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Treatment-related pulmonary adverse events induced by chemoradiation and Durvalumab affect survival in locally advanced non-small cell lung cancer

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Abstract

Purpose: We compared treatment-related pulmonary adverse events (TRPAE), progression-free survival (PFS), and overall survival (OS) among locally advanced non-small cell lung cancer (NSCLC) patients who received concurrent chemoradiotherapy (CRT) versus CRT followed by immune check point inhibitor (ICI) immunotherapy (CRTI).

Materials and methods: TRPAE was defined as any pulmonary events as defined in CTCAE v.5 occurring within 12 months after completion of radiotherapy. Outcomes were compared between CRT and CTRI by Cox proportional hazard regression and Kaplan-Meier analyses. We also assessed if TRPAE-induced discontinuation of ICI affected survival.

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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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.10.002.

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Results: We analyzed 326 patients treated between July 2010 and November 2019; 195 patients received CRT and 131 received CRTI. The incidences of severe grade ≥ 3 TRPAE were similar between the two groups, however, symptomatic TRPAE was almost doubled in CRTI group (65.7 % CTRI vs 35.9 % CRT, $P < 0.0001$). The rates of 4-year OS and PFS were 54.5 % vs 36.7 % ($P = 0.0003$) and 43.8 % vs 35.8 % ($P = 0.038$) in CRT + Durvalumab and CRT group, respectively. Receipt of ICI Durvalumab was associated with better 4-year OS (HR 0.53, 95 % CI 0.36–0.78, $P = 0.001$) and PFS (HR 0.55, 95 % CI 0.38–0.80, $P = 0.002$). Patients who discontinued ICI because of TRPAE had worse 4-year OS ($P = 0.001$) and higher rates of distant metastasis ($P = 0.003$) than those who completed planned ICI after developing TRPAE.

Conclusion: CRT followed by adjuvant ICI led to improved 4-year OS and PFS consistent with published data. CRTI was associated with higher incidence of grade ≥ 2 TRPAE in both high and low mean lung dose groups without significant difference in grade ≥ 3 TRPAE. Discontinuation of ICI due to TRPAE was associated with poorer OS and distant disease control than completing ICI as planned after developing TRPAE.

Keywords

Concurrent chemoradiotherapy; Adjuvant immunotherapy; Disease outcome; Pulmonary toxicities; Non-small cell lung cancer

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The use of immune checkpoint inhibitors (ICI) represents a breakthrough in the treatment of locally advanced non-small cell lung cancer (LA-NSCLC). The median overall survival (OS) time for these patients has improved to 47.5 months with standard concurrent chemoradiotherapy (CRT) and adjuvant ICI immunotherapy with Durvalumab [1,2]. Findings from the landmark PACIFIC trial led to Durvalumab being granted approval by the US Food and Drug Administration as consolidation therapy for patients with unresectable stage III NSCLC [3,4]. However, both CRT and adjuvant ICI carry risks of adverse effects on healthy lung tissue. Moreover, in the PACIFIC trial, only patients who did not develop symptomatic pneumonitis, disease progression, unresolved symptomatic adverse events from CRT were included in the randomization for ICI, which may have excluded up to 55 % of patients who might benefit from ICI immunotherapy [5].

Findings from other prospective studies have also shown increased pulmonary toxicity among patients who receive thoracic RT with concurrent or sequential PD-1/PD-L1 inhibitor, suggesting that these therapies may interact in ways that increase the risk of pulmonary toxicity [6,7]. A meta-analysis published in abstract form showed that receipt of thoracic RT with ICI for NSCLC led to a higher incidence of ICI-related pneumonitis than that without receiving CRT [8]. Clinically, treatment-related pulmonary adverse events (TRPAE) after CRT or other cancer treatment can present in many different forms including cough, dyspnea, pleural effusion, hypoxia, respiratory distress, infection, even though pneumonitis has been most commonly reported. It is important for clinicians to understand the whole spectrum of possible TRPAE after cancer treatment. Several reports (including the PACIFIC trial) have shown that consolidation ICI can improve survival, however, little “real-world” evidence is available on the incidence of TRPAE and their impacts on survival.

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In this study, we hypothesized that consolidation ICI and TRPAE affect disease outcomes after CRT. We retrospectively assessed (1) the effects of CRT followed by adjuvant ICI on TRPAE and rates of 4-year OS and disease progression in patients with LA-NSCLC and (2) whether discontinuation of ICI due to TRPAE would affect OS and disease progression.

Materials and methods

Patients

This was a retrospective analysis of outcomes in 361 patients with inoperable LA-NSCLC who were consecutively treated either with concurrent CRT or CRT plus consolidation ICI immunotherapy (CRTI, routinely use after November 2017) at a single institution. Inclusion criteria includes: 1) NSCLC patients with stage II-III or recurrent disease after initial lung surgery; 2) received concurrent CRT ± adjuvant ICI for the first time; 3) radiation total tumor dose ≥ 60 Gy. Exclusion criteria were 1) active or previous autoimmune diseases or infections (n = 15); 2) history of primary immunodeficiency (n = 2); 3) active steroids treatment (n = 3, also have immune diseases). Finally, 326 patients were included in this analysis (Suppl. Fig. S1). Information on patient-, disease-, and treatment-characteristics and outcomes (survival and lung toxicities) were collected under an IRB-approved protocol for retrospective chart review, and informed consent was waived.

Treatment and follow-up

All patients received definitive concurrent CRT. Chemotherapy regimen was mainly platinum-based doublets with taxanes. Radiation was delivered in daily 2-Gy fractions by photon or proton therapy (median dose 66 Gy, range 60–78 Gy). Patients received radiation doses 66 Gy or higher routinely from 2010. After publication of the RTOG0617 [9,10], our radiation prescription has been changed to give GTV 66 Gy, while maintaining 60 Gy/30 fractions for the PTV. In 2016, we also started treating LA-NSCLC patients using protons as our routine practice. The selection of radiation modality was based on dosimetric comparison demonstrating potential benefit of the selected modality, either proton or photons, or if patient was treated on previously completed proton protocol. Patients who are currently enrolled to therapeutic protocols are not included in the current study. Adjuvant ICI immunotherapy usually started at 4–6 weeks after completion of CRT and continued for 1 year. ICI agents include Durvalumab (n = 118, 90.1 %), Pembrolizumab (n = 6, 4.6 %), Atezolizumab (n = 5, 3.9 %), and Nivolumab (n = 2, 1.5 %). The non-Durvalumab ICIs were mostly used before the FDA approval of Durvalumab as standard consolidation ICI treatment after CRT. ICI may be discontinued due to adverse events or disease progression.

Follow-up evaluations after treatment included surveillance chest CTs or PET/CTs performed at 4–8 weeks after RT completion, and then every 3–4 months thereafter for the next 2 years. Findings documented in diagnostic radiology reports were confirmed independently by a board-certified radiation oncologist.

Treatment-related pulmonary adverse events (TRPAE) were diagnosed and graded by two radiation oncologists or pulmonologists according to the CTCAE 5.0 including pneumonia, pneumonitis, fibrosis, pleural effusion, hypoxia, and respiratory distress. Patients who were

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diagnosed with pneumonia simultaneously with pneumonitis, or when it was difficult to rule out pneumonitis when patients were diagnosed with pneumonia after RT were included as TRPAE events in this analysis. Patients developed severe respiratory distress needing intubation without clear evidence of pneumonitis (e.g. no imaging changes to indicate inflammation in the lung) were categorized as respiratory distress. Similarly, patients developed hypoxia without clear evidence of pneumonitis were categorized as hypoxia.

Statistical analyses

The endpoints of this study were symptomatic (grade ≥ 2) TRPAE, OS, and progression-free survival (PFS). Time to TRPAE was computed from the start of CRT to the date of the first documented lung toxicity. Maximum grade of TRPAE was used for analysis. Patients who did not develop TRPAE were censored at the time of the last follow-up or death within 1 year after CRT. Demographics and clinical characteristics were compared with *t* test (for continuous variables) or χ^2 test (for categorical variables) between treatment groups. Endpoints were estimated by Kaplan-Meier method and compared with log-rank test. Cox proportional hazard regression models were applied to identify associated factors, including clinical factors (age, sex, smoking status, clinical disease stage, tumor location and histology, radiation dose, receipt of chemotherapy, and receipt of ICI), lung and tumor dose parameters, and radiation modalities. Risk factors were entered multivariable model if $P < 0.1$ in univariable analysis or clinically relevant to the endpoint. $P < 0.05$ was the threshold for statistical significance. Statistical analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patients' characteristics are shown in Table 1. A total of 326 inoperable LA-NSCLC patients treated from July 2010 through November 2019 were included in this study. Among them, 195 (59.8 %) were treated with CRT from 2010 to 2019, and 131 (40.2 %) were treated with CRTI from 2014 to 2019. Pretreatment patient-related variables (age, sex, smoking status, ECOG performance status score) and disease-related variables (disease stage, tumor histology and location, gross tumor volume [GTV]) were well balanced between the two groups except more white ethnic in CRT group (92.3 % vs 82.4 %).

As for treatment characteristics, majority of patients received standard radiation dose of 60–66 Gy (64.4 %) with photon therapy (75.8 %). A small portion of patients received > 66 Gy (35.6 %) and treated with proton therapy (24.2 %) when dosimetric plan comparison suggested better sparing or neighboring normal organs such as lung, heart, and esophagus. More patients in CRTI group received standard radiation dose compared to CRT group (83.2 % vs 51.8 %, $P < 0.0001$). However, the mean lung dose (MLD) was similar between the two groups (CRTI vs CRT, 14.3 Gy vs 15.1 Gy, $P = 0.084$). Seventeen percent of total patients received induction chemotherapy. No significant difference was found in induction chemotherapy between the two groups. There were 57 (29.2 %) patients in CRT group received adjuvant chemotherapy. All patients in CTRI group received ICI in an adjuvant setting except for 3 (2.3 %) patients who received consolidation immunotherapy with chemotherapy.

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The grades and incidences of TRPAE are listed in Table 2. The incidence of grade ≥2 TRPAE was nearly doubled in CRTI group comparing to CRT group (65.7 % vs 35.9 %, $P < 0.0001$). However, there was no significant difference in grade ≥ 3 TRPAE between the CRT and CRTI groups (26.2% vs 32.1%, $P = 0.247$). The median time to grade ≥ 2 TRPAE was 5.1 months (IQR 2.8–7.7) after the start of CRT in the entire population; 5.8 months (IQR 3.5–8.2) for the CRTI group; and 4.3 months (IQR 2.1–6.7) for the CRT group ($P = 0.019$). In the CRT group, 85.7 % TRPAE occurred ≤ 8 months and 14.3 % occurred > 8 months after RT. However, more patients in the CRTI group developed TRPAE > 8 months after RT (72.1 % ≤8 months and 27.9 % >8 months, $P = 0.040$). The incidences of pneumonitis were 62.9 %, 52.3 %, and 78.6 % for the whole, the CRT, and the CRTI groups, respectively.

The cumulative incidences of grade ≥ 2 TRPAE are plotted in Fig. 1A. Curves for patients with and without ICI started to diverge at about 5 months after CRT. Because MLD is an established radiation dosimetric risk factor for TRPAE after CRT for NSCLC [11], we also considered possible interactions between ICI and MLD in this study. We used the mean MLD value of the entire study population (14.8 Gy) as the cutoff to define high and low MLD subgroups. The incidences of grade ≥ 2 TRPAE were 51.1 % in high MLD group and 43.9 % in low MLD group with marginally significant difference ($P = 0.062$, Fig. 1B). However, MLD was a strong predictor of TRPAE for CRT patients only (high vs low MLD, 43.9 % vs 24.7 %, $P = 0.017$, Fig. 1C) but not for CRTI patients. In another word, reduced MLD did not lower the incidences of TRPAE in CRTI group (high vs low MLD, 64.7 % vs 66.7 %, $P = 0.717$, Fig. 1C), suggesting that ICI induced TRPAE may have a different mechanism independent of radiation induced lung injury.

Univariable Cox regression analysis (Suppl. Table S1) showed that CRTI (Durvalumab) doubled the risk of grade ≥ 2 TRPAE compared to CRT (hazard ratio [HR] = 2.00, 95 % confidence interval [CI] 1.45–2.75, $P < 0.0001$). Number of ICI cycle was also a strong risk factor for grade ≥ 2 TRPAE (HR 1.02, 95 % CI 1.004–1.035, $P = 0.016$). Other clinical factors associated with grade ≥ 2 TRPAE were age (≥67 years), race (other ethnicities), GTV, ECOG score (≥1), and MLD (≥14.8 Gy). In multivariable Cox regression analysis (Table 3), receipt of ICI Durvalumab was independently associated with more than 2-fold of risk of grade ≥ 2 TRPAE (HR = 2.37, 95 % CI 1.56–3.40, $P < 0.0001$) after adjusting for age, race, GTV, tumor location, ECOG score, smoking status, MLD, total tumor dose and radiation technique. Race, GTV, and radiation technique were significant risk factors for grade ≥ 2 TRPAE after adjustment.

The median times of PFS were 12.4 and 16.7 months for CRT and CRTI group respectively. The median time of OS was 31.0 months for CRT group, while it was not reached but longer than 48 months for CRTI group. Kaplan-Meier estimates for the disease outcomes, including PFS, local–regional progression–free survival (LPFS), distant metastasis–free survival (DMFS), and OS at 4 years by treatment groups are shown in Fig. 2. All rates of 4-year survival outcomes excluding DMFS were significantly higher in the CRT + Durvalumab group than those of the CRT group: PFS, 43.8 % CRTI and 35.8 % CRT ($P = 0.038$); LPFS, 73.1 % CRTI and 59.7 % CRT ($P = 0.016$); DMFS, 52.1 % CRTI and 45.4 % CRT ($P = 0.102$); and OS, 54.5 % CRTI and 36.7 % CRT ($P = 0.0003$). However, in patients who received CRT + other ICI agent (n = 13), only the rate of 4-year OS was higher than

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that of CRT group (53.9 % vs 36.7 %, $P = 0.001$), and no significant differences in the rates of PFS, LPFS, or DMFS. Twelve patients (92.3 %) in this ICI subgroup had local–regional failure (53.8 %, $P = 0.280$) or distant failure (61.5 %, $P = 0.401$) within 4 years after CRT. The median time of OS for CRTI group was longer than 4 years, while it was 31 months for CRT group ().

Univariable Cox regression analyses for OS and PFS at 4 years are shown in Suppl. Table S1. Receipt of Durvalumab as consolidation ICI was associated with significantly improved 4-year OS (HR = 0.52, 95 % CI 0.36–0.75, $P = 0.0005$) and PFS (HR = 0.70, 95 % CI 0.51–0.97, $P = 0.031$) compared with CRT only patients. Number of ICI cycle was also a strong factor for OS (HR = 0.95, 95 % CI 0.93–0.97, $P < 0.0001$) and PFS (HR = 0.70, 95 % CI 0.51–0.97, $P = 0.031$). Kaplan-Meier estimates of OS, LRFS, DMFS and PFS stratified by cycles of ICI were plotted in Suppl. Fig. S2. Patients received > 12 cycles of ICI had better OS (62.0 % vs 46.3 %, $P = 0.002$), DMFS (59.6 % vs 36.6 %, $P = 0.0002$) and PFS (49.0 % vs 25.4 %, $P = 0.0001$) than patients received ≤ 12 cycles of ICI. Other clinical factors associated with 4-year OS were disease stage, tumor histology, GTV, ECOG score, smoking status, and MLD. Clinical factors associated with 4-year PFS were age, disease stage, GTV, and MLD (Suppl. Table S1).

In multivariable Cox regression analysis (Table 3), receipt of Durvalumab was independently associated with improved 4-year OS (HR = 0.53, 95 % CI 0.36–0.78, $P = 0.001$) and PFS (HR = 0.55, 95 % CI 0.38–0.80, $P = 0.002$) after adjustment for selected clinical factors. GTV, ECOG score, smoking status, and MLD were clinical factors significantly associated with 4-year OS after adjustment. Age, GTV, tumor location and MLD were clinical factors significantly associated with 4-year PFS after adjustment (Table 3).

Finally, we conducted a subgroup analysis to evaluate the effects of TRPAE-caused discontinuation of ICI on disease outcomes. Of the 131 patients in the CTRI group, 55 (42.0 %) completed 1 year adjuvant ICI (50 [38.2 %] patients with TRPAE and 5 [3.8 %] without TRPAE); 72 patients (55.0 %) discontinued ICI; 2 patients (1.5 %) lost follow up. There were a variety of reasons for discontinuation of ICI, chief among them being toxicity events (32 events (24.4 %): 27 TRPAE [20.6 %]; 1 skin toxicity [0.8 %]; 2 arthritis or joint/muscle pain [1.5 %]; 1 cognitive issues and fatigue [0.8 %]; and 1 vomiting and weakness [0.8 %]). The second reason was disease progression (25 patients [19.1 %]). Ten patients (7.6 %) discontinued ICI for other reasons, such as death, change in health status and patient's decision. Among patients developed TRPAE, 50 (38.2 %) completed ICI therapy and 27 (20.6 %) discontinued ICI therapy because of TRPAE. Discontinuation of ICI had significant negative effects on 4-year DMFS (ICI discontinued vs continued, 45.4 % vs 60.2 %, $P = 0.003$) and 4-year OS (ICI discontinued vs continued, 52.3 % vs 62.9 %, $P = 0.001$) relative to those patients who continued ICI after developing TRPAE (Fig. 3). Representative radiographic features of severe TRPAE leading to discontinuation of ICI in two patients are shown in Suppl. Fig. S3.

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Discussion

In this real-world, single-institution analysis, receipt of consolidation ICI immunotherapy after CRT significantly increased the incidence of symptomatic (grade 2) TRPAE. Patients who received CRTI had more TRPAE despite receiving lower radiation dose when compared with CRT group. MLD was a strong predictor of TRPAE risk for patients who received CRT, but not for patients who received CRTI. The risk of TRPAE in CRTI treated patients was uniformly high in both high and low MLD subgroups, which implies that ICI immunotherapy was indeed an independent risk factor for TRPAE. We also showed that receipt of Durvalumab immunotherapy led to significantly improved 4-year OS and PFS compared with CRT only. We further found that among the CRTI group, discontinuation of ICI immunotherapy because of TRPAE had significant negative effects on 4-year DMFS and OS.

Clinical data from prospective trials suggested that thoracic RT could increase pulmonary toxicities of ICI, given concurrently or sequentially, for NSCLC [6,7] In the PACIFIC trial, the incidence of pneumonitis/pneumonia among patients receiving Durvalumab was 46.1 % (any grade) and 7.8 % (grade 3/4) compared with 31.2 % (any grade) and 6.0 % (grade 3/4) among patients given placebo [4]. In real-world retrospective studies, there is inconsistency in the reported incidence of pneumonitis [5,6,12–23] (Suppl. Table S2). For examples, Hassanzadeh et al. [21] reported 2/34 (6 %) grade 3 pneumonitis; Bruni et al. [23] reported 7/155 (5 %) grade ≥ 3 pneumonitis; Perna et al. [16] reported 7/187 (4 %) grade ≥ 3 pneumonitis, consistent with that reported from PACIFIC trial. However, there are studies reported high rates of grade ≥ 3 pneumonitis [5,12,13,15,17,18,24]. For examples, Jung et al. [5] reported 9/21 (43 %) grade ≥ 2 and 3/21 (14.3 %) grade 3 pneumonitis versus 8/40 (20 %) grade ≥2 and 1/40 (2.5 %) grade 3 pneumonitis in Durvalumab versus observation group. Thomas et al. [13] reported 26/123 (21 %) grade ≥ 2 and 17/123 (13 %) grade 3/4 pneumonitis in CRTI patients. Mayahara et al. [18] reported 50/56 (89 %) grade ≥ 2 and 22/56 (39 %) grade ≥ 3 pneumonitis. Similarly, the incidences of pneumonitis grades 2 and 3 in our study were largely increased in CRTI group as listed in Suppl. Table S2. There were 76/131 (58 %) grade ≥ 2 and 33/131 (25 %) grade ≥ 3 pneumonitis versus 44/195 (23 %) grade ≥ 2 and 33/195 (14 %) grade ≥ 3 pneumonitis in CRTI versus CRT group. These differences in the incidences of pneumonitis between the real-world reports including our study and PACIFIC trial could reflect the use of strict patient selection criteria and the exclusion of patients who developed symptomatic pneumonitis in the PACIFIC trial. Small sample size and different inclusion criteria of real-world retrospective studies were also potential reasons for the wide range of reported incidences.

In our study, we found 65.7 % grade ≥ 2 TRPAE and 32.1 % grade ≥ 3 TRPAE in CRTI treated patients. This high incidence of TRPAE was due to the inclusion of all possible pulmonary adverse events that were attributable to CRT or CRTI in the definition of events in the current study. These pulmonary adverse events included not only pneumonitis but also fibrosis, pleural effusion, hypoxia, respiratory distress, and pneumonia. In a study reported by Reibnitz et al. [12], there were 34/79 (43 %) grade 2 + and 15/79 (19 %) grade 3 + TRPAE in NSCLC patients received CRTI, including pneumonitis, pneumonia, dyspnea, cough, pleural effusion, pulmonary embolism, and bronchopulmonary aspergillosis. Our

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motivation to include all pulmonary adverse events in this report was to provide a more comprehensive description of all possible pulmonary adverse events that can impact on patient quality of life and even the treatment outcomes. Therefore, incidences of TRPAEs from the current study should not be considered as equivalent to “radiation induced pneumonitis” and should not be directly compared with those reports that only included pneumonitis. In fact, the incidence of grade 3 or higher pneumonitis in our study after CRT or CRTI were quite consistent with our previous reports [25–27] and reports from others listed in Suppl. Table S2 [5,12,18].

Use of the PD-L1 inhibitor Durvalumab as consolidation therapy after concurrent CRT has significantly extended survival times and now represents the current standard of care for unresected stage III NSCLC [28]. In Jung et al.’s analysis [5], use of Durvalumab for consolidation was associated with favorable PFS in the entire population as well as a subgroup of patients who did not meet the criteria for the PACIFIC study. Similarly, Desilets et al. [22] reported an improved median OS time for patients given Durvalumab for historical patients. Our findings of improved OS with median > 48 months (vs. 31 months) and improved PFS with median of 16.7 months (vs. 12.4 months) in the CRTI group seems to agree with the results of both the PACIFIC trial and the reported real-world evidences.

Discontinuation of cancer therapy could be expected to negatively affect survival outcomes. In the PACIFIC trial, 15.4 % patients in Durvalumab group and 9.8 % in placebo group discontinued the trial regimen because of grade 3/4 adverse events [3]. Pneumonitis was the most common adverse events for ICI discontinuation. In our study, 24.4 % patients discontinued ICI immunotherapy because of adverse events (mainly grade 3/4 TRPAE), 18 % were discontinued because of pneumonitis, which is consistent with previous reports listed in Suppl. Table S2 [5,6,13–15,17,18,21,22]. These patients had poorer OS and DMFS relative to those who completed ICI even after developing TRPAE. These findings underscore the importance of identifying risk factors, means of early diagnosis, and effective management for TRPAE to allow more patients to complete ICI therapy and, potentially, experience survival and disease control benefits.

We identified MLD was only a risk factor for TRPAE in CRT group but not CRTI group. The radiation dose to certain threshold volumes of the lung has been well established as a risk factor for radiation-induced TRPAE [11]. However, using stricter lung-dose constraints may not be as effective in reducing pneumonitis in the setting of CRTI as it has been in the setting of CRT, because lung injury induced by ICI may involve different pathophysiologic pathways. The precise means by which immunotherapy leads to adverse events is largely unknown, some have proposed that it relates to the temporal process of how immune checkpoints maintain immunologic homeostasis; the point at which PD1 inhibits T cells in peripheral tissues, for example, is thought to be related to the type of tissue injury induced by ICI with anti-PD1 [29]. Recent study also suggested that Th17 mediated inflammation may play a critical role in the pathophysiology of ICI-related pulmonary complications [30]. Additional preclinical and translational research is needed to better understand the mechanisms underlying various types of immunotherapy-related toxicities to develop more specific interventions for TRPAE induced by ICI immunotherapy.

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We acknowledged that this retrospective single-center study was subject to all the limitations inherent in retrospective analyses. For example, patients in the CRT group were treated from 2010, and all patients in the CRTI group were treated more recently because of the practice changes resulting from the PACIFIC trial findings. However, the standard work-up and concurrent CRT regimens for LA-NSCLC have been quite consistent for the past 2 decades, and the CRTI group had similar preclinical characteristics to those treated earlier. We also included patients who were diagnosed with pneumonia but also had findings that indistinguishable from TRPAE because of the difficulty in ruling out pneumonitis from pneumonia based on clinical symptoms or diagnostic images, and because these two events often co-exist. We realize that this approach, though more conservative and safer, may add noise to the analysis and contribute to the higher incidence of the TRPAE in our study. Since it is extremely challenging to differential pneumonitis and pneumonia clinically, it might be warranted to perform bronchial airway lavage in all cases of pneumonitis to exclude pneumonia, and to develop tests that “diagnose” pneumonitis and distinguish from pneumonia. Furthermore, as additional patients are treated with this new standard of care, our findings will need to be confirmed by larger, prospective multicenter studies.

In conclusion, we found that concurrent CRT followed by consolidation immunotherapy with ICI led to improved survival and disease control relative to concurrent CRT only for patients with LA-NSCLC, consistent with published data. Compared with CRT, CRTI was associated with increased grade 2 TRPAE without significant increase in severe grade ≥ 3 TRPAE regardless of radiation MLD. Discontinuation of ICI resulting from TRPAE was associated with poorer disease outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

TRPAE	Treatment-related pulmonary adverse events
PFS	Progression-free survival
OS	Overall survival
LA-NSCLC	Locally advanced non-small cell lung cancer

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CRT	Chemoradiotherapy
ICI	Immune checkpoint inhibitor
CRTI	Chemoradiotherapy plus consolidation immune checkpoint inhibitor immunotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed tomography
PET	Positron emission tomography
GTV	Gross tumor volume
MLD	Mean lung dose

References

[1]. Faivre-Finn C, Vicente D, Kurata T, Planchard D, Paz-Ares L, Vansteenkiste JF, et al. Four-year survival with Durvalumab after chemoradiotherapy in stage III NSCLC-an update from the PACIFIC trial. J Thorac Oncol 2021;16:860–7. 10.1016/j.jtho.2020.12.015. [PubMed: 33476803]

[2]. 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;40:1301–11. 10.1200/JCO.21.01308. [PubMed: 35108059]

[3]. 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;379:2342–50. 10.1056/NEJMoa1809697. [PubMed: 30280658]

[4]. 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;377:1919–29. 10.1056/NEJMoa1709937. [PubMed: 28885881]

[5]. Jung HA, Noh JM, Sun J-M, Lee S-H, Ahn JS, Ahn M-J, et al. Real world data of durvalumab consolidation after chemoradiotherapy in stage III non-small-cell lung cancer. Lung Cancer 2020;146:23–9. 10.1016/j.lungcan.2020.05.035. [PubMed: 32505077]

[6]. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 2017;18:895–903. 10.1016/s1470-2045(17)30380-7. [PubMed: 28551359]

[7]. Theelen W, Peulen HMU, Lalezari F, van der Noort V, de Vries JF, Aerts J, et al. Effect of Pembrolizumab after stereotactic body radiotherapy vs Pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: results of the PEMBRO-RT phase 2 randomized clinical trial. JAMA Oncol 2019;5:1276–82. 10.1001/jamaoncol.2019.1478. [PubMed: 31294749]

[8]. Jie Y, Gu A, Fu P, Kong F-M. Does radiation increase the risk of immunotherapy related pneumonitis in cancer patients with thorax radiotherapy combined immune checkpoint inhibitors: a meta-analysis. J Clin Oncol 2020;38:e15099. 10.1200/JCO.2020.38.15_suppl.e15099.

[9]. Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187–99. 10.1016/S1470-2045(14)71207-0. [PubMed: 25601342]

[10]. Bradley JD, Hu C, Komaki RR, Masters GA, Blumenschein GR, Schild SE, et al. Long-term results of NRG oncology RTOG 0617: standard-versus high-dose chemoradiotherapy with or without Cetuximab for unresectable stage III non-small-cell lung cancer. J Clin Oncol 2020;38:706–14. 10.1200/JCO.19.01162. [PubMed: 31841363]

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[11]. 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:S70–6. 10.1016/j.ijrobp.2009.06.091. [PubMed: 20171521]

[12]. von Reibnitz D, Chaft JE, Wu AJ, Samstein R, Hellmann MD, Plodkowski AJ, et al. Safety of combining thoracic radiation therapy with concurrent versus sequential immune checkpoint inhibition. Adv Radiat Oncol 2018;3:391–8. 10.1016/j.adro.2018.05.001. [PubMed: 30202807]

[13]. Thomas TS, Luo S, Knoche EM, Sanfilippo KM, Keller JW. Evaluation of the incidence of pneumonitis in United States veterans with non-small cell lung cancer receiving durvalumab following chemoradiation. J Clin Oncol 2020;38:9034. 10.1200/JCO.2020.38.15_suppl.9034.

[14]. Shintani T, Kishi N, Matsuo Y, Ogura M, Mitsuyoshi T, Araki N, et al. Incidence and risk factors of symptomatic radiation pneumonitis in non-small-cell lung cancer patients treated with concurrent chemoradiotherapy and consolidation Durvalumab. Clin Lung Cancer 2021;22:401–10. 10.1016/j.cllc.2021.01.017. [PubMed: 33678582]

[15]. Saito S, Abe T, Kobayashi N, Aoshika T, Ryuno Y, Igari M, et al. Incidence and dose-volume relationship of radiation pneumonitis after concurrent chemoradiotherapy followed by durvalumab for locally advanced non-small cell lung cancer. Clin Transl Radiat Oncol 2020;23:85–8. 10.1016/j.ctro.2020.05.006. [PubMed: 32529055]

[16]. Perna M, Scotti V, Ciammella P, Borghetti P, D'Angelo E, Levra NG, et al. The NIPRO study: an observational, retrospective, multicenter study on the safety of the radiotherapy and immunotherapy combination for advanced-stage NSCLC. Clin Lung Cancer 2021;22:e767–73. 10.1016/j.cllc.2021.02.005. [PubMed: 33766477]

[17]. Moore R, Lau S, Bezjak A, Sacher AG, Liu Z, Hope AJ, et al. The clinical relevance and management of grade 2 Pneumonitis in stage III non-small cell lung cancer patients on adjuvant Durvalumab. Int J Radiat Oncol Biol Phys 2020;108:E100.

[18]. Mayahara H, Uehara K, Harada A, Kitatani K, Yabuuchi T, Miyazaki S, et al. Predicting factors of symptomatic radiation pneumonitis induced by durvalumab following concurrent chemoradiotherapy in locally advanced non-small cell lung cancer. Radiat Oncol 2022;17:7. 10.1186/s13014-021-01979-z. [PubMed: 35033139]

[19]. Lu X, Wang J, Zhang T, Zhou Z, Deng L, Wang X, et al. Comprehensive Pneumonitis profile of thoracic radiotherapy followed by immune checkpoint inhibitor and risk factors for radiation recall pneumonitis in lung cancer. Front Immunol 2022;13:918787. 10.3389/fimmu.2022.918787. [PubMed: 35795657]

[20]. Jang JY, Kim SS, Song SY, Kim YJ, Kim SW, Choi EK. Radiation pneumonitis in patients with non-small-cell lung cancer receiving chemoradiotherapy and an immune checkpoint inhibitor: a retrospective study. Radiat Oncol 2021;16:231. 10.1186/s13014-021-01930-2. [PubMed: 34863244]

[21]. Hassanzadeh C, Sita T, Savoor R, Samson PP, Bradley J, Gentile M, et al. Implications of pneumonitis after chemoradiation and durvalumab for locally advanced non-small cell lung cancer. J Thorac Dis 2020;12:6690–700. 10.21037/jtd-20-1792. [PubMed: 33282370]

[22]. Desilets A, Blanc-Durand F, Lau S, Hakozaki T, Kitadai R, Malo J, et al. Durvalumab therapy following chemoradiation compared with a historical cohort treated with chemoradiation alone in patients with stage III non–small cell lung cancer: a real-world multicentre study. Eur J Cancer 2021;142:83–91. 10.1016/j.ejca.2020.10.008. [PubMed: 33242835]

[23]. Bruni A, Scotti V, Borghetti P, Vagge S, Cozzi S, D'Angelo E, et al. A real-world, multicenter, observational retrospective study of Durvalumab after concomitant or sequential chemoradiation for unresectable stage III non-small cell lung cancer. Front Oncol 2021;11:. 10.3389/fonc.2021.744956744956.

[24]. Suresh K, Voong KR, Shankar B, Forde PM, Ettinger DS, Marrone KA, et al. Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: incidence and risk factors. J Thorac Oncol 2018;13:1930–9. 10.1016/j.jtho.2018.08.2035. [PubMed: 30267842]

[25]. Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, et al. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. J Clin Oncol 2018;36:1813–22. 10.1200/JCO.2017.74.0720. [PubMed: 29293386]

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[26]. Pang Q, Wei Q, Xu T, Yuan X, Lopez Guerra JL, Levy LB, et al. Functional promoter variant rs2868371 of HSPB1 is associated with risk of radiation pneumonitis after chemoradiation for non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2013;85:1332–9. 10.1016/j.ijrobp.2012.10.011. [PubMed: 23374503]

[27]. Tucker SL, Li M, Xu T, Gomez D, Yuan X, Yu J, et al. Incorporating single-nucleotide polymorphisms into the Lyman model to improve prediction of radiation pneumonitis. Int J Radiat Oncol Biol Phys 2013;85:251–7. 10.1016/j.ijrobp.2012.02.021. [PubMed: 22541966]

[28]. Brahmer JR, Govindan R, Anders RA, Antonia SJ, Sagorsky S, Davies MJ, et al. The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). J ImmunoTher Cancer 2018;6:75. 10.1186/s40425-018-0382-2. [PubMed: 30012210]

[29]. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158–68. [PubMed: 29320654]

[30]. Kim ST, Sheshadri A, Shannon V, Kontoyiannis DP, Kantarjian H, Garcia-Manero G, et al. Distinct IMMUNOPHENOTYPES of T cells in Bronchoalveolar Lavage fluid from Leukemia patients with immune checkpoint inhibitors-related pulmonary complications. Front Immunol 2021;11. 10.3389/fimmu.2020.590494.

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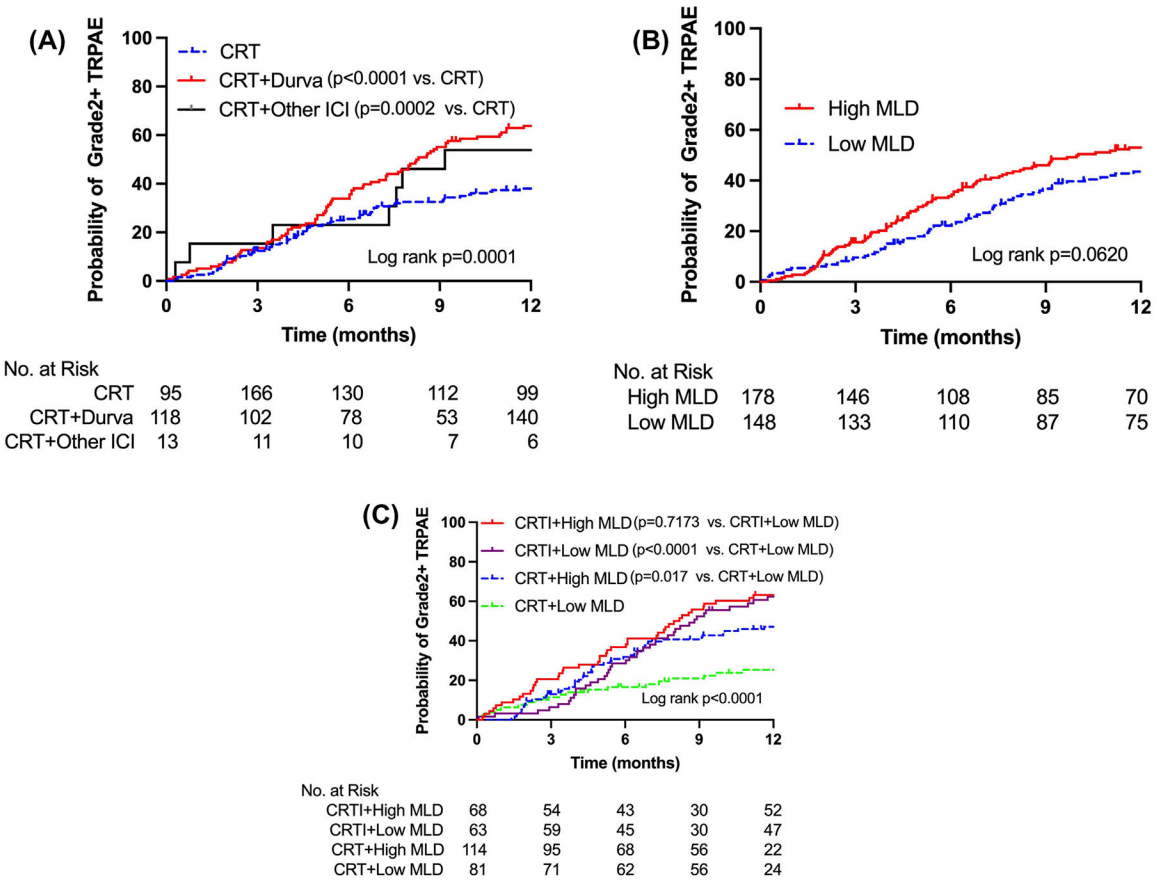

Fig. 1.

Cumulative incidence of grade ≥ 2 treatment-related pulmonary adverse events (TRPAE) in all patients stratified by (A) treatment (CRT vs CRTI), (B) mean lung dose (MLD), and (C) a combination of the two. Significant increases in the incidence of grade ≥ 2 TRPAE were associated with receipt of immune checkpoint inhibitors (ICI) (A) and in patients with a high (≥14.8 Gy) MLD (B). Receipt of ICI was associated with significantly higher incidence of grade ≥ 2 TRPAE regardless of the MLD. MLD was a strong predictor of grade ≥ 2 TRPAE among patients who received CRT, but not among patients given CRTI (C), because all patients given ICI had a high incidence of TRPAE regardless of whether the MLD was high or low.

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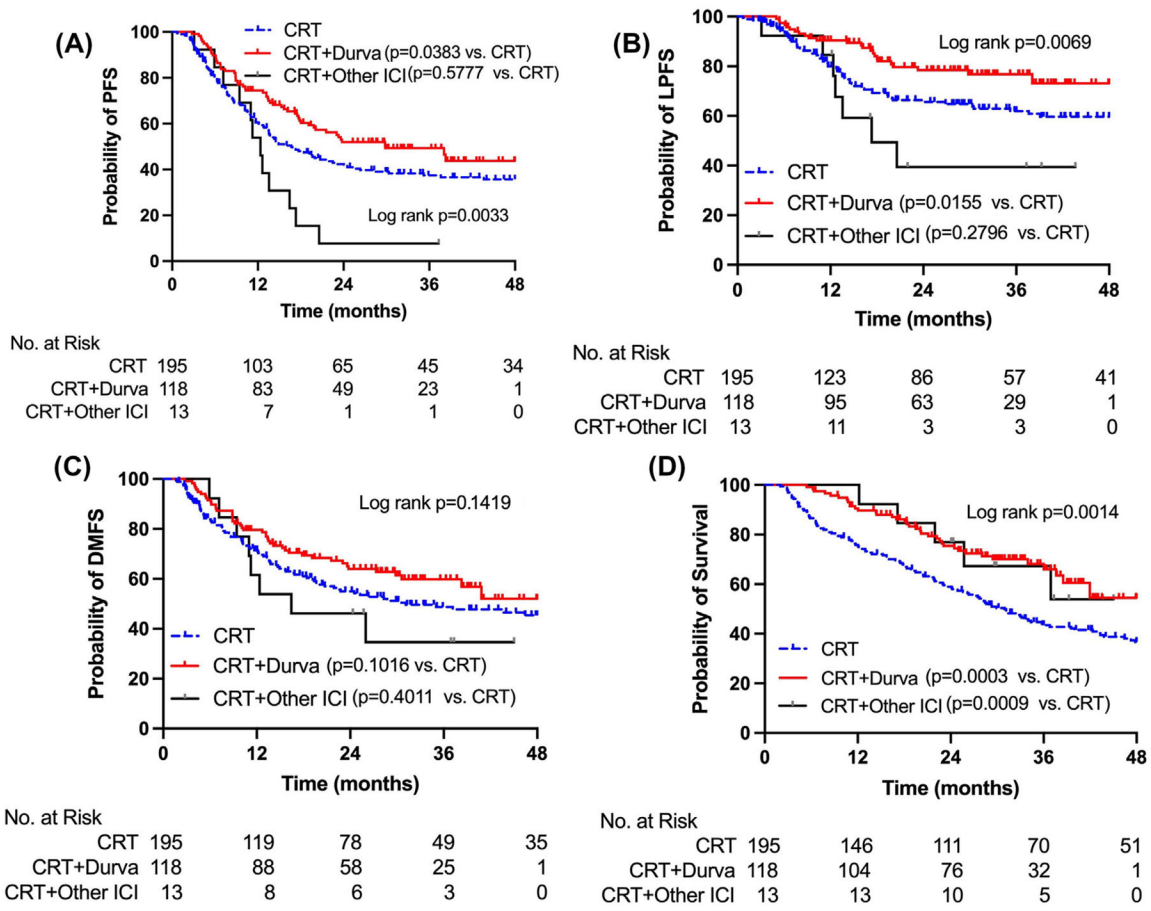

Fig. 2.

Four-year disease outcomes stratified by receipt of chemoradiotherapy (CRT) or chemoradiotherapy followed by adjuvant immune checkpoint inhibitor Durvalumab or other ICI immunotherapy (CRTI). (A) Progression-free survival (PFS); (B) local-regional progression-free survival (LPFS); (C) distant metastasis-free survival (DMFS); and (D) overall survival for patients with non-small cell lung cancer. Receipt of Durvalumab ICI immunotherapy led to improved local and distant progression-free survival and overall survival.

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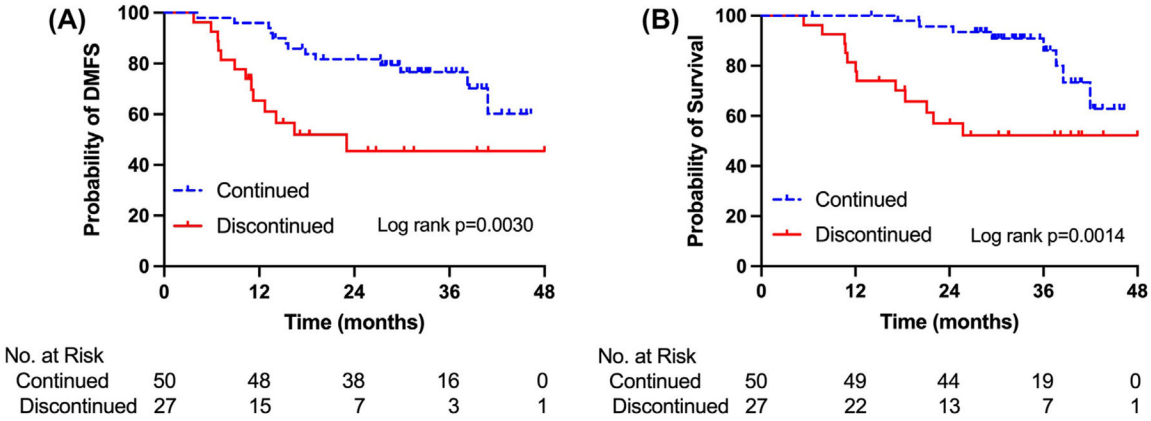

Fig. 3.

Four-year disease outcomes in patients with non-small cell lung cancer who developed treatment-related pulmonary adverse events (TRPAE), grouped by completion of immunotherapy. Patients who discontinued immunotherapy had worse (A) distant metastasis-free survival and (B) overall survival than did those who continued ICI therapy after developing TRPAE.

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Table 1

Patient, disease, and treatment characteristics.

Variables	CRTI Group (n = 131)	CRT Group (n = 195)	All Patients (n = 326)	*P* Values*
Age, years, mean (SD)	67 (8.9)	67 (10.0)	67 (9.4)	0.617
Sex				0.310
Female	53 (40.5 %)	90 (46.1 %)	143 (43.9 %)	
Male	78 (59.5 %)	105 (53.9 %)	183 (56.1 %)	
Race				0.007
White	108 (82.4 %)	180 (92.3 %)	286 (88.3 %)	
Others	23 (17.6 %)	15 (7.7 %)	37 (11.7 %)	
Smoking Status				0.770
Never	19 (14.5 %)	23 (11.8 %)	42 (12.9 %)	
Former	84 (64.1 %)	132 (67.7 %)	216 (66.2 %)	
Current	28 (21.4 %)	40 (20.5 %)	68 (20.9 %)	
ECOG Score				0.875
≤ 1	128 (97.7 %)	190 (97.4 %)	315 (97.6 %)	
> 1	3 (2.3 %)	5 (2.6 %)	8 (2.4 %)	
Disease Stage				0.423
II	15 (11.4 %)	27 (13.9 %)	42 (12.9 %)	
IIIA	74 (56.5 %)	100 (51.3 %)	174 (53.4 %)	
IIIB	42(32.1 %)	65 (33.3 %)	107 (32.8 %)	
Recurrent	0 (0 %)	3 (1.5 %)	3 (0.9 %)	
Tumor Histology				0.173
Adenocarcinoma	76 (58.0 %)	106 (54.4 %)	182 (55.8 %)	
Squamous cell carcinoma	50 (38.2 %)	71 (36.4 %)	121 (37.1 %)	
Others	5 (3.8 %)	18 (9.2 %)	23 (7.1 %)	
Tumor Location				0.261
Left	58 (44.3 %)	74 (37.9 %)	132 (40.5 %)	
Right	67 (51.1 %)	116 (59.5 %)	183 (56.1 %)	
Others	6 (4.6 %)	5 (2.6 %)	11 (3.4 %)	
GTV, cm^3, mean (SD)	114.4 (120.1)	133.3 (131.4)	125.7 (127.1)	0.189

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Variables	CRTI Group (n = 131)	CRT Group (n = 195)	All Patients (n = 326)	*P* Values*
MLD, Gy, mean (SD)	14.3 (3.9)	15.1 (4.5)	14.8 (4.3)	0.136
Total dose, Gy, mean (SD)				<0.0001
60–66	109 (83.2 %)	101 (51.8 %)	210 (64.4 %)	
>66	22 (16.8 %)	94 (48.2 %)	116 (35.6 %)	
Chemotherapy Induction	24 (18.3 %)	30 (15.4 %)	54 (16.6 %)	0.485
Adjuvant	3 (2.3 %)	57 (29.2 %)	60 (18.4 %)	-
Technique				0.0003
Photon	113 (86.3 %)	134 (68.7 %)	247 (75.8 %)	
Proton	18 (14.0 %)	61 (30.9 %)	79 (24.2 %)	

Abbreviations: CRT, chemoradiotherapy; CRTI, chemoradiotherapy with consolidation immune checkpoint inhibitor immunotherapy; SD, standard deviation; GTV, gross tumor volume; ECOG, Eastern Cooperative Oncology [performance status] score; MLD, mean lung dose.

*Differences between categorical variables are compared with Chi-square test; differences between continuous variables are compared with *t* test.

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Table 2

Summary of treatment-related pulmonary adverse events.

TRPAE CTCAE v5.0 Severity	CRTI Group (n = 131)	CRT Group (n = 195)	All Patients (n = 326)	*P* Values
Grade 0	12 (9.2 %)	42 (21.5 %)	54 (16.6 %)	
Grade 1	33 (25.2 %)	83 (42.6 %)	116 (35.6 %)	
Grade 2	44 (33.6 %)	19 (9.7 %)	63 (19.3 %)	
Grade 3	34 (26.0 %)	49 (25.1 %)	83 (25.5 %)	
Grade 4	5 (3.8 %)	1 (0.5 %)	6 (1.8 %)	
Grade 5	3 (2.3 %)	1 (0.5 %)	4 (1.2 %)	
Grade 2+	86 (65.7 %)	70 (35.9 %)	156 (47.9 %)	<0.0001
Grade 3+	42 (32.1 %)	51 (26.2 %)	93 (28.5 %)	0.247

Abbreviations: TRPAE, treatment-related pulmonary adverse events; CTCAE, Common Terminology Criteria for Adverse Events; CRT, chemoradiotherapy; CRTI, chemoradiotherapy plus consolidation immune checkpoint inhibitor immunotherapy.

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Table 3

Multivariable Cox proportional hazard regression models for treatment-related pulmonary adverse events (TRPAE) and disease outcomes.

Variables	4-year OS			4-year PFS			Grade ≥ 2 TRPAE		
	HR	95 % CI	*P*	HR	95 % CI	*P*	HR	95 % CI	*P*
Immunotherapy									
CRT	Ref								
CRT + Durvalumab	0.53	0.36–0.78	0.001	0.55	0.38–0.80	0.002	2.37	1.65–3.40	<0.0001
CRT + Other ICI	0.61	0.25–1.53	0.293	1.66	0.89–3.10	0.108	1.75	0.77–3.97	0.180
Age, years	1.00	0.98–1.02	0.918	0.98	0.96–0.99	0.005			
≥67 vs < 67							1.30	0.92–1.83	0.143
Sex (Female vs Male)	0.78	0.55–1.10	0.161	0.95	0.68–1.31	0.736			
Race (White vs Others)							0.52	0.28–0.96	0.036
Disease Stage									
II	0.85	0.48–1.49	0.561	0.97	0.56–1.68	0.911			
IIIA	0.81	0.56–1.16	0.249	0.66	0.46–0.94	0.021			
IIIB	Ref			Ref					
Recurrent	2.29	0.53–9.95	0.268	0.90	0.12–6.73	0.917			
Tumor Histology									
Adenocarcinoma	Ref			Ref					
Squamous cell carcinoma	1.03	0.72–1.49	0.863	0.78	0.54–1.13	0.192			
Others	1.13	0.59–2.14	0.720	0.64	0.32–1.27	0.201			
GTV, cm^3	1.002	1.001–1.004	<0.0001	1.002	1.001–1.004	<0.0001	1.002	1.001–1.004	<0.0001
Tumor Location									
Right	Ref			Ref			Ref		
Left	1.16	0.83–1.62	0.397	1.41	1.02–1.96	0.038	1.03	0.73–1.44	0.873
Mediastinum	1.11	0.14–8.59	0.920	4.20	0.56–31.73	0.164	-	-	-
Both sides	1.63	0.56–4.79	0.372	1.38	0.47–4.07	0.564	1.34	0.53–3.39	0.543
ECOG (≥1 vs < 1)	3.54	1.38–9.09	0.009	2.08	0.74–5.85	0.165	2.20	0.87–5.55	0.094
Smoking status									
Current	Ref			Ref			Ref		
Never	0.25	0.12–0.56	0.001	0.96	0.54–1.69	0.883	1.36	0.74–2.48	0.325

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Variables	4-year OS			4-year PFS			Grade ≥ 2 TRPAE		
	HR	95 % CI	*P*	HR	95 % CI	*P*	HR	95 % CI	*P*
Previous	0.76	0.51–1.12	0.168	1.06	0.70–1.58	0.794	1.32	0.86–2.02	0.207
MLD, Gy Continuous	1.06	1.01–1.11	0.011	1.05	1.00–1.09	0.035			
≥14.8 vs < 14.8							1.34	0.96–1.87	0.090
Total dose (>66 Gy vs 60–66 Gy)							0.84	0.57–1.23	0.367
Technique (Photon vs Proton)	1.12	0.77–1.63	0.543	1.30	0.88–1.91	0.185	0.59	0.40–0.87	0.007

Abbreviations: TRPAE, treatment-related pulmonary adverse events; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; CRT, chemoradiotherapy; CRTI, chemoradiotherapy with consolidation immune checkpoint inhibitor immunotherapy; GTV, gross tumor volume; ECOG, Eastern Cooperative Oncology [performance status] score; MLD, mean lung dose.

Note: Clinical covariates were entered into multivariable models if $p < 0.1$ in univariable analysis or relevant to endpoint.