



The efficacy profiles of concurrent chemoradiotherapy with intensity-modulated radiotherapy followed by durvalumab in patients with unresectable stage III non–small cell lung cancer: A multicenter retrospective cohort study

Yuichiro Takeda^{a,*}, Yusaku Kusaba^a, Yoko Tsukita^b, Yukari Uemura^c, Eisaku Miyauchi^b, Takaya Yamamoto^d, Hiroshi Mayahara^e, Akito Hata^f, Hidetsugu Nakayama^g, Satoshi Tanaka^h, Junji Uchida^h, Kazuhiro Usuiⁱ, Tatsuya Toyoda^j, Motohiro Tamiya^k, Masahiro Morimoto^l, Yuko Oya^m, Takeshi Kodairaⁿ, Keiichi Jingu^d, Hisatoshi Sugiura^b

^a Department of Respiratory Medicine, National Center for Global Health and Medicine, 1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan

^b Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-Ku, Sendai 980-8574, Japan

^c Section of Biostatistics, Department of Clinical Research Center, National Center for Global Health and Medicine, 1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan

^d Department of Radiation Oncology, Tohoku University Graduate School of Medicine, 1-1 Seiryomachi, Aoba-Ku, Sendai 980-8574, Japan

^e Department of Radiation Oncology, Kobe Minimally Invasive Cancer Center, 8-5-1, Minatojimanakamachi, Chuo-ku, Kobe, Hyogo 650-0046, Japan

^f Department of Respiratory Medical Oncology, Kobe Minimally Invasive Cancer Center, 8-5-1, Minatojimanakamachi, Chuo-ku, Kobe, Hyogo 650-0046, Japan

^g Department of Radiation Oncology, National Center for Global Health and Medicine, 1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan

^h Department of Respiratory Medicine, Osaka General Medical Center, 3-1-56, Bandaihigashi, Sumiyoshi-Ku, Osaka 558-0056, Japan

ⁱ Division of Respiriology, NTT Medical Center Tokyo, 5-9-22, Higashigotanda, Shinagawa, Tokyo 141-8625, Japan

^j Department of Radiology, NTT Medical Center Tokyo, 5-9-22, Higashigotanda, Shinagawa, Tokyo 141-8625, Japan

^k Department of Thoracic Oncology, Osaka International Cancer Institute, 3-1-69, Otemae, Chuo-ku, Osaka 541-8567, Japan

^l Department of Radiation Oncology, Osaka International Cancer Institute, 3-1-69, Otemae, Chuo-ku, Osaka 541-8567, Japan

^m Department of Thoracic Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-Ku, Nagoya 464-8681, Japan

ⁿ Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-Ku, Nagoya 464-8681, Japan

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ABSTRACT

Purpose: Intensity-modulated radiotherapy (IMRT) is currently used more commonly than 3-dimensional conformal radiation for definitive thoracic radiation. We examined the efficacy profiles of concurrent chemoradiotherapy (CCRT) with IMRT after durvalumab became clinically available.

Methods: We reviewed the clinical records of patients with stage III non-small cell lung cancer (NSCLC) treated with CCRT and IMRT at seven centers in Japan and investigated relapse and survival from May 2018 to December 2019. The primary endpoint of this report was progression-free survival (PFS).

Results: Among 107 patients enrolled in the study, 87 were sequentially administered durvalumab. From CCRT commencement, patients were followed up for a median period of 29.7 months. The median PFS at the end of the CCRT was 20.7 months. Among the 87 patients, 58 experienced disease relapses, of whom 36 (62.1 %) had distant metastases. Multivariate Cox regression analysis revealed that a favorable response to CCRT, a radiation dose ≥ 62 Gy, and stage IIIA NSCLC were associated with prolonged PFS (all $P = 0.04$). Multivariate logistic regression by landmark analysis revealed that mortality risk factors were durvalumab treatment duration ≤ 11.7 months, a lower maximum grade of immune-related adverse events, $FEV_1 < 2805$ mL, and radiation dose < 62 Gy ($P = 0.01, 0.01, 0.03, \text{ and } 0.04$, respectively).

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; 95% CI, 95% confidence interval; AE, adverse event; AIC, Akaike's information criterion; CCRT, concurrent chemoradiotherapy; FEV_1 , forced expiratory volume in 1 second; HR, hazard ratio; OR, odds ratio; IMRT, intensity-modulated radiotherapy; IO, immune-oncology; irAE, immune-related adverse event; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; ROC, receiver operating characteristic.

* Corresponding author at: Department of Respiratory Medicine, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.

E-mail address: ytakeda@hosp.ncgm.go.jp (Y. Takeda).

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Conclusions: In patients with NSCLC receiving CCRT using IMRT, long PFS was associated with a better response to CCRT, stage IIIA NSCLC, and an increased radiation dose. The duration of durvalumab consolidation also played an essential role in the survival of patients receiving CCRT with IMRT. (250 words)

Introduction

Until November 2017, the standard of care for patients with a good performance status (PS) and unresectable stage III non-small cell lung cancer (NSCLC) was concurrent chemoradiotherapy (CCRT) [1]. However, CCRT has a higher rate of radiation-induced adverse events (AEs) than sequential chemoradiation [2]. Intensity-modulated radiation therapy (IMRT) is a recent advancement in radiation therapy. This treatment aims to improve the efficacy and reduce the toxicity of radiation therapy [3]. RTOG 0617 established that IMRT is associated with significantly reduced grade 3 pneumonitis [4], which led to the widespread adoption of IMRT for stage III NSCLC.

According to the phase 3 PACIFIC study, the sequential use of durvalumab, a human IgG1 monoclonal anti-PD-L1 antibody, after platinum-based CCRT prolonged the progression-free survival (PFS) and overall survival (OS) of patients with unresectable stage III NSCLC [5,6]. After the publication of the results of the PACIFIC trial in November 2017, the standard of care for stage III NSCLC became CCRT, followed by consolidative durvalumab treatment for 1 year. However, the PACIFIC study protocol did not specify its radiation program details, except for the lower limit of the radiation dose used [5]. The present standard of care for unresectable stage III NSCLC is a tri-modal combination of thoracic irradiation, cytotoxic chemotherapy, and immuno-oncology (IO). However, information on the optimal settings for each modality is inadequate and limited data are available regarding the prognostic factors for relapse or survival in real-world settings.

Thus, this observational study of patients with stage 3 NSCLC sought to evaluate the PFS from the end of CCRT after durvalumab was approved by medical insurance since we reported the incidence of symptomatic pneumonitis in detail in a previous study [7]. In this study, we report the efficacy of CCRT with IMRT by identifying factors favoring PFS in patients who received the tri-modal combination, which is CCRT with IMRT followed by durvalumab consolidation. The findings of this study will facilitate the management of patients receiving durvalumab consolidation following platinum-based CCRT with IMRT and will help to maintain its efficacy.

Materials and methods

Patients

This retrospective, multicenter, observational study reviewed the medical records of patients treated with CCRT using IMRT at seven centers in Japan from May 2018 to December 2019. The procedures were detailed in our previous report [7].

Ethical considerations

This study was conducted in accordance with the World Medical Association's Declaration of Helsinki. The institutional review board of each center approved our study protocol. The National Center for Global Health and Medicine certified review board approved the study protocol on January 8th, 2021 (NCGM-G-003529-01). By displaying the disclosure document at each hospital, the opt-out method was used to obtain informed consent from the participants for using their medical data.

Data collection

Patient characteristics including age, sex, smoking index, comorbidities, and Eastern Cooperative Oncology Group PS upon starting

CCRT were recorded. Clinically, we obtained blood and pulmonary function test results. For oncological data, we recorded histological type, clinical stage according to the TNM Classification of Thoracic Oncology, version 8 [8], mutation status, and PD-L1 expression status. We also recorded the chemotherapy regimen for CCRT and its treatment plan along with details of IMRT delivery, including radiation dosage, initial planning target volume (PTV), percentage of total lung volume (lung volume minus gross tumor volume; > 40 [V40], 20 [V20], and 5 Gy [V5]), mean lung dose, and radiation therapy interruption or discontinuation.

To assess CCRT outcomes, we recorded the objective overall response rate (ORR), PFS, PFS 2 (see below), OS, AEs, immune-related AEs (irAEs), and use of corticosteroids for pneumonitis. Each investigator evaluated the tumor response according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Treatment-related AEs were assessed using the National Cancer Institute Common Terminology Criteria version 5.0. PFS was defined as the time from the end of CCRT to the first disease progression, the last day of follow-up, or death from any cause. PFS 2 was defined as the time from the end of CCRT to the second disease progression, the last day of follow-up, or death for any reason. OS was defined as the time from the start of CCRT to the last day of follow-up or death from any cause. The data cutoff date was September 15, 2021.

Statistical analyses

The primary endpoints were PFS from the end of CCRT after durvalumab became clinically available. The secondary endpoints were OS, PFS2, and AEs.

For continuous variables, receiver operating characteristic (ROC) curves were analyzed using SigmaPlot version 14.5 (Systat Software Inc., San Jose, CA, USA). The optimal cutoff values were set to a pre-test probability of 0.5 and a cost ratio of 1.0 [9]. PFS and OS were estimated using the Kaplan–Meier method. Cox regression analysis was performed to investigate factors favoring PFS from the end of CCRT. According to a previously described model selection method [10], we included variables with a p-value < 0.1 in univariate analysis, in the multivariate analysis. We identified both statistically dependent variables by Spearman's rank test and clinically clarified dependent variables to prevent including dependent variables in the same model. A correlation coefficient (rho) with an absolute value > 0.3 was considered a significant correlation. We constructed models including only independent variables as candidates and used Akaike's information criterion (AIC) to choose the best candidate model. After selecting the best model, we reduced variables one by one to minimize each AIC. The final model was composed of the number of variables that achieved a minimum AIC among each best model. Using a two-sided test, we defined each factor with a p-value < 0.05 as statistically significant in the final multivariate analysis. In addition, a sensitivity analysis was conducted using a model with one less variable than the final model.

We considered that survival length would most likely be influenced by the duration of durvalumab therapy in patients undergoing tri-modal therapy, and typical survival analyses would include this bias [11–13]. We performed a landmark analysis to minimize the immortal time bias induced by events that occurred after CCRT commencement. The landmark was set 12 months after the end of CCRT and included patients surviving then. We performed a multivariate landmark analysis using logistic regression to evaluate the impact of the tri-modal combined therapy on survival. All analyses were performed using SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA).

Results

Patients' characteristics and treatment information

We enrolled 107 patients in this study, 87 of whom were administered durvalumab consolidation treatment. Fig. 1 shows a flow chart of all the analyses performed in this study. The median duration of the follow-up from the start of CCRT was 29.7 months (95 % confidence interval [95 % CI]: 27.4–32.1 months). As of September 15, 2021, 46 patients had relapsed, and subsequent anticancer treatments were administered to 41 patients. Table S1 presents the background characteristics of the patients and the CCRT treatment information. Our prior report describes this information briefly [7]. Twenty (18.7 %) patients were not administered durvalumab consolidation due to disease progression (10 %), durvalumab rejection (25 %), comorbidities (45 %), or doctors' decision (5 %) (Table S2). The medication was terminated in all patients upon data cutoff. Forty-seven (54 %) patients continued durvalumab for 1 year, and 29 (61.7 %) completed it without interruption. Forty (46 %) patients discontinued the drug during the study, 15 due to disease progression, one each due to the patient's and the doctor's decision, and 23 due to adverse events (Table S2, right column). Six (6.9 %) patients had AEs \geq grade 3 (Table S3). irAEs \geq grade 2, such as pneumonitis, hepatic disorders, and thyroid disorders, occurred at low frequency.

Efficacy profile of CCRT using IMRT

The median OS from the start of CCRT was not achieved (Fig. 2a). The median PFS from the end of CCRT was 20.7 (95 % CI 14.4–27) months (Fig. 2b). Fifty-eight patients had disease relapse, of whom 36 (62.1 %) had distant metastasis (Table S4).

Factors favoring PFS after CCRT completion

To evaluate the efficacy profile of CCRT using IMRT, we conducted Cox regression analyses to identify the factors favoring PFS. As part of the screening, we performed univariate Cox analyses for PFS on the 54 clinical variables described in the data collection section (Table 1, left column). Twenty variables had p-values $<$ 0.10. We then constructed four sets of multivariate candidate models comprising variables that were not correlated with each other and chose the final model, which

included seven variables, based on the AIC (Table 1, right column). A sensitivity analysis demonstrated the same tendency as the final model. Through this model, we identified factors favoring PFS: a better response to CCRT based on RECIST (hazard ratio [HR]: 0.62; 95 % CI 0.39–0.94; $p = 0.043$), low stage III substage (HR: 0.63; 95 % CI 0.40–0.97; $p = 0.038$), and radiation dose ≥ 62 Gy (HR: 0.36; 95 % CI 0.14–0.97; $p = 0.043$).

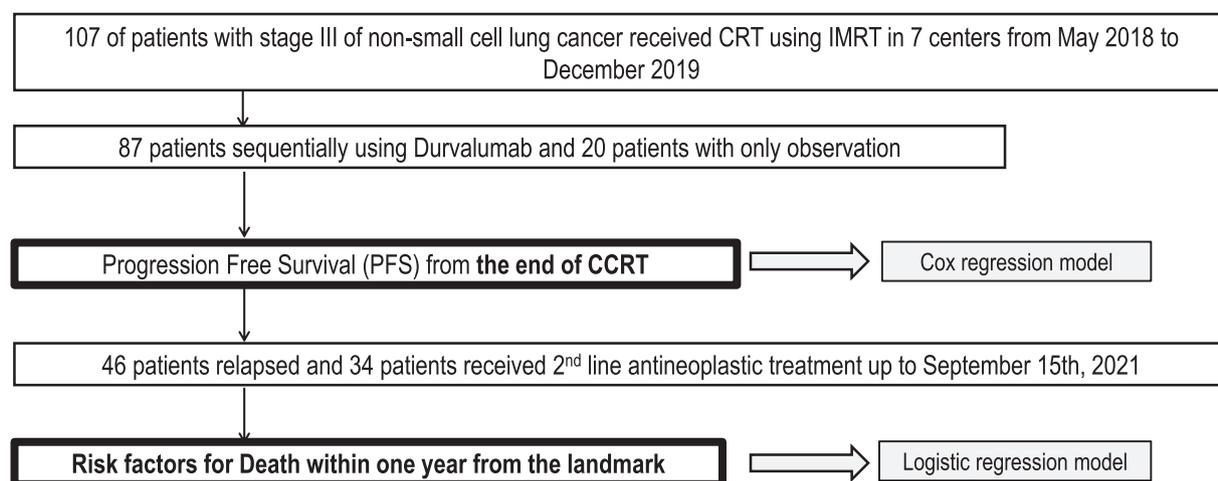
Subsequent anticancer therapy

Table S5 presents the subsequent treatment in detail. Among 107 patients, 41 (38.3 %) received subsequent anticancer therapy, corresponding to 70.7 % of the 58 relapsed patients (Table S5). Eight relapsed patients had an actionable mutation, five of whom were given molecular-targeted agents. Among the relapsed patients, 18 (44 %) received regimens including IO therapy, and 18 (44 %) received only cytotoxic regimens as second-line therapy.

The median PFS 2 was not reached (Fig. 2c). Seventy-five percent of PFS2 had 18.8 months.

Risk factors for death within 1 year from the landmark

Through a landmark analysis, we evaluated the impact of the trimodal combination treatment on patients' survival. We set the landmark at 12 months after the end of CCRT, when durvalumab consolidation had been completed. At that point, 93 patients (86.9 %) were alive. Since there were only 21 (19.6 %) OS events, we conducted a landmark analysis through a logistic regression model to identify the risk factors for death within 1 year from the landmark. For screening, we performed univariate logistic analyses of 69 clinical variables and identified 15 variables with p-values $<$ 0.10 (Table 2, left column). We constructed 20 sets of multivariate candidate models composed of clinically and statistically independent variables. After choosing the best model, the final model included only the variables that achieved a minimum AIC among each best model. The sensitivity analysis yielded the same trend as the final analysis. The final model (Table 2, right column) identified the following risk factors for death within 1 year from the landmark: a duration of durvalumab use ≥ 11.8 months (odds ratio [OR]: 0.20; 95 % CI: 0.06–0.69; $p = 0.01$), high maximum grade for any irAE (OR: 0.36; 95 % CI: 0.17–0.79; $p = 0.01$), forced expiratory volume in 1 second (FEV₁) $>$ 2805 mL (OR: 0.08; 95 % CI: 0.008–0.72; $p = 0.01$).



CCRT; concurrent chemoradiotherapy IMRT ; Intensity-modulated radiation therapy
Landmark; time at 12 months after the end of the CCRT

Fig. 1. The flow chart of the study. CCRT: concurrent chemoradiotherapy; IMRT: intensity-modulated radiation therapy.

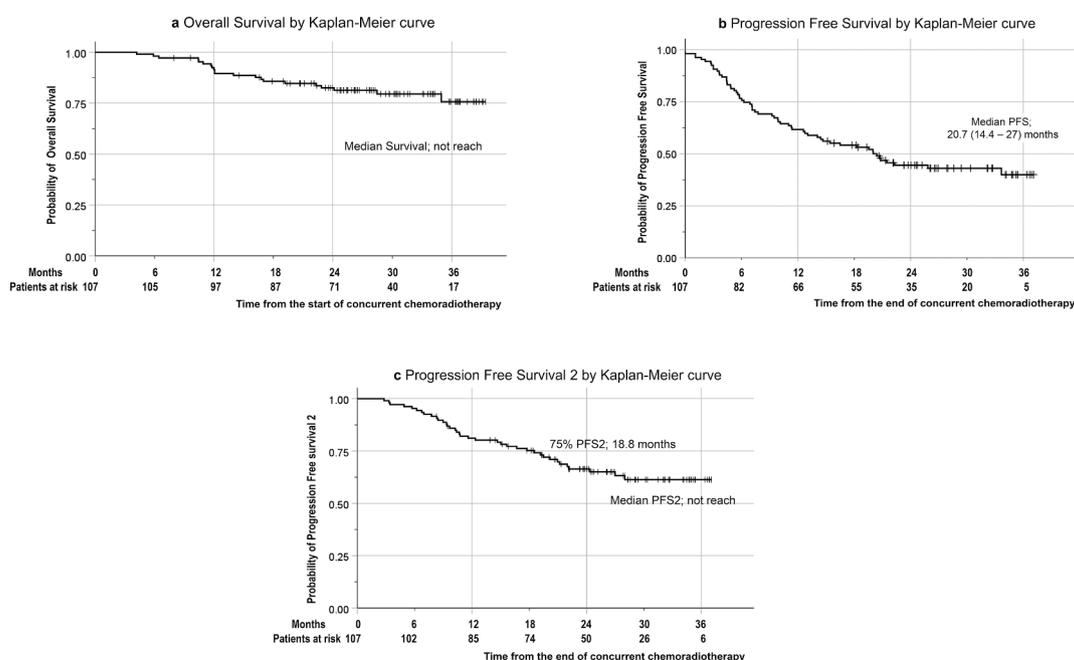


Fig. 2. Survival in this study. a) Overall survival (OS) by Kaplan–Meier analysis OS was defined as the time from the start of CCRT to death by any cause or the last day of follow-up. b) Progression-free survival (PFS) by Kaplan–Meier analysis PFS was defined as the time from the end of CCRT to disease progression, death from any cause, or the last day of follow-up. c) PFS 2 by Kaplan–Meier curve PFS 2 was defined as the time from the end of CCRT to the second disease progression, death from any cause, or the last day of follow-up.

Table 1
Progression free survival from the end of CRT by COX regression analysis.

Univariate Analyses				Multivariate Analysis			
Variables	HR	95 %CI	p-value	Variables	HR	95 %CI	p-value
RECIST of CCRT (PD,NE < SD < PR < CR)	0.54	0.35 – 0.84	0.006	RECIST of CCRT (PD,NE < SD < PR < CR)	0.62	0.39 – 0.94	0.043
Stage (3C < 3B < 3A)	0.61	0.42 – 0.88	0.008	Stage (3C < 3B < 3A)	0.63	0.40 – 0.97	0.038
Radiation dose (<62 vs 62 Gy≤)	0.29	0.12 – 0.73	0.008	Radiation dose (<62 vs 62 Gy≤)	0.36	0.14 – 0.97	0.043
Duration of radiation pause (7 → 0 day)	0.85	0.75 – 0.96	0.008	V5 (47.2 ≤ vs <47.2 %)	NI		
V5 (47.2 ≤ vs <47.2 %)	0.50	0.29 – 0.86	0.012	V5 (47.2 ≤ vs <47.2 %)	0.65	0.36 – 1.19	0.17
Duration of radiation (40≤ vs ≤39 days)	0.39	0.18 – 0.82	0.013	Chemotherapy discontinuation (+ vs –)	0.46	0.195 – 1.82	0.075
Chemotherapy discontinuation (+ vs –)	0.40	0.19 – 0.84	0.016	NI			
DCR of CCRT (NE,PD vs SD,PR,CR)	0.24	0.07 – 0.76	0.016	NI			
Mean Lung Dose (11.5≤ vs <11.5 Gy)	0.53	0.31 – 0.90	0.018	NI			
Radiation pause (+ vs –)	0.46	0.25 – 0.88	0.018	NI			
N factor of TNM ver.8 (3 < 2 < 1 < 0)	0.65	0.45–0.94	0.023	Percent VC (≤89.5 vs 89.6 %≤)	0.63	0.37 – 1.09	0.097
Percent VC (≤89.5 vs 89.6 %≤)	0.55	0.32 – 0.94	0.027	NI			
ORR of CCRT (NE,PD,SD vs CR,PR)	0.56	0.33 – 0.94	0.029	NI			
Cycle of Chemotherapy (≤3 vs 4 cycles≤)	0.54	0.30 – 0.95	0.033	NI			
Combined Platinum regimen (CDDP vs CBDCA)	0.60	0.35 – 1.03	0.064	Combined Platinum regimen (CDDP vs CBDCA)	0.68	0.39 – 1.20	0.185
PTX included regimen (other vs PTX)	0.60	0.35 – 1.03	0.066	NI			
V20 (17.3≤ vs <17.3 %)	0.63	0.37 – 1.07	0.086	NI			
Chemotherapy interval (every 4 W vs every 1 W)	0.62	0.36 – 1.07	0.087	NI			
Dose reduction or skip (– vs +)	0.61	0.34 – 1.09	0.093	NI			
Fraction of radiation (≤32 vs 32 times≤)	0.19	0.03 – 1.34	0.094	NI			

Abbreviations: HR, Hazard ratio; CI, confidence interval; Variables with a p-value < 0.10 on univariate analysis were entered into multivariate logistical analysis by a simultaneous method. NI, not included in the final multivariate COX regression model. CCRT, Concurrent chemoradiotherapy; RECIST, Response Evaluation Criteria in Solid Tumors; VC, Vital Capacity; FVC, Forced Vital Capacity; PTV, Planning Target Volume; CDDP, Cisplatin; CBDCA, Carboplatin; PTX, Paclitaxel; VNR, Vinorelbine; DCR, Disease Control Rate; RR, Objective Response Rate.

= 0.03), and radiation dose > 62 Gy (OR: 0.16; 95 % CI: 0.03–0.88; p = 0.04).

Discussion

In this study, PFS after the end of CCRT was one of the endpoints; thus, we sought to find factors favoring PFS in patients using tri-modal therapy. PFS was prolonged in patients with locally advanced stage IIIA NSCLC who received tri-modal treatment with a radiation dose ≥62 Gy and had a better response to CCRT. We also performed survival

analyses as secondary endpoints. To reduce bias, we performed landmark analyses using a multivariate logistic regression model and identified risk factors for death within 1 year from the landmark, namely, a duration of durvalumab use ≤11.7 months, low maximum grade irAEs, FEV₁ < 2805 mL, and radiation dose <62 Gy. The median PFS from the end of CCRT was 20.7 months (Fig. 2b). Kaplan–Meier analysis with the log-rank test showed slightly better PFS with durvalumab than that without durvalumab regardless of no statistical significance in our previous report [7]. In this updated data, the median PFS of patients receiving CCRT using IMRT with and without durvalumab consolidation

Table 2
Risk factors for Death within 1 year from landmark by logistic regression analysis.

Univariate Analyses				Multivariate Analysis			
Variables	OR	95 %CI	p-value	Variables	OR	95 %CI	p-value
Duration of Durvalumab use (≤ 11.7 vs 11.8 months \leq)	0.16	0.05–0.46	<0.001	Duration of Durvalumab use (≤ 11.7 vs 11.8 months \leq)	0.20	0.06 – 0.69	0.011
Durvalumab discontinuation (no use or discontinuance vs continuance)	0.23	0.09–0.59	0.002		NI		
Durvalumab cycles (≤ 13 vs 14 cycles \leq)	0.31	0.13–0.76	0.01		NI		
Max Grade of Any irAE ($0 < 1 < 2 < 3 < 4$)	0.38	0.18–0.80	0.01	Max Grade of Any irAE ($0 < 1 < 2 < 3 < 4$)	0.36	0.17 – 0.79	0.011
Any irAE (G0 to 1 vs G2 to 4)	0.14	0.03–0.64	0.012		NI		
Durvalumab cycles (≤ 14 vs 15 cycles \leq): Median	0.33	0.14 – 0.81	0.015		NI		
Duration of Durvalumab use (≤ 7.5 vs 7.5 months \leq): Median	0.33	0.14–0.81	0.015		NI		
FEV1 (< 2805 vs 2805 mL \leq)	0.097	0.01–0.78	0.028	FEV1 (< 2805 vs 2805 mL \leq)	0.08	0.008 – 0.72	0.025
Radiation dose (< 62 vs 62 Gy \leq)	0.18	0.04–0.83	0.028	Radiation dose (< 62 vs 62 Gy \leq)	0.16	0.03 – 0.88	0.035
Duration of radiation ($43 \leq$ vs 42 days)	0.38	0.16–0.93	0.033		NI		
PTV Dose prescription ($72.5 \leq$ vs < 72.5 %)	0.37	0.15–0.95	0.038		NI		
Neutrophile count ($3927 \leq$ vs < 3927 μ L)	0.38	0.14–1.07	0.068	Neutrophile count ($3927 \leq$ vs < 3927 μ L)	0.39	0.11 – 1.35	0.14
Steroid for pneumonitis (use vs no use)	0.42	0.16 – 1.08	0.072		NI		
Age ($72 \leq$ vs ≤ 71)	0.47	0.20 – 1.12	0.089		NI		
Max Grade of Hematological toxicities on CCRT ($4 < 3 < 2 < 1 < 0$)	0.75	0.54 – 1.05	0.09		NI		

Abbreviations: Landmark was set to time at 12 months from the end of CCRT; OR, Odds ratio; CI, confidence interval; Variables with a p-value < 0.10 on univariate analysis were entered into multivariate logistical analysis by a simultaneous method. NI is not included in the final multivariate logistic regression model. CCRT, Concurrent chemoradiotherapy; irAE, immune-related adverse events; FEV1, Forced Expiratory Volume in 1 second; PTV, Planning Target Volume; Toxicities grade; NIH-CTC AE ver.5.0.

was 20.9 and 9.3 months, respectively. The median PFS thus tended to be longer with this consolidation treatment. It was also longer than the 16.9 months reported in the PACIFIC study for patients receiving CCRT with durvalumab [14]. Similar to the multivariate analyses of the PACIFIC study, tumor stage was a prognostic factor for PFS, although the TNM classification differed between the studies. The favorable PFS in our study was likely attributable to the use of IMRT by all patients, a high proportion of stage IIIA in our study, and differences in medical care [14].

Several studies have reported prognostic factors for survival post-CCRT. The identified survival predictors included age, sex, tumor histology, smoking history, comorbidities, pulmonary function, cancer stage, radiation dose, gross tumor volume, PTV, and radiation treatment interruption [15–18]. Koshy et al. reported that IMRT was associated with a significant survival benefit in patients with stage III NSCLC [19].

Our multivariate analyses provide vital information for improving the efficacy of CCRT using IMRT (Tables 1 and 2). First, we identified the relationship between radiation dose and treatment efficacy. RTOG 0617 trial data demonstrated that radiation doses > 60 Gy may be associated with a worse treatment efficacy [20]. However, our multivariate Cox regression analysis of PFS indicated that PFS was better in patients who received radiation doses ≥ 62 Gy than in those who received radiation doses < 62 Gy (HR 0.36; Table 1 and Figure S1). The logistic regression analysis of death within 1 year from the landmark also indicated a significant effect of radiation dose, with an OR of 0.16 (Table 2): patients who received radiation doses ≥ 62 Gy had a lower frequency of death within 1 year from the landmark than those who received radiation doses < 62 Gy. Second, the multivariate analyses of the PACIFIC study revealed that PFS was associated with the degree of stage IIIA, based on TNM Classification, version 7 [14]. In our study, patients with a lower stage III subtype had significantly better PFS than those with a higher stage (HR 0.63; Table 1 and Figure S2). Third, the PACIFIC study reported that the best response to CCRT by RECIST was not significantly associated with PFS [14]. However, in our study, patients with a better CCRT response had a significantly better PFS than those with a poor CCRT response (HR 0.62; Table 1 and Figure S3). The degree of CCRT response is likely related to the efficacy of CCRT with IMRT followed by durvalumab consolidation.

In the PACIFIC study [5], patients received at least two cycles of

platinum-based CCRT and a total radiation dose of at least 60 Gy. There were no restrictions on the radiation program besides the fixed lower limit of radiation dosage. In contrast, our study even included patients who received a single dose of any platinum-based chemotherapy regimen. The median radiation dose was 60 Gy (range 54–75 Gy) (Table S1). Twenty patients did not receive durvalumab consolidation because of disease progression, comorbidity, and the patients' or doctors' decision (Table S2). Consequently, we found no significant difference in PFS between CCRT with and without durvalumab consolidation. However, almost completing the planned duration (11.7 months) of durvalumab consolidation was associated with better survival (Table 2).

According to the landmark analysis by multivariate logistic regression, a higher FEV₁ at CCRT inception was associated with better survival (Table 2). Whether pulmonary function testing improves survival prediction is debatable; however, higher FEV₁ or percent FEV₁ has been reported to be a favorable survival predictor [21,22], in agreement with our results.

Some studies have reported that irAE development was associated with improved survival in patients with advanced NSCLC receiving IO treatment [23,24]. In our study, irAE severity was also associated with improved survival in patients with unresectable stage III NSCLC undergoing CCRT using IMRT with durvalumab consolidation (Table 2).

We provided subsequent anticancer therapy to 41 (38.3 %) of our patients (Table S5). Half of these patients received subsequent IO treatment, excluding those who received a molecular-targeted treatment. Most of these patients were treated with regimens including an anti-PD-1 antibody. These factors may have influenced the favorable PFS 2 (Fig. 2c) and OS (Fig. 2a).

This study had some limitations. Despite being a multicenter observational study, it was also a real-world, retrospective study, with associated bias. To minimize this bias, we selected institutes that had expertise in providing IMRT to patients with lung cancer. The median number of accrued patients at each institution was 14 (range 9–24), and only three (2.8 %) were lost to follow-up, which was a low loss rate (Table S4). Second, in the inclusion criteria, we defined the thoracic irradiation method as only IMRT with curative intent, without specifying the radiation program. In fact, in this study, around 80 % of the patients in the PFS analysis and the landmark analysis received a radiation dose of 60 Gy and only 20 % were determined by the physician or

radiotherapy doctor choice. There were also no significant differences between the radiation dose and key background characteristics listed in Table S1. Therefore, the effect of selection for radiation doses was considered minor. However, variation in the IMRT method and radiation dose was a limitation in this study. In the future, the effects of IMRT factors and radiation doses should be investigated. We considered that radiation doses were not a critical factor but rather represented the possibility of dose-escalation in the tri-modality era.

Nonetheless, this study had several strengths. This study offered indications for improving the efficacy of CCRT using IMRT, although the standard radiation dose with CCRT using either 3D-CRT or IMRT remains 60 Gy [20]. A radiation dose ≥ 62 Gy would lead to a favorable PFS and prolonged survival. Despite being a nonrandomized study, the recent IDEAL-CRT phase 1/2 trial reported that moderately dose-escalated CCRT administered in a 6-week schedule resulted in good patient compliance, acceptable toxicity, and promising survival [25]. A slight increase in the radiation dose may improve relapse-free survival and OS in the case of tri-modal treatment. However, it is essential to keep the lung dose as low as possible to avoid increasing radiation pneumonitis even at high doses [7]. In the future, it will be necessary to validate the factors identified in this study with large-scale, prospective, real-world data.

In conclusion, in this study, an excellent relapse-free status was associated with a better response to CCRT based on RECIST, stage IIIA, and an increased radiation dose. The duration of durvalumab consolidation also played an essential role in the survival of patients receiving CCRT with IMRT followed by durvalumab consolidation.

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Declaration of Competing Interest

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Appendix A. Supplementary data

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