Predictive factors of symptomatic radiation pneumonitis induced by durvalumab following concurrent chemoradiotherapy in locally advanced non-small cell lung cancer

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Research

Keywords: locally advanced non-small cell lung cancer, concurrent chemoradiotherapy, radiation pneumonitis, dosimetric factor, durvalumab

Posted Date: August 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-840895/v1

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Running title: Predictive factors of radiation pneumonitis after CCRT and durvalumab in LA-NSCLC

0. Abstract:

Background: Concurrent chemoradiotherapy (CCRT) followed by durvalumab is the standard of care for unresectable locally advanced non-small cell cancer (LA-NSCLC). However, a major concern about the administration of durvalumab after CCRT is whether the incidence of symptomatic radiation pneumonitis (RP) increases. In the present analysis, we report the initial results of CCRT followed by durvalumab in patients with LA-NSCLC in a real-world setting with a focus on predictive factors for symptomatic RP.

Methods: Patients who were pathologically diagnosed with NSCLC and initiated treatment with CCRT followed by durvalumab between July 2018 and December 2019 were eligible for this study. Patients were included if they completed the planned CRT course and were administered at least one course of durvalumab. We retrospectively investigated the preliminary survival outcome and incidence and predictive factors for symptomatic RP.

Results: Of the 67 patients who were scheduled to receive CCRT, 63 completed the entire CCRT course. Of these patients, 56 proceeded to consolidation with durvalumab. The median time to eternal discontinuation of durvalumab was 9.7 months. The cumulative proportions of patients who exhibited symptomatic RP were 30, 40 and 44% at 3, 6 and 12 months, respectively. In multivariate analyses, the pulmonary fibrosis score and lung V40 were significant predictive factors for symptomatic RP ($p < 0.001$, HR: 7.83, 95% CI: 3.38-18.13, and $p = 0.034$, HR: 3.17, 95% CI: 1.09-9.19, respectively).

Conclusions: The pulmonary fibrosis sore and lung V40 are significant predictive factors for symptomatic RP. We should be cautious about the administration of durvalumab for patients with subclinical pulmonary fibrosis. To the best of our knowledge, this is one of the first reports showing the predictive value of high dose volumes to the lung in patients with LA-NSCLC who receive CCRT followed by durvalumab.

Keywords:

locally advanced non-small cell lung cancer, concurrent chemoradiotherapy, radiation pneumonitis, dosimetric factor, durvalumab

1. Introduction

Lung cancer is the most frequently diagnosed cancer and the leading cause of cancer-related mortality worldwide [1]. Locally advanced stage 3 non-small cell lung cancer (LA-NSCLC) accounts for 20% of all lung cancer cases [2]. Because of the frequencies of both locoregional and distant recurrences, for decades, concurrent chemoradiotherapy (CCRT) has been the standard of care [3, 4]. The 5-year overall survival (OS) rate is estimated to be only 15-30% [5, 6, 7, 8, 9, 10]. Numerous studies tested the combination of new systemic agents or dose escalation and failed to improve outcomes [6, 8, 9, 11, 12]. Several studies investigated consolidative chemotherapy after CCRT and showed no apparent clinical benefit [13, 14, 15, 16, 17].

The PACIFIC phase 3 randomized controlled trial demonstrated the efficacy of consolidation therapy with durvalumab [18, 19, 20]. Durvalumab is a selective human IgG1 monoclonal antibody that blocks programmed death ligand-1 (PD-L1) binding to the PD-1 receptor and CD80 and increases the antitumor activity of T cells [21, 22, 23]. In the PACIFIC study, for patients with LA-NSCLC, durvalumab administered after CCRT improved the median progression-free survival (PFS) by 17.2 months compared to placebo (5.6 months). The median OS was 47.5 months with durvalumab but 29.1 months with placebo [20]. Currently, the administration of durvalumab after CCRT has become the standard of care [24].

A major concern about the administration of durvalumab after CCRT is whether the incidence and severity of radiation pneumonitis (RP) increase. In the PACIFIC study, RP was observed in 34% and

25% of the patients treated with durvalumab and placebo, respectively [18]. In particular, grade 3 and 4 RP occurred in 3.4% and 2.6% of patients treated with durvalumab and placebo, respectively. In the PACIFIC study, patients were randomly assigned to groups after the successful completion of CCRT, and those who exhibited symptomatic RP during and immediately after CCRT were excluded from the study [18]. The reported incidence of RP in the PACIFIC study may not represent a real-world incidence because it might include only patients in good condition. Additionally, actual dosimetric factors, such as lung dose, target coverage, irradiation techniques, and quality of radiotherapy plans, were not evaluated because CCRT was not included in the protocol of the PACIFIC study [18].

In the present analysis, we report the results of CCRT followed by durvalumab in patients with unresectable LA-NSCLC in a real-world setting with a focus on predictive factors for symptomatic RP.

2. Materials and Methods

2.1. Study subjects

Patients with either unresectable primary LA-NSCLC or locoregional recurrent NSCLC after primary resection were included in this study. Patients who were pathologically diagnosed with NSCLC and initiated CCRT followed by durvalumab between July 2018 and December 2019 were eligible for this study. The data cutoff date was September 30, 2020. Patient consent for treatment was obtained in written form. Clinical staging was performed by fluorodeoxyglucose-positron emission tomography, contrast-enhanced computed tomography (CT) and gadolinium-enhanced magnetic resonance imaging (MRI) of the brain according to the Union for International Cancer Control criteria (8th ed.). Patients were included if they completed the planned CRT course and were administered at least one course of durvalumab. We retrospectively investigated the incidence and predictive factors for symptomatic RP. This study was approved by our institutional review board and was conducted in accordance with the Declaration of Helsinki.

2.2. Statistical analysis

The primary objective of this analysis was to determine the clinical outcomes associated with CRT followed by durvalumab. OS and PFS were estimated as the time from starting CRT to death or disease progression by using the Kaplan-Meier method.

Possible clinical and dosimetric factors that may predict symptomatic RP were statistically investigated. Symptomatic RP was defined as grade 2 or higher RP (G2RP) by the Common Toxicity Criteria for Adverse Events (version 5.0). The time to G2RP was defined as the time from the completion of CRT to the development of G2RP and was calculated by using the Kaplan–Meier estimator and compared by using the log-rank test. Time to discontinue durvalumab (TTDD) was defined as the time from the first administration of durvalumab to 14 days after the last administration of durvalumab. Temporary postponement of durvalumab due to toxicity or completion after 12 months of administration was not counted as an event. Disease progression and discontinuation of durvalumab for any reason other than RP were treated as competing risks for TTDD due to RP, and the hazard ratio (HR) was estimated using the Fine-Gray method.

In regard to the evaluation of baseline lung fibrosis, we used the pulmonary fibrosis score, which was introduced by Kazerooni EA et al. and modified by Tsujino et al. [25, 26]. The pulmonary fibrosis scores were independently reviewed by an experienced diagnostic radiologist (CS), pulmonary medical oncologist (AK) and radiation oncologist (KK) who were blinded to the patients' medical records. If there was any discordance in the pulmonary fibrosis score, the score was decided upon a discussion.

The percentage of the lung volume receiving the various dose levels described above was statistically evaluated. To determine the optimal cutoff values of continuous variables, we performed receiver operating characteristic (ROC) curve analyses, and the optimal cutoff values were determined by the Youden index. Then, the areas under the curves (AUCs) of each value were calculated. Associations between dosimetric variables were evaluated by using the Pearson correlation coefficients. A correlation coefficient of more than 0.6 was regarded as some correlation between variables. When we considered factors that were correlated with each other, we selected the factor that had the highest AUC in the ROC curve analyses. Multivariate analyses were performed by using the Fine-Gray model and included factors that showed significant associations ($p < 0.05$) in the univariate Gray's test.

All analyses were performed in R, version 3.6.3 (R Foundation for Statistical Computing). All hypothesis tests were 2-sided, and $p < 0.05$ was considered statistically significant.

2.3. Radiotherapy

Radiotherapy was delivered using a 10- or 6-MV X-ray with the TrueBeam system (Varian Medical Systems, CA, USA). Four-dimensional CT (4D CT) was used to evaluate respiratory tumor motion. Varian's RPM respiratory gating irradiation system was used if respiratory tumor motion encompassed 7 mm. For dose calculations, images of the expiratory phase (2 mm thickness) were used. Eclipse treatment planning software (ARIA 11.0.42, Varian Medical Systems, CA, USA) was used for dose optimization and calculation. Irradiation techniques included both intensity-modulated radiotherapy (IMRT) and three-dimensional conformal radiotherapy (3D-CRT). The irradiation technique was decided at the discretion of the attending radiation oncologist, who considered the anatomical tumor location, tumor extension and treatment schedule. All irradiations were delivered under image guidance with an orthogonal on-board imager (OBI) and kV cone beam CT (CBCT). The gross target volume (GTV) of the primary lesion was defined in simulated CT images of the lung window. The internal target volume (ITV) was determined by the summation of GTVs in 4D CT images to encompass whole respiratory tumor motion. Upon respiratory gating, the ITV was calculated as the summation of GTVs in only the end-respiratory phase (typically 40-60% of the respiratory cycle). The clinical target volume (CTV) included a 5 mm margin in all directions from the ITV. Essentially, prophylactic regional irradiation was not applied. The planning target volume (PTV) was defined as the CTV with a 4-5 mm margin to compensate for any setup error. The prescribed dose was 60 Gy in 30 fractions for all the patients, except for one patient who discontinued irradiation at a dose of 54 Gy in 27 fractions due to infectious pneumonitis. The dose was prescribed to the isocenter in a patient who received 3D-CRT, whereas the dose was prescribed to D50% of the PTV in a patient who received IMRT until April 2019. Then, the dose was switched to D95% of the PTV thereafter, in accordance with the protocol of another prospective observational clinical study. Dose-volume parameters such as the mean lung dose (MLD), percentage of the normal lung volume (lung - GTV) that received more than 5 Gy (V5), 10 Gy (V10), 15 Gy (V15), 20 Gy (V20), 30 Gy (V30), 40 Gy (V40), and 50 Gy (V50), volume of the lung that received less than 5 Gy (Vs5), MLD and initial PTV volume (ml) were recorded prior to treatment. Dose constraints for organs at risk were <45 Gy to the spinal cord, and V20 and V5 of the lung were < 30% and < 65%, respectively.

2.4. Chemotherapy

The concurrent chemotherapy regimens included weekly CBDCA + paclitaxel (PTX), cisplatin (CDDP) +S-1, CDDP + vinorelbine and CDDP + pemetrexed. The regimen was determined at the discretion of the attending medical oncologists and depended on the patients' age, general condition, organ functions and tumor histology.

2.5. Durvalumab

Diagnostic CT scans were taken immediately after completing CCRT to evaluate its efficacy and to detect RP. If no abnormalities were found on CT and blood tests, durvalumab was started. Durvalumab (10 mg/kg) was administered intravenously every 2 weeks until 1 year [18]. The administration of durvalumab was continued until disease progression, the emergence of unacceptable toxicities such as G2RP or withdrawal of consent. If patients developed G2RP, they typically were treated with corticosteroids with prednisolone at 0.5-1.0 mg/kg, and the administration of durvalumab was postponed until the symptoms were resolved, and prednisolone was reduced to a dose of less than 5-10 mg/kg body.

2.6. Follow-up

After starting durvalumab, patients were recommended to receive chest X-ray and blood tests for every biweekly visit for durvalumab. Chest and upper abdominal CT images were taken every 2 months for the first year and every 3-4 months thereafter. Brain MR images were taken every 6 months.

3. Results

3.1. Patient characteristics

Fifty-six patients with LA-NSCLC who completed CCRT and received maintenance therapy with durvalumab were eligible for this analysis. The patients' baseline characteristics are summarized in Table 1. Between July 2018 and December 2019, a total of 78 patients received definitive radiotherapy in our single institution. Among them, 63 had unresectable primary LA-NSCLC, and 15 had unresectable locoregional recurrent NSCLC after primary resection. Upon the exclusion of 12 patients who were scheduled to be treated with radiotherapy alone, 67 patients were scheduled to receive CCRT. Sixty-three patients completed the planned CCRT course, whereas 4 patients discontinued CCRT because of massive respiratory bleeding, a tracheoesophageal fistula, chemotherapy-induced pneumonitis, and refusal to receive chemotherapy. Upon the exclusion of these 4 patients, 63 patients completed CCRT. Of these patients, 56 received durvalumab after a median of 19 days from the last day of irradiation. Seven patients did not receive durvalumab due to surgical resection (n=2), a comorbidity (n=2), early symptomatic RP (n=1), a deteriorated performance status (n=1) and patient refusal (n= 1). These patients were excluded from further analysis to maintain comparability with the results of the PACIFIC study. Thus, 56 of 67 (84%) patients who were scheduled to receive CCRT proceeded to maintenance therapy with durvalumab. The applied irradiation techniques were IMRT for 28 patients and 3D-CRT for 28 patients.

3.2. OS, PFS and causes of morbidity

With a median follow-up period of 14.0 months among the living patients, the 12- and 18-month OS rates were 87 and 84%, respectively (Fig. 1A). At the time of analysis, 9 patients had died; six had died from primary disease progression, 1 from another cancer and 2 from treatment-related toxicities (lung toxicity in one and toxic epidermal necrolysis in one). The 12- and 18-month PFS rates were 57 and 46%, respectively (Fig 1B).

3.3. Continuity of durvalumab

At the time of analysis, 19 patients completed 1 year of durvalumab administration, whereas 8 patients were currently under administration. Twenty-nine patients discontinued durvalumab. Of these, 15 discontinued durvalumab due to disease progression, 11 due to toxicity, and 3 due to patient refusal. The proportions of patients who were continuing durvalumab at 3, 6 and 12 months were 70, 63 and 48%, respectively (Fig. 2). The median TTDD was 9.7 months.

3.4. Incidence of RP

The numbers of patients who developed grade 0, 1, 2, 3 and 5 RP were 6 (10.7%), 28 (50%), 17

(30.4%), 4 (7.1%) and 1 (1.8%), respectively. The cumulative proportions of patients who developed G2RP were 30, 40 and 44% at 3, 6 and 12 months, respectively (Fig. 3). The proportions of patients who eternally discontinued durvalumab due to G2RP were 14, 14 and 14% at 3, 6 and 12 months, respectively (Fig. 4).

3.5. ROC curve analysis of dose-volume histogram parameters of the lung for the risk of G2RP

The results of the ROC curve analysis of G2RP are summarized in Table 2. The patients were dichotomized according to the threshold levels determined by the ROC curve analysis. The cumulative incidences of G2RP were estimated by Gray's test. Discontinuation of durvalumab due to causes other than G2RP was treated as a competing risk for G2RP. Lung V30, V40, and V50, the MLD and the initial PTV were significant predictors for G2RP. Lung V20, V10 and V5 did not significantly predict G2RP. The Pearson correlation coefficients between lung V30/V40, V40/V50 and V30/V50 were 0.730, 0.853, and 0.629, respectively. The Pearson correlation coefficients between MLD/V30, MLD/V40 and MLD/V50 were 0.762, 0.802, and 0.661, respectively. Because lung V30, V40, and V50 and the MLD were correlated with each other, we selected lung V40, which had the highest AUC among these parameters, for further analysis.

3.6. Univariate and multivariate analyses of factors affecting the risk of G2RP

Univariate analyses revealed that sex (male), the pulmonary fibrosis score (≥2), smoking history (present), lung V40 (≥10%) and the initial PTV (≥398 ml) were significant predictors for G2RP (Table

3). There was no difference in the incidence of G2RP between IMRT and 3D-CRT. Pulmonary function was also not a predictive factor for G2RP. In multivariate analyses, the pulmonary fibrosis score and lung V40 remained significant factors for G2RP ($p < 0.001$, HR: 7.83, 95% CI: 3.38-18.13, and $p = 0.034$, HR: 3.17, 95% CI: 1.09-9.19, respectively). The cumulative incidences of G2RP at 6 months were 16.7% and 57.3% with lung V40s below and above the threshold level of 10%, respectively (Fig. 5).

3.7. Univariate and multivariate analyses of factors affecting the risk of eternal discontinuation of durvalumab due to RP

Univariate analyses revealed that sex (male), the pulmonary fibrosis score (≥ 2) and the initial PTV (≥398 ml) were significant factors for eternal discontinuation of durvalumab (Table 3). There was no difference in the incidence of G2RP between IMRT and 3D-CRT. Pulmonary function was also not a predictive factor. In the multivariate analysis, only the pulmonary fibrosis score remained a significant factor (< 0.001, HR: 5.89, 95% CI: 1.53-22.68).

3.8. Cumulative incidence of G2RP according to the lung V20 level

The 6-month cumulative incidences of G2RP among patients with lung V20s of <20%, 20-25% or ≥25% were 25.0, 46.7 and 51.8%, respectively (Fig. 6). There were no significant differences among them ($p = 0.51$).

4. Discussion

In the current study, the incidence of G2RP was 39.3% after CCRT followed by durvalumab for LA-NSCLC. The incidence of G2RP seems to be higher than that in previous reports without durvalumab [26, 27, 28, 29]. In a recent multi-institutional retrospective analysis in Japan, Horinouchi et al. reported a G2RP incidence of 24% before the introduction of durvalumab [29]. Few analyses have reported the real-world incidence of G2RP when durvalumab is administered after CCRT. Consistent with the current study, reports from several institutions revealed the incidence to be 36-43% [30, 31, 32]. Jung et al reported a higher incidence of G2RP among patients administered durvalumab than among patients under observation (42.9% vs. 20%) [31]. They also reported a higher incidence of grade 3 RP in patients treated with durvalumab than in those under observation (14.3% vs. 2.5%). A recently described multi-institutional study in Japan revealed that the incidence of G2RP was 37.7% with durvalumab [32]. Consolidation with durvalumab should increase the incidence of symptomatic RP, especially in patients of Asian ethnicity. Among the considerations for durvalumab, the development of G2RP is a clinically important endpoint. One of the frequent reasons for discontinuing durvalumab is symptomatic RP. When a patient develops G2RP, durvalumab is interrupted, and the patients is typically treated with corticosteroids. Interruption of durvalumab as well as immunologic inhibition by corticosteroids may impair the antitumor activity of T cells, which has been enhanced by durvalumab. Therefore, the prediction and prevention of G2RP are crucial.

The dosimetric analysis in this study showed that the percentage of the lung irradiated exceeding 40 Gy (V40) and the baseline presence of pulmonary fibrosis were independent predictors for G2RP.

Various predictive factors for RP have been reported thus far [33, 34, 35]. Among them, the lung dose has been regarded as the most distinct predictive factor for RP. The relationship between the radiation dose to the lung and RP in radiotherapy for LA-NSCLC has frequently been investigated by many researchers. In 1999, Graham et al. initially reported strong relationships between lung V20 and RP in radiotherapy alone for LA-NSCLC [27]. A lung V20 higher than 40% led to a remarkable increase in the incidence of G2RP. The threshold level of lung V20 for predicting G2RP was further lowered with the concurrent use of chemotherapy. In 2003, Tsujino et al. reported the relationships between lung V20 and the incidence of G2RP following CCRT for LA-NSCLC [23]. The CCRT regimen was predominantly a platinum agent plus taxanes. A lung V20 higher than 25% significantly increased the incidence of G2RP [23].

To reduce the incidence of RP, the introduction of new irradiation techniques, such as IMRT or respiratory motion management, would be useful. In a retrospective analysis of CCRT for LA-NSCLC, Liao et al. reported a significant reduction in the incidence of grade 3 RP by the combined use of IMRT and 4D CT planning [36]. In a meta-analysis of patients who received CCRT, IMRT significantly reduced the incidence of G2RP [37]. Several investigators reported a reduction in lung V20 by using IMRT compared to 3D-CRT [38]. However, there is another concern about the risk of excessive low-dose irradiation to the lung from the reports of post extrapleural pneumonectomy radiotherapy for pleural mesothelioma. Allen et al. found that the median lung V5 in patients who developed grade 5 RP was as high as 98.6% [39]. By introducing an optimal dose constraint for lung V5, the incidence of fatal RP after IMRT was drastically decreased in patients with pleural mesothelioma [40]. Additionally, in a patient with LA-NSCLC who received CCRT using IMRT, the incidence of grade 3 RP significantly increased when lung V5 exceeded 70% [41]. In this study, there was no difference in the incidence of grade 2 or 3 RP between patients who received IMRT or 3D-CRT, and neither V20 nor V5 was a significant predictor for G2RP. One possible explanation for the nonsignificant effects of V20 and V5 in the current study is that both lung V20 and V5 are highly restricted during treatment planning in our general practice, irrespective of the irradiation techniques used. This may have led to nonsignificant effects of V20 and V5 for predicting G2RP in the current study.

In contrast to previous studies, in the current study, the volume of the lung irradiated at medium to high doses (V30-50) was found to be an independent significant predictor of G2RP. In accordance with our study, Jin et al reported a high dose constraint of V50 (≤10%) along with V20 (≤25%), V25 (≤20%) and V35 (≤15%) in patients with LA-NSCLC who received either radiotherapy alone or CCRT [42]. However, this high dose constraint to the lung was not often highlighted in later reports. In line with the current study, Saito et al recently suggested a significant association of medium to high dose volumes to the lung and G2RP in patients with LA-NSCLC treated with CCRT followed by durvalumab [30]. From ROC curve analysis, they observed high AUCs with V40 (AUC = 0.759) and V30 (AUC = 0.779), as well as V20 (AUC = 0.756) and the MLD (AUC = 0.742), for G2RP. Medium to high dose volumes to the lung should be associated with the incidence of G2RP in patients with LA-NSCLC treated with CCRT followed by durvalumab.

Associations of high dose volumes and G2RP were also reported in patients with LA-NSCLC treated by CCRT with protons [43]. From ROC curve analysis, Harris et al. found that V35Gy to V50Gy had higher AUCs than other dose levels. It is technically difficult to restrict V30-50 because a high dose area to the lung would largely be determined by the shape of the target. The introduction of involved-field radiotherapy and the application of modern techniques, such as image-guided radiotherapy (IGRT), IMRT and respiratory motion management, may lead to a reduction in the lung volumes irradiated at high doses. Every effort should be practiced to reduce high dose-irradiation volumes to the lung.

In the current study, the baseline existence of pulmonary fibrosis was the strongest predictor of G2RP and only an independent predictor of permanent discontinuation of durvalumab due to RP. The association between subclinical interstitial lung disease and fatal RP has been described in several reports [44, 45, 46]. Tsujino et al advocated the predictive risk score including subclinical interstitial lung disease for grade 3 RP [26]. A pulmonary fibrosis score of 2 or more, which indicates honeycombing, was revealed as an independent predictor for grade 3 RP. When the pulmonary fibrosis score was combined with other predictors (age≥68 years, lung V20≥26% and lung Vs5 <1500 cc), its predictability for grade 3 RP was significantly improved. Taking into consideration this predictive risk sore in the treatment planning for LA-NSCLC, the incidences of grade 3 or higher RP radically decreased over time at their institution (personal communication). Multivariate analyses in the current study showed that a pulmonary fibrosis score of 2 or more was a significant predictor of G2RP and permanent discontinuation of durvalumab due to RP. The cumulative incidence of G2RP in patients with a pulmonary fibrosis score of 2 or more was as high as 85% at 6 months. The cumulative incidence of permanent discontinuation of durvalumab due to RP in patients with a pulmonary fibrosis score of 2 or more was also high (65% at 6 months). One patient who had baseline interstitial lung disease developed grade 5 RP 15 days after the first administration of durvalumab and 51 days after the completion of CCRT. He received CCRT using 3D-CRT with a lung V40 of 8.7%, a V20 of 17.7% and a V5 of 37.1%. All of these lung dose volumes were under the median value of the entire cohort.

From the specific surveillance of durvalumab use in Japan, of the 550 Japanese patients administered durvalumab, 10 (1.8%) developed grade 5 RP (unpublished in-house data from AstraZeneca). Baseline interstitial lung disease, symptomatic RP and a poor performance status after CCRT were reported to be associated with grade 5 RP, and patients with these factors are warned of the use of durvalumab. Careful patient selection for durvalumab is crucial, especially for patients who are suspected of having subclinical interstitial lung disease.

The preliminary OS and PFS results of the current study seem to be comparable to those of the initial report of the PACIFIC study [18]. However, there were nonnegligible differences in the baseline characteristics of the patients included in the PACIFIC study and the current study. Our study included relatively older patients, with a median age of 72 years, compared to 64 years in the PACIFIC study. Additionally, patients with more unfavorable prognosis (clinical stage IIIC; 10 patients (18%)) were included in this study and not in the PACIFIC study. Regardless of the considerable patient selection biases, the preliminary survival outcomes of patients in the current study were similar to those of patients in the PACIFIC study. The results of the current study suggest the reproducible survival benefit of durvalumab in a real-world setting.

We know there are several limitations to the current study. First, because of the retrospective nature of this study, patient selection criteria for both CCRT and durvalumab may have varied among the attending physicians. Additionally, the grade of RP, which was based on medical records, may have affected interpretation of the results. Second, because the irradiation technique was determined at the discretion of the attending radiation oncologists, the baseline characteristics of the patients who received CCRT with IMRT or 3D-CRT were not matched with other patients. Third, the optimal cutoff value of the lung dose-volume still needs to be investigated because of the limited number of patients included in the current study. Last, possible biomarkers that may predict the incidence or severity of RP were not investigated in the current study, although some of the patients' sera were sequentially cryopreserved for future assays after obtaining informed consent. We also conducted a multi-institutional prospective clinical trial, WJOG12019L (UMIN000038366), that is currently ongoing to investigate the efficacy and safety of CCRT using IMRT followed by durvalumab for LA-NSCLC.

5. Conclusions

The pulmonary fibrosis sore and lung V40 are significant predictive factors for symptomatic RP in patients with LA-NSCLC after CCRT followed by durvalumab. We should be cautious about the administration of durvalumab for patients with subclinical pulmonary fibrosis. To the best of our knowledge, this is one of the first reports showing the predictive value of high-dose volumes to the lung in patients with LA-NSCLC who receive CCRT followed by durvalumab.

Figure legends

Fig. 1A: Kaplan-Meier overall survival curve of the eligible patients

Fig. 1B: Kaplan-Meier progression-free survival curve of the eligible patients

Fig. 2: Kaplan-Meier curve for the proportion of patients who were continuing durvalumab

Fig. 3: Cumulative incidence of grade 2 or higher radiation pneumonitis

Fig. 4: Cumulative incidence of patients who eternally discontinued durvalumab due to radiation pneumonitis

Fig. 5: Cumulative incidence of grade 2 or higher radiation pneumonitis stratified by lung V40. The dichotomizing value was based on ROC curve analysis. Lung V40: percentage of the lung volume exceeding 40 Gy

Fig. 6: Cumulative incidence of grade 2 or higher radiation pneumonitis according to the lung V20 level

Lung V20: percentage of the lung volume exceeding 20 Gy

Competing interests

Hiroshi Mayahara reports personal fees from Accuray Japan, Inc., Hitachi, Ltd., and Eisai Co., Ltd., grants from MSD, and grants and personal fees from AstraZeneca PLC outside the submitted work. Akito Hata reports grants and personal fees from Eli Lilly, Boehringer Ingelheim and AstraZeneca, personal fees from Chugai, and grants from MSD outside the submitted work.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

Study concept and design: HM, KU and AK; Data acquisition and date interpretation: AH, KK, TY, SM, TI, HK, HK, HO, TN and CS; statistical analysis: HM and AK; Writing the first draft: HM; Supervision study: AH; All authors read and approved the final manuscript.

Acknowledgements

The authors thank American Journal Experts (www.aje.com) for English language editing.

Ethics declarations

The current study was approved by the institutional review board of our institution (2020-Kenkyu05-03), and the requirement for written informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and analyzed during the current study are not publicly available as individual privacy could be compromised but are available from the corresponding author on reasonable request.

Figures

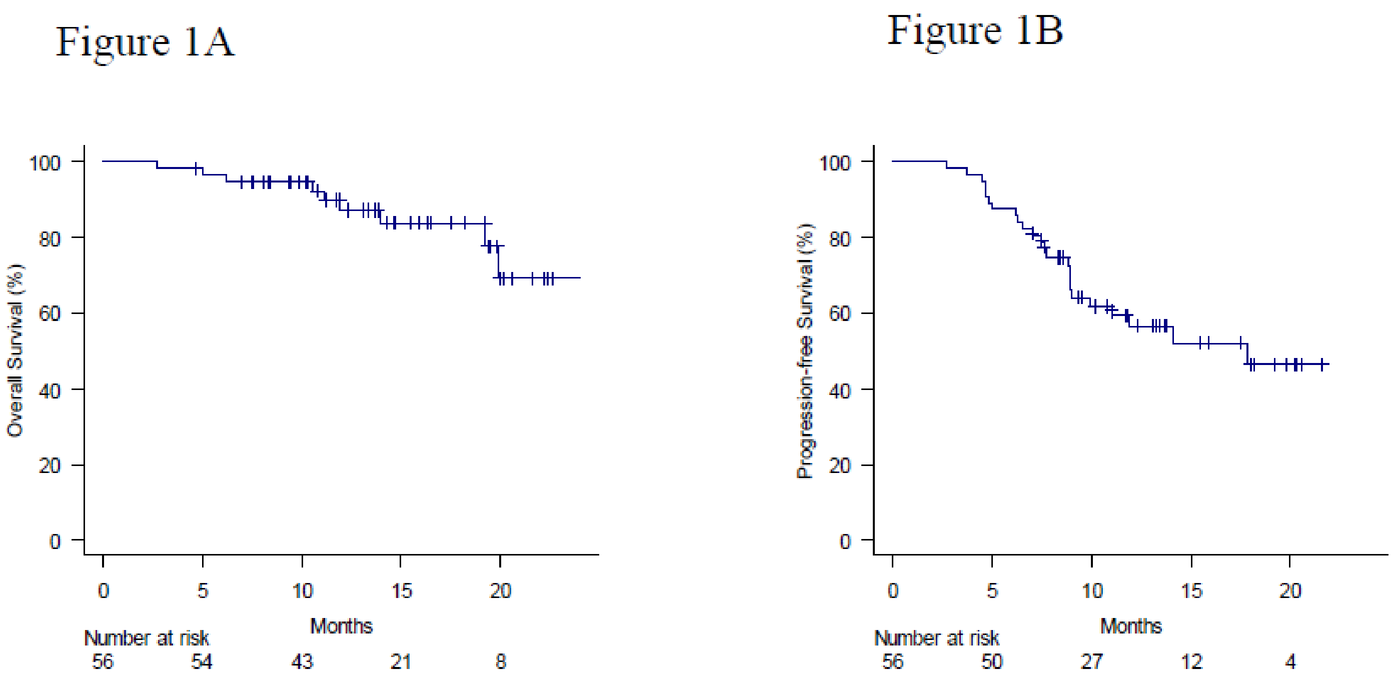

Figure 1

1A: Kaplan-Meier overall survival curve of the eligible patients. 1B: Kaplan-Meier progression-free survival curve of the eligible patients

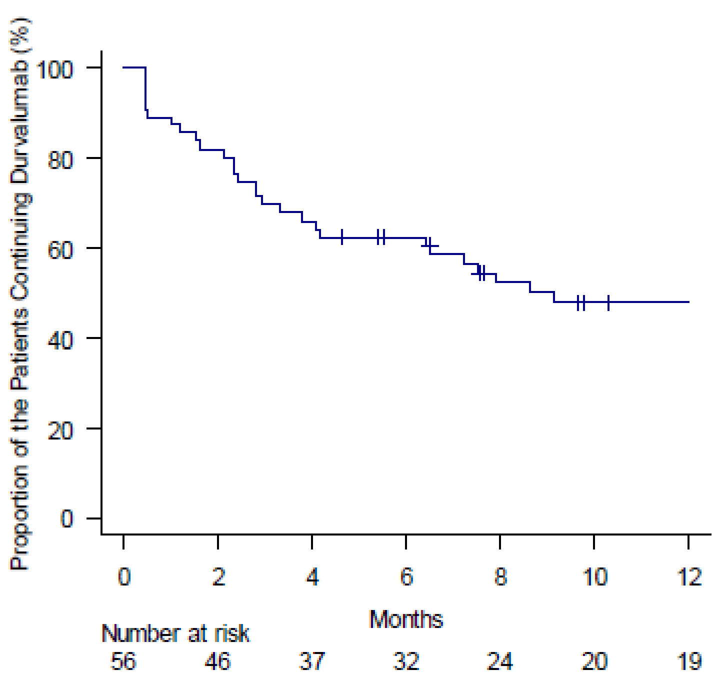

Figure 2

Kaplan-Meier curve for the proportion of patients who were continuing durvalumab

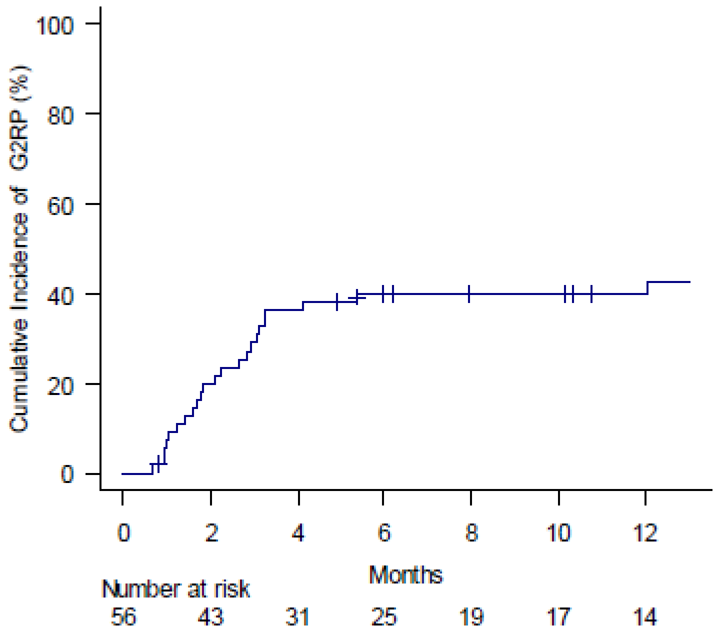

Figure 3

Cumulative incidence of grade 2 or higher radiation pneumonitis

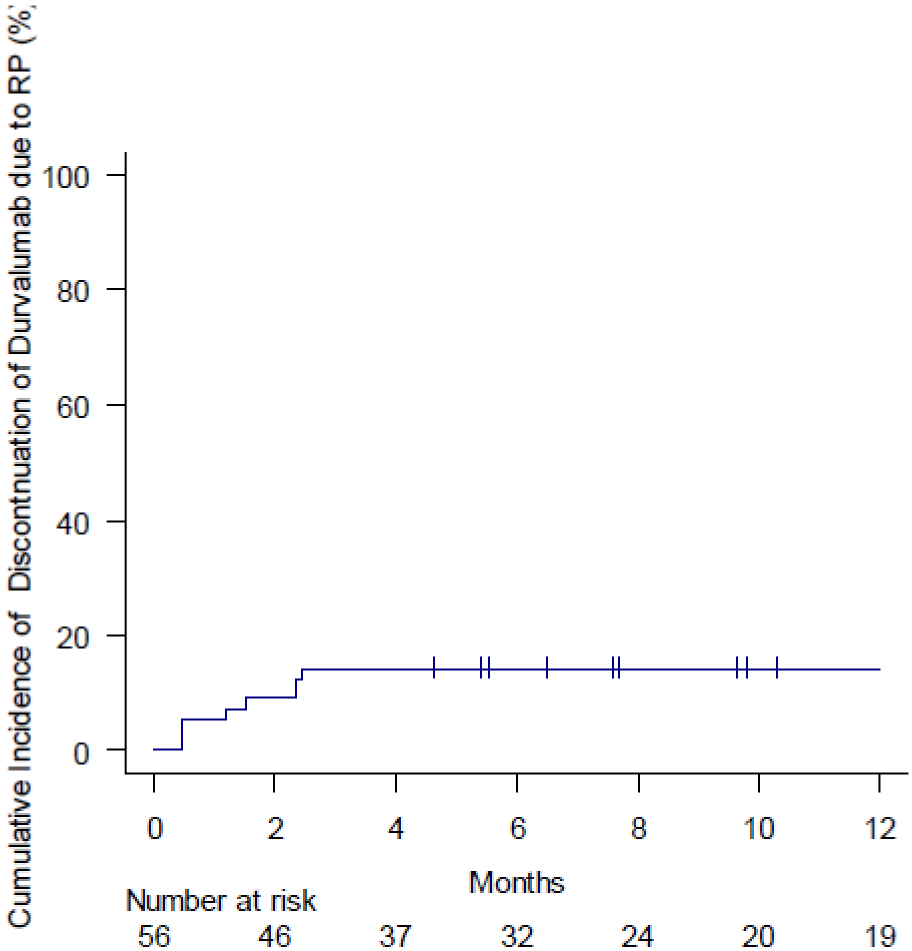

Figure 4

Cumulative incidence of patients who eternally discontinued durvalumab due to radiation pneumonitis

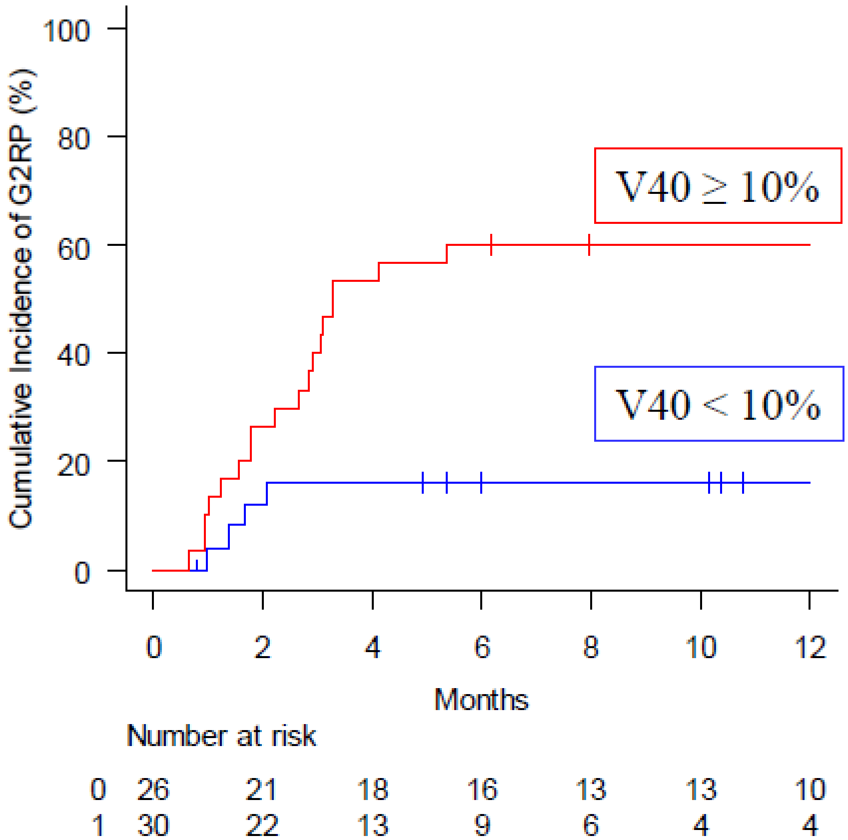

Figure 5

Cumulative incidence of grade 2 or higher radiation pneumonitis stratified by lung V40. The dichotomizing value was based on ROC curve analysis. Lung V40: percentage of the lung volume exceeding 40 Gy

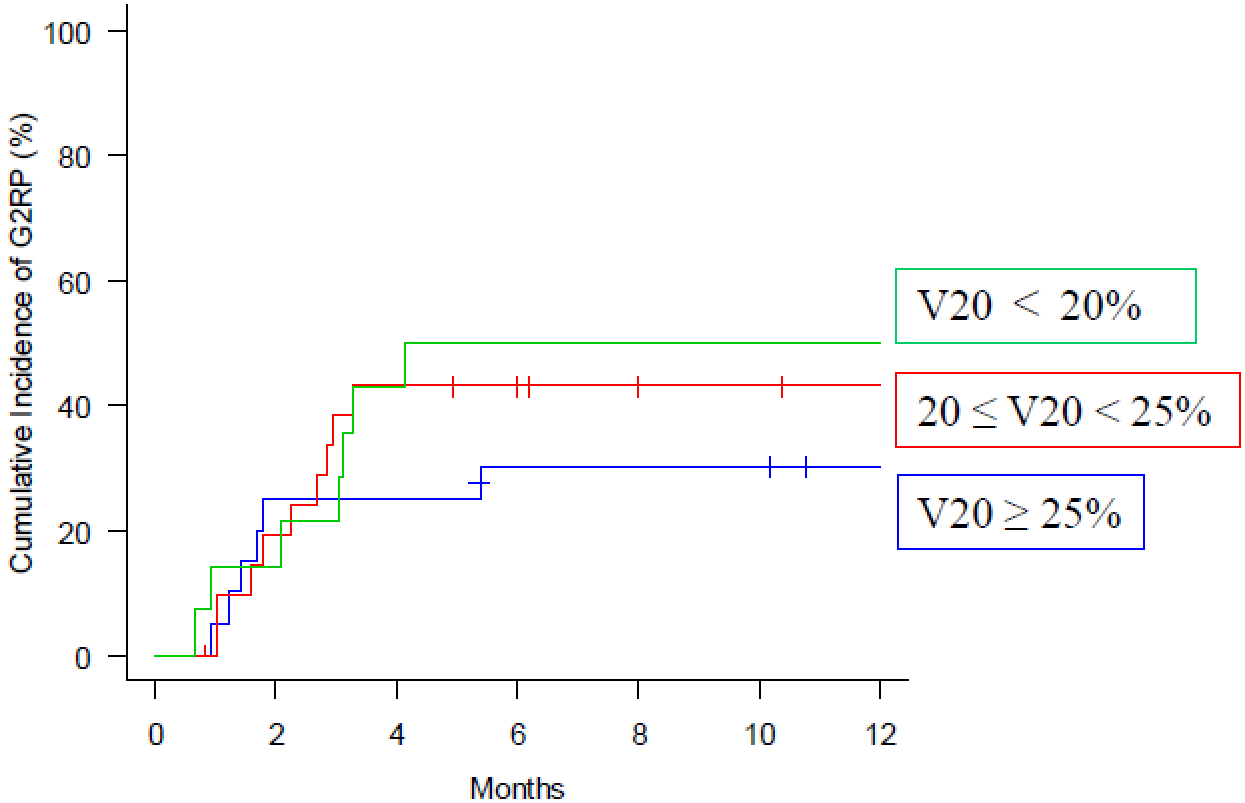

Figure 6

Cumulative incidence of grade 2 or higher radiation pneumonitis according to the lung V20 level Lung V20: percentage of the lung volume exceeding 20 Gy

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 210821Tablesmayaharaetal.pdf