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Relationship Between Radiation Pneumonitis Following Definitive Radiotherapy for Non-small Cell Lung Cancer and Isodose Line

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Abstract. *Background/Aim: It is important to identify radiation pneumonitis above Common Terminology Criteria for Adverse Events Grade 2 (G2) in order to safely continue durvalumab maintenance after chemoradiotherapy for advanced lung cancer. The aim of this study was to discover factors that predict pneumonitis above G2. Patients and Methods: A follow-up computed tomography (CT) image was superimposed on the planning CT image using deformable image registration (DIR). The pneumonitis area was contoured on follow-up CT after DIR and the dose-volume histogram parameters of the contoured pneumonitis area were calculated. Results: V5 (Percentage of total volume receiving ≥5 Gy) to V50 of pneumonitis were significantly lower in patients with G2 pneumonitis than in those with G1 pneumonitis. The pneumonitis V15 was the most significant. The group with pneumonitis V15 <87.10% had significantly more G2 pneumonitis than the group with pneumonitis V15 ≥87.10%. Conclusion: Pneumonitis V15 <87.10% was a risk factor for G2 pneumonitis.*

Radiation pneumonitis is a serious adverse event after radiotherapy for lung cancer. V30 (percentage of total volume receiving ≥30 Gy), V20, V5 of lungs and mean lung dose (MLD) have been established as risk factors for radiation pneumonitis development after radiotherapy for lung cancer (1-3).

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In recent years, durvalumab has been used after concurrent chemoradiotherapy (CCRT) as the standard treatment for non-small cell lung cancer. However, data are limited on radiation pneumonitis when combined with immune checkpoint inhibitors (ICI) such as durvalumab (4, 5). It is important to identify radiation pneumonitis above Grade 2 (G2) in order to safely continue durvalumab.

In the simple radiotherapy with two opposed beams, radiation pneumonitis that spreads to the outside of the irradiated field is generally considered to have a poor prognosis (6). At present, multiport three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy are performed as radiotherapy for lung cancer (7), and several risk factors for radiation pneumonitis have been reported (3, 8). However, using modern radiotherapy techniques, the low-dose area is wide; therefore, the spread of pneumonitis out of the irradiated field cannot be used as a prognostic factor for radiation pneumonitis.

Radiotherapy planning is performed using computed tomography (CT) under shallow breathing or four-dimensional computed tomography (4D-CT) (9). On the other hand, CT for diagnosing radiation pneumonitis is performed with deep inspiratory breath hold (10). As the lung volume is different between CT at rest or 4D-CT and CT in the deep inspiratory state, the positions do not match even if the images are superimposed. Therefore, it is not possible to confirm whether the isodose line on treatment planning CT and the area of pneumonitis on diagnostic CT match. However, deformable image registration (DIR) was recently developed and it has become possible to superimpose images of different respiratory phases (11).

The purpose of this study lies in the following two points. The first was to identify the dose applied to the area of radiation pneumonitis by superimposing planning CT and diagnostic CT at the time of appearance of radiation pneumonitis using DIR. The second was to identify risk factors for G2 or higher pneumonitis by investigating

differences in the extent of pneumonitis between severe radiation pneumonitis and mild radiation pneumonitis cases.

Patients and Methods

Patients and design. In this retrospective study, we reviewed the medical records of 42 consecutive patients who received definitive radiotherapy for Non-small cell lung cancer (NSCLC) between August 2018, when durvalumab became available in Japan, and May 2020 at Yokohama City University Medical Center and were followed up for 5 months or longer. All patients had a definitive pathological diagnosis and were stage IIB to IIIC by the UICC TNM classification 8th edition (12). All patients received definitive radiotherapy. Radiotherapy was delivered five days per week, with daily doses ranging from 1.8 to 2.0 Gy. A total irradiation dose ranging from 59.4 to 64.8 Gy (median, 59.4 Gy) was used (13). All patients were treated using 3D-CRT. Of the 42 patients, 37 for whom planning CT and diagnostic CT at the time of the appearance of radiation pneumonitis were able to be collated or for whom it was confirmed that pneumonitis did not develop after radiotherapy were included. Five patients were excluded from the analysis because there was no image after the end of radiotherapy. Pulmonologists decided whether to use concurrent chemotherapy and durvalumab after concurrent chemotherapy. The follow-up time was defined as the first date of radiotherapy to the date of the final confirmation of survival. CT and laboratory tests were performed as pretreatment evaluations for all patients. Evaluations after treatment were performed every 1 to 3 months, and comprised provisional medical history and physical examination, laboratory tests, and CT or positron emission tomography-CT. At each follow-up visit, treatment-related toxicities were assessed and scored according to the National Cancer Institute's common terminology criteria for adverse events version 5.0.

Data collection. The gross tumor volume (GTV) was defined as the primary lesion in the lung and clinically involved lymph nodes, and the clinical target volume (CTV) was defined as the micro-infiltrated area around the primary lesion. Adjacent lymph node areas were not normally included in the CTV. The planning target volume (PTV) was set with an appropriate margin on the CTV and the irradiation field was set with a leaf margin of 7 mm on the PTV. X-rays at 6 to 10 MV were used for treatment. Image-guided radiotherapy using cone-beam CT was performed during daily treatment for all patients. During radiotherapy, all patients were immobilized in a supine position with vacuum immobilizers for simulation and treatment. Planning CT images were obtained using a Lightspeed RT Scanner (GE Healthcare UK) with a 2.5-mm slice thickness under shallow breathing. During the planning of 3D-CRT, contouring of the GTV, CTV, PTV and organs at risk was performed, and external beam fields were planned with 4 to 8 ports at different gantry angles by radiation oncologists. Dose distributions were calculated using the Pinnacle 3 software program (Philips, Amsterdam, Netherlands). No patients received induction chemotherapy. Thirty-two patients received CCRT and 5 patients received radiotherapy alone. Follow-up CT images after radiotherapy were obtained with 5-mm thickness under deep inspiratory breath hold every 1-3 months or when symptoms of pneumonitis were noted. The pneumonitis grade was evaluated at the time of clinical exacerbation. A follow-up 5-mm-thick CT image when pneumonitis was first confirmed was superimposed on the 2.5-mm-thick planning CT image. Then, the superimposed follow-up CT image was complemented and reconstructed at a thickness of 2.5 mm. Images were processed using the Velocity software program (Varian Medical Systems USA) (14). Rigid image registration was performed first and DIR was then performed with the region of interest only in the thoracic cavity (Figure 1). The area with pneumonitis was contoured on imaging CT after DIR and the dose-volume histogram (DVH) parameters of the contoured pneumonitis area were calculated (Figure 2).

Statistical analysis. Fisher's exact test and the Mann–Whitney *U*-test were used to evaluate associations between the pneumonitis grade and examined characteristics. Descriptive statistics were calculated, and logistic regression analysis was used to analyze the relationship between DVH parameters of the contoured pneumonitis area and the grade of pneumonitis. Receiver operating characteristics (ROC) curves were created based on the results of logistic regression analysis and the cutoff value was determined. For all analyses, a two-tailed *p*-value of <0.05 was considered significant. All statistical analyses were performed using the JMP pro version 15.0 software package (SAS Institute, Tokyo, Japan).

Ethical considerations. This retrospective study protocol was approved by Institutional Review Board in Yokohama City University (approval number: B170700047), and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and relevant guidelines and regulations. All patients included in the study provided written informed consent for treatment.

Results

Patients. This study included 27 males and 10 females, with a median age of 71 years. The median observation period was 15 months (range=5-33 months). The median observation period for patients who only underwent durvalumab maintenance was 16 months (range=11-33 months).

Thirty-two patients received CCRT and five received radiotherapy alone. Details of the treatment of 32 patients who underwent CCRT are presented below. Carboplatin and paclitaxel chemotherapy (CP) (15) was administered to 28 patients. Among the 28 patients who received CP, 13 were administered more than 6 courses, 9 were administered 5 courses, and the remaining 6 discontinued after less than 4 courses due to adverse events. Two courses of cisplatin and docetaxel chemotherapy (16) were administered to 1 patient. Daily low-dose carboplatin chemotherapy (low- dose CBDCA) (17) was administered to 3 patients. Of the 3 patients treated using low-dose CBDCA, 2 completed the scheduled 20 doses and 1 was censored after 14 doses. Of the 32 patients who underwent CCRT, 21 received durvalumab maintenance. The other 11 patients were withdrawn at the discretion of the pulmonologist because of a history of interstitial pneumonia, high V20 of the radiotherapy plan (*e.g.* 35% or higher), or the development of pneumonitis before the administration of durvalumab.

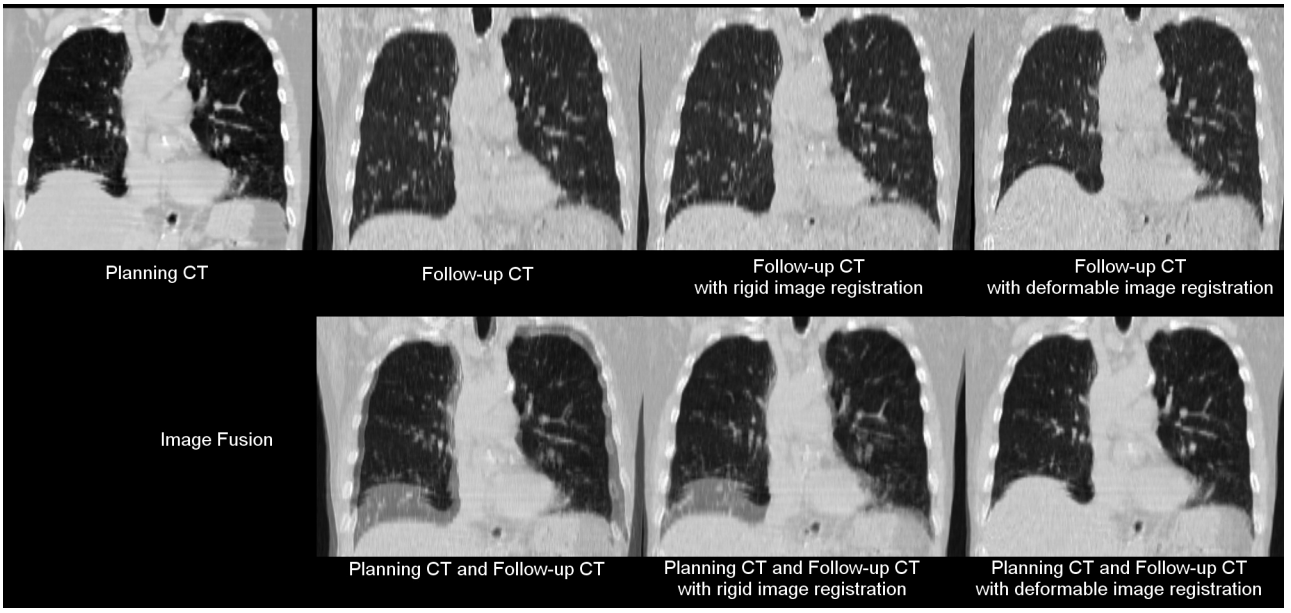

Figure 1. *The procedure for merging follow-up CT with planning CT.*

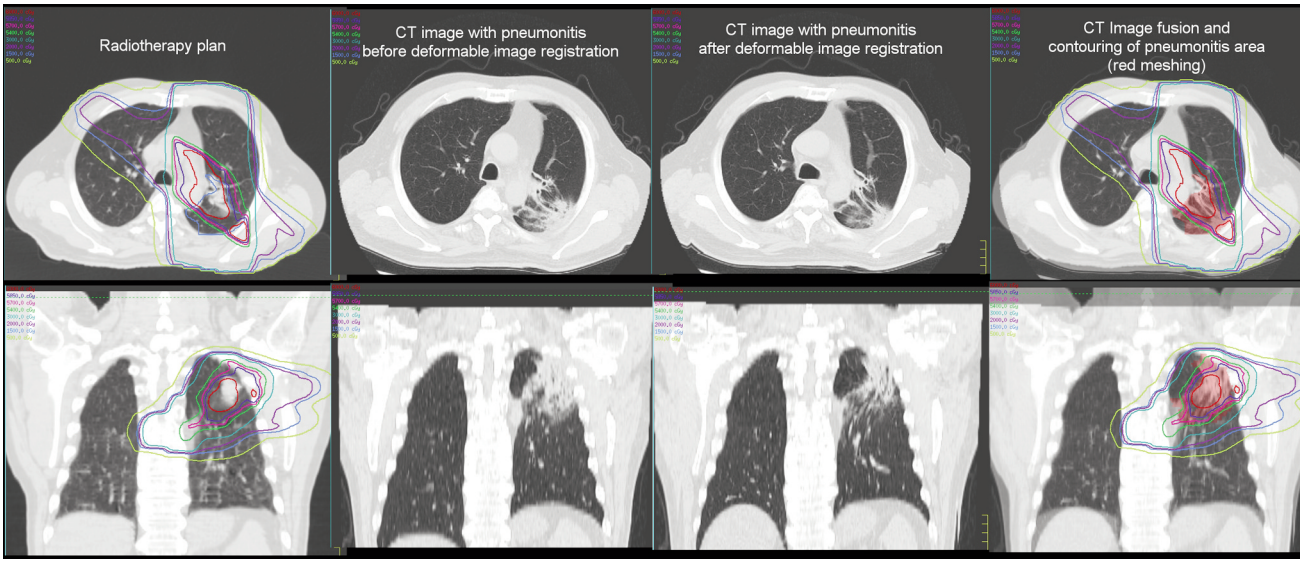

Figure 2. *Radiotherapy plan, CT images with pneumonitis before and after deformable image registration, and contoured pneumonitis area.*

Pneumonitis and DVH parameters. Six patients had G2 pneumonitis, 27 had G1 pneumonitis and four had no confirmed pneumonitis. Eighteen of the 21 patients who underwent durvalumab maintenance after CCRT developed pneumonitis. Four developed pneumonitis before the first dose of durvalumab and 18 developed pneumonitis after the first dose of durvalumab. On the other hand, it was not possible to determine whether the pneumonitis that developed after the first dose of durvalumab was an immune-related adverse event or pure radiation pneumonitis (18). The detailed characteristics of the patients divided into two groups, G2 or higher and G1 or lower, are presented in Table I. The results of laboratory tests are those before the start of radiotherapy. There was no significant difference between the two groups in all of the factors analyzed.

Table I. *Patient characteristics*.

Grade at the time of exacerbation of pneumonitis	Grade 1 or no pneumonitis n=31 (%)	Grade 2 pneumonitis n=6 (%)	*p*-Value
Gender			
Male	21 (67.7)	6 (100)	0.1621
Female	10 (32.3)	0 (0)	
Age (years)			
Mean (range)	69 (51-87)	76 (70-80)	0.0693
Prescription dose (Gy)			
Mean (range)	59.4 (59.4-64.8)	59.4 (59.4-64)	0.8636
Concurrent chemotherapy			
With	28 (90.3)	4 (66.7)	0.1771
Without	3 (9.7)	2 (33.3)	
Durvalumab maintenance			
With	18 (58.1)	3 (50)	1.0000
Without	13 (41.9)	3 (50)	
White blood cells (×1,000/μl)			
Mean (range)	7.0 (3.7-18.5)	9.0 (4.2-12.7)	0.2656
Red blood cells (×10,000/μl)			
Mean (range)	4.05 (2.75-5.04)	4.55 (3.53-5.25)	0.1491
Hemoglobin (g/dl)			
Mean (range)	12.9 (8.5-15.1)	13.6 (11-15.4)	0.0871
Platelet (×1,000/μl)			
Mean (range)	253 (129-664)	336.5 (203-491)	0.0637
C-reactive protein (mg/dl)			
Mean (range)	0.264 (0.015-11.749)	1.3185 (0.294-14.809)	0.0993
Sialylated carbohydrate antigen KL-6 (U/ml)			
Mean (range)	287.5 (137-902)	569.5 (204-1,910)	0.1327
Surfactant protein D (ng/mL)			
Mean (range)	65.7 (17.2-126)	149 (41.6-239)	0.0884
Observation period (months)			
Mean (range)	14 (5-33)	16 (12-19)	

The relationship between the pneumonitis grade and DVH parameters of the lung at the time of treatment planning is shown in Table II. There was no significant difference between the two groups in DVH parameters of the lung.

The relationship between pneumonitis grade and DVH parameters of the pneumonitis area at the time of appearance of pneumonitis is shown in Table III. All DVH parameters of the pneumonitis area were significantly lower in patients with G2 pneumonitis. Therefore, G2 pneumonitis extends beyond each isodose line compared with G1 pneumonitis.

Logistic regression analysis was performed to determine whether G2 pneumonitis can be predicted from the DVH parameters of the pneumonitis area. The odds ratio (OR), 95% confidence interval (CI) of the odds ratio, cutoff value and *p*-value are shown in Table IV. The ROC curve and area under the curve (AUC) of the DVH parameters of the pneumonitis area are shown in Figure 3. Among the DVH parameters of the pneumonitis area analyzed, significant odds ratios were derived except for V20. The AUC at pneumonitis V15 was the largest and significant. Fisher's exact test was performed in two groups, above 87.10% and below 87.10%. The group with V15 <87.10% had significantly more G2 pneumonitis than that with V15 ≥87.10% (OR=130, 95%CI=6.9249892-2,440.437, p=0.0011).

Discussion

There are numerous reports on the risk factors for radiation pneumonitis in many diseases. V5, V20, V30, MLD and PTV volume are considered to be risk factors for the development of radiation pneumonitis after definitive radiotherapy for advanced lung cancer (1, 19-21). In stereotactic body radiotherapy for early-stage lung cancer, V20, V5 and V2.5 are considered to be risk factors for the development of radiation pneumonitis (22). The presence of interstitial pneumonitis on CT images, serum surfactant protein D (SP-D) and serum Krebs von den Lungen-6 (KL-6) are also considered risk factors for radiation pneumonitis (23, 24). An increasing central lung distance and MLD are considered to be risk factors for the development of radiation pneumonitis in postoperative irradiation of breast cancer (25, 26). For definitive radiotherapy for esophageal cancer, V20, MLD and

Table II. *The pneumonitis grade and the DVH parameters of the lung at the time of treatment planning*.

	Grade 1 or no pneumonitis n=31	Grade 2 pneumonitis n=6	*p*-Value
Lung V20 (%)			
Mean (range)	28.57 (7.80-37.37)	24.04 (16.10-32.15)	0.9671
Lung V10 (%)			
Mean (range)	38.58 (10.37-62.88)	41.15 (25.96-54.42)	0.4583
Lung V5 (%)			
Mean (range)	47.76 (13.96-78.88)	51.97 (36.00-71.70)	0.3647
Lung mean dose (cGy)			
Mean (range)	1,575.4 (479.7-2,042.3)	1,460.5 (1,050.2-1,825.6)	0.8047

DVH: Dose-volume histogram; Vxx: Percentage of total volume receiving ≥xx Gy.

Table III. *The pneumonitis grade and the DVH parameters of the pneumonitis area*.

	Grade 1 or no pneumonitis n=31	Grade 2 pneumonitis n=6	*p*-Value
Pneumonitis V50 (%)			
Mean (range)	72.04 (12.12-97.25)	25.96 (13.75-54.32)	0.0051
Pneumonitis V40 (%)			
Mean (range)	86.08 (44.15-100.00)	39.45 (25.79-62.85)	0.0006
Pneumonitis V30 (%)			
Mean (range)	91.69 (59.58-100.00)	45.18 (30.83-71.74)	0.0002
Pneumonitis V20 (%)			
Mean (range)	96.66 (78.98-100.00)	54.17 (38.22-80.03)	0.0002
Pneumonitis V15 (%)			
Mean (range)	98.48 (82.11-100.00)	62.21 (45.08-87.10)	0.0002
Pneumonitis V10 (%)			
Mean (range)	99.94 (82.43-100.00)	70.00 (52.74-92.31)	0.0002
Pneumonitis V5 (%)			
Mean (range)	100.00 (83.27-100.00)	85.21 (65.32-96.87)	0.0001
Pneumonitis mean dose (cGy)			
Mean (range)	5,162.5 (1,367.4-5,950.0)	2,927.3 (2,065.3-4,238.8)	0.0011

DVH: Dose-volume histogram; Vxx: Percentage of total volume receiving ≥xx Gy.

Table IV. *Logistic regression analysis of DVH parameters of the pneumonitis area and the pneumonitis grade*.

	Odds ratio	95% Confidence interval			Cut-off value	*p*-Value
Pneumonitis V50	0.000916	3.08E-06	-	0.272377	33.15%	0.0161
Pneumonitis V40	0.000002597	1.32E-10	-	0.050946	62.85%	0.0108
Pneumonitis V30	1.477E-08	1.90E-15	-	0.114771	71.74%	0.0259
Pneumonitis V20	1.43E-32	0	-	1.43E+24	80.03%	0.265
Pneumonitis V15	1.243E-09	2.41E-18	-	0.641389	87.10%	0.0451
Pneumonitis V10	2.33E-13	1.52E-23	-	0.003575	92.31%	0.0151
Pneumonitis V5	2.17E-14	7.26E-24	-	6.46E-05	96.87%	0.0047
Pneumonitis mean dose	0.998493	0.998493	-	0.999595	4,238.8 cGy	0.0073

DVH: Dose-volume histogram; Vxx: Percentage of total volume receiving ≥xx Gy.

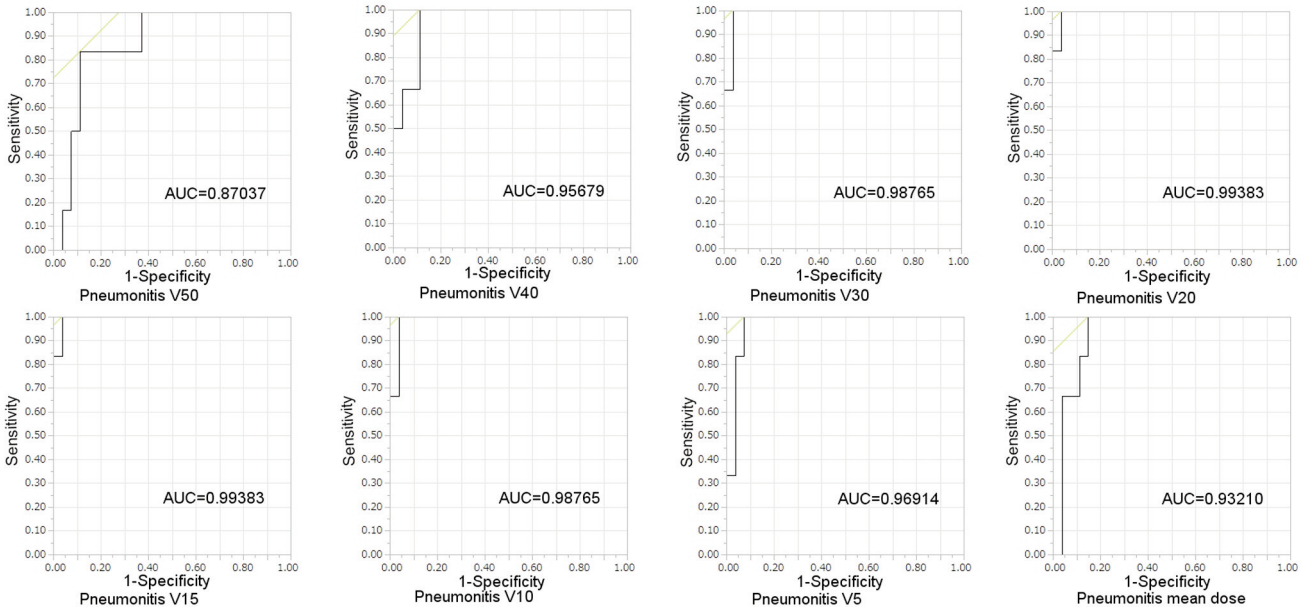

Figure 3. *Receiver operating characteristics curve and area under the curve of the DVH parameters of the pneumonitis area.*

PTV volume are considered risk factors for the development of radiation pneumonitis (27). However, these are all risk factors related to DVH parameters at the time of treatment planning for the development of radiation pneumonitis.

There is limited evidence that radiation pneumonitis protruding from the irradiated field (edge of the irradiated field) becomes more severe in the case of tangential irradiation of breast cancer or two opposite irradiation fields for lung cancer (6, 28). However, the edge of the irradiated field is not defined by the isodose line. The irradiated field was previously defined as V5 (2, 5). This definition is not generally accepted as a risk factor for radiation pneumonitis because the low-dose area of the lung (V5) and intermediate-dose area (V20) are related, and attempts to reduce the V5 may lead to an inability to reduce the V20 using modern radiotherapy techniques (7). There are few reports on the relationship between the area where radiation pneumonitis developed and the dose irradiated (29). As these previous studies did not use the deformable registration of diagnostic CT, the collation accuracy between the isodose line or irradiation field and the area where pneumonitis developed is expected to be inferior. One previous study investigated the relationship between the definition inside and outside the irradiated field and the DVH parameters in animal experiments, but no clear results were obtained (30).

In this study, G2 radiation pneumonitis had smaller DVH parameters, such as V15 and V20, than G1 radiation pneumonitis in the area where pneumonitis developed. In addition, the predictive ability of V15 for G2 radiation pneumonitis was less than 87.10%. Thus, "G2 radiation pneumonitis occurs when 12.90% or more of the pneumonitis spreads outside the 15-Gy isodose line. Although the definition of the irradiated field at the time of multiport irradiation in radiotherapy for lung cancer has not been established, we propose that the "irradiated field=the 15-Gy isodose line" based on this study. As durvalumab maintenance has been established as standard treatment and its continued use is not permitted for pneumonitis of G2 or higher, it is important to distinguish pneumonitis of G2 or higher using imaging findings.

Combined therapy with ICI and radiotherapy has been used in recent years, but data are limited. One study of combination of chest radiotherapy and ICI for melanoma revealed that the combination of ICI is more likely to cause pneumonitis with less V20 (5). The combination of radiotherapy and ICI for lung cancer does not significantly increase pneumonitis during durvalumab maintenance, but the details of the irradiation method and the definition of the irradiated field have not been clarified (4). Radiation recall pneumonitis was reported after the sequential use of ICI and resulted in death in cases that spread outside the irradiation field (31), but the details of the irradiation method and the definition of the irradiated field are unknown. In our study, durvalumab maintenance was not a significant risk factor for the development of G2 radiation pneumonitis and there was no death due to radiation pneumonitis.

Patients with high levels of biomarkers (KL-6 and SP-D) are more likely to develop severe radiation pneumonitis (22,

24). In our study, KL-6 was not a significant risk factor for G2 radiation pneumonitis. SP-D was a significant risk factor for G2 pneumonitis, but its OR was 1.027857; therefore, it was considered to be of low clinical significance.

To the best of our knowledge, this is the first study to investigate the relationship between radiation pneumonitis and DVH parameters of the pneumonitis area after definitive radiotherapy for stage IIB to IIIC lung cancer using DIR. The strength point derived from our results is that it is possible to easily determine whether radiation pneumonitis worsens to G2 by comparing the pneumonitis area with the isodose line. However, our approach has certain limitations. First, this was a small single-center retrospective study with a short observation period. Second, combination therapies other than radiation therapy varied among patients. Third, the DIR algorithm remains incomplete (32). Fourth, the blurred contours of pneumonitis in the process of DIR and reconstruction of imaging CT may have affected the accuracy of contouring. Additional studies, such as interventional clinical trials, are necessary for conclusive results.

Conclusion

This study was conducted to establish a means of discriminating pneumonitis above G2 using imaging findings. G2 radiation pneumonitis had smaller DVH parameters, such as V15 and V20, than G1 radiation pneumonitis. In these parameters, V15 of pneumonitis <87.10% was the most significant risk factor for G2 pneumonitis. The 15-Gy isodose line may serve as a definition of the irradiated field that predicts the risk of pneumonitis on multiport 3D-CRT.

Conflicts of Interest

The Authors report no conflicts of interest related to this study.

Authors' Contributions

S.W designed the study. S.W and D.S collected and analyzed the data. S.W wrote the manuscript with support from I.O, and M.H., I.O and M.H supervised the study. All Authors discussed the results and contributed to the final manuscript.

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