicity (n = 10), and other patients (n = 35) were compared. One-way ANOVA testing was used to compare the depicted groups and their mean heart radiotherapy doses.

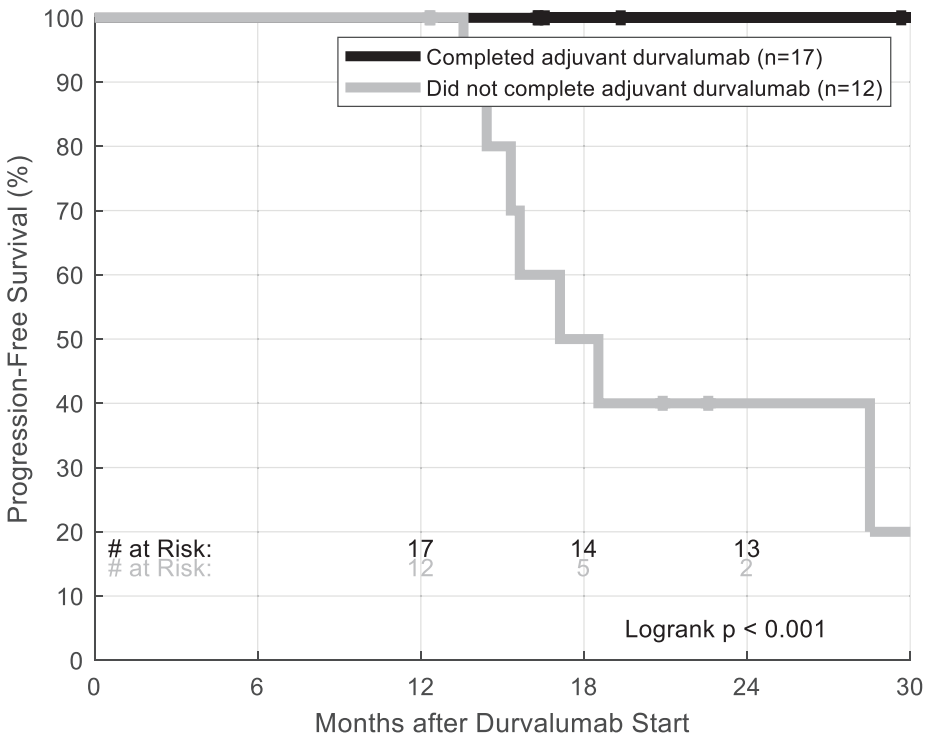

Fig. 2. Landmark analysis, with Kaplan-Meier curves depicting progression-free survival rates after durvalumab initiation for patients who completed a one-year course of durvalumab, compared to patients who did not complete one year of adjuvant durvalumab. Patients who developed disease progression or death within one year after durvalumab initiation were excluded from this analysis. Patients with follow-up duration of less than one year after durvalumab initiation were also excluded.

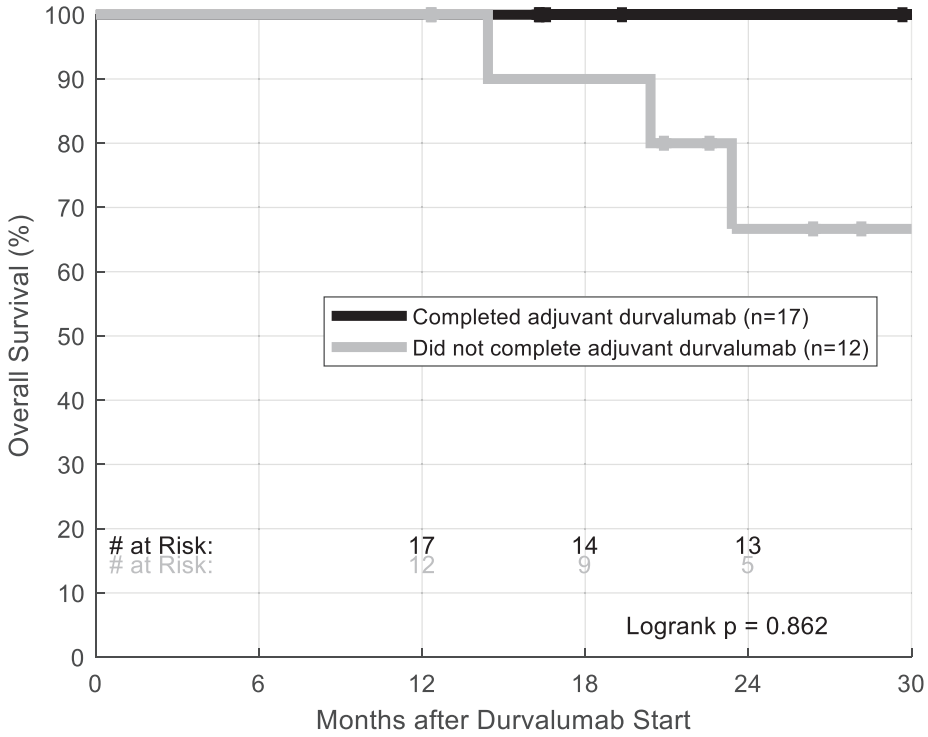

Fig. 3. Landmark analysis, with Kaplan-Meier curves depicting overall survival rates after durvalumab initiation for patients who completed a one-year course of durvalumab, compared to patients who did not complete one year of adjuvant durvalumab. Patients who developed disease progression or death within one year after durvalumab initiation were excluded from this analysis. Patients with follow-up duration of less than one year after durvalumab initiation were also excluded.

cascade leading to cardiac disease, coronary artery stenosis, myocardial atrophy, and pericardial constriction[12,13]. Using large datasets, several groups have identified extent of cardiac irradiation as predictive of subsequent cardiac events[14–18] and impaired OS[17,19,20], with recent data suggesting pericardial dose is a significant predictor of OS, rather than cardiac substructure dose[17,18]. A range of increasing cardiac volumetric doses (V5 to $\geq$ V50) have been shown to predict survival[17,19]. Recent retrospective studies have shown cardiac-event incidence was related to cardiac substructure dose in cancer[21–24]. There is a lack of randomized, prospective evidence that sparing cardiac substructures has a survival advantage over sparing the entire heart or is different from sparing portions of the heart as a single structure. Newer

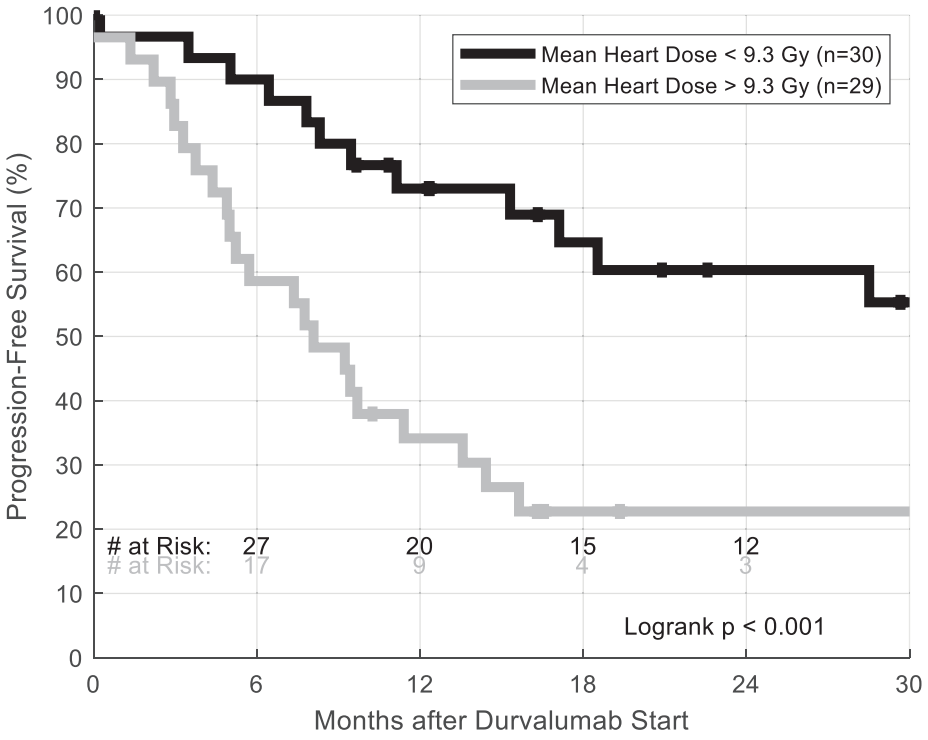

Fig. 4. Kaplan Meier curves depicting rates of progression-free survival after durvalumab initiation for patients who received mean heart radiotherapy doses above or below the cohort median of 9.3 Gy.

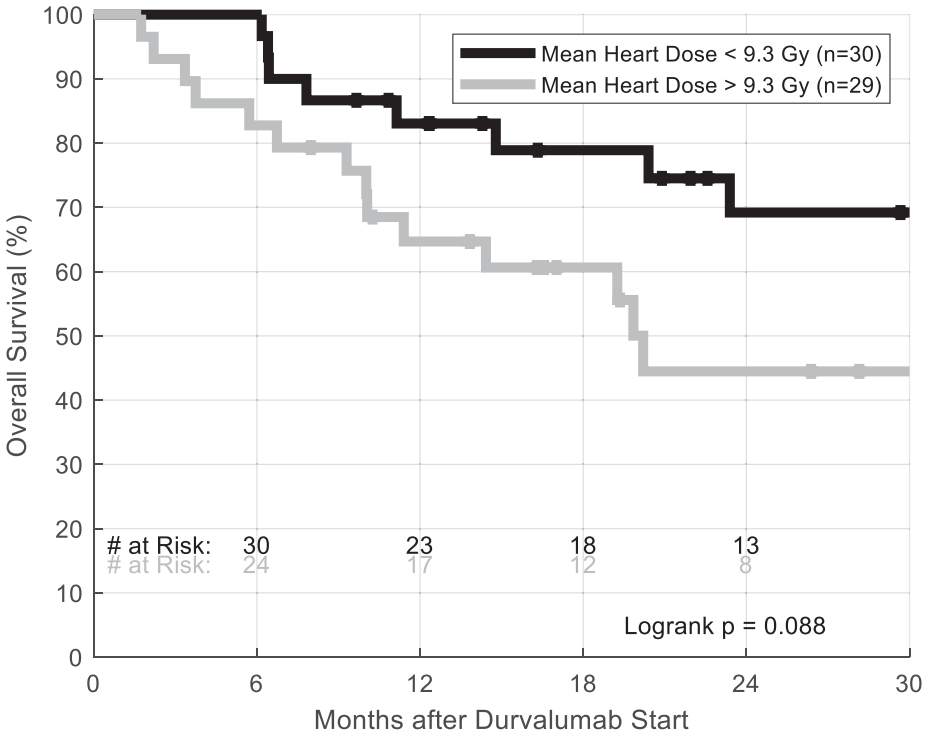

Fig. 5. Kaplan Meier curves depicting rates of overall survival after durvalumab initiation for patients who received mean heart radiotherapy doses above or below the cohort median of 9.3 Gy.

data suggest radiation-induced cardiotoxicity may be modulated by the PD-1/PD-L1 axis[25,26]. Therefore, we chose MHD as an established predictor[14–20] of clinical outcomes and representation of heart dose. We acknowledge incoming evidence for the predictive value of cardiac substructures is compelling[21–24], and substructures can be analyzed in future studies once their predictive value is established in large, prospective, randomized trials.

Cardiac irradiation may detract from immunotherapy efficacy

Numerous studies have demonstrated associations between extent of cardiac irradiation and lymphopenia[27–30]. Lymphopenia and the related observation of elevated neutrophil-to-lymphocyte ratio (NLR) have been identified as poor prognostic factors for survival and progression in many cancer settings[31], including in patients recently treated with CRT for NSCLC[27,32,33] and patients treated with immune-checkpoint inhibitors for advanced NSCLC[34,35]. Radiotherapy-induced lymphopenia (RIL) has recently been implicated in reducing efficacy of adjuvant durvalumab and increasing risk of progression and death, adding further importance to reducing cardiac irradiation[36]. Our findings suggest that MHD as an estimate of cardiac irradiation may estimate blood-volume radiation exposure and subsequent NLR destabilization, and this may be why it is predictive of progression. The relationship between NLR and cardiac subsites remains unexplored.

Cardiac irradiation may lead to lung toxicity and immunotherapy discontinuation

Pulmonary complications typically occur several months after completing thoracic radiotherapy and can affect quality-of-life and functional status. Pulmonary toxicity is now a common reason for withholding or discontinuing durvalumab after CRT for LA-NSCLC, and discontinuation worsens outcomes[37,38], as seen in our landmark results. The most recent PACIFIC safety data showed 1.9% of patients receiving durvalumab experienced pneumonitis, the most frequent adverse event prompting discontinuation, and pulmonary toxicity contributed to mortality[2].

Before durvalumab was added to the treatment paradigm for LA-NSCLC, numerous analyses established associations between extent of lung irradiation and risk of radiation pneumonitis[39,40]. Several studies also suggest that lung toxicity following radiotherapy can be a consequence of cardiac irradiation[41–44]. Murine studies have demonstrated that cardiac irradiation can cause diastolic dysfunction, pulmonary congestion, and pulmonary fibrosis[45]. The current study detected a potential trend for MHD to influence durvalumab discontinuation through lung toxicity, and multiple studies have found MHD of approximately $\geq$9 – 10 Gy predicts Grade 2+ pneumonitis [41–44,46,47].

Unexpectedly, the current study did not show that extent of lung irradiation predicted durvalumab discontinuation from lung toxicity. Several studies have suggested a range of lung parameters predict pneumonitis during durvalumab maintenance after CRT[48–53], sometimes causing durvalumab discontinuation[46,47,54]. This emerging data, as well as the current study, illustrate the need for high-quality, real-world data to better define lung parameters in the immunotherapy era.

Effect 4.1 is likely a key factor in the established association between cardiac irradiation and mortality risk in patients treated with CRT for LA-NSCLC. It is likely that effects 4.2 and 4.3 will amplify the deleterious effects of cardiac irradiation in modern LA-NSCLC patients who are treated with CRT followed by immunotherapy, and it is possible that one or a combination of the three effects contributed to this study's findings.

The current study's median OS and PFS values were below those in the PACIFIC 5-year update[3], likely due to difference in patients discontinuing durvalumab (69% in the current study, 46.4% in PACIFIC), worse outcomes for patients who discontinued durvalumab, and our inclusion of patients with ECOG performance status of 2 +. This study reflects the 5-year PACIFIC update in that the main reason for durvalumab discontinuation was progression, and our landmark analyses confirm the survival advantages of completing durvalumab seen in PACIFIC[3].

As adjuvant immunotherapy reduces the risk of recurrence and distant metastases following CRT for LA-NSCLC, there will be increased opportunity for direct cardiac toxicity to become clinically relevant. These considerations suggest that minimizing cardiac irradiation should be a priority when treating LA-NSCLC with CRT, also to not compromise tolerance of adjuvant durvalumab.

Avoiding elective nodal irradiation[55] and employing intensity-modulated radiotherapy[56] are now common practices that reduce cardiac irradiation. Treatment with proton radiotherapy in the ongoing RTOG 1308 trial (NCT01993810)[57] and dose-painted or de-escalated radiotherapy[10,58] are being studied as techniques to reduce heart parameters.

There are several limitations to this hypothesis-generating study. It is retrospective, sample size is modest, and follow-up is limited. This real-world analysis included patients who would not have been eligible for PACIFIC, which established durvalumab as adjuvant therapy after CRT, including 3 oligometastatic Stage IV patients (5%), although the number of these patients was small enough to likely not drive statistical analysis. Causes for durvalumab discontinuation were identified using clinicians' notes rather than formal toxicity scoring or objective physiologic data, due to missing real-time adverse-event grading and to represent a real-world experience. Our patients did not obtain routine electrocardiograms or echocardiograms in follow-up. We are evolving our practices to include these measures for current-day patients based on cardiac irradiation and risk factors for heart disease. A larger multi-institutional analysis to validate our findings and address these concerns is underway, as well as incorporate more detailed parameters such as cardiac subsites, immune-cell counts, more lung volumetric parameters, tumor location, first progression location, RIL prediction models[59], causes of death, and chemotherapy regimens contributing to lung toxicity[39,60].

Conclusion

For LA-NSCLC patients treated with chemoradiotherapy followed by immunotherapy, extent of cardiac irradiation may be an important risk factor for affecting early immunotherapy discontinuation via progression or lung toxicity, disease recurrence, and death, and should be further explored in multi-institutional, prospective, and randomized studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70 (1):7–30. https://doi.org/10.3322/caac.21590.
[2] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. N Engl J Med 2018;379(24):2342–50.
[3] Spigel DR, Faivre-Finn C, Gray JE, Vicente D, Planchard D, Paz-Ares L, et al. Five-year survival outcomes from the PACIFIC trial: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. J Clin Oncol 2022;40 (12):1301–11.
[4] Raben D, Rimner A, Senan S, Broadhurst H, Pellas T, Dennis PA, et al. Patterns of disease progression with durvalumab in stage III non-small cell lung cancer (PACIFIC). Int J Radiat Oncol 2019;105(3):683.
[5] Faivre-Finn C, Vicente D, Kurata T, et al. Four-year survival with durvalumab after chemoradiotherapy in Stage III NSCLC - an update from the PACIFIC trial. J Thorac Oncol 2021;S1556–0864(21):00022–8. https://doi.org/10.1016/j.jtho.2020.12.015.
[6] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. N Engl J Med 2017;377(20):1919–29.
[7] Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: Epidemiology, management and surveillance. Nat Rev Clin Oncol 2019;16(9):563–80.
[8] Matson DR, Accola MA, Rehrauer WM, et al. Fatal myocarditis following treatment with the PD-1 inhibitor nivolumab. J Forensic Sci 2018;63(3). https://doi.org/10.1111/1556-4029.13633.

[9] Chuzi S, Tavora F, Cruz M, et al. Clinical features, diagnostic challenges, and management strategies in checkpoint inhibitor-related pneumonitis. CancerManag Res 2017:9. https://doi.org/10.2147/CMAR.S136818.

[10] Ohri N, Bodner WR, Kabarriti R, Shankar V, Cheng H, Abraham T, et al. Positron emission tomography–adjusted intensity modulated radiation therapy for locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2018;102(4):709–15.

[11] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17(4):343–6.

[12] Wang K, Eblan MJ, Deal AM, Lipner M, Zagar TM, Wang Y, et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: Pooled analysis of dose-escalation trials delivering 70 to 90 Gy. J Clin Oncol 2017;35(13):1387–94.

[13] Banfill K, Giuliani M, Aznar M, Franks K, McWilliam A, Schmitt M, et al. Cardiac toxicity of thoracic radiotherapy: Existing evidence and future directions. J Thorac Oncol 2021;16(2):216–27.

[14] Wang EH, Corso CD, Rutter CE, Park HS, Chen AB, Kim AW, et al. Postoperative radiation therapy is associated with improved overall survival in incompletely resected Stage II and III non–small-cell lung cancer. J Clin Oncol 2015;33(25):2727–34.

[15] Dess RT, Sun Y, Matuszak MM, Sun G, Soni PD, Bazzi L, et al. Cardiac events after radiation therapy: Combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer. J Clin Oncol 2017;35(13):1395–402.

[16] Atkins KM, Chaunzwa TL, Lamba N, Bitterman DS, Rawal B, Bredfeldt J, et al. Association of left anterior descending coronary artery radiation dose with major adverse cardiac events and mortality in patients with non-small cell lung cancer. JAMAOncol 2021;7(2):206.

[17] Bradley JD, Hu C, Komaki RU, Masters G, Blumenschein GR, Schild SE, et al. Long-term results of RTOG 0617: A randomized phase 3 comparison of standard dose versus high dose conformal chemoradiation therapy +/- cetuximab for stage III NSCLC. Int. J Radiat Oncol 2017;99(2):S105.

[18] Xue J, Han C, Jackson A, Hu C, Yao H, Wang W, et al. Doses of radiation to the pericardium, instead of heart, are significant for survival in patients with non-small cell lung cancer. Radiother Oncol 2019;133:213–9.

[19] Speirs CK, DeWees TA, Rehman S, Molotievschi A, Velez MA, Mullen D, et al. Heart dose is an independent dosimetric predictor of overall survival in locally advanced non–small cell lung cancer. J Thorac Oncol 2017;12(2):293–301.

[20] Stam B, van der Bijl E, van Diessen J, Rossi MMG, Tijhuis A, Belderbos JSA, et al. Heart dose associated with overall survival in locally advanced NSCLC patients treated with hypofractionated chemoradiotherapy. Radiother Oncol 2017;125(1):62–5.

[21] Wang X, Palaskas NL, Hobbs BP, Abe J-I, Nead KT, Yusuf SW, et al. The impact of radiation dose to heart substructures on major coronary events and patient survival after chemoradiation therapy for esophageal cancer. Cancers (Basel) 2022;14(5):1304.

[22] Hahn E, Jiang H, Ng A, Bashir S, Ahmed S, Tsang R, et al. Late cardiac toxicity after mediastinal radiation therapy for hodgkin lymphoma: Contributions of coronary artery and whole heart dose-volume variables to risk prediction. Int J Radiat Oncol Biol Phys 2017;98(5):1116–23.

[23] Atkins KM, Chaunzwa TL, Lamba N, Bitterman DS, Rawal B, Bredfeldt J, et al. Association of left anterior descending coronary artery radiation dose with major adverse cardiac events and mortality in patients with non–small cell lung cancer. JAMAOncol 2021;7(2):206.

[24] van den Bogaard VAB, Ta BDP, van der Schaaf A, Bouma AB, Middag AMH, Bantema-Joppe EJ, et al. Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. J Clin Oncol 2017;35(11):1171–8.

[25] Du S, Zhou L, Alexander GS, Park K, Yang L, Wang N, et al. PD-1 Modulates radiation-induced cardiac toxicity through cytotoxic T lymphocytes. J Thorac Oncol 2018;13(4):510–20.

[26] Du S, Zhou L, Shukla G, Wang N, Yang L, Ma X, et al. Pharmacological inhibition of PD-1 exacerbates radiation-induced cardiac toxicity through cytotoxic T Cell–mediated myocarditis. Int. J Radiat Oncol 2016;96(2):S88.

[27] Contreras JA, Lin AJ, Weiner A, Speirs C, Samson P, Mullen D, et al. Cardiac dose is associated with immunosuppression and poor survival in locally advanced non-small cell lung cancer. Radiother Oncol 2018;128(3):498–504.

[28] Ladbury CJ, Rusthoven CG, Camidge DR, Kavanagh BD, Nath SK. Impact of radiation dose to the host immune system on tumor control and survival for stage III non-small cell lung cancer treated with definitive radiation therapy. Int J Radiat Oncol Biol Phys 2019;105(2):346–55. https://doi.org/10.1016/j.ijrobp.2019.05.064.

[29] Abravan A, Faivre-Finn C, Kennedy J, McWilliam A, van Herk M. Radiotherapy-related lymphopenia affects overall survival in patients with lung cancer. J Thorac Oncol 2020;15(10):1624–35. https://doi.org/10.1016/j.jtho.2020.06.008.

[30] Joseph N, McWilliam A, Kennedy J, Haslett K, Mahil J, Gavarraju A, et al. Post-treatment lymphocytopaenia, integral body dose and overall survival in lung cancer patients treated with radical radiotherapy. Radiother Oncol 2019;135:115–9.

[31] Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis. J Natl Cancer Inst. 2014. 10.1093/jnci/dju124.

[32] Friedes C, Chakrabarti T, Olson S, Prichett L, Brahmer JR, Forde PM, et al. Association of severe lymphopenia and disease progression in unresectable locally advanced non-small cell lung cancer treated with definitive chemoradiation and immunotherapy. Lung Cancer 2021;154:36–43.

[33] Ohri N, Halmos B, Bodner WR, Cheng H, Garg MK, Gucalp R, et al. Who benefits the most from adjuvant durvalumab after chemoradiotherapy for non-small cell lung cancer? An exploratory analysis Pract Radiat Oncol 2021;11(2):e172. e179.

[34] Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer 2017;111:176–81.

[35] Mezquita L, Auclin E, Ferrara R, Charrier M, Remon J, Planchard D, et al. Association of the lung immune prognostic index with immune checkpoint inhibitor outcomes in patients with advanced non-small cell lung cancer. JAMAOncol 2018;4(3):351.

[36] Jing W, Xu T, Wu L, Lopez PB, Grassberger C, Ellsworth SG, et al. Severe radiation-induced lymphopenia attenuates the benefit of durvalumab after concurrent chemoradiotherapy for NSCLC. JTO Clin Res Reports 2022;3(9):100391.

[37] Sakaguchi T, Ito K, Furuhashi K, Nakamura Y, Suzuki Y, Nishii Y, et al. Patients with unresectable stage III non-small cell lung cancer eligible to receive consolidation therapy with durvalumab in clinical practice based on PACIFIC study criteria. Respir Investig 2019;57(5):466–71.

[38] Shaverdian N, Offin MD, Rimner A, Shepherd AF, Wu AJ, Rudin CM, et al. Utilization and factors precluding the initiation of consolidative durvalumab in unresectable stage III non-small cell lung cancer. Radiother Oncol 2020;144:101–4.

[39] Palma DA, Senan S, Tsujino K, Barriger RB, Rengan R, Moreno M, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: An international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys 2013;85(2):444–50.

[40] Marks LB, Bentzen SM, Deasy JO, Kong F-M, Bradley JD, Vogelius IS, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010;76(3):S70. S76.

[41] Huang EX, Hope AJ, Lindsay PE, Trovo M, El Naqa I, Deasy JO, et al. Heart irradiation as a risk factor for radiation pneumonitis. Acta Oncol (Madr) 2011;50(1):51–60.

[42] Dang J, Li G, Zang S, Zhang S, Yao L. Comparison of risk and predictors for early radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with radiotherapy with or without surgery. Lung Cancer 2014;86(3):329–33.

[43] Shepherd AF, Iocolano M, Leeman J, Imber BS, Wild AT, Offin M, et al. Clinical and dosimetric predictors of radiation pneumonitis in patients with non-small cell lung cancer undergoing postoperative radiation therapy. Pract Radiat Oncol 2021;11(1):e52–62.

[44] Tomita N, Okuda K, Ogawa Y, Iida M, Eguchi Y, Kitagawa Y, et al. Relationship between radiation doses to heart substructures and radiation pneumonitis in patients with thymic epithelial tumors. Sci Rep 2020;10(1). https://doi.org/10.1038/s41598-020-68168-y.

[45] Ghobadi G, van der Veen S, Bartelds B, de Boer RA, Dickinson MG, de Jong JR, et al. Physiological interaction of heart and lung in thoracic irradiation. Int J Radiat Oncol Biol Phys 2012;84(5):e639. e646.

[46] Diamond BH, Belani N, Masel R, DeCarli K, DiPetrillo T, Hepel JT, et al. Predictors of pneumonitis in patients with locally advanced non-small cell lung cancer treated with definitive chemoradiation followed by consolidative durvalumab. Adv Radiat Oncol 2023;8(2):101130.

[47] Gao RW, Day CN, Yu NY, Bush A, Amundson AC, Prodduturvar P, et al. Dosimetric predictors of pneumonitis in locally advanced non-small cell lung cancer patients treated with chemoradiation followed by durvalumab. Lung Cancer 2022;170:58–64.

[48] Landman Y, Jacobi O, Kurman N, Yariv O, Peretz I, Rotem O, et al. Durvalumab after concurrent chemotherapy and high-dose radiotherapy for locally advanced non-small cell lung cancer. Oncoimmunology 2021;10(1). https://doi.org/10.1080/2162402X.2021.1959979.

[49] Tatsuno S, Doi H, Okada W, Inoue E, Nakamatsu K, Tanooka M, et al. Risk factors for radiation pneumonitis after rotating gantry intensity-modulated radiation therapy for lung cancer. Sci Rep 2022;12(1). https://doi.org/10.1038/s41598-021-04601-0.

[50] Katsui K, Ogata T, Watanabe K, Katayama N, Kuroda M, Kiura K, et al. Radiation pneumonitis after definitive concurrent chemoradiotherapy with cisplatin/docetaxel for non-small cell lung cancer: Analysis of dose-volume parameters. Cancer Med 2020;9(13):4540–9.

[51] Heskel M, Xanthopoulos E, Corradetti M, et al. Radiation pneumonitis in IMRT vs. 3D conformal radiation therapy. S1144 J Thorac Oncol 2013;8:S1143. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71397626.

[52] Hirama N, Yamamoto M, Kanaoka H, et al. A retrospective analysis of risk factors for Durvalumab related interstitial lung disease after chemoradiotherapy in Stage III NSCLC. European Respiratory. Society 2020;1638. https://doi.org/10.1183/13993003.congress-2020.1638.

[53] Wang Yu, Zhang T, Huang Y, Li W, Zhao J, Yang Y, et al. Real-world safety and efficacy of consolidation Durvalumab after chemoradiation therapy for stage III non-small cell lung cancer: A systematic review and meta-analysis. Int J Radiat Oncol 2022;112(5):1154–64.

[54] Shaverdian N, Offin M, Shepherd AF, Hellmann MD, Gomez DR, Chaft JE, et al. Association between the early discontinuation of Durvalumab and poor survival in patients with stage III NSCLC. JTO Clin Res Reports 2021;2(7):100197.

[55] Nestle U, Schimek-Jasch T, Kremp S, et al. Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial. LancetOncol 2020;21(4):581–92. https://doi.org/10.1016/S1470-2045(20)30013-9.

[56] Chun SG, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: A secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. J Clin Oncol 2017;35(1):56–62.
[57] Giaddui T, Chen W, Yu J, Lin L, Simone CB, Yuan L, et al. Establishing the feasibility of the dosimetric compliance criteria of RTOG 1308: Phase III randomized trial comparing overall survival after photon versus proton radiochemotherapy for inoperable stage II-IIIB NSCLC. Radiat Oncol 2016;11(1). https://doi.org/10.1186/s13014-016-0640-8.
[58] Ohri N, Cheng H, Jolly S, Gadgeel SM, Cooper BT, Shum E, et al. The selective personalized radioimmunotherapy for locally advanced NSCLC trial (SPRINT). J Clin Oncol 2019;37(15_suppl):TPS8571–.
[59] van Rossum PSN, Stam B, Juan-Cruz C, Rossi MMG, Belderbos J, Sonke JJ. Severe radiation-induced lymphopenia during concurrent chemoradiotherapy for lung cancer: External validation of two prediction models. Int J Radiat Oncol 2022;114(3):e394.
[60] Liang J, Bi N, Wu S, Chen M, Lv C, Zhao L, et al. Etoposide and cisplatin versus paclitaxel and carboplatin with concurrent thoracic radiotherapy in unresectable stage III non-small cell lung cancer: A multicenter randomized phase III trial. Ann Oncol 2017;28(4):777–83.