ORIGINAL ARTICLE

Intensity-Modulated Radiotherapy for Locally Advanced Lung Cancer in the Immunotherapy Era: A Prospective Study WJOG12019L

Hideyuki Harada, MD, PhD,[a] Akito Hata, MD,[b,*] Masahiro Konno, PhD,[a] Nobuaki Mamesaya, MD, PhD,[c] Kiyoshi Nakamatsu, MD, PhD,[d] Koji Haratani, MD, PhD,[e] Takaya Yamamoto, MD, PhD,[f] Ryota Saito, MD, PhD,[g] Hiroshi Mayahara, MD, PhD,[h] Masaki Kokubo, MD, PhD,[i] Yuki Sato, MD,[j] Nobuki Imano, MD, PhD,[k] Takeshi Masuda, PD, PhD,[l] Haruyuki Fukuda, MD, PhD,[m] Toshikatsu Sado, MD, PhD,[n] Kenichi Yoshimura, PhD,[o] Yasumasa Nishimura, MD, PhD,[p] Kazuhiko Nakagawa, MD, PhD,[e] Isamu Okamoto, MD, PhD,[q] Nobuyuki Yamamoto, MD, PhD,[r] for the West Japan Oncology Group (WJOG)

[a]*Radiation and Proton Therapy Center, Shizuoka Cancer Center, Nagaizumi, Japan*
[b]*Division of Thoracic Oncology, Kobe Minimally Invasive Cancer Center, Kobe, Japan*
[c]*Division of Thoracic Oncology, Shizuoka Cancer Center, Nagaizumi, Japan*
[d]*Department of Radiation Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan*
[e]*Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Japan*
[f]*Department of Radiation Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan*
[g]*Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan*
[h]*Department of Radiation Oncology, Kobe Minimally Invasive Cancer Center, Kobe, Japan*
[i]*Department of Radiation Oncology, Kobe City Medical Center General Hospital, Kobe, Japan*
[j]*Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, Japan*
[k]*Department of Radiation Oncology, Hiroshima University Hospital, Hiroshima, Japan*
[l]*Department of Respiratory Medicine, Hiroshima University Hospital, Hiroshima, Japan*
[m]*Department of Radiation Oncology, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan*
[n]*Department of Respiratory Medicine, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan*
[o]*Department of Biostatistics and Health Data Science, Graduate School of Medical Science, Nagoya City University, Nagoya, Japan*
[p]*Radiation Therapy Center, Fuchu Hospital, Izumi, Japan*
[q]*Department of Respiratory Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*
[r]*Internal Medicine III, Wakayama Medical University, Wakayama, Japan*

Received 27 January 2025; revised 26 February 2025; accepted 14 March 2025
Available online - 20 March 2025

ABSTRACT

Introduction: Chemoradiotherapy (CRT) followed by durvalumab is the standard of care for unresectable locally advanced NSCLC. Limited prospective data have been reported on intensity-modulated radiotherapy (IMRT)–adapted CRT in the immunotherapy era.

Methods: In this multicenter prospective observational study, patients underwent IMRT-adapted CRT (platinum-doublet chemotherapy plus 60 Gy IMRT in 30 fractions under a prespecified radiation protocol), followed by consolidative durvalumab. The primary outcome was the durvalumab introduction rate within 42 days post-CRT.

Results: Thirty-two patients with unresectable locally advanced NSCLC were enrolled between November 2019

***Corresponding author.**

Presented at European Lung Cancer Congress 2024 in Prague, Czech Republic, March 22, 2024.

Address for correspondence: Akito Hata, MD, Division of Thoracic Oncology, Kobe Minimally Invasive Cancer Center, 8-5-1, Minatojima-nakamachi, Chuo-ku, Kobe 650-0047, Japan. E-mail: akitohata@hotmail.com

Cite this article as: Harada H, Hata A, Konno M, et al. Intensity-modulated radiotherapy for locally advanced lung cancer in the immunotherapy era: a prospective study WJOG12019L. *JTO Clin Res Rep*. 2025;6:100828.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2025.100828

and February 2021. Among the 28 evaluable cases, durvalumab was introduced in 24 (85.7%, 90% confidence interval: 70.2%–95.0%) of 28 patients after CRT, achieving the primary end point. All 29 patients who received IMRT completed the scheduled 60 Gy radiotherapy dose. One year of durvalumab treatment was completed in 12 of 24 patients (50%). In the 24 patients who were durvalumab-introduced, the median progression-free survival and overall survival were 20.9 (95% confidence interval: 6.9–not evaluable) months and not reached, respectively. Two-year progression-free survival and overall survival rates were 44% and 73%, respectively. Among the 29 patients in the safety analysis set, there were no treatment-related deaths or grade 4 nonhematological adverse events. Pneumonitis grade 1 was observed in 13 patients (45%), grade 2 in seven (24%), and grade 3 in one (3%).

Conclusions: High durvalumab introduction rate was reported after the completion of IMRT-adapted CRT under a prespecified radiation protocol. Its efficacy has been suggested, with favorable safety profiles, including a low incidence of severe pneumonitis.

Trial Registration: University Hospital Medical Information Network database ID: UMIN000038366

Keywords: Intensity-modulated radiation therapy; Chemoradiotherapy; Durvalumab; Non–small cell lung cancer; Immunotherapy

Introduction

On the basis of the results of the PACIFIC trial, a randomized phase 3 study, chemoradiotherapy (CRT) followed by durvalumab is the standard of care for unresectable locally advanced NSCLC (uLA-NSCLC).[1,2] Nevertheless, 20% to 30% of patients receiving CRT cannot receive durvalumab treatment owing to progressive disease (PD), performance status regression, or intolerable adverse events (AEs), including treatment-related deaths (TRDs) and severe radiation pneumonitis (RP).[3,4] To administer durvalumab to more patients after CRT, safer and more effective methodologies should be developed.

Intensity-modulated radiotherapy (IMRT)-adapted CRT may provide this methodology. IMRT can irradiate more target lesions and fewer surrounding normal organs, resulting in better local control and fewer AEs. In a pivotal phase 3 study (RTOG0617), IMRT was associated with significantly less frequent grade 3 RP and fewer cardiovascular complications compared with conventional three-dimensional–conformal radiotherapy (3D-cRT).[5] Moreover, long-term follow-up data reported that IMRT significantly reduced heart V40 compared with 3D-cRT, and heart V40 (<20%) was associated with better overall survival (OS) than heart V40 (20%).[6] Another meta-analysis reported a lower frequency of grade 2 or higher RP with IMRT than with 3D-cRT.[7] In the PACIFIC study, randomization was performed after the completion of CRT; thus, no information regarding the radiation procedure was collected. According to the protocol of the PACIFIC study, patients must have received a total dose of radiation of 60 Gy (±10%) (54 Gy–66 Gy) to be randomized as part of the chemoradiation therapy. Sites were encouraged to adhere to mean organ radiation dosing as follows: the mean lung dose must be less than 20 Gy and V20 must be less than 35%, the mean esophagus dose must be less than 34 Gy, and heart V45 less than 35% or V30 less than 30%. IMRT is currently utilized in thoracic CRT, but few prospective data have been reported regarding durvalumab after IMRT-adapted CRT.

On the basis of the above background, we hypothesized that IMRT reduces radiation-induced AEs, especially severe RP, while maximizing local effects. We also assume that durvalumab can be introduced owing to these favorable effects, contributing to better survival outcomes in the immunotherapy era.

Materials and Methods

Study Design and Participants

This multicenter, prospective, hospital-based observational study was conducted by the West Japan Oncology Group (WJOG). Participants were enrolled from eight institutes in Japan. The eight participating institutes had adopted IMRT before this study. This study was approved by the ethics and institutional review board of each participating institution and was conducted in compliance with the principles of the Declaration of Helsinki under the registration of the University Hospital Medical Information Network database (UMIN000038366). All patients provided written informed consent before enrollment.

The primary outcome was the durvalumab introduction rate, defined as the number of durvalumab-introduced cases within 42 days after CRT completion per the number of cases receiving IMRT-adapted CRT. The secondary outcomes were progression-free survival (PFS), OS, overall response rate (ORR), disease control rate (DCR), and safety.

The key inclusion criteria were written informed consent, cytologically or histologically confirmed NSCLC, uLA disease (stage III or recurrence after surgery),

European Cooperative Oncology Group performance status of 0 or 1, age below 75 years, presence of measurable lesions, no history of thoracic radiation, and scheduled treatment with IMRT (60 gray in 30 fractions [60 Gy/30 Fr]). The key exclusion criteria were as follows: active double cancer, systemic infection requiring antibiotics, interstitial lung disease detected by chest computed tomography (CT), uncontrolled comorbidities, human immunodeficiency virus infection, and prescription of steroids or immunosuppressants.

Treatment

The enrolled patients received CRT consisting of concurrent 60 Gy/30 Fr IMRT plus platinum-doublet chemotherapy. The chemotherapy regimens were selected by the doctors in charge. After the completion of CRT, durvalumab was administered at a dose of 10 mg/kg every 2 weeks for 1 year.

Radiotherapy

Radiation procedures were performed according to a prespecified radiation protocol (Supplement 1). IMRT with inverse planning and image-guided RT were mandatory. A dose calculation algorithm that included inhomogeneity correction was used. The prescribed dose for the planning target volume (PTV) was 60 Gy/30 Fr, and 95% of the PTV received the prescribed dose. Four-dimensional CT was used to assess the respiratory movement of the tumor. Reevaluation with CT simulation at the midpoint of treatment was mandatory, and treatment plans were adapted if needed. The dose constraints, criteria for quality assurance scores, organs at risk, and acceptable deviations were specified in the protocol.

To control the quality of IMRT, this study required a credentialing process from all participating institutions. The process consisted of two components: (1) irradiation of a phantom consisting of heterogeneous tissue such as the mediastinum and lungs to check the institution's IMRT process, beginning with CT simulation through treatment planning and irradiation, and (2) a dummy run study on treatment planning. After all participating institutions passed this credentialing process, patient enrollment began, and the planning data for the enrolled patients were reviewed centrally.

Efficacy and Safety Evaluation

To confirm definitive uLA disease, CT or magnetic resonance imaging of the brain, CT of the chest and abdomen, and a bone scan or positron emission tomography scan were performed before enrollment. Regular tumor assessments using CT were recommended at baseline, after CRT, before durvalumab introduction, and after every six to 12 weeks. Tumor response was evaluated in accordance with the Response Evaluation Criteria in Solid Tumors version 1.1. AEs were evaluated using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0.

Statistical Analysis

We determined the threshold durvalumab introduction rate to be 70% and expected it to reach 90%. On the basis of this assumption, the number of patients required to provide 80% power for a one-sided 0.05 level of type I error was calculated to be 28. Considering ineligible patients, the sample size was set to 30. The 90% confidence intervals (CIs) for durvalumab introduction rates were calculated using the Clopper-Pearson method. PFS was defined as the time from enrollment to the date of disease progression or death from any cause. OS was defined as the time from enrollment to death from any cause. PFS and OS were analyzed using the Kaplan-Meier method, and median values and corresponding 95% CIs were calculated using the Brookmeyer–Crowley method. All statistical analyses were performed using SAS V.9.4 (SAS Institute).

Results

Patients

Thirty-two patients were enrolled in the study between November 2019 and February 2021. Two patients withdrew informed consent after enrollment. The baseline characteristics of the 30 full analysis set patients, excluding the two withdrawn patients, are shown in Table 1. The median patient age was 69 years (range: 49–74 y). Twenty-six patients (87%) were male individuals, and 97% had a history of smoking. The clinical stages were recurrence, IIIA, IIIB, and IIIC in one (3%), 13 (43%), 13 (43%), and three (10%) patients, respectively. On the basis of histologic characteristics, 14 (46%) adenocarcinomas, 12 (40%) squamous cell carcinomas, and four (13%) not otherwise specified were included. Figure 1 shows a patient flow diagram. One patient did not receive IMRT but received 3D-cRT after enrollment because disease progression was too rapid to afford IMRT planning. Two patients were enrolled in another clinical trial after CRT during this study. Except for two consent withdrawal patients and these three patients, the per-protocol set population was determined to be 27 patients. The median follow-up was 24.3 months (range: 6.5–36.6 mo).

Durvalumab Introduction Rate

With the exception of four patients (two patients withdrew and two enrolled in another clinical trial after CRT), durvalumab was introduced in 24 (85.7%, 90% CI:

Table 1. Baseline Characteristics

Characteristics	Number (%)
Age (y)	
Median, range	69, 49-74
<65	7 (23)
≥65	23 (77)
Sex	
Male	26 (87)
Female	4 (13)
ECOG performance status	
0	17 (23)
1	13 (77)
Smoking status	
Former/current	10/19 (33/63)
Never	1 (3)
Stage	
Recurrence/IIIA	1/13 (3/43)
IIIB/IIIC	13/3 (43/10)
Histology	
Adeno	14 (47)
Squamous/NOS	12/4 (40/13)
EGFR mutation	
Negative	10 (33)
Unknown	20 (67)
ALK fusion	
Positive	1 (3)
Negative/Unknown	8/21 (27/70)
PD-L1 TPS	
<50%	9 (30)
≥50%	9 (30)
Unknown	12 (40)

ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; PD-L1 TPS, programmed death-ligand 1 total proportion score.

70.2%–95.0%) of 28 patients, achieving the primary end point. The reasons for four patients not receiving durvalumab were as follows: two had PD, one had intolerable AEs, and one received 3D-cRT rather than IMRT because of rapid PD.

Completion of RT, Chemotherapy, and Durvalumab

All 29 patients (100%) receiving IMRT completed the initially planned RT of 60 Gy/30 Fr. Eight (33%) cisplatin plus vinorelbine and 21 (67%) weekly carboplatin plus paclitaxel chemo-regimens were selected. All eight patients (100%) completed two cycles of cisplatin plus vinorelbine. All 21 patients (100%) received at least two cycles of weekly carboplatin plus paclitaxel, and 10 of them (48%) completed a total of six cycles. One year of durvalumab administration was completed in 12 of the 24 patients (50%) administered with durvalumab. The reasons for durvalumab discontinuation were nine PD and three AEs (two pneumonitis and one uveitis).

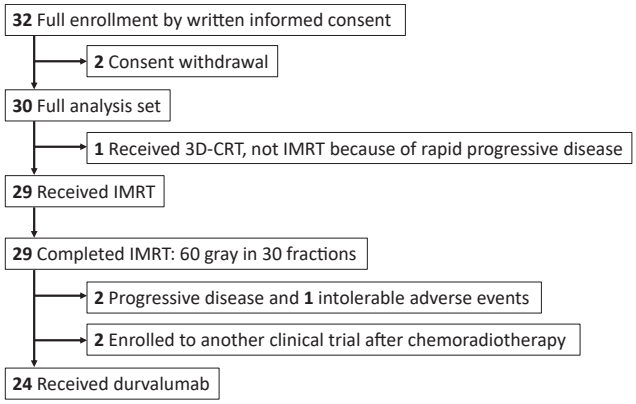

Figure 1. Patient flow diagram. 3D-cRT, three-dimensional-conformal radiotherapy; IMRT, Intensity-modulated radiotherapy.

Survival and Tumor Response

In 24 patients treated with durvalumab, efficacy was evaluated from the day of CT scanning after CRT before durvalumab initiation. Median PFS (Fig. 2*A*) and OS (Fig. 2*B*) were 20.9 months (95% CI: 5.3–not evaluable [NE]) and not reached, respectively. One- and 2-year PFS and OS rates were 58% and 100%, and 44% and 73%, respectively. One case (4%) of complete response, two (8%) of partial response, 18 (75%) of stable disease, and three (13%) of PD cases were confirmed, resulting in an ORR of 13% and a DCR of 88%. In 27 patients with per-protocol set, the efficacy was evaluated from the day of enrollment. The median PFS (Fig. 3*A*) and OS (Fig. 3*B*) were 14.3 months (95% CI: 6.9–NE) and not reached, respectively. One- and 2-year PFS and OS rates were 52% and 93%, and 40% and 64%, respectively. One (4%) complete response, 17 (63%) partial response, seven (26%) stable disease, and two (7%) PD cases were confirmed, resulting in an ORR of 67% and a DCR of 93%.

Radiation Quality Assurance Analysis

A total of 29 cases treated with IMRT were included in the quality assurance analysis, with three cases being excluded (two owing to withdrawal and one receiving 3D-cRT). Table 2 presents the dose constraints, criteria for quality assurance scores, organs at risk, and acceptable deviations as specified in the protocol. The prescribed dose aimed to achieve PTV D95 coverage, with a median dose of 60 Gy (interquartile range [IQR]: 59.5–60 Gy). High-dose regions within the PTV were assessed using D2, with a median value of 64 Gy (IQR: 63.3–65.7 Gy). The low-dose regions within the PTV and internal target volume were evaluated using PTV D98 and internal target volume D98, with median doses of 58.9 Gy (IQR: 57.9–59.3 Gy) and 60.6 Gy (IQR: 60.2–61.1 Gy), respectively.

Regarding organs at risk, the maximum spinal cord dose remained below 50.0 Gy. For the lungs, V20 had a

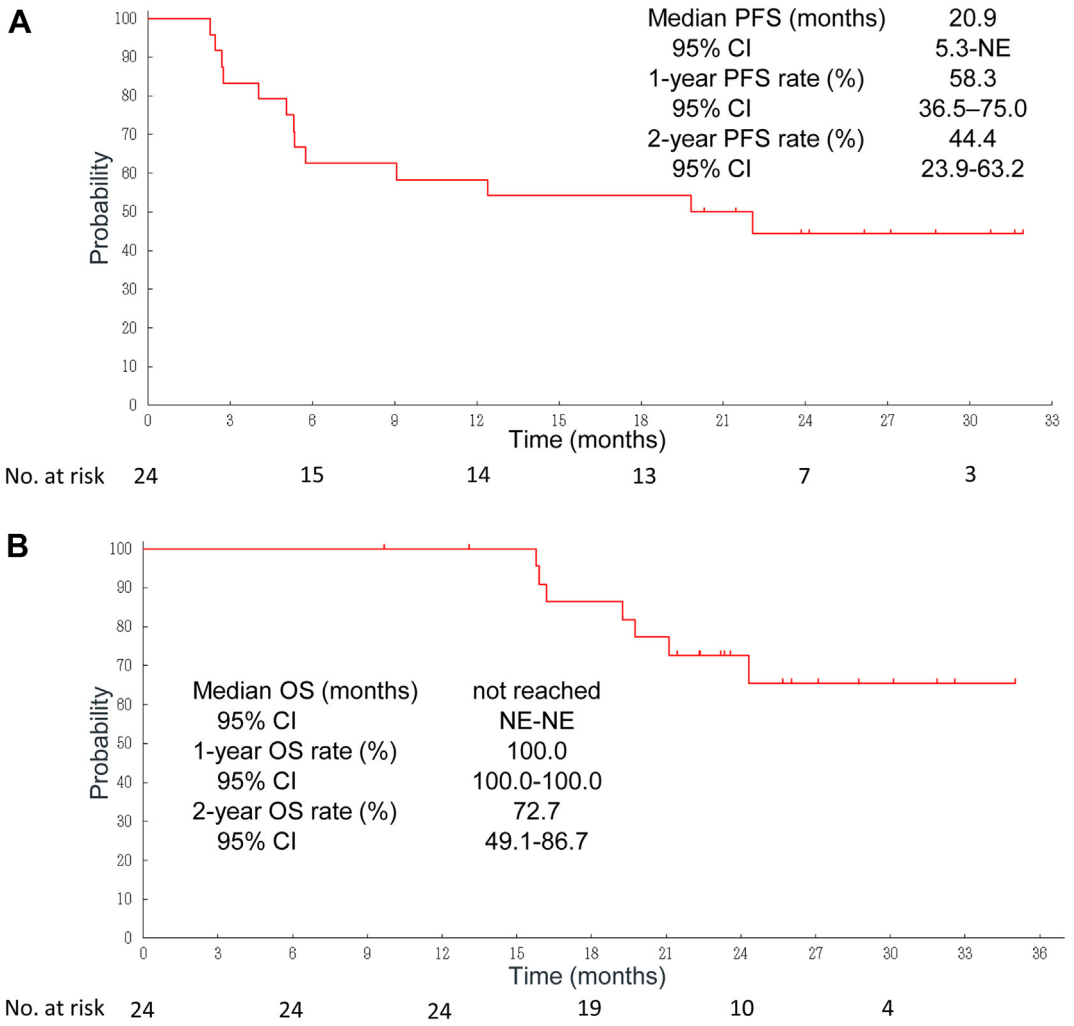

Figure 2. PFS *(A)* and OS *(B)* curves in 24 patients who were durvalumab-introduced. Median follow-up was 24.3 months (range: 6.5–36.6 mo). CI, confidence interval; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

median value of 20.6% (IQR: 17.8–26.3%), whereas V5 had a median value of 45.9% (IQR: 38.2%–55.9%). The mean lung dose had a median value of 12.4 Gy (IQR: 10.4–15.1 Gy). For the esophagus, the maximum dose was within an IQR of 63.8 to 65.1 Gy, with a maximum observed value of 69.9 Gy. For the heart, V30 and V45 were assessed, with median values of 9 and 2.7 Gy, respectively.

Adaptive planning was performed in 13 cases (45%) on the basis of midtreatment evaluations. Among these, 11 cases required a single replan, whereas two cases underwent multiple replans (two and five times, respectively).

Safety

Safety analysis was performed since enrollment in 29 patients receiving IMRT-adapted CRT, except for two patients who withdrew consent and one who received 3D-cRT. Table 3 shows the safety profile, including AEs: incidence of 10% or higher for any grade 3 or higher. No TRDs or grade 4 nonhematological AEs were observed. RP was confirmed in 13 (45%) patients with grade 1, seven (24 %) with grade 2, and one (3 %) with grade 3. Other grade 3 AEs included pulmonary infections in two patients (7%), esophagitis in one (3%), thromboembolism in one (3%), and oral mucositis in one (3%).

Discussion

To the best of our knowledge, this is the first report evaluating the effectiveness of IMRT-adapted CRT followed by durvalumab treatment for uLA-NSCLC under a prespecified protocol for radiation procedures in the immunotherapy era. Although several retrospective studies have suggested the possible effectiveness of IMRT in CRT followed by durvalumab for uLA-NSCLC,[8,9] these studies did not adopt a prespecified protocol; thus, radiation procedures were quite variable. In thoracic CRT, pulmonary RT dose restriction is extremely

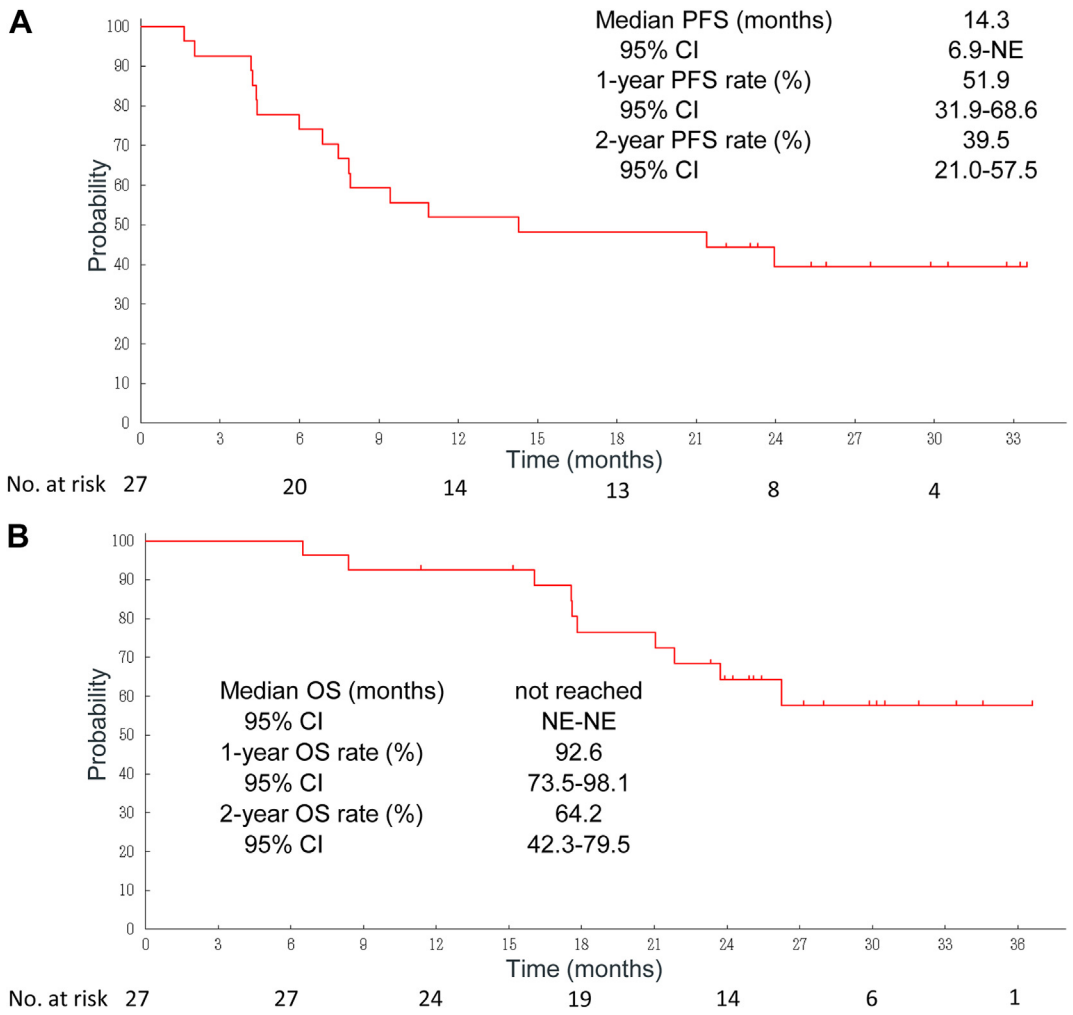

Figure 3. PFS *(A)* and OS *(B)* curves from enrollment before chemoradiation. Median follow-up was 24.3 months (range: 6.5–36.6 mo). CI, confidence interval; NE, not evaluable; OS, overall survival; PFS, progression-free survival; PPS, per-protocol set.

important for preventing RT-induced severe RP. Our study strictly enforced lung V20 of 35% or less, mean dose of 20 Gy or less, and V5 of 60% or less, resulting in the reduction of RPs of grade 2 and 3. The observed median values for V20 and V5 were 20.6% (IQR: 17.8%–26.3%) and 45.9% (IQR: 38.2%–55.9%), respectively, demonstrating successful adherence to these constraints. In addition, only one (3%) grade 3 esophagitis and no cardiac complications were observed during the study period. IMRT under a prespecified protocol could improve safety, which is associated with the favorable results of our study, including a 60 Gy/30 Fr RT completion rate of 100% and a high durvalumab introduction rate.

The durvalumab introduction rate was 85.7% (90% CI: 70.2%–95.0%), representing a positive statistical significance of the primary end point. Previous studies

Table 2. Dose Prescription and Organs at Risk

Metrics	Per Protocol	Acceptable Deviation
PTV	D98 $\geq$ 85%, 98% $\leq$ D95 $\leq$ 102%, D2 $\leq$ 115%	D98 $\geq$ 75%, 95% $\leq$ D95 $\leq$ 105%, D2 $\leq$ 120%
CTV	D98 $\geq$ 100%	D98 $\geq$ 95%
Organ	Target dose	Acceptable deviation
Lung	V20 $\leq$ 35%, mean dose $\leq$ 20 Gy, V5 $\leq$ 60%	V20 $\leq$ 37%, Mean dose $\leq$ 22 Gy, V5 $\leq$ 65%
Esophagus	66 Gy $\leq$ 1 cm^3	70 Gy $\leq$ 1 cm^3
Spinal cord	V48 $<$ D0.03 cm^3	V52 $<$ D0.03 cm^3 and V48 $<$ 1 cm^3
Heart	V30 $\leq$ 50%, V45 $\leq$ 35%, D0.03 cc $\leq$ 66 Gy	V30 $\leq$ 55%, V45 $\leq$ 40%, D0.03 cm^3 $\leq$ 72 Gy

CTV, clinical target volume; PTV, planning target volume.

Table 3. Safety Profile

Adverse Events	Any Grade, n (%)	Grade ≥3, n (%)
Laboratory		
Leukopenia	25 (86)	13 (45)
Anemia	24 (83)	2 (7)
Thrombocytopenia	18 (62)	0 (0)
Neutropenia	24 (83)	6 (21)
AST elevation	8 (28)	0 (0)
ALT elevation	10 (35)	0 (0)
T-bilirubin elevation	3 (10)	0 (0)
Albumin decrease	20 (69)	0 (0)
Creatinine elevation	5 (17)	0 (0)
Hypo-sodium	17 (59)	0 (0)
Hyper-potassium	11 (38)	0 (0)
Hypo-potassium	4 (14)	1 (3)
Hypo-calcium	3 (10)	0 (0)
Nonhematological		
Pneumonitis	21 (72)	1 (3)
Esophagitis	17 (59)	1 (3)
Dermatitis	17 (59)	0 (0)
Constipation	13 (45)	0 (0)
Nausea	10 (35)	0 (0)
Malaise	9 (31)	0 (0)
Anorexia	7 (24)	0 (0)
Diarrhea	5 (17)	0 (0)
Fever	5 (17)	0 (0)
Vomiting	4 (14)	0 (0)
Gastritis	3 (10)	0 (0)
Oral mucositis	3 (10)	1 (3)
Lung infection	2 (7)	2 (7)
Thromboembolism	1 (3)	1 (3)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

have reported a durvalumab introduction rate of 70% to 80%.[3,4] Reduced progression and severe AEs, especially grade 2 RPs, using IMRT may have contributed to the higher durvalumab introduction rates in our study.

Survival analyses from the same time point as in the PACIFIC study (after CRT before durvalumab introduction) found that the median PFS and OS were 20.9 months and not reached, respectively. One- and 2-year PFS and OS rates were 58% and 100%, and 44% and 73%, respectively. These results were comparable or slightly better than those of the PACIFIC study: median PFS of 16.9 months; 1-year PFS and OS rate of 56% and 83%, respectively; and 2-year PFS and OS rate of 45% and 66%, respectively.[10] The favorable results of our study using IMRT should be validated in further studies with larger sample sizes. We expect more patients to benefit from consolidative durvalumab therapy after IMRT-adapted CRT in the immunotherapy era.

Contrastingly, in survival analyses from enrollment, which was the basic time point before the immunotherapy era, the median PFS and OS were 14.3 months and not reached, respectively. One- and 2-year PFS and OS rates were 52% and 93%, and 40% and 64%, respectively. In our previously conducted WJTOG0105 study before the immunotherapy era, the median PFS and OS and one- and 2-year PFS and OS rates were 9.5 and 22.0 months, approximately 40% and 70%, and 20% and 50%, respectively, in the weekly carboplatin plus paclitaxel arm.[11] Although the results of our study seem to be superior to those before the immunotherapy era, it is currently difficult to evaluate its actual effectiveness.

Our study reported that there were no TRDs or grade 4 nonhematological AEs. Grade 3 AEs were observed in five of the 29 patients (17%) subjected to the safety analysis. In the PACIFIC study, 31% of patients in the durvalumab arm experienced grade 3 or 4 AEs of any cause.[1,2] IMRT-adapted CRT followed by durvalumab treatment could improve safety and reduce severe AEs induced by RT and subsequent immune-related AEs caused by durvalumab.

Our study had several limitations. First, the small sample size and nonrandomized design may have induced potential biases. Second, the interpretation of the primary end point was modified in the final analysis. The initial presentation at the 2022 European Society of Medical Oncology annual meeting reported a statistical negativity of the primary end point, the durvalumab introduction rate. Initially, two patients who were enrolled in another clinical trial after CRT during this study were included as participants without durvalumab introduction. Although these two patients were able to receive consolidative immunotherapies under another clinical trial, it was not possible to determine whether durvalumab was administered under our study protocol. After discussion with the WJOG respiratory and radiation group committees, the patients were excluded from the primary end point analysis. Such modifications could be unfavorable in clinical trials, but these cases should not be scientifically included.

In conclusion, high durvalumab introduction rate was reported after the completion of IMRT-adapted CRT under a prespecified radiation protocol for uLA-NSCLC. Its efficacy has been suggested, with favorable safety profiles, including a low incidence of severe pneumonitis. Further randomized studies versus 3D-cRT are required to validate the clinical effectiveness of IMRT-adapted CRT followed by durvalumab treatment in the immunotherapy era.

CRediT Authorship Contribution Statement

Hideyuki Harada: Supervision, Project administration, Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization.

Akito Hata: Supervision, Project administration, Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Funding acquisition.

Masahiro Konno: Methodology, Investigation, Data curation, Writing - original draft, Writing - review & editing.

Nobuaki Mamesaya: Investigation, Data curation, Writing - original draft, Writing - review & editing.

Kiyoshi Nakamatsu: Investigation, Resources, Writing - original draft, Writing - review & editing.

Koji Haratani: Investigation, Resources, Writing - original draft, Writing - review & editing.

Takaya Yamamoto: Investigation, Resources, Writing - original draft, Writing - review & editing.

Ryota Saito: Investigation, Resources, Writing - original draft, Writing - review & editing.

Hiroshi Mayahara: Investigation, Resources, Writing - original draft, Writing - review & editing.

Masaki Kokubo: Investigation, Resources, Writing - original draft, Writing - review & editing.

Yuki Sato: Investigation, Resources, Writing - original draft, Writing - review & editing.

Nobuki Imano: Investigation, Resources, Writing - original draft, Writing - review & editing.

Takeshi Masuda: Investigation, Resources, Writing - original draft, Writing - review & editing.

Haruyuki Fukuda: Investigation, Resources, Writing - original draft, Writing - review & editing.

Toshikatsu Sado: Investigation, Resources, Writing - original draft, Writing - review & editing.

Kenichi Yoshimura: Investigation, Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualization.

Yasumasa Nishimura: Supervision, Project administration, Investigation, Resources, Writing - original draft, Writing - review & editing.

Kazuhiko Nakagawa: Supervision, Project administration, Investigation, Writing - original draft, Writing - review & editing, Funding acquisition.

Isamu Okamoto: Supervision, Project administration, Investigation, Writing - original draft, Writing - review & editing.

Nobuyuki Yamamoto: Supervision, Project administration, Investigation, Writing - original draft, Writing - review & editing, Funding acquisition.

Disclosure

Dr. Harada has received personal fees from AstraZeneca, Accuray, Chugai, Takeda, Merck Sharp & Dohme, Pfizer, Brainlab, Hitachi, Novartis, Guerbet Japan, GE Healthcare, Nihon Medi-Physics, and Taiho. Dr. Hata has received grants from Merck Sharp & Dohme, Eli Lilly, Chugai, Taiho, Boehringer Ingelheim, AstraZeneca, AbbVie, and personal fees from AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Chugai, Pfizer, Boehringer Ingelheim, and Taiho. Dr. Mamesaya has received grants from Merck Sharp & Dohme, Chugai, Arrivent Biopharma, and personal fees from Chugai, Boehringer Ingelheim, AstraZeneca, Taiho, Merck Sharp & Dohme, Ono, and Novartis. Dr. Haratani has received grants from AstraZeneca, Mochida Memorial Foundation, Nakatomi Foundation, KANAE Foundation for the Promotion of Medical Science, Osaka Cancer Society, SGH Foundation, YOKOYAMA Foundation for Clinical Pharmacology, Takeda Science Foundation, The Osaka Medical Research Foundation for Intractable Disease, and personal fees from AstraZeneca; Dr. Yamamoto has received personal fees from AstraZeneca, Amgen, AiRato Inc., and Takeda. Dr. Saito has received personal fees from AstraZeneca, Merck Sharp & Dohme, Chugai, and Taiho. Dr. Mayahara has received personal fees from AstraZeneca. Dr. Kokubo has received personal fees from AstraZeneca, Varian, Daiichi Sankyo, and Hitachi. Dr. Sato has received personal fees from AstraZeneca, Merck Sharp & Dohme, Novartis, Chugai, Ono, Pfizer, Taiho, Nippon Kayaku, Bristol-Myers Squibb, Eli Lilly, Takeda, Kyowa Kirin, Daiichi Sankyo, and Boehringer Ingelheim. Dr. Masuda has received personal fees from Daiichi Sankyo, Taiho, Boehringer Ingelheim, Kyowa Kirin, Ono, Eli Lilly, Otsuka, Chugai, and AstraZeneca. Dr. Yoshimura has received personal fees from AstraZeneca. Dr. Nakagawa has received grants from AstraZeneca, Merck Sharp & Dohme, Ono, Boehringer Ingelheim, Novartis, Pfizer, Bristol-Myers Squibb, Eli Lilly, Chugai, Daiichi Sankyo, Merck, Parexel International, PRA Health Sciences, EPS Corporation., Kissei, EPS International, Taiho, PPD-SNBL, SymBio, IQVIA Services Japan, Syneos Health Clinical, Nippon Kayaku, EP-CRSU, Mebix, Janssen, AbbVie, Bayer, Eisai, Mochida, Covance Japan, Japan Clinical Research Operations, Takeda, GlaxoSmithKline, Sanofi, Sysmex, Medical Reserch Support, Otsuka, SRL, Amgen, personal fees from Ono, Amgen, Nippon Kayaku, AstraZeneca, Chugai, Eli Lilly, Merck Sharp & Dohme, Pfizer, Boehringer Ingelheim, Taiho, Bayer, CMIC ShiftZero, Life Technologies Japan, Neo Communication, Roche Diagnostics, AbbVie, Merck, Kyowa hakko Kirin, Takeda, 3H Clinical Trial, Care Net, Medical Review, Medical Mobile Communications, YODOSHA, Nikkei Business Publications, Japan Clinical Research Operations, CMIC, Novartis, Taiyo Pharma, Kyorin Pharmaceutical, Bristol-Myers Squibb, and patents from Daiichi Sankyo. Dr. Okamoto has received grants from AstraZeneca, Taiho, Boehringer Ingelheim, Ono, Merck Sharp & Dohme, Eli Lilly, Astellas, Bristol-Myers Squibb, Novartis, Pfizer,

AbbVie, and personal fees from AstraZeneca, Taiho, Boehringer Ingelheim, Ono, Merck Sharp & Dohme, Eli Lilly, Bristol-Myers Squibb, Novartis, Pfizer, and AbbVie. Dr. Yamamoto has received grants from Boehringer Ingelheim, Taiho, Chugai, Shionogi, Eli Lilly, Daiichi Sankyo, Tsumura, Nippon Kayaku, Asahikasei-pharma, AstraZeneca, Janssen, Sanofi, Amgen, Novartis, Astellas, Merck Sharp & Dohme, Esai, Bristol-Myers Squibb, AbbVie, Tosoh, and personal fees from Merck Sharp & Dohme, AstraZeneca, Amgen, Ono, Otsuka, Guardant Health Japan, Tsumura, Kyowa Hakko Kirin, Kyorin, GlaxoSmithKline, Sanofi, Daiichi Sankyo, Taiho, Takeda, Chugai, Eli Lilly, Nippon Kayaku, Boehringer Ingelheim, Novartis, Pfizer, Bristol-Myers Squibb, Miyarisan, Merck, and Janssen. The remaining authors declare no conflict of interest.

Acknowledgments

This study was supported by a research grant from AstraZeneca. We thank the patients, their families, and all the investigators who participated in the present study. We thank Mr. David Martin for English language support. We would like to thank Editage (www.editage.jp) for English language editing. Data management and monitoring for this study were conducted by the WJOG under a funding contract with AstraZeneca.

Data Availability Statement

The original data for this study are available on request from the corresponding author.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2025.100828.

References

1. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med*. 2017;377:1919–1929.
2. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342–2350.
3. Hosoya K, Fujimoto D, Kawachi H, et al. Ineligibility for the PACIFIC trial in unresectable stage III non-small cell lung cancer patients. *Cancer Chemother Pharmacol*. 2019;84:275–280.
4. Sakaguchi T, Ito K, Furuhashi K, et al. Patients with unresectable stage III non-small cell lung cancer eligible to receive consolidation therapy with durvalumab in clinical practice based on PACIFIC study criteria. *Respir Investig*. 2019;57:466–471.
5. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: A secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. *J Clin Oncol*. 2017;35:56–62.
6. Chun SG, Hu C, Komaki RU, et al. Long-term prospective outcomes of intensity modulated radiotherapy for locally advanced lung cancer: A secondary analysis of a randomized clinical trial. *JAMA Oncol*. 2024;10:1111–1115.
7. Hu X, He W, Wen S, et al. Is IMRT superior or inferior to 3DCRT in radiotherapy for NSCLC? A meta-analysis. *PLoS One*. 2016;11:e0151988.
8. Tsukita Y, Yamamoto T, Mayahara H, et al. Intensity-modulated radiation therapy with concurrent chemotherapy followed by durvalumab for stage III non-small cell lung cancer: a multi-center retrospective study. *Radiother Oncol*. 2021;160:266–272.
9. Masuo M, Shinohara E, Kitano M, et al. A comparison of the incidence of $\geq$ grade 2 radiation pneumonitis between intensity-modulated radiotherapy and three-dimensional conformal radiotherapy in patients with unresectable non-small cell lung cancer treated with durvalumab after concurrent chemoradiotherapy. *Jpn J Clin Oncol*. 2024;54:312–318.
10. Spigel DR, Faivre-Finn C, Gray JE, 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;40:1301–1311.
11. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol*. 2010;28:3739–3745.