Elective Nodal Irradiation for Non-small Cell Lung Cancer Complicated With Chronic Obstructive Pulmonary Disease Affects Immunotherapy After Definitive Chemoradiotherapy

MASAHIRO MORIMOTO¹, KAZUMI NISHINO², KENTARO WADA¹, FUMIO IMAMURA², KOJI KONISHI¹, HANAKO KUHARA², MOTOHIRO TAMIYA², TAKAKO INOUE², KEI KUNIMASA², MADOKA KIMURA², TAKERO HIRATA^{1,3}, NAOYUKI KANAYAMA¹, MASAYASU TORATANI¹, HAYATO KAWACHI², KIKI OHIRA², ERINA NAKANISHI^{1,3}, SHINGO OHIRA¹, TOMOHIRO SAGAWA¹, MASAYOSHI MIYAZAKI¹, TAKASHI MATSUNAGA⁴, TORU KUMAGAI² and TERUKI TESHIMA¹

Department of ¹Radiation Oncology, ²Thoracic Oncology, ⁴Medical Informatics,
Osaka International Cancer Institute, Osaka, Japan;

³Department of Radiation Oncology, Osaka University Graduate School of Medicine, Osaka, Japan

Abstract. *Background/Aim:* The aim of this retrospective study was to detect the frequency, reasons, and significant factors for not receiving immunotherapy after chemoradiotherapy in non-small cell lung cancer (NSCLC) patients. *Patients and Methods:* Thirty-four patients with NSCLC received definitive chemoradiotherapy. The endpoint of this study was receiving durvalumab within 45 days after chemoradiotherapy for NSCLC. *Results:* Twenty-five of 34 (73%) patients received immunotherapy within 45 days after chemoradiotherapy. The reasons for not receiving immunotherapy were radiation pneumonitis (50%), radiation esophagitis (10%), and four other reasons (40%). Univariate analysis showed that significant factors for not receiving immunotherapy were elective nodal irradiation (ENI)+ and chronic obstructive pulmonary disease (COPD)+. The rate of immunotherapy was 100% (17/17 cases) in the COPD– and ENI– group, and 16% (1/6 cases) in the COPD+ and ENI+ group. *Conclusion:* ENI for NSCLC complicated with COPD decreased the rate of immunotherapy after definitive chemoradiotherapy.

This article is freely accessible online.

Correspondence to: Masahiro Morimoto, Department of Radiation Oncology, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka 541-8567, Japan. Tel: +81 669451181, Fax: +81 69451900, e-mail: morimoto-ken@umin.ac.jp

Key Words: Volumetric modulated arc therapy (VMAT), intensity modulated radiation therapy (IMRT), involved field radiotherapy irradiation (IFR-IFI), twice-daily thoracic radiotherapy (BID-TRT), accelerated hyperfractionated thoracic radiotherapy (AHTRT), anti-programmed cell death ligand-1 immune checkpoint inhibitor (ICIs).

The anti-programmed cell death ligand-1 immune checkpoint inhibitor, durvalumab, is a standard treatment for locally advanced non-small cell lung cancer (NSCLC) after chemoradiotherapy (1, 2). However, not all NSCLC patients can receive immunotherapy after chemoradiotherapy for various reasons. In clinical practice, reasons include adverse events from chemoradiotherapy, progressive disease, or other factors.

The characteristics of patients who cannot receive immunotherapy and the significant factors that are correlated with not receiving immunotherapy are not clear. The aim of this retrospective study was to detect the frequency, reasons, and significant factors for not receiving immunotherapy after chemoradiotherapy in NSCLC patients.

Patients and Methods

A total of 34 patients with NSCLC received definitive chemoradiotherapy between May 2018 and January 2019. Institutional review board approval was obtained for this study (number 19020). The patient characteristics and treatment factors are listed in Table I. The diagnosis of NSCLC was confirmed by histologic findings. The patients underwent the following pre-therapeutic procedures: a physical examination and chest radiography; fiberoptic bronchoscopy and endobronchial ultrasonography as needed; complete blood cell count and biochemical tests including tumor markers; electrocardiography; computed tomography (CT) imaging of the chest and abdomen; positron emission tomography/CT. A hematologic status, which included a white blood cell count $>3,500/\text{mm}^3$, platelet count $>100,000/\text{mm}^3$, and hemoglobin level $>10 \text{ g/dl}$, was generally required. When febrile neutropenia or grade 3 non-hematologic adverse events excluding nausea, vomiting, appetite loss, and elevated creatinine or liver enzymes developed, radiotherapy was generally interrupted. Adverse events were evaluated using Common Terminology Criteria for Adverse Events, Version 4.0.

Table I. Patient characteristics and treatment factors.

	N		N
Number of patients	34	Hemoglobin (g/dl)	
Age (years)		Median	13.4
Median	73	Range	9.6-15.7
Range	30-87	White blood cell count/mm ³	
Gender		Median	6,520
Male	25 (73%)	Range	3,890-10,790
Female	9 (26%)	Neutrophil cell count/mm ³	
Performance status		Median	4,140
0	27 (79%)	Range	2,060-9,080
1	7 (20%)	Platelet cell count/mm ³	
Location of primary site		Median	229,500
Upper lobe	22 (64%)	Range	150,000-451,000
Middle lobe	1 (2%)	C-reactive protein (mg/dl)	
Lower lobe	11 (32%)	Median	0.16
T classification		Range	0.02-9.45
0	1 (2%)	Creatinine clearance (ml/min)	
1a	1 (2%)	Median	73
1b	6 (17%)	Range	31-128
1c	1 (2%)	Carcinoembryonic antigen (ng/ml)	
2a	5 (14%)	Median	4.7
2b	6 (17%)	Range	1-322
3	6 (17%)	Cytokeratin 19 fragment (ng/ml)	
4	8 (23%)	Median	3.4
N classification		Range	0.9-25.1
0	5 (14%)	Sialylated carbohydrate antigen KL-6 (U/ml)	
1	8 (23%)	Median	259
2	17 (50%)	Range	103-669
3	4 (11%)	Number of patients with epidermal growth factor receptor mutation	2 (5%)
Stage		Number of patients with anaplastic lymphoma kinase fusion gene	2 (5%)
IA2	2 (5%)	Number of patients with c-ros oncogene 1 fusion gene	3 (8%)
IB	1 (2%)	Programmed cell death 1 ligand 1 expression level (%)	
IIA	1 (2%)	Median	50
IIB	5 (14%)	Range	0-95
IIIA	14 (41%)	Vital capacity (l)	
IIIB	9 (26%)	Median	3.14
IIIC	2 (5%)	Range	1.68-5.42
Histology		%vital capacity	
Adenocarcinoma	18 (52%)	Median	100
Squamous cell carcinoma	15 (44%)	Range	60.7-134
Pleomorphic carcinoma	1 (2%)	Forced expiratory volume in 1 sec (l)	
Positron emission tomography standardized maximum uptake value		Median	1.92
Median	12	Range	1.17-4.2
Range	2-37.5	Forced expiratory volume in 1 sec %	
Brinkman index		Median	75
Median	945	Range	42-91
Range	0-4200	% predicted forced expiratory volume in 1 sec	
Number of patients with asthma	2 (5%)	Median	75
Number of patients with diabetes mellitus	6 (17%)	Range	52-164
Number of patients complicated with interstitial pneumonia	2 (5%)	Number of patients complicated with chronic obstructive pulmonary disease	11 (32%)
Number of patients complicated with emphysematous change on computed tomography	18 (52%)	Number of patients complicated with mild chronic obstructive pulmonary disease (% predicted forced expiratory volume in 1 second ≥80%)	5 (14%)
Number of patients with post-operative recurrence	7 (20%)		
Number of patients with a history of drinking	23 (67%)		
Body mass index (kg/m ²)			
Median	21.5		
Range	16.3-30.1		

Table I. Continued

Table I. *Continued*

	N		N
Number of patients complicated with intermediate chronic obstructive pulmonary disease (% predicted forced expiratory volume in 1 second $\geq 50\%$ to $<80\%$)	6 (17%)	Lung V50Gy (%)	
		Median	2
		Range	0-8.3
Number of patients using inhaled medicine for chronic obstructive pulmonary disease	9 (26%)	Lung V60Gy (%)	
Number of patients received endobronchial ultrasonography	24 (70%)	Median	0
Prescribed radiation dose		Range	0-2.4
60 Gy/30 fractions/6 weeks once daily	16 (47%)	Mean lung dose (Gy)	
64 Gy/40 fractions/4 weeks twice daily; in the morning 2 Gy, with or without elective nodal irradiation, and in the evening, 1.2 Gy with tumor boost	13 (38%)	Median	7.8
66 Gy/30 fractions/6 weeks once daily	3 (8%)	Range	3.2-14.9
60 Gy/25 fractions/5 weeks once daily	1 (2%)	Esophagus V10Gy (%) (percentage volume of the esophagus irradiated more than or equal to 10 Gy)	
40 Gy/20 fractions and 30 Gy/10 fractions once daily	1 (2%)	Median	45.1
Prescribed method		Range	0-94
Dmean	32 (94%)	Esophagus V20Gy (%)	
D95	2 (5%)	Median	35.1
Radiotherapy methods		Range	0-79
Volumetric modulated arc therapy	31 (91%)	Esophagus V30Gy (%)	
Three-dimensional conformal radiotherapy	3 (8%)	Median	29.8
Elective nodal irradiation		Range	0-72.8
Yes	12 (35%)	Esophagus V40Gy (%)	
No	22 (64%)	Median	17.4
Radiotherapy duration (days)		Range	0-66.3
Median	41	Esophagus V50Gy (%)	
Range	15 ^a -61	Median	5.1
Planning target volume (cc)		Range	0-59.5
Median	289	Esophagus V60Gy (%)	
Range	64-1,087	Median	0
Lung V5Gy (%) (percentage volume of the lung irradiated more than or equal to 5 Gy)		Range	0-33
Median	32	Mean esophagus dose (Gy)	
Range	9-63.5	Median	17.5
Lung VS5Gy (cc) (absolute volume of the lung spared from 5 Gy)		Range	1.1-44.6
Median	2,001	Chemotherapy	
Range	580-3,998	Cisplatin 80 mg/m ² day 1, vinorelbine	14 (41%)
Lung V10Gy (%)		20 mg/m ² days 1, 8 triweekly	
Median	20.5	Carboplatin AUC 2, paclitaxel	14 (41%)
Range	6.3-36.9	40 mg/m ² days 1, 8, 15, 22, 29, 35	
Lung V20Gy (%)		Carboplatin AUC 6 day 1, nab-paclitaxel	6 (17%)
Median	12.5	100 mg/m ² days 1, 8, 15 triweekly	
Range	4.4-27	Chemotherapy cycle	
Lung V30Gy (%)		1	2 (5%)
Median	8.4	2	18 (52%)
Range	1.6-19.9	3	5 (14%)
Lung V40Gy (%)		4	6 (17%)
Median	4.2	5	0
Range	0.4-14	6	3 (8%)
		Radiotherapy and chemotherapy timing	
		Concurrent	32 (94%)
		Sequential	2 (5%)
		Number of patients receiving the full dose of chemotherapy	17 (50%)
		Number of patients receiving granulocyte-colony stimulating factor	7 (20%)

AUC: Area under the curve. ^aThe patient finished radiotherapy at 24.2 Gy/11 fractions over 15 days because of radiation pneumonitis.

Tumor staging was based on TMN classification 7th and 8th edition. The follow-up time was from the day radiotherapy or chemotherapy was started. Any death was counted as an event in the overall survival rate. Any deaths or progression, including distant

metastases, were counted as an event in the progression-free survival rate. Any progression in the radiotherapy field was counted as an event in the local control rate. Isolated elective nodal failures (*i.e.*, recurrences) were investigated in all thirty-four patients.

Table II. Univariate and multivariate logistic regression analyses for no use of durvalumab after definitive chemoradiotherapy in non-small cell lung cancer patients.

Factors	Univariate analyses			Multivariate analyses		
	<i>p</i> -Value	Odds ratio	95% confidence interval	<i>p</i> -Value	Odds ratio	95% confidence interval
Chronic obstructive pulmonary disease (vs. no chronic obstructive pulmonary disease)	0.003	18.37	2.74-122.94	0.022	17.25	1.51-196.64
Elective nodal irradiation (vs. no elective nodal irradiation)	0.005	14	2.19-89.21	0.016	19.81	1.98-252.82
Forced expiratory volume in 1 second (l)	0.031	0.14	0.024-0.83	Not included		
Forced expiratory volume in 1 second %	0.007	0.89	0.82-0.96	Not included		
% predicted forced expiratory volume in 1 sec	0.019	0.93	0.88-0.98	Not included		
Use of inhaled medicine for chronic obstructive pulmonary disease (vs. no use of inhaled medicine)	0.03	6.56	1.2-35.73	Not included		
Radiation pneumonitis ≥Grade 2 (vs. Grade 1 or no radiation pneumonitis)	0.016	8	1.46-43.67	Not included		
Radiation esophagitis ≥Grade 2 (vs. Grade 1 or no radiation esophagitis)	0.045	12	1.05-136.79	Not included		
Age	0.094			0.404		
Male (vs. female)	0.24			Not included		
Performance status 1 (vs. 0)	0.28			Not included		
Location of primary site in upper or middle lobe (vs. in lower lobe)	0.94			Not included		
T3 or T4 (vs. T0 or T1 or T2)	0.65			Not included		
N2 or N3 (vs. N0 or N1)	0.65			Not included		
Stage III (vs. Stage I or II)	0.67			Not included		
Adenocarcinoma (vs. squamous cell carcinoma or pleomorphic carcinoma)	0.17			Not included		
Epidermal growth factor receptor mutation (vs. no epidermal growth factor receptor mutation)	0.44			Not included		
Anaplastic lymphoma kinase fusion gene (vs. no anaplastic lymphoma kinase fusion gene)	0.37			Not included		
C-ros oncogene 1 fusion gene (vs. no c-ros oncogene 1 fusion gene)	0.86			Not included		
Programmed cell death 1 ligand 1 expression high (≥50%) (vs. low <50%)	0.16			Not included		
Positron emission tomography standardized maximum uptake value	0.29			Not included		
Brinkman index	0.49			Not included		
Alcohol history (vs. no alcohol history)	0.94			Not included		
Body mass index	0.086			Not included		
Pulmonary emphysema (vs. no pulmonary emphysema)	0.34			Not included		
Interstitial pneumonia (vs. no interstitial pneumonia)	0.99			Not included		
Asthma (vs. no asthma)	0.45			Not included		
Vital capacity (l)	0.23			Not included		
%vital capacity	0.24			Not included		
Intermediate chronic obstructive pulmonary disease (vs. no chronic obstructive pulmonary disease or mild chronic obstructive pulmonary disease)	0.16			Not included		
Diabetes mellitus (vs. no diabetes mellitus)	0.67			Not included		
White blood cell count/mm ³	0.61			Not included		
Neutrophil cell count/mm ³	0.45			Not included		
Hemoglobin (g/dl)	0.13			Not included		
Platelet cell count/mm ³	0.4			Not included		
C-reactive protein (mg/dl)	0.37			Not included		
Creatinine clearance (ml/min)	0.077			Not included		
Carcinoembryonic antigen (ng/ml)	0.24			Not included		
Cytokeratin 19 fragment (ng/ml)	0.3			Not included		
Sialylated carbohydrate antigen KL-6 (U/ml)	0.45			Not included		
Post-operative recurrences (vs. new cases)	0.42			Not included		

Table II. Continued

Table II. *Continued*

Factors	Univariate analyses			Multivariate analyses		
	<i>p</i> -Value	Odds ratio	95% confidence interval	<i>p</i> -Value	Odds ratio	95% confidence interval
Use of carboplatin (<i>vs.</i> use of cisplatin)	0.057			Not included		
No use of full dose of chemotherapy (<i>vs.</i> use of full dose of chemotherapy)	0.99			Not included		
Number of chemotherapy cycles	0.52			Not included		
Use of granulocyte-colony stimulating factor (<i>vs.</i> no use of granulocyte-colony stimulating factor)	0.42			Not included		
Axillary temperature of $\geq 37.5^{\circ}\text{C}$ during chemoradiotherapy (<i>vs.</i> $< 37.5^{\circ}\text{C}$)	0.76			Not included		
Febrile neutropenia (<i>vs.</i> no febrile neutropenia)	0.99			Not included		
White blood cells decreased $\geq$ Grade 3 (<i>vs.</i> Grade 1 or 2 or no white blood cells decreased)	0.34			Not included		
Neutropenia $\geq$ Grade 3 (<i>vs.</i> Grade 1 or 2 or no neutropenia)	0.34			Not included		
Anemia $\geq$ Grade 2 (<i>vs.</i> Grade 1 or no anemia)	0.91			Not included		
Thrombocytopenia $\geq$ Grade 1 (<i>vs.</i> no thrombocytopenia)	0.81			Not included		
Twice-daily thoracic radiotherapy (<i>vs.</i> once-daily thoracic radiotherapy)	0.26			Not included		
Volumetric modulated arc therapy (<i>vs.</i> three-dimensional conformal radiotherapy)	0.77			Not included		
Radiotherapy duration (days)	0.41			Not included		
Planning target volume (cc)	0.45			Not included		
Lung V5Gy (%) (percentage volume of the lung irradiated more than or equal to 5 Gy)	0.58			Not included		
Lung VS5Gy (cc) (absolute volume of the lung spared from 5 Gy)	0.068			Not included		
Lung V10Gy (%)	0.59			Not included		
Lung V20Gy (%)	0.74			Not included		
Lung V30Gy (%)	0.93			Not included		
Lung V40Gy (%)	0.95			Not included		
Lung V50Gy (%)	0.98			Not included		
Lung V60Gy (%)	0.081			Not included		
Mean lung dose (Gy)	0.58			Not included		
Esophagus V10Gy (%) (percentage volume of the esophagus irradiated more than or equal to 10 Gy)	0.76			Not included		
Esophagus V20Gy (%)	0.58			Not included		
Esophagus V30Gy (%)	0.46			Not included		
Esophagus V40Gy (%)	0.28			Not included		
Esophagus V50Gy (%)	0.71			Not included		
Esophagus V60Gy (%)	0.67			Not included		
Mean esophagus dose (Gy)	0.55			Not included		

Values in italics are statistically significant ($p < 0.05$). Multivariate analyses were done as reference only because the study size included only 34 cases, and the result might be unstable.

Radiotherapy. Volumetric modulated arc therapy (VMAT) with mainly Dmean prescription was generally performed. All patients received four-dimensional or three-dimensional CT simulation. Clinical target volume (CTV) 1 was typically a 0.5-cm expansion of the gross tumor volume including the primary tumor and metastatic lymph nodes; planning target volume (PTV) 1 was then a 0.5-cm expansion of CTV1. Then, the radiation oncologist determined whether CTV2 should include elective hilar, mediastinal, or supraclavicular lymph nodes plus CTV1 based on the information of the patient, tumor, and treatment. This protocol is called elective nodal irradiation (ENI) and

is intended to treat potential metastatic lymph nodes. The target of the elective nodal area was delineated based on the Japan Lung Cancer Society-Japanese Society for Radiation Oncology consensus-based computed tomographic atlas for defining regional lymph node stations in radiotherapy for lung cancer (3, 4). The total radiation dose of 60 Gy/30 fractions/6 weeks once daily was mainly administered to the patients. Alternatively, a more aggressive dose of 64 Gy/40 fractions/4 weeks twice daily (accelerated hyperfractionated thoracic radiotherapy) was given (5-7); in the morning, 2 Gy with or without ENI, and in the evening, 1.2 Gy with tumor boost radiotherapy were

Table III. Frequency and reasons for not receiving durvalumab within 45 days after chemoradiotherapy.

Number of patients who did not receive durvalumab within 45 days after radiotherapy	Nine of 34 patients (26%)
The reasons for not receiving durvalumab	
Radiation pneumonitis ^a	Five of 10 reasons (50%)
Radiation esophagitis ^b	One of 10 reasons (10%)
Progression of disease	One of 10 reasons (10%)
Death from heart attack	One of 10 reasons (10%)
Leg bone fracture	One of 10 reasons (10%)
Not coming to the hospital	One of 10 reasons (10%)

^{a,b}One patient had two reasons.

administered to other patients. ENI was performed for a median of 40 Gy/20 fractions/4 weeks. ENI was preferably adopted in good performance patients or patients in whom the tumor was located in the upper lobe, which requires a smaller lung dose compared to those with a primary location in the lower lobe.

Chemotherapy and immunotherapy. The chemotherapy regimen mainly consisted of cisplatin and vinorelbine or carboplatin and paclitaxel. Cisplatin (80 mg/m²) on day 1 combined with vinorelbine (20 mg/m²) on days 1 and 8 in 3- to 4-week intervals were delivered concurrently with radiotherapy. In patients aged >75 years or those with a low performance status, low renal function (creatinine clearance <60 ml/min), or other severe complications, the second choice for concurrent chemotherapy consisted of weekly carboplatin (area under the curve=2) plus paclitaxel (40 mg/m²), which were administered concurrently with radiotherapy. Another regimen, carboplatin (area under the curve=6) on day 1 combined with nab-paclitaxel (100 mg/m²) on days 1, 8, and 15 delivered concurrently with radiotherapy or pre-radiotherapy, was used. After chemoradiotherapy, durvalumab (10 mg/kg) every 2 weeks for up to 12 months was given if possible.

Statistical analysis. The endpoint of this study was that durvalumab was given to patients within 45 days after chemoradiotherapy. Although 42 days (6 weeks) was the longest interval between the end of chemoradiotherapy and start of durvalumab in a previous phase III study (1, 2), the one and a half-month (45 days) interval was adopted in this daily clinical practice study. Univariate logistic regression analyses were performed for 71 clinical and therapeutic factors. Then, selected factors were entered into the multivariate logistic regression analyses. However, the results of multivariate analyses are shown in Table II for reference only, because the sample size was 34 cases, and thus, results might be unstable. Statistical analyses were performed using SPSS, version 24.0 (IBM, Armonk, NY, USA). The 1-year overall survival, 1-year local control, and 1-year progression-free survival rates were estimated, and percentages were calculated with the Kaplan-Meier method.

Results

The median follow-up time was 13 months (range=0-17 months). The 1-year overall survival rate was 89%

Table IV. Adverse events due to chemoradiotherapy.

Adverse events	N
Pneumonitis	
Grade 1	14 (41%)
Grade 2	10 (29%)
Grade 3	0
Grade 4	1 (2%)
Grade 5	0
Esophagitis	
Grade 1	14 (41%)
Grade 2	1 (2%)
Grade 3	3 (8%)
Grade 4	0
Grade 5	0
Febrile neutropenia	
Grade 3	2 (5%)
Grade 4	0
Grade 5	0
White blood cells decreased	
Grade 1	2 (5%)
Grade 2	10 (29%)
Grade 3	16 (47%)
Grade 4	2 (5%)
Grade 5	0
Neutropenia	
Grade 1	2 (5%)
Grade 2	13 (38%)
Grade 3	9 (26%)
Grade 4	3 (8%)
Grade 5	0
Anemia	
Grade 1	24 (70%)
Grade 2	8 (23%)
Grade 3	0
Grade 4	0
Grade 5	0
Thrombocytopenia	
Grade 1	19 (55%)
Grade 2	1 (2%)
Grade 3	0
Grade 4	0
Grade 5	0
Number of patients with an axillary temperature of ≥37.5°C during chemoradiotherapy	10 (29%)

(range=79-100%). The 1-year progression-free survival rate was 72% (range=56-87%). The 1-year local control rate was 76% (range=60-92%). No isolated elective nodal failures were found in all thirty-four patients.

Twenty-five of 34 (73%) patients received immunotherapy after a median of 8 days (range=1-45 days) from the end of chemoradiotherapy. The reasons for not receiving immunotherapy are shown in Table III. The most frequent reason for not receiving immunotherapy was radiation pneumonitis, which accounted for 50% (5/10 reasons). Adverse events including hematologic toxicities due to

Table V. Univariate logistic regression analyses for not receiving durvalumab after definitive chemoradiotherapy in thirty-four non-small cell lung cancer patients.

Factors	Univariate analyses		
	<i>p</i> -Value	Odds ratio	95% confidence interval
Chronic obstructive pulmonary disease (vs. no chronic obstructive pulmonary disease)	0.003	18.37	2.74-122.94
Elective nodal irradiation (vs. no elective nodal irradiation)	0.005	14	2.19-89.21
Forced expiratory volume in 1 second (l)	0.031	0.14	0.024-0.83
Forced expiratory volume in 1 second %	0.007	0.89	0.82-0.96
% predicted forced expiratory volume in 1 second	0.019	0.93	0.88-0.98
Use of inhaled medicine for chronic obstructive pulmonary disease (vs. no use of inhaled medicine)	0.03	6.56	1.2-35.73
Radiation pneumonitis ≥Grade 2 (vs. Grade 1 or no radiation pneumonitis)	0.016	8	1.46-43.67
Radiation esophagitis ≥Grade 2 (vs. Grade 1 or no radiation esophagitis)	0.045	12	1.05-136.79
Age	0.094		
Male (vs. female)	0.24		
Performance status 1 (vs. 0)	0.28		
Location of primary site in upper or middle lobe (vs. in lower lobe)	0.94		
T3 or T4 (vs. T0 or T1 or T2)	0.65		
N2 or N3 (vs. N0 or N1)	0.65		
Stage III (vs. Stage I or II)	0.67		
Adenocarcinoma (vs. squamous cell carcinoma or pleomorphic carcinoma)	0.17		
Epidermal growth factor receptor mutation (vs. no epidermal growth factor receptor mutation)	0.44		
Anaplastic lymphoma kinase fusion gene (vs. no anaplastic lymphoma kinase fusion gene)	0.37		
C-ros oncogene 1 fusion gene (vs. no c-ros oncogene 1 fusion gene)	0.86		
Programmed cell death 1 ligand 1 expression high (≥50%) (vs. low <50%)	0.16		
Positron emission tomography standardized maximum uptake value	0.29		
Brinkman index	0.49		
Alcohol history (vs. no alcohol history)	0.94		
Body mass index	0.086		
Pulmonary emphysema (vs. no pulmonary emphysema)	0.34		
Interstitial pneumonia (vs. no interstitial pneumonia)	0.99		
Asthma (vs. no asthma)	0.45		
Vital capacity (l)	0.23		
%vital capacity	0.24		
Intermediate chronic obstructive pulmonary disease (vs. no chronic obstructive pulmonary disease or mild chronic obstructive pulmonary disease)	0.16		
Diabetes mellitus (vs. no diabetes mellitus)	0.67		
White blood cell count/mm ³	0.61		
Neutrophil cell count/mm ³	0.45		
Hemoglobin (g/dl)	0.13		
Platelet cell count/mm ³	0.4		
C-reactive protein (mg/dl)	0.37		
Creatinine clearance (ml/min)	0.077		
Carcinoembryonic antigen (ng/ml)	0.24		
Cytokeratin 19 fragment (ng/ml)	0.3		
Sialylated carbohydrate antigen KL-6 (U/ml)	0.45		
Post-operative recurrences (vs. new cases)	0.42		
Use of Carboplatin (vs. use of cisplatin)	0.057		
No use of full dose of chemotherapy (vs. use of full dose of chemotherapy)	0.99		
Number of chemotherapy cycles	0.52		
Use of granulocyte-colony stimulating factor (vs. no use of granulocyte-colony stimulating factor)	0.42		
Axillary temperature of ≥37.5°C during chemoradiotherapy (vs. <37.5°C)	0.76		
Febrile neutropenia (vs. no febrile neutropenia)	0.99		
White blood cells decreased ≥Grade 3 (vs. Grade 1 or 2 or no white blood cells decreased)	0.34		
Neutropenia ≥Grade 3 (vs. Grade 1 or 2 or no neutropenia)	0.34		
Anemia ≥Grade 2 (vs. Grade 1 or no anemia)	0.91		
Thrombocytopenia ≥Grade 1 (vs. no thrombocytopenia)	0.81		
Twice-daily thoracic radiotherapy (vs. once-daily thoracic radiotherapy)	0.26		

Table V. Continued

Table V. *Continued*

Factors	Univariate analyses		
	<i>p</i> -Value	Odds ratio	95% confidence interval
Volumetric modulated arc therapy (vs. three-dimensional conformal radiotherapy)	0.77		
Radiotherapy duration (days)	0.41		
Planning target volume (cc)	0.45		
Lung V5Gy (%) (percentage volume of the lung irradiated more than or equal to 5 Gy)	0.58		
Lung VS5Gy (cc) (absolute volume of the lung spared from 5 Gy)	0.068		
Lung V10Gy (%)	0.59		
Lung V20Gy (%)	0.74		
Lung V30Gy (%)	0.93		
Lung V40Gy (%)	0.95		
Lung V50Gy (%)	0.98		
Lung V60Gy (%)	0.081		
Mean lung dose (Gy)	0.58		
Esophagus V10Gy (%) (percentage volume of the esophagus irradiated more than or equal to 10 Gy)	0.76		
Esophagus V20Gy (%)	0.58		
Esophagus V30Gy (%)	0.46		
Esophagus V40Gy (%)	0.28		
Esophagus V50Gy (%)	0.71		
Esophagus V60Gy (%)	0.67		
Mean esophagus dose (Gy)	0.55		

Values in italics are statistically significant ($p < 0.05$).

chemoradiotherapy are shown in Table IV. Radiation pneumonitis $\geq$ Grade 2 and radiation esophagitis $\geq$ Grade 2 were found in 32% (11/34 cases) and 11% (4/34 cases), respectively. The eight significant factors in univariate analysis that affected administration of immunotherapy are listed in Table V and are as follows: chronic obstructive pulmonary disease (COPD)+, ENI+, using inhaled medicine for COPD, forced expiratory volume in 1 second (FEV1), FEV1%, %FEV1, radiation pneumonitis $\geq$ Grade 2, and radiation esophagitis $\geq$ Grade 2. COPD was defined as FEV1% $< 70\%$ in this study. Lung dose parameters including lung VS5Gy (cc) (absolute volume of the lung spared from 5 Gy) (8) were not significant factors. To avoid multicollinearity, COPD+, ENI+, and age, were included in the multivariate logistic regression analyses. Although age was not a significant factor in univariate analysis, age was important in clinical practice. After multivariate logistic regression analysis, two significant factors affecting immunotherapy were identified as COPD+ and ENI+ (for reference only; Table II). The actual rates of immunotherapy based on COPD (+ or –) or ENI (+ or –) are shown in Table VI. The rate of immunotherapy was 100% (17/17 cases) in the COPD– and ENI– group, and 16% (1/6 cases) in the COPD+ and ENI+ group. The choice of ENI area and the background of the patients are shown in Table VII. The comparison of lung dose parameters between the group that

Table VI. *The rate of use of durvalumab with or without chronic obstructive pulmonary diseases (COPD), and with or without elective nodal irradiation (ENI) after definitive chemoradiotherapy in thirty-four non-small cell lung cancer patients.*

	ENI (+)	ENI (–)	Total
COPD (+)	1/6 (16%)	3/5 (60%)	4/11 (36%)
COPD (–)	4/6 (66%)	17/17 (100%)	21/23 (91%)
Total	5/12 (41%)	20/22 (90%)	25/34 (73%)

received durvalumab and the group that did not is shown in Table VIII. No significant differences were found in any of the average lung doses between the two groups.

Five patients could not receive immunotherapy because of radiation pneumonitis. Four of these five patients with radiation pneumonitis received ENI. Therefore, for these four patients, the virtual radiation therapy planning was done without ENI (*i.e.*, without PTV2) in order to prove the reduction of the lung dose parameters using their past radiation therapy planning CT with fusion of diagnostic CT images of emergence of their radiation pneumonitis. The radiation pneumonitis area on diagnostic CT with fusion on the radiation therapy planning CT was delineated, and a virtual radiation therapy plan without ENI was made. For all four patients, reduction of the dose in

Table VII. Choice of elective nodal irradiation area and background of twelve patients.

Age (years)	Performance status	Tumor location	T	N	Stage	Histology	Tumor status	Chronic obstructive pulmonary disease	Diabetes mellitus	Lymph node area with gross tumor involved	Elective nodal irradiation area	Lung V20 (%)	Radiotherapy regimen	Combined chemotherapy regimen	Use of durvalumab
78	0	Right lower lobe	2b	1	IIB	Squamous cell carcinoma	New case	No	No	#11i, #10R	#7, #4R, #4L	8.8	Once a day	Carboplatin and paclitaxel	No
72	0	Left upper lobe	4	3	IIIC	Squamous cell carcinoma	New case	Yes	Yes	#11L, #4R	#10L, #5, #6, #4L, #2L, #3a, #2R, #1L	17.3	Twice a day	Carboplatin and paclitaxel	No
74	0	Left upper lobe	4	1	IIIA	Adenocarcinoma	New case	Yes	No	#11L	#10L, #5, #6, #4L, #4R, #3a, #2L, #2R, #1L	14.9	Twice a day	Carboplatin and paclitaxel	No
79	0	Left upper lobe	4	2	IIIB	Squamous cell carcinoma	New case	No	No	#11L, #10L, #7, #5, #6	#4L, #4R, #3p, #2L, #2R	14.2	Once a day	Carboplatin and nab-paclitaxel	No
76	0	Left upper lobe	4	3	IIIC	Squamous cell carcinoma	New case	No	No	#11L, #10L, #4L, #4R, #1L	#7, #5, #6, #3p, #3a, #2L, #2R, #1R	27	Twice a day	Cisplatin and vinorelbine	Yes
76	0	Right upper lobe	1b	2	IIIA	Squamous cell carcinoma	New case	Yes	Yes	#11s, #11i, #10R, #4R	#7, #3p, #2R	15.9	Once a day	Carboplatin and paclitaxel	No
77	0	Right upper lobe	2b	2	IIIA	Adenocarcinoma	New case	No	No	#11s, #10R, #7, #4R, #2R	#4L, #2L, #1R	14.4	Once a day	Carboplatin and nab-paclitaxel	Yes
76	0	Right upper lobe	1a	1	IIB	Adenocarcinoma	New case	Yes	No	#11s, #11i	#10R, #7, #4R, #4L, #3p, #3a, #2R, #2L, #1R	17.4	Once a day	Carboplatin and nab-paclitaxel	Yes
75	0	Right lower lobe	4	0	IIIA	Adenocarcinoma	Post-operative recurrence	No	No	#11i, #11s	#10R, #7, #4R, #4L, #2R, #2L	11.6	Once a day	Carboplatin and nab-paclitaxel	Yes
78	1	Left lower lobe	3	2	IIIB	Adenocarcinoma	Post-operative recurrence	Yes	No	#11L, #7	#10L, #5, #6, #4L, #4R, #3p, #2L, #2R	10.3	Once a day	Carboplatin and nab-paclitaxel	No
74	0	Left upper lobe	2a	0	IB	Adenocarcinoma	New case	Yes	No	none	#5, #6	5.9	Once a day	Carboplatin and paclitaxel	No
72	1	Right upper lobe	4	1	IIIA	Adenocarcinoma	New case	No	No	#10R, #4R ^a	#7, #4L, #3a, #2R	14.2	Twice a day	Cisplatin and vinorelbine	Yes

Eleven patients received volumetric modulated arc therapy. The other one patient received three-dimensional conformal radiotherapy. ^a#4R was irradiated as metastatic lymph node.

Table VIII. Comparison of dosimetric parameters of lung dose between group that used durvalumab and group that did not.

Lung dose	Use of durvalumab (N=25)	No use of durvalumab (N=9)	p-Value
Average V5Gy (%) (percentage volume of the lung irradiated more than or equal to 5 Gy)	34	36.8	0.523
Average VS5Gy (cc) (absolute volume of the lung spared from 5 Gy)	1847	2383	0.093
Average V10Gy (%)	21.1	22.7	0.536
Average V20Gy (%)	12.4	13.1	0.742
Average V30Gy (%)	8.4	8.6	0.941
Average V40Gy (%)	5.3	5.2	0.964
Average V50Gy (%)	2.6	2.6	0.984
Average V60Gy (%)	0.2	0.6	0.191
Average mean lung dose (Gy)	7.9	8.5	0.555

the radiation pneumonitis area, lung dose parameters, and esophagus dose parameters could be achieved by maintaining the effective dose to PTV1 (*i.e.*, the primary tumor and metastatic lymph nodes) (Table IX).

Discussion

Although our study size was small, this study calculated the actual rate of immunotherapy, analyzed clinical and dosimetric factors, and demonstrated that ENI and COPD affected whether NSCLC patients did or did not receive immunotherapy after definitive chemoradiotherapy. Radiation pneumonitis was the most common reason for not receiving immunotherapy. Virtual radiation therapy plan without ENI in patients treated with ENI who could not receive immunotherapy because of their radiation pneumonitis, achieved a reduction in the dose parameters of the lung. The results showed the possibility of palliation for their radiation pneumonitis without ENI. Although the follow-up time was short, no isolated elective nodal failures were found in all patients in the current study.

ENI has not been recommended for NSCLC in the guidelines of the European Organization for Research and Treatment of Cancer (9). In the International Atomic Energy Agency report (10), the clinical value of ENI was uncertain. The clinical trial Radiation Therapy Oncology Group 0617 did not permit ENI (11). On the other hand, ENI was regarded as an alternative standard therapy for locally advanced lung cancer in the Japanese radiation therapy planning guideline in 2016 (12) when immunotherapy was not available after definitive chemoradiotherapy. Although ENI has been used traditionally (13), its effectiveness has not been established. Yuan *et al.* reported that high-dose involved field irradiation (IFI) achieves a better overall response rate (90% *vs.* 79%, $p=0.032$), better 5-year local control rate (51% *vs.* 36%, $p=0.032$), and better 2-year overall survival rate (39.4% *vs.* 25.6%, $p=0.048$) than low-dose ENI in a randomized trial of 200 patients (14). The radiation

pneumonitis rate in the IFI group was also lower than that in the ENI group (17% *vs.* 29%, $p=0.044$). Topkan *et al.* reported that isolated elective nodal failures were present in 2.5% of the ENI group (21/844 cases) *vs.* 2.1% (3/143 cases) of the IFI group (15). They also reported that the overall survival rate (22.3 *vs.* 23.7 months, $p=0.47$), locoregional progression-free survival rate (12.6 *vs.* 13.2 months, $p=0.58$), and progression-free survival rate (10.7 *vs.* 10.4 months, $p=0.82$) were not significantly different between the two groups. In a meta-analysis, Li *et al.* reported no significant difference in the incidence of elective nodal failure between the IFI and ENI groups in three randomized controlled trials and three cohort studies (16). Schild *et al.* reported that ENI is associated with worse survival than IFI (median survival 16 *vs.* 24 months, $p=0.002$) in a pooled analysis of 16 cooperative group trials involving 3,600 patients (17).

Staging accuracy was achieved with positron emission tomography/CT and endobronchial ultrasonography. The progressed supportive care recommendation for NSCLC patients receiving chemoradiotherapy has been described (18). Radiotherapy technology was developed by four-dimensional CT, intensity modulated radiation therapy (IMRT), VMAT, and daily cone-beam CT. Although ENI compensates for the developing staging accuracy or radiation technology, omission of ENI for decreasing radiation-induced adverse events including pneumonitis is a reasonable idea for introducing immunotherapy after chemoradiotherapy in this era. Although the radiation oncologist should decrease the normal tissue dose including the dose to the lung and concentrate the effective dose on the gross tumor, they should remember which lymph nodes lung cancers tend to spread. This way of thinking may encourage another future study such as a study that includes post-operative radiotherapy.

Around 39-62% of lung cancer patients also have COPD (19, 20). In the current study, one-third of NSCLC patients had COPD, and most of them received an acting anti-muscarinic antagonist, acting beta agonist, or inhaled corticosteroid. COPD and radiation pneumonitis are

Table IX. Comparison of dosimetric factors between virtual radiation therapy plans without elective nodal irradiation (ENI) and actual radiation therapy plans with ENI in the four radiation pneumonitis patients who could not receive durvalumab (N=4).

Dosimetric factors		Actual radiation therapy plan with ENI	Virtual radiation therapy plan without ENI
Patient 1	Planning target volume (cc)	501	262
	Lung V5Gy (%) (percentage volume of the lung irradiated more than or equal to 5 Gy)	42.4	32.1
	Lung VS5Gy (cc) (absolute volume of the lung spared from 5 Gy)	2299	2708
	Lung V10Gy (%)	27.6	20.2
	Lung V20Gy (%)	14.2	12.3
	Lung V30Gy (%)	9.3	8.1
	Lung V40Gy (%)	5.7	5.4
	Lung V50Gy (%)	1.6	1.3
	Lung V60Gy (%)	0	0
	Mean lung dose (Gy)	10.3	7.7
	Mean dose of radiation pneumonitis area (Gy)	19.6	18.6
	Esophagus V10Gy (%) (percentage volume of the esophagus irradiated more than or equal to 10 Gy)	53	39.4
	Esophagus V20Gy (%)	50.5	36.6
	Esophagus V30Gy (%)	49.4	34.8
	Esophagus V40Gy (%)	48.3	31.7
	Esophagus V50Gy (%)	31.6	28.8
	Esophagus V60Gy (%)	14.2	10.2
	Mean esophagus dose (Gy)	27.6	21
Patient 2	Planning target volume (cc)	326	76
	Lung V5Gy (%)	33.9	12.8
	Lung VS5Gy (cc)	2457	3249
	Lung V10Gy (%)	19.3	8.8
	Lung V20Gy (%)	10.3	5.7
	Lung V30Gy (%)	5.8	2.7
	Lung V40Gy (%)	2.6	0.9
	Lung V50Gy (%)	1.4	0.1
	Lung V60Gy (%)	0.8	0
	Mean lung dose (Gy)	7.3	3.5
	Mean dose of radiation pneumonitis area (Gy)	18.9	17.7
	Esophagus V10Gy (%)	45.8	15.8
	Esophagus V20Gy (%)	42.3	12.1
	Esophagus V30Gy (%)	39.9	8.6
	Esophagus V40Gy (%)	30.9	5.2
	Esophagus V50Gy (%)	8.8	3.1
	Esophagus V60Gy (%)	3.4	1.5
	Mean esophagus dose (Gy)	19.8	6.1
Patient 3	Planning target volume (cc)	703	430
	Lung V5Gy (%)	39	27.2
	Lung VS5Gy (cc)	2321	2776
	Lung V10Gy (%)	24.6	15.3
	Lung V20Gy (%)	14.9	9.4
	Lung V30Gy (%)	9.3	7.1
	Lung V40Gy (%)	5.6	4.9
	Lung V50Gy (%)	3	2.7
	Lung V60Gy (%)	0.4	0.3
	Mean lung dose (Gy)	8.9	6.5
	Mean dose of radiation pneumonitis area (Gy)	34.6	30.7
	Esophagus V10Gy (%)	55.7	40.6
	Esophagus V20Gy (%)	45.8	29.7
	Esophagus V30Gy (%)	39.9	19.1
	Esophagus V40Gy (%)	32.4	13.5
	Esophagus V50Gy (%)	15.3	9.5
	Esophagus V60Gy (%)	7.3	5.5
	Mean esophagus dose (Gy)	23.4	15

Table IX. Continued

Table IX. *Continued*

Dosimetric factors		Actual radiation therapy plan with ENI	Virtual radiation therapy plan without ENI
Patient 4	Planning target volume (cc)	423	186
	Lung V5Gy (%)	54.5	52.4
	Lung VS5Gy (cc)	1089	1259
	Lung V10Gy (%)	28.9	26.8
	Lung V20Gy (%)	15.9	12
	Lung V30Gy (%)	9.3	7.1
	Lung V40Gy (%)	4	2.9
	Lung V50Gy (%)	0.5	0.3
	Lung V60Gy (%)	0	0
	Mean lung dose (Gy)	9.9	8.7
	Mean dose of radiation pneumonitis area (Gy)	31.2	29.8
	Esophagus V10Gy (%)	55.4	41.8
	Esophagus V20Gy (%)	53.1	26.5
	Esophagus V30Gy (%)	51.2	17.9
	Esophagus V40Gy (%)	48.4	9.9
	Esophagus V50Gy (%)	7	4.5
	Esophagus V60Gy (%)	0	0
	Mean esophagus dose (Gy)	25.1	13

All the four patients received volumetric modulated arc therapy.

inflammatory diseases caused mainly by smoking and radiation therapy, respectively. Using univariate analysis, Shi *et al.* reported that COPD was a significant factor ($p<0.05$) in 11 patients with severe acute radiation pneumonitis among 94 NSCLC patients treated with IMRT (21). Using multivariate analysis, Inoue *et al.* reported that COPD was a significant factor ($p=0.002$) in 44 patients with prolonged minimal radiation-induced pneumonitis after stereotactic body radiation therapy among 136 stage I lung cancer patients (22). Therefore, COPD might be a risk factor in relation to radiation pneumonitis. COPD should be treated along with lung cancer to minimize the influence of loss of normal lung function by chemoradiotherapy. Continuing medications such as an acting anti-muscarinic antagonist, acting beta agonist, or inhaled corticosteroid for COPD is important before and after chemoradiotherapy for NSCLC. Prohibiting smoking and vaccination against influenza and *Streptococcus pneumoniae* are also important (23).

Conclusion

ENI for NSCLC complicated with COPD decreased the rate of immunotherapy after definitive chemoradiotherapy. To increase the possibility of introducing immunotherapy, ENI should not be used for NSCLC complicated with COPD. Supportive care for NSCLC patients complicated with COPD should be done to minimize the loss of normal tissue function by chemoradiotherapy.

Conflicts of Interest

K Nishino had honoraria from Nippon Boehringer Ingelheim Co., Ltd., AstraZeneca K.K., Novartis Pharma K.K., Eli Lilly Japan K.K., Roche Diagnostics K.K., Chugai Pharma, and ONO PHARMACEUTICAL CO., LTD. K Nishino had research funding from Nippon Boehringer Ingelheim Co., Ltd. F Imamura had research funding from AstraZeneca. T Kumagai received a grant from Ono Pharmaceutical., MSD K.K., Chugai Pharmaceutical Co. Ltd., AstraZeneca K.K., Takeda Pharmaceutical Company Limited., Merck Serono Co., Ltd., Pfizer Japan Inc., Taiho Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., and The Osaka Foundation for The Prevention of Cancer and Life-style related Diseases (Public Interest Incorporated Foundation). T Kumagai received personal fee from Ono Pharmaceutical., AstraZeneca K. K., Taiho Pharmaceutical Co. Ltd., MSD K.K., TEIJIN PHARMA LIMITED, Novartis Pharma K.K., Nippon Boehringer Ingelheim Co., Ltd., Eli Lilly Japan K.K., Pfizer Inc., Chugai Pharmaceutical Co. Ltd., Bristol-Myers Squibb K.K., and Takeda Pharmaceutical Company Limited.

Authors' Contributions

Conception and design: M Morimoto, and K Nishino. Acquisition of data: M Morimoto, K Nishino, K Wada, F Imamura, K Konishi, H Kuhara, M Tamiya, T Inoue, K Kunimasa, M Kimura, T Hirata, N Kanayama, M Toratani, H Kawachi, K Ohira, E Nakanishi, S Ohira, T Sagawa, M Miyazaki, T Kumagai, and T Teshima. Analysis and interpretation of data: M Morimoto, K Nishino, K Wada, F Imamura, K Konishi, H Kuhara, M Tamiya, T Inoue, K Kunimasa, M Kimura, T Hirata, N Kanayama, M Toratani, H Kawachi, K Ohira, E Nakanishi,

S Ohira, T Sagawa, M Miyazaki, T Matsunaga (statistician), T Kumagai, and T Teshima. Writing, review, and/or revision of the manuscript: M Morimoto, K Nishino, K Wada, and K Kunimasa.

Acknowledgements

This study was supported by JSPS KAKENHI Grant Number 18K15616. The Authors deeply appreciate the investigator Toshiki Ikawa M.D. (Department of Radiation Oncology, Osaka International Cancer Institute, Osaka, Japan) who contributed to this study.

References

- 1 Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hiet S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA and Özgüroğlu M: Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 377: 1919-1929, 2017. PMID: 28885881. DOI: 10.1056/NEJMoa1709937
- 2 Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Kurata T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hiet S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Faivre-Finn C, Reck M, Vansteenkiste J, Spigel DR, Wadsworth C, Melillo G, Taboada M, Dennis PA and Özgüroğlu M: Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med* 379: 2342-2350, 2018. PMID: 30280658. DOI: 10.1056/NEJMoa1809697
- 3 Itazawa T, Tamaki Y, Komiyama T, Nishimura Y, Nakayama Y, Ito H, Ohde Y, Kusumoto M, Sakai S, Suzuki K, Watanabe H and Asamura H: The Japan Lung Cancer Society-Japanese Society for Radiation Oncology consensus-based computed tomographic atlas for defining regional lymph node stations in radiotherapy for lung cancer. *J Radiat Res* 58: 86-105, 2017. PMID: 27609192. DOI: 10.1093/jrr/rrw076
- 4 The JLCS – JASTRO joint committee for developing an atlas of the regional lymph node stations in radiotherapy treatment planning for lung cancer, Komiyama T, Itazawa T, Tamaki Y, Nishimura Y, Nakayama Y, Ito H, Ohde Y, Kusumoto M, Sakai S, Suzuki K, Watanabe H and Asamura H: A consensus-based computed tomographic atlas for defining the regional lymph node stations in radiotherapy for lung cancer (in Japanese). *Haigan* 55: 189-205, 2015.
- 5 Imamura F, Konishi K, Uchida J, Nishino K, Okuyama T, Kumagai T, Kawaguchi Y and Nishiyama K: Novel chemoradiotherapy with concomitant boost thoracic radiation and concurrent cisplatin and vinorelbine for stage IIIA and IIIB non-small-cell lung cancer. *Clin Lung Cancer* 15: 281-286, 2014. PMID: 24656641. DOI: 10.1016/j.clcc.2014.02.001
- 6 Wada K, Kishi N, Kanayama N, Hirata T, Morimoto M, Konishi K, Imamura F, Teshima T and Ogawa K: Radiation dose escalation in accelerated hyperfractionated radiotherapy for stage III non-small-cell lung cancer. *Anticancer Res* 38: 5951-5958, 2018. PMID: 30275224. DOI: 10.21873/anticancer.12941
- 7 Wada K, Kishi N, Kanayama N, Hirata T, Ueda Y, Kawaguchi Y, Morimoto M, Konishi K, Imamura F, Ogawa K and Teshima T: Predictors of acute radiation esophagitis in non-small cell lung cancer patients treated with accelerated hyperfractionated chemoradiotherapy. *Anticancer Res* 39: 491-497, 2019. PMID: 30591500. DOI: 10.21873/anticancer.13139
- 8 Tsujino K, Hashimoto T, Shimada T, Yoden E, Fujii O, Ota Y, Satouchi M, Negoro S, Adachi S and Soejima T: Combined analysis of V20, VS5, pulmonary fibrosis score on baseline computed tomography, and patient age improves prediction of severe radiation pneumonitis after concurrent chemoradiotherapy for locally advanced non-small-cell lung cancer. *J Thorac Oncol* 9: 983-990, 2014. PMID: 24922010. DOI: 10.1097/JTO.0000000000000187
- 9 De Ruysscher D, Faivre-Finn C, Moeller D, Nestle U, Hurkmans CW, Le Péchoux C, Belderbos J, Guckenberger M and Senan S: European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. *Radiother Oncol* 124: 1-10, 2017. PMID: 28666551. DOI: 10.1016/j.radonc.2017.06.003
- 10 Belderbos JS, Kepka L, Spring Kong FM, Martel MK, Videtic GM and Jeremic B: Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small-cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 72: 335-342, 2008. PMID: 18793953. DOI: 10.1016/j.ijrobp.2008.04.081
- 11 Bradley JD, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, Bogart J, Hu C, Forster K, Magliocco A, Kavadi V, Garces YI, Narayan S, Iyengar P, Robinson C, Wynn RB, Koprowski C, Meng J, Beitler J, Gaur R, Curran W Jr. and Choy H: Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 16: 187-199, 2015. PMID: 25601342. DOI: 10.1016/S1470-2045(14)71207-0
- 12 Japanese Society for Radiation Oncology: Radiation therapy planning guideline 2016 edition. Tokyo: Kanahara Co., Ltd., 2016.
- 13 Perez CA, Stanley K, Grundy G, Hanson W, Rubin P, Kramer S, Brady LW, Marks JE, Perez-Tamayo R, Brown GS, Concannon JP and Rotman M: Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung: report by the Radiation Therapy Oncology Group. *Cancer* 50: 1091-1099, 1982. PMID: 6286087. DOI: 10.1002/1097-0142(19820915)50:6<1091::aid-cncr2820500612>3.0.co;2-0
- 14 Yuan S, Sun X, Li M, Yu J, Ren R, Yu Y, Li J, Liu X, Wang R, Li B, Kong L and Yin Y: A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III non-small cell lung cancer. *Am J Clin Oncol* 30: 239-244, 2007. PMID: 17551299. DOI: 10.1097/01.coc.0000256691.27796.24
- 15 Topkan E, Guler OC and Yildirim BA: Omission of elective nodal irradiation has no impact on isolated elective nodal failure and survival outcomes in stage III non-small-cell lung cancer patients treated with definitive concurrent chemoradiotherapy. *Ann Oncol* 26: i24, 2015. DOI: <https://doi.org/10.1093/annonc/mdv049.08>
- 16 Li R, Yu L, Lin S, Wang L, Dong X, Yu L, Li W and Li B: Involved field radiotherapy (IFRT) versus elective nodal irradiation (ENI) for locally advanced non-small cell lung cancer: a meta-analysis of incidence of elective nodal failure

- (ENF). *Radiat Oncol* 11: 124, 2016. PMID: 27655339. DOI: 10.1186/s13014-016-0698-3
- 17 Schild SE, Pang HH, Fan W, Stinchcombe TE, Vokes EE, Ramalingam SS, Bradley JD, Kelly K and Wang X: Exploring radiotherapy targeting strategy and dose: A pooled analysis of cooperative group trials of combined modality therapy for stage III NSCLC. *J Thorac Oncol* 13: 1171-1182, 2018. PMID: 29689435. DOI: 10.1016/j.jtho.2018.04.011
 - 18 De Ruysscher D, Faivre-Finn C, Nackaerts K, Jordan K, Arends J, Douillard JY, Ricardi U and Peters S: Recommendation for supportive care in patients receiving concurrent chemotherapy and radiotherapy for lung cancer. *Ann Oncol* 31: 41-49, 2020. PMID: 31912794. DOI: 10.1016/j.annonc.2019.10.003
 - 19 Abal Arca J, Parente Lamelas I, Almazán Ortega R, Blanco Pérez J, Toubes Navarro ME and Marcos Velázquez P: Cáncer de pulmón y EPOC: una asociación frecuente [Lung cancer and COPD: a common combination] (in Spanish, abstract). *Arch Bronconeumol* 45: 502-507, 2009. PMID: 19748721. DOI: 10.1016/j.arbres.2009.07.005
 - 20 Loganathan RS, Stover DE, Shi W and Venkatraman E: Prevalence of COPD in women compared to men around the time of diagnosis of primary lung cancer. *Chest* 129: 1305-1312, 2006. PMID: 16685023. DOI: 10.1378/chest.129.5.1305
 - 21 Shi A, Zhu G, Wu H, Yu R, Li F and Xu B: Analysis of clinical and dosimetric factors associated with severe acute radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with concurrent chemotherapy and intensity-modulated radiotherapy. *Radiat Oncol* 5: 35, 2010. PMID: 20462424. DOI: 10.1186/1748-717X-5-35
 - 22 Inoue T, Shiomi H and Oh RJ: Stereotactic body radiotherapy for Stage I lung cancer with chronic obstructive pulmonary disease: special reference to survival and radiation-induced pneumonitis. *J Radiat Res* 56: 727-734, 2015. PMID: 25887042. DOI: 10.1093/jrr/rrv019
 - 23 The Japanese Respiratory Society: The JRS Guidelines for the Management of Chronic Obstructive Pulmonary Disease 5th edition. Tokyo: Medical Review Co., Ltd., 2018.

Received October 3, 2020

Revised October 8, 2020

Accepted October 9, 2020