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Risk factor of pneumonitis on dose-volume relationship for chemoradiotherapy with durvalumab: Multi-institutional research in Japan

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ABSTRACT

Objectives: To estimate appropriate dose-volume parameters for avoidance of pneumonitis in use of chemoradiotherapy and durvalumab for treatment of lung cancer.

Materials and methods: Patients with non-small cell lung cancer treated with concurrent chemoradiotherapy followed by durvalumab at 9 centers were enrolled in the study. Three-dimensional radiotherapy, intensity modulated radiotherapy, and proton beam therapy were used. The frequency and severity of pneumonitis and the dose-volume relationship for normal lung were evaluated. Univariable and multivariable analyses were conducted to identify risk factors. A covariate adjusted hazard ratio was then estimated for the percentages of normal lung volume irradiated at $\geq$ X Gy (Vx) (X = 5–40) and lung volume non-irradiated at $\geq$ X Gy (X = 5–40), with the covariates selected in the variable selection. Cumulative incidence functions and covariate adjusted hazard ratios were also estimated for dichotomized variables, with estimated cut-off points.

Results: A total of 91 patients were enrolled in the study. The median time from the start of radiotherapy to development of pneumonitis was 4.1 months. Pneumonitis was observed in 80 patients (88%), including grade 2 or severe pneumonitis in 31 (34%) and $\geq$ grade 3 pneumonitis in 11 (12%). Pneumonitis was inside the irradiation field in 73 of the 80 patients (91%). The selected factors for $\geq$ grade 2 pneumonitis were V_{20}, and primary site (upper lobe) in multivariable analysis. The cut off value of V_{20} was 18.99%, and there was a significant difference between V_{20} of < 18.77 and $\geq$ 18.77.

Conclusion: Though there are some limitation of this study, the basic concept of concurrent chemoradiotherapy with an emphasis on V_{20} remains unchanged in use of durvalumab. However, we recommend reduction of V_{20} to as small a value as possible in use of this therapy.

Introduction

With recent progress of immune therapy, the indication for immune checkpoint inhibitors (ICIs) has expanded in cancer treatment. In 2017, the efficacy of durvalumab after concurrent chemoradiotherapy (CCRT) was suggested in the phase III PACIFIC

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study [1–2], and this approach is now widely used as a standard therapy for unresectable locally advanced non-small cell lung cancer (NSCLC). However, an ICI has a risk of an autoimmune response, including interstitial pneumonitis, and this raises a concern about an increased risk of radiation pneumonitis with use of durvalumab.

The risk of radiation pneumonitis is correlated with various factors, such as combined chemotherapy, radiotherapy, age, poor performance status, smoking history, poor lung function, co-existence lung disease of chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), cytokines or biomarker level, and dosimetric factors of radiotherapy [3–9]. In radiotherapy, the dose-volume relationship for the normal lung is one of the most important factors, and this has been evaluated using a dose-volume histogram (DVH) in previous studies of CCRT. The importance of the lung volume irradiated at $\geq$ 20 Gy (V_{20}) has been established for radiation pneumonitis [7,10], and parameters such as V_{10}, V_{30}, and mean lung dose (MLD) have also been suggested as significant risk factors for radiation pneumonitis [7,10–19]. In the PACIFIC study, the incidence of pneumonitis was infrequent [2]; however, it is unclear if previous dose-volume parameters can be used for radiotherapy with durvalumab. In this study, we evaluated DVHs of patients with locally advanced NSCLC who received CCRT followed by durvalumab at 9 centers, and we analyzed risk factors for pneumonitis.

Material and methods

Patients

Patients who received durvalumab following CCRT at 9 centers in Ibaraki prefecture from March 2018 to August 2020 were enrolled in this study. Each institutional review board approved this study. Written informed consent was obtained from all patients before treatment was administrated.

Radiation therapy

Three-dimensional radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT) including tomotherapy, and proton beam therapy (PBT) were available at the 9 centers, and patients were treated with all these modalities. In PBT, an equivalent dose to photon therapy was used based on a relative biological effectiveness of 1.1 [20]. The target policy differed among the centers and elective nodal irradiation (ENI) was performed at some centers. Respiratory synchronization, breath holding, and abdominal compression were used for respiratory control. Normal lung volume was contoured as the bilateral lung volume minus the clinical target volume (CTV). Lasso-based variable selection with Bayesian information criteria was also performed.

Analysis

The DVH was calculated on a treatment planning system at each center. Pneumonitis was graded according to CTCAE version 4.0. The end point was defined as the time to occurrence of pneumonitis ($\geq$grade 2 or $\geq$ grade 3) while treating death as a competing risk. A univariable subdistribution hazard model was used for explanatory variables [21–22] of age ($\geq$68 vs. < 68), gender, performance status (PS, 0 or 1 vs. 2 or 3), stage (stage II vs. III vs. others), pathology (adenocarcinoma vs. squamous cell carcinoma vs. others), programmed cell death ligand-1 (PDL-1) status, serum value of sialylated carbohydrate antigen (KL-6), smoking history, Brinkman index, presence of COPD, ILD, pulmonary infection, chemotherapy regimen (cisplatin (CDDP) + vinorelbine (VNR) vs. carboplatin (CBDCA) + paclitaxel (PTX) vs. CDDP + pemetrexed (PEM) vs. CDDP + tegafur, gimeracil, oteracil potassium (TS-1) vs. others), radiotherapy modality (3D-CRT vs. 3DCRT + IMRT vs. IMRT vs. PBT), respiratory control method (synchronization vs. depression vs. abdominal compression vs. none), treatment field (ENI vs. involved field radiation therapy (IFRT), number of treatment fields shrinkage times, total dose, CTV, planning target volume (PTV), MLD, and percentages of normal lung volume irradiated at $\geq$ X Gy (Vx) (X = 5–40) and lung volume not irradiated at $\geq$ X Gy (remnant lung volume, RLVx) (X = 5–40).

Lasso-based variable selection based on Bayesian information criteria was conducted using the above candidate explanatory variables to identify risk factors [23–24]. The covariate adjusted hazard ratios (HR) for Vx and RLVx were then estimated using a subdistribution hazard model with the covariates selected in the variable selection. In these analyses, Vx and RLVx (X = 5–40) were treated as categorical variables divided into four with estimated quartiles. The following parameters previously reported as significant factors for radiation pneumonitis were also evaluated: V_5 (>40% [15], >60% [13]) V_{10} (>30% [15], >35% [15]) V_{20} (>25% [7], 35% [6,11]), V_{30} (>20% [15]), and MLD (15 Gy, 18 Gy [11,19]). A cumulative incidence function was also estimated for each level of the above categorized variables. Time-dependent ROC curve analysis [25–26] was then applied for Vx and RLVx (X = 5–40), and the time-dependent AUC and cut-off points that maximized sensitivities and specificities at 6 months from irradiation were estimated. Cumulative incidence functions and covariate adjusted HRs were all estimated for the dichotomized variables with determination of cut-off points. $P < 0.05$ was defined as significant in all statistical tests. R ver. 4.0.3 (R Core Team) and SAS (SAS Institute Inc.) were used for the analyses.

Results

Patients

The characteristics of the 91 patients enrolled in the study are shown in Table 1. The cohort included 67 males and 24 females, and the median age was 68 years old (range, 37 to 86 years). Performance status was 0, 1, 2, and 3 for 63, 22, 4, and 2 cases; the tumor stage was II, IIIA, IIIB, IIIC and IV in 2, 35, 35, 12, and 1 cases, and there was postoperative recurrence in 6 cases. One stage IV case had a small brain metastasis and was treated with stereotactic radiotherapy, after which CCRT followed by durvalumab was indicated. The pathology was adenocarcinoma, squamous cell carcinoma, and others in 34, 37 and 20 cases, respectively.

Of the 74 cases in which PD-L1 was evaluated, the level was < 1%, 1–10%, 12.5–50%, 65–75%, 80–90%, and 95–100% in 15, 16, 25, 5, 9, and 4 cases, respectively. KL-6 was also measured in 74 cases, and the median value was 305 U/ml (range, 138–2103 U/ml). COPD was present in 27 patients, 5 had ILD, and one patient had mycobacterium intracellulare before the start of CCRT. A total of 82 patients had a smoking history and 26 were current smokers. The median Brinkmann index was 900 (range, 0 to 3300).

A summary of treatment is shown in Table 2. Radiotherapy with 3DRT, IMRT, a combination of 3DRT and IMRT, and PBT was conducted in 67, 12, 10 and 2 patients, respectively. The treatment field was ENI in 33 cases and IFRT in 58. The median treatment dose was 60 Gy (range, 45 to 66 Gy). Adaptive radiotherapy was performed and the number of shrunk targets were 0, 1, 2, 3, and 4 in 3, 68, 17, 2, and 2 cases, respectively.

The mean follow-up period was 14.8 months (range, 3.1 to 31.5 months) and 81 patients (89%) were alive at the last follow up. Durvalumab were administered 1–26 times (median, 11 times). At the last follow-up, durvalumab was ongoing in 27 cases, and 23 had completed administration for 1 year. However, durvalumab

Table 1
Patient characteristics.

Item		Value
Gender	Male	67
	Female	24
Age	Median	68
	Range	37–86
Performance status	0	63
	1	22
	2	4
	3	2
TMN Stage	II	2
	IIIA	35
	IIIB	35
	IIIC	12
	IV	1
	Recurrent disease	6
Pathology	Adenocarcinoma	34
	Squamous cell carcinoma	37
	Others	20
PDL-1	<1%	15
	1.0–10%	16
	12.5–50%	25
	65–75%	5
	80–90%	9
	95–100%	4
	Not measured	17
KL-6 (U/ml)	Median	305
	Range	138–2103
Smoking	Current smoker	26
	Ex-smoker	56
	Non smoker	9
Brinkman index	Median	900
	Range	0–300
Co-existing lung disease	ILD	5
	COPD	27
	Infection	1

Table 2
Treatment strategy.

Item		Value
Chemotherapy Regimen		
	CDDP + VNR	23
	CBDCA + PTX	37
	CDDP + PEM	4
	CDDP + TS-1	20
	Others	7
Radiotherapy		
	3D-CRT	67
	3DCRT + IMRT	10
	IMRT	12
	PBT	2
Respiratory control		
	Synchronization	39
	Depression	16
	Abdominal compression	5
	None	31
Treatment field		
	ENI	33
	IFT	58
Treatment dose		
	Median	60 Gy
	45 Gy	1
	60 Gy	50
	62 Gy	1
	65.4 Gy	1
	66 Gy	38
Median Clinical Target Volume (CTV) (cc)		
	Total	193.2 (13.1–896.1)
	3DCRT	184.0 (13.1–878.9)
	3DCRT + IMRT	262.4 (27.9–896.1)
	IMRT	227.0 (51.5–607.0)
	PBT	68.9 (57.2–80.6)
Planning Target Volume (PTV) (cc)		
	Total	351.6 (68.7–1241.4)
	3DCRT	346.0 (68.7–1241.4)
	3DCRT + IMRT	460.5 (157.6–1219.2)
	IMRT	347.1 (189.7–660.0)
	PBT	351.6 (68.7–1241.4)
Number of field shrinkage		
	None	3
	Once	68
	Twice	17
	Third	2
	Fourth	2

was interrupted in 41 patients due to disease progression or toxicities.

Pneumonitis

The median time from the start of therapy to development of pneumonitis was 4.1 months (range, 1.9 to 16.4 months). Pneumonitis developed in 80 cases (88%), including grade 2 or severe pneumonitis in 31 (34%) and ≥ grade 3 pneumonitis in 11 (12%). Pneumonitis was inside the irradiation field in 73 of the 80 cases (91%). In the 7 cases with pneumonitis spreading outside the irradiation field, grade 3 or severer pneumonitis occurred in 5 (grade 1: 2: 3: 4: 5 = 1: 1: 2: 2: 1) (Table 3).

In univariable analysis, tumor location (upper lobe), ILD, PBT, total dose, Vx (x = 10–40), and remnant lung dose of < 10 Gy and 15 Gy were significantly associated with the incidence of ≥ grade 2 pneumonitis; and PS, location, chemotherapy (CDDP + VNR vs. CDDP + PEM or others), radiation modality (3DCRT vs. others), respiratory control, PTV, and Vx (x = 10–40) were significant factors associated with the incidence of ≥ Grade 3 pneumonitis (Table 4).

Based on lasso variable selection, V_{20} and primary site (upper lobe) were selected as the prognostic factors for ≥ grade 2 pneumonitis, however no variable was selected for ≥ grade3 pneumonitis. So the primary site was treated as a covariate factors for estimating covariate adjusted HR for ≥ grade 2 pneumonitis. The mean V_{20} was 19.4% in all patients, and the mean V_{20} levels by pneumonitis grade were 16.6%, 18.5%, 21.3%, 28.8%, 18.3%, and 20% for grades 0 to 5, respectively (Table 5). The cut-off for V_{20} was estimated as 18.77% (AUC 0.701) and there was a significant difference in the incidence of pneumonitis between V_{20} of < 18.77% and ≥ 18.77% (adjusted HR: 2.840, p = 0.015; Fig. 1). Since this cut-off was smaller than in previous studies, the sensitivity and specificity were calculated for V_{20} = 20%, 25%, 30%, and 35%. The sensitivity was reduced and specificity was enhanced as the cut-off value increased (Fig. 2). The cut-off values for Vx (x = 5–40) are shown in Fig. 3. The AUCs were all > 0.7, indicating that they were relatively reliable.

Among previously suggested parameters, V_{10} > 30% (p = 0.037 for ≥ grade 2), > 35% (p =0.017 for ≥ grade 3)V_{20} > 25% (p = 0.026 for ≥ grade 3), 30% (p = 0.011 and 0.009 for ≥ grade 2 and 3), and 35% (p < 0.001 for ≥ grade 2), and MLD > 15 Gy (p = 0.017 for ≥ grade 2) and 18 Gy (p = 0.003 for ≥ grade 3) were also significant factors according to cummulative incidence analysis.

Discussion

In chemoradiotherapy for lung cancer, radiation pneumonitis is one of the most important toxicity. Many parameters have been proposed as significant factors for radiation pneumonitis, with the best known being V_{20}. In 1999, Graham et al. found that V_{20} was significantly correlated with the incidence and grade of radiation pneumonitis, and suggested that a treatment plan with V_{20} > 35% should not be used because fatal pneumonitis occurred

Table 3
Outcome of treatment.

Item	Value
Follow-up time	
Median	14.8 months
Range	3.1–31.5 months
Number of doses of durvalumab	
Median	11
Range	1–26
Status of durvalumab	
Complete	23
Ongoing	27
Interruption	41
Pneumonitis	
None (Grade 0)	11
Grade 1	49
Grade 2	20
Grade 3	6
Grade 4	4
Grade 5	1
Time from start of radiotherapy to pneumonitis	
Median	4.2 months
Range	1.9 to 16.4 months
Pneumonitis (N = 80)	
Symptoms	
Symptomatic	31
Asymptomatic	49
Relation to irradiation field	
Inside radiation field	73
Outside radiation field	7
Use of steroids	
Yes	54
No	26
Maximum dose of steroids	
20–25 mg	7
30–35 mg	5
40 mg	4
60 mg	2
80 mg	2
125 mg	1
1000 mg	5

Table 4
Univariate analysis of factors related to pneumonitis.

Factors	P-value	
	≥ Grade 2	≥ Grade 3
Age (≤68 vs. > 68)	0.280	0.275
Gender	0.890	0.910
Performance Status (0/1 vs. 2 or 3)	0.313	*<0.001*
KL-6	0.315	0.449
Stage (II vs III)	0.596	0.103
Stage (II vs others)	0.577	0.279
Pathology (adenocarcinoma vs. squamous cell carcinoma)	0.687	0.810
Smoking history (current vs. non-smoker)	0.737	0.662
Smoking history (current vs. ex-smoker)	0.348	0.519
Location (upper lobe vs. other)	*0.007*	*0.025*
Brinkman Index	0.928	0.930
COPD	0.989	0.569
ILD	*0.017*	0.633
Chemotherapy (CDDP + VNR vs. CBDCA + PTX)	0.679	0.654
Chemotherapy (CDDP + VNR vs. CDDP + PEM)	0.672	*<0.001*
Chemotherapy (CDDP + VNR vs. TS—1)	0.676	0.343
Chemotherapy (CDDP + VNR vs. others)	0.244	*<0.001*
Irradiation modality (3DCRT vs. IMRT)	0.101	*<0.001*
Irradiation modality (3DCRT vs. 3DCRT + IMRT)	0.394	*<0.001*
Radiation modality (3DCRT vs. PBT)	*<0.001*	*<0.001*
Respiratory control (None vs. synchronization)	0.099	0.503
Respiratory control (None vs. suppression)	0.608	0.805
Respiratory control (None vs. abdominal compression)	0.374	*<0.001*
Treatment field (ENI vs. IFRT)	0.711	0.491
Total dose	*<0.001*	0.847
CTV	0.310	0.072
PTV	0.289	*0.018*
Target shrinking	0.283	0.543
Mean lung dose	*0.033*	0.104
V_5	0.052	0.074
V_{10}	*<0.001*	*0.002*
V_{15}	*<0.001*	*0.004*
V_{20}	*<0.001*	*0.004*
V_{25}	*<0.001*	*0.008*
V_{30}	*<0.001*	*0.022*
V_{35}	*<0.001*	*0.026*
V_{40}	*0.002*	*0.041*
Remnant lung volume (RLV) < 5 Gy	0.096	0.345
RLV < 10 Gy	*0.026*	0.197
RLV < 15 Gy	*0.043*	0.283
RLV < 20 Gy	*0.049*	0.328
RLV < 25 Gy	0.056	0.382
RLV < 30 Gy	0.063	0.436
RLV < 35 Gy	0.069	0.466
RLV < 40 Gy	0.080	0.506

Table 5
Incidence of pneumonitis.

Pneumonitis grade	n	Mean V_{20} ± SD(%)
0	11	16.6 ± 9.2
1	49	18.5 ± 5.7
2	20	21.3 ± 5.8
3	6	28.8 ± 5.1
4	4	17.8 ± 1.2
5	1	20.0
Total	91	19.4 ± 7.0

in a patient at this V_{20} value. In this report [10], 42% of the patients received some form of chemotherapy, and most received concurrent or pre-irradiation chemotherapy with a cisplatin regimen. Then, in 2005, Tsujino et al. reported the significance of V_{20} in CCRT [7]. The incidence and grade of radiation pneumonitis were shown to be significantly related to the V_{20} value and the incidence of radiation pneumonitis differed significantly between V_{20} > 25% and ≤ 25% [7].

The efficacy of ICIs has subsequently been established in cancer treatment, and durvalumab is now used after CCRT. However, ICIs have off-target effects and toxicities, including interstitial pneumonitis. Thus, there may be an increased risk of pneumonitis due to potential overlapping radiation and chemical pneumonitis in CCRT plus durvalumab for NSCLC. However, criteria for DVH parameters have not been established for this procedure.

Biologically, radiation pneumonitis occurs between 3 weeks up to 6 months after radiation exposure [27]. In our study, the median time from the start of therapy to development of pneumonitis was 4.1 months, and compatible to this report. In our study, ≥grade 2 and ≥ grade 3 pneumonitis occurred in 34% and 12% of cases, respectively, which are relatively high compared to previous studies. The incidence of ≥ grade 3 pneumonitis was 4.5% in the PACIFIC trial [2], and the incidences of ≥ grade 2 and ≥ grade 3 pneumonitis were 24% (17/71) and 4.2% (3/71) in the CCRT reported by Tsujino et al. [7]. The reason for the higher incidences in the current study is unclear. Pneumonitis caused by factors other than radiotherapy was also present, including drug induced pneumonitis, and we did not separate this from radiation pneumonitis because it is difficult to distinguish these conditions. However, a certain number of severe pneumonitis that were not dependent on radiotherapy were thought to occur, considering that 5 of the 7 cases of pneumonitis outside the irradiation field was ≥ grade 3, and that the mean V_{20} increased with severity of pneumonitis increased up to grade 3, but V_{20} in grades 4 and 5 was rather low. The incidences of ≥ grade 2 and ≥ grade 3

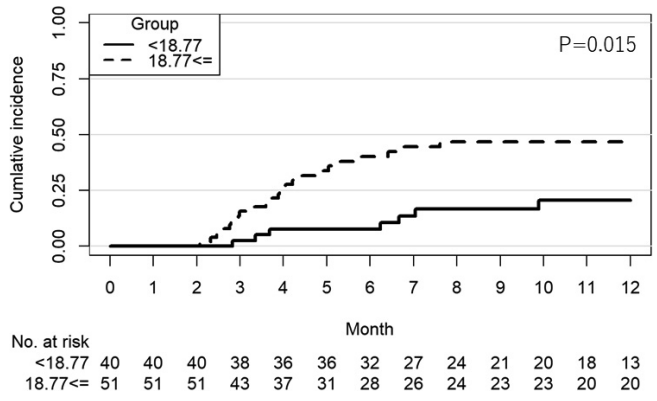

Fig. 1. Cumulative incidence curve for ≥ grade 2 pneumonitis stratified by V_{20}.

in-field pneumonitis were 28% and 6.5%, respectively, which are similar to those found by Tsujino et al. The high general incidence of pneumonitis may have been due to the lack of strictly defined criteria for administration of steroids due to the retrospective multicenter study design.

In our study, V_{20} was the only dosimetry factor that was significantly associated with pneumonitis in multivariable analysis. Since the V_{20} cut-off value was 18.77% for prediction of grade 2 pneumonitis was much lower than previously reported values, we evaluated the sensitivity and specificity for V_{20} values of 20%, 25%, 30%, and 35%. The specificity increased, but sensitivity was reduced as this value increased. This suggests that severe pneumonitis that is not related to radiotherapy occurs with a constant probability. Other previously suggested criteria, including V_{10} of 30% and 35%, and MLD of 10 Gy, 15 Gy, and 18 Gy, were significant

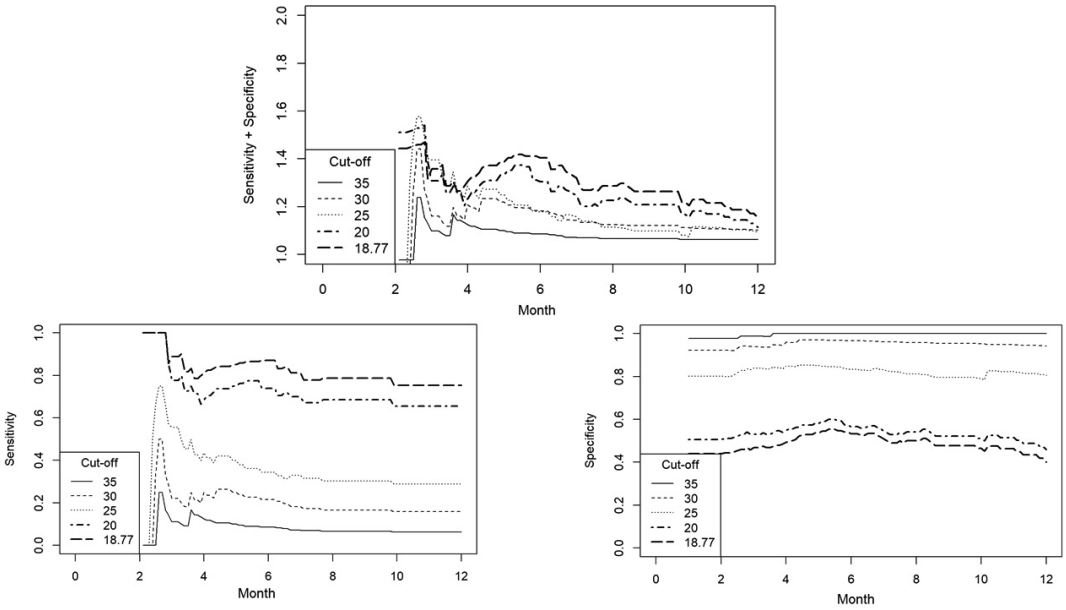

Fig. 2. Sensitivity and specificity for V_{20} = 20%, 25%, 30%, and 35%.

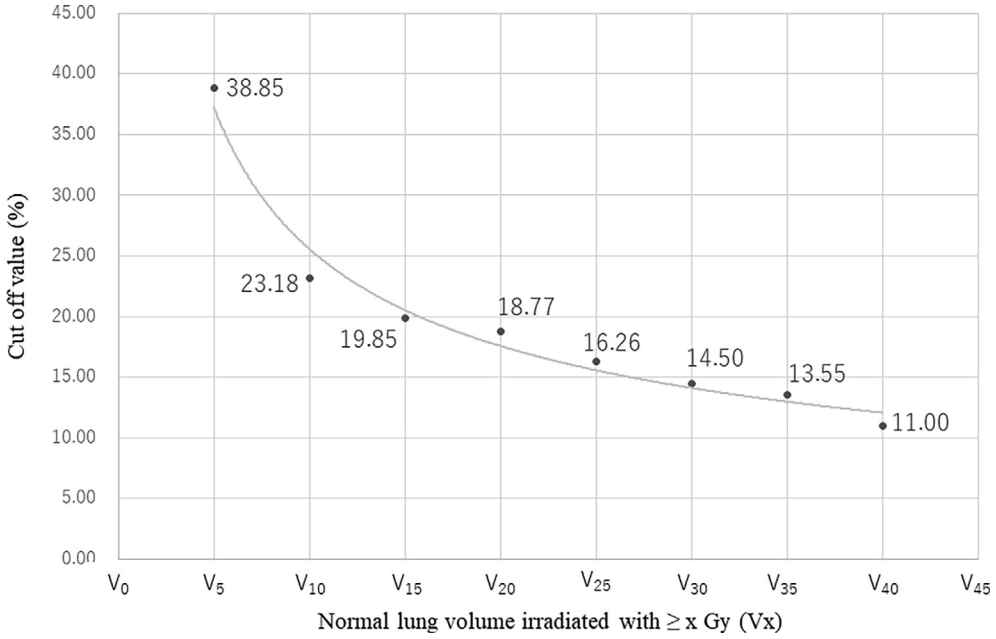

Fig. 3. Cut-off values for Vx (x = 5–40).

factors for pneumonitis in univariate analysis; however, these factors are closely correlated with V_{20}.

There are some limitations of the study, including the retrospective design, short follow up period, and absence of a defined policy to evaluate pneumontis. The severity of pneumonitis was followed by CTCAE, but diagnosed by each pulmonologist or radiation oncologist. Therefore, the classification of grades 2 and 3 pneumonitis may be ambiguous. Also, in clinical practice, it is difficult to keep V_{20} at < 19% for bulky NSCLC. Within these limitations, we conclude that the basic concept of radiotherapy with emphasis on V_{20} is unchanged in CCRT followed by durvalumab, but that an effort to reduce V_{20} with any modality should be made in use of this therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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