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Original Article

Dose-Volume Parameters Predict Radiation Pneumonitis after Surgery with Induction Concurrent Chemoradiotherapy for Non-small Cell Lung Cancer

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To clarify the relationship between dose-volume histogram (DVH) parameters and radiation pneumonitis (RP) after surgery in cases of non-small cell lung cancer (NSCLC) treated with induction concurrent chemoradiotherapy (CCRT). Patients with NSCLC treated with induction CCRT (chemotherapy: cisplatin and docetaxel; radiotherapy: 2.0 Gy fractions once daily for a total of 46 Gy) before surgery were reviewed. We calculated the percentage of lung volume receiving at least 20 Gy (V20) and the mean lung dose (MLD) for the total lung volume and the lung remaining after resection. Factors affecting the incidence of RP at grade 2 or higher (≥ G2 RP) were analyzed. Eighteen of 49 patients (37%) experienced ≥ G2 RP. The V20 and MLD for the lung remaining after resection (V20r and MLDr) were significant predictors according to the multivariate analysis ($p = 0.007$ and 0.041, respectively). The incidence of ≥ G2 RP was 8% in patients with V20r < 10%, and 13% in patients with MLDr < 5.6 Gy, respectively. The optimal approach to reduce the rate of postoperative RP in patients with induction CCRT for NSCLC is to keep the V20r below 10% and/or the MLDr below 5.6 Gy in the radiotherapy planning.

Key words: radiation pneumonitis, V20, mean lung dose, induction chemoradiotherapy, non-small cell lung cancer

The therapy for locally advanced non-small-cell lung cancer (NSCLC) remains controversial [1-7]. Definitive chemoradiotherapy (CRT) is considered a standard therapy in the curative management of the disease, and concurrent administration of taxanes with radiotherapy (RT) has shown good results [8,9]. However, inadequate local control outcomes have led to various treatment strategies that incorporate surgical resection [1]. Meta-analyses of individual participant data regarding preoperative chemotherapy have shown improved survival for patients with mainly stage IB-IIIA NSCLC [10]. In addition, some attempts at incorporating radiotherapy into the induction program have

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been made. In INT0139, a phase III randomized controlled trial compared the concurrent CRT (CCRT) followed by surgery with definitive CCRT in patients with stage III NSCLC, and found that OS was not significantly improved in patients who underwent trimodal treatment. In an exploratory analysis, in comparison to patients who received definitive CCRT, OS was improved for patients who underwent lobectomy, but not pneumonectomy [7]. Toyooka *et al*. showed that the 3-year and 5-year OS of patients who underwent induction CCRT were significantly higher than those of patients who underwent induction chemotherapy [6]. In the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: version 3.2018 <https://www.nccn.org/professionals/physician_gls/pdf/nscl_blocks.pdf>(accessed April, 208), induction CCRT is recommended for resectable superior sulcus tumors and is an option for patients with resectable stage IIIA tumors (minimal N2 and treatable with lobectomy).

Symptomatic radiation pneumonitis (RP) is a clinically important toxicity in patients undergoing CRT for NSCLC [11]. Several previous studies have reported correlations between radiation dose-volume histogram (DVH) parameters and pneumonitis [11-13]. The percentage of lung volume receiving at least 20 Gy (V20) and mean lung dose (MLD) are frequently associated with pneumonitis and are the most commonly used DVH parameters in clinical practice. Recently, Takahashi *et al.* published the first report to examine the relationship between RP and DVH parameters in patients with NSCLC undergoing induction CRT [14]. The V20 values of the lung remaining after resection (V20r) and lobectomy were significant factors according to a univariate analysis, but no factor was found to be significant based on multivariate analysis. In addition, there were some problems in their report. For example, the regimen of chemotherapy was not unified. Chemotherapy is a risk factor for RP [11], and therefore the variation in the chemotherapy regimen may have influenced the results of their analysis. In addition, their study included some patients who experienced RP before surgery. Because V20r is determined by the results of surgery, V20r cannot be a predictor of preoperative RP.

In the present study, we investigated the predictors of RP after surgery with induction CCRT for NSCLC patients. We selected the patients who received the same chemotherapy regimen and who had an onset of RP only after surgery.

Materials and Methods

Patients. Data on 84 NSCLC patients who received induction CCRT at Okayama University Hospital between January 2003 and December 2011 were reviewed. NSCLC was confirmed histologically before treatment. Induction CCRT was given for patients with potentially resectable N2/3 or bulky N1 tumors. Eligible patients were required to be treated with RT with a total dose of 46 Gy in 23 fractions, chemotherapy using cisplatin/docetaxel administered concurrently with RT, and the surgery conducted following induction CCRT. Patients who had an onset of pneumonia or pneumonitis before surgery were excluded. This retrospective study complied with the Declaration of Helsinki 1989 recommendations. Patients who received induction CCRT provided consent to participate in the study through an opt-out methodology, by displaying a notice in the outpatient ward and on the website. The institutional review board of Okayama University approved this study (approval number 2214).

Treatment. The staging workup included a physical examination, chest X-ray, CT scan of the chest and abdomen, MRI scan of the brain, and a bone scan or positron emission tomography integrated with a fluorodeoxyglucose-computed tomography scan. The RT treatment planning was based on 2-10 mm thick, and 2-10 mm-interval CT scans obtained in the supine position with both arms up, breathing freely. RT targets were defined according to the International Commission on Radiation Units and Measurements Report Numbers 50 and 62. The gross tumor volume (GTV) included the primary tumors and clinically diagnosed metastatic lymph nodes. The clinical target volume (CTV) included the GTV with a 5-10 mm margin and uninvolved subcarinal and ipsilateral hilar lymph nodes. The planning target volume (PTV) included the clinical target volume with a 5-10 mm margin, with consideration for the internal and setup margin. All patients underwent 3D treatment planning using computer software (Xio version 4.8.0, Elekta, Sweden) with a superposition dose calculation algorithm for heterogeneity correction. RT was delivered using a linear accelerator (Mevatron KD2, Canon, Japan) with a 10-MV photon beam and with conven-

tional fractionation. Generally, the prescribed dose to the isocenter or reference point in the PTV was 46 Gy at 2-Gy fractions once daily, 5 days/week. The beam arrangements were typically 2 opposed anterior-posterior fields followed by off-cord oblique fields. Chemotherapy was given concurrently with RT as the initial treatment. The chemotherapy regimen was cisplatin/docetaxel. Surgery was conducted about one month after completion of RT. Consolidation chemotherapy was not executed.

Evaluation. The lungs were considered together as a single-paired organ. Lung contours were obtained automatically by the CT threshold, the trachea and bronchi were excluded manually, and the GTV within the lung was also excluded. As DVH parameters, V20 and MLD were calculated from the total lung volume and the lung volume remaining after resection (V20r and MLDr). The terms "V20r" and "MLDr" were adapted from Takahahi's article [14]. Portions of the lung resected at the initial surgery were determined according to the surgical records.

After treatment completion, patients were followed-up every 1-2 months on an outpatient basis while the patient's general status was stable. The RP was graded according to the Common Terminology Criteria for Adverse Events, version 4.0. The association between grade 2 or higher RP (≥G2 RP) and DVH parameters was analyzed. Univariate analyses by Fisher's exact test and a multivariate analysis by the Cox proportional hazards model were performed using R software, version 3.2.0 (R Foundation for Statistical Computing) to assess patient- and treatment-related factors in addition to DVH parameters. We used the median cut-off value in order to convert continuous parameters into binomial parameters before executing Fisher's exact test. A p value of less than 0.05 was considered significant. The cumulative incidence rate of RP was presented as a Kaplan-Meier curve with stratification of significant factors in the multivariate analysis.

Results

Forty-nine patients were examined in this study. The patient characteristics are shown in Table 1. The clinical stage according to the 7th edition of the Union for International Cancer Control TNM classification

Table 1 Patient characteristics

			%
Age (year)	Median (range)	60 (46–79)	–
Gender	Male	34	69
	Female	15	31
ECOG-PS	0	30	61
	1	19	39
Smoking history (pack-year)[a]	Median (range)	41 (0–135)	–
Lobe	Upper	30	61
	Middle	4	8
	Lower	15	31
Histology	Adenocarcinoma	24	49
	Squamous cell carcinoma	17	35
	Non-small cell carcinoma	8	16
c-stage	IIA	2	4
	IIB	3	6
	IIIA	26	53
	IIIB	18	37
FEV1 (L)[a]	Median (range)	2.5 (1.4–3.9)	–
Period from completion of RT to surgery (weeks)	Median (range)	5 (3–9)	–
Surgery	Pneumonectomy	5	10
	Bilobectomy	7	14
	Lobectomy	37	76

ECOG-PS, Eastern Cooperative Oncology Group-Performance Status; FEV1, forced expiratory volume in 1 sec; RT, radiotherapy.
[a]These factors have missing values.

was IIA in 2 patients, IIB in 3 patients, IIIA in 26 patients and IIIB in 18 patients. All of the 49 patients were pathologically diagnosed before surgery; 24 had adenocarcinoma, 17 had squamous cell carcinoma and the remaining 8 had non-small cell lung carcinoma. The median baseline forced expiratory volume in 1 second was 2.5 l (range: 1.4-3.9). All the patients received induction CCRT with a dose of 46 Gy. The median interval to surgery was 5 weeks (range: 3-9 weeks). A lobectomy was performed in 37 patients, a bilobectomy in 7 patients and a pneumonectomy in 5 patients.

The median follow-up period was 28.9 months (range: 2.7-108.3). RP developed in the study patients as follows: grade 0 in 16 patients, grade 1 in 15, grade 2 in 17, and grade 3 in 1 patient. Eighteen (37%) patients experienced ≥G2 RP. The median period from completion of RT to the onset of ≥G2 RP was 8.1 weeks (range: 4.6-18.6 weeks). The cumulative incidence rate of ≥G2 RP is presented as a Kaplan-Meier curve (Fig. 1). The rate at 6 months was 37% (32-49%, 95% confidential interval). The results of univariate or multivariate analyses of factors associated with ≥G2 RP are shown in Table 2. A V20≥23% and V20r≥10% were found to be statistically significant factors in the univariate analyses ($p=0.016$ and 0.0002, respectively). An MLD≥10.8 Gy and MLDr≥5.6 Gy were also found to be significant factors in the univariate analysis ($p=0.002$ and 0.009, respectively). Patient age, smoking history, gender, and tumor location, which were associated with a risk of developing RP after CRT in the previous report [15], did not make a significant contribution to the development of≥G2 RP in our study. V20r and MLDr were also significant factors in the multivariate analysis ($p=0.007$ and 0.041, respectively). With stratification for V20r and MLDr, the cumulative incidence rate of ≥G2 RP is presented as a Kaplan-Meier curve (Fig. 2A, 2B). The rates at 6 months were 8% and 62% in patients with V20r<10% and≥10%, respectively, and 13% and 60% in patients with MLDr<5.6 Gy and≥5.6 Gy, respectively.

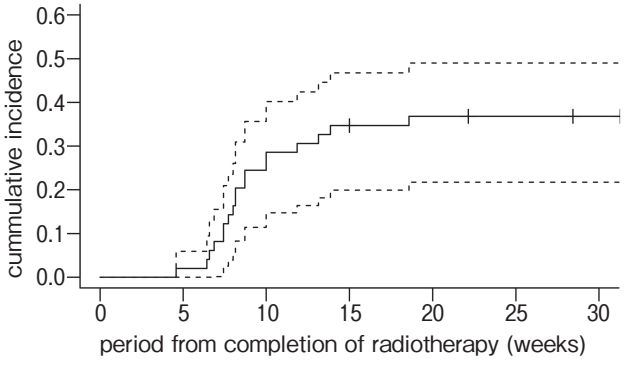

Fig. 1 Cumulative incidence rate of radiation pneumonitis at grade 2 or higher after completion of radiotherapy. The broken lines indicate 95% confidential intervals.

Discussion

In the treatment of NSCLC, RP often occurs after surgery with induction CRT [7, 14, 16]. The DVH parameters, such as V20 and MLD, are useful predictors of RP in the definitive RT with or without chemotherapy [11-13, 15, 17-21]. Graham *et al.* reported that V20 was the only single independent predictor of RP in their patients undergoing definitive RT [17]. In their report, when the V20 was less than 22%, there was no pneumonitis, and when the V20 was 22-31% there was an 8% chance of developing grade 2 pneumonitis, but no higher severity. Tsujino *et al.* showed that V20 was the only factor associated with ≥G2 RP after CCRT [13]. The 6-month cumulative incidence of ≥G2 RP was 14% in their patients with V20 ≤25% and 63% in those with V20 ≥26%. Palma *et al.* reported that the rate of RP was 18.6% in patients with V20<20% in their meta-analysis [11]. According to these researchers, the incidence of fatal pneumonitis was 2.9% and 3.5% in patients with V20 30-40% and≥40%, respectively. Some authors have reported observing a relationship between MLD and RP after definitive radiotherapy with or without chemotherapy [11, 13, 15, 18, 21]. Barriger *et al.* reported that 2.2% of patients with MLD<18 Gy had ≥G2 RP compared to 19% of patients with MLD>18 Gy [13]. As the result of a recursive partitioning analysis, Palma *et al.* showed that the rates of RP in patients aged≤65 years and treated with carboplatin/paclitaxel chemotherapy were 0-9% and 41-48% in those with MLD<10 Gy and≥10 Gy, respectively [11]. In our study, the cumulative rates of ≥G2 RP at 6 months were 8% and 62% in patients with V20r<10% and≥10%, respectively. In patients with MLDr<5.6 Gy and≥5.6 Gy, the rates were 13% and 60%, respectively. These cut-off values were lower than those of previous studies on definitive CRT.

Recently, Takahashi *et al.* issued the first report to examine the relationship between radiation pneumonitis and DVH parameters in patients with NSCLC with

Table 2 Univariate and multivariate analyses of factors associated with radiation pneumonitis at grade 2 or higher

Factor		n	Univariate *p*-value	Odds ratio (95% CI)	Multivariate *p*-value
Age (year)	<60	9/26	0.775	-	NE
	≥60	9/23			
Gender	Male	13/34	1.000	-	NE
	Female	5/15			
ECOG-PS	0	10/30	0.559	-	NE
	1	8/19			
Smoking history	<41	10/23	0.542	-	NE
(pack-year)[a]	≥41	7/23			
Lower lobe		9/15	0.051	-	NE
Upper/Middle lobe		9/34			
Lobectomy		11/37	0.094	-	NE
Bilobectomy/Pneumonectomy		7/12			
FEV 1 (L)[a]	<2.5	7/21	0.759	-	NE
	≥2.5	10/24			
Total lung	<3,171	10/24	0.561	-	NE
Volume (ml)	≥3,171	8/25			
V20 (%)	<23	5/25	0.016	5.34	0.351
	≥23	13/24		(1.27-27.74)	
MLD (Gy)	<10.8	3/23	0.002	8.65	0.107
	≥10.8	15/26		(1.88-56.90)	
Total lung volume	<2,429	10/24	0.561	-	NE
Remaining after resection (ml)	≥2,429	8/25			
V20r (%)	<10	2/23	0.0002	15.73	0.007
	≥10	16/26		(2.86-167.11)	
MLDr (Gy)	<5.6	3/24	0.0009	9.94	0.041
	≥5.6	15/25		(2.14-66.08)	

CI, confidence interval; NE, not entered; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; FEV 1, forced expiratory volume in 1 sec; MLD, mean lung dose of the total lung; MLDr, mean lung dose of the lung remaining after resection; V20, percentage of the total lung volume receiving at least 20 Gy; V20r, percentage of the lung volume remaining after resection receiving at least 20 Gy.
[a]These factors have missing values.

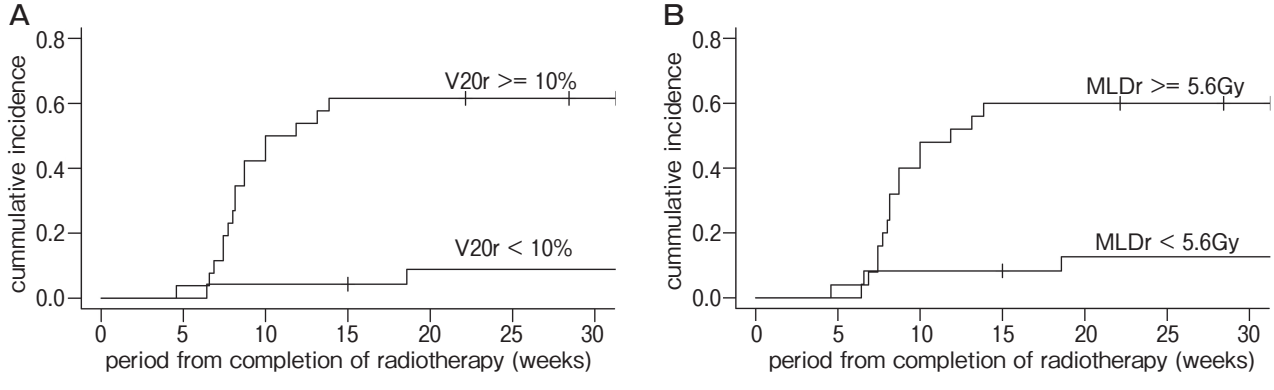

Fig. 2 **A**, Cumulative incidence rate of radiation pneumonitis at grade 2 or higher after completion of radiotherapy, stratified according to the percentage of the lung volume remaining after resection receiving at least 20 Gy (V20r); **B**, Cumulative incidence rate of radiation pneumonitis at grade 2 or higher after completion of radiotherapy, stratified according to the mean lung dose of the lung remaining after resection (MLDr).

induction CCRT [14]. In their report, the rates of ≥G2 RP were 22% and 55% in patients with V20r≤11% and≥12%, respectively. A V20r≥12% and lobectomy were significant factors in the univariate analysis, but these factors were not found to be significant in the multivariate analysis. The MLD was not a significant factor even in the univariate analysis. We have shown that the risk of ≥G2 RP is significantly higher when V20r≥10% and/or MLDr≥5.6 Gy in univariate and multivariate analyses.

Palma *et al*. found that the predictors of radiation pneumonitis were V20 (odds ratio [OR] 1.03) and chemotherapy regimen (OR for carboplatin/paclitaxel 3.33, relative to cisplatin/etoposide) on multivariate analysis [11]. Barriger *et al*. reported that consolidation chemotherapy with docetaxel after CCRT was a predictive factor for RP [13]. These reports suggest that the use of taxane agents is a risk factor for RP. Whereas the chemotherapy regimen was cisplatin/docetaxel in all patients in our study, the regimens of Takahashi's study were various, including regimens without taxane. The difference in chemotherapy regimens may account for the different results between their study and ours. In addition, ≥G2 RP occurred preoperatively in 9 out of 16 patients with ≥G2 RP in Takahashi's report [14]. RP typically occurs within radiation fields, and thus RP that occurred preoperatively would be expected to locate mostly within the lung around the tumor, which would be resected thereafter. We think that in the case of preoperative RP patients, it is appropriate to investigate the risk of RP in relation to the V20 or MLD from the total lung volume, including the volume of the later resected parts, as in other studies concerning definitive RT. Because the risk factors of RP may be different between preoperative and postoperative cases, to lump both cases together might lead to unreliable results.

Takahashi *et al*. reported that a lobectomy was another significant factor compared to a bilobectomy/pneumonectomy in a univariate analysis [14], but in our study, it was not a significant factor. In their report, the incidence of RP was 40% in those with a lobectomy and 14% in those with a bilobectomy/pneumonectomy, whereas in our report, the incidence was 30% and 58%, respectively. Because patients with preoperative RP were included in their study, this may account for the difference. In an exploratory analysis of INT0139, OS was improved for patients who underwent lobectomy after induction CRT versus definitive CRT [7]. From the point of view of not only treatment prognosis but also adverse events, induction CRT should be indicated in cases treatable with lobectomy.

Some authors have reported that the rate of ≥G2 RP was 7-35% in patients with definitive CRT [12,13,21]. In our study, although the total radiation dose was no more than 46 Gy and much of the lung exposed to a relatively high radiation dose was resected, the rate of RP was 36% and higher than those in previous reports. Sugiura *et al*. reported that 4.8% of patients who were histologically diagnosed with usual interstitial pneumonia experienced postoperative acute exacerbation [22]. In the INT0139 trial, 6% of patients who underwent surgery after induction CRT died of acute respiratory distress syndrome and other types of respiratory failure [7]. In addition to chemotherapy including taxane agents, surgical invasion may account for the relatively high rate of RP in our study.

Acute RP most commonly manifests in the first 6 months after RT completion [15]. The median period before onset of RP after definite radiotherapy was reported to be 41 days [19] or 2.7 months [20]. In our study, the period after induction CRT was 8.1 weeks, which is almost the same as in the above reports but longer than the 5.5 weeks reported in Takahashi's study [14]. Excluding patients with preoperative RP in our study may account for this difference.

To the best of our knowledge, ours is the first study to indicate that V20r and MLDr are significant predictors of RP after surgery with induction CCRT for NSCLC. However, our study has certain limitations. This was a retrospective study and the diagnosis of RP was somewhat uncertain. We determined the diagnostic criteria of RP before reviewing patient records, but grading of RP was sometimes confusing because it was based on past medical records. Kocak *et al*. reported that scoring of radiation pneumonitis was difficult in 28% of patients treated for lung cancer owing to confounding medical conditions [23]. The uncertainty in grading RP might also have had some influence over the results of our analysis.

In conclusion, we found that V20r and MLDr were the predictors of ≥G2 RP after surgery with induction CCRT for our NSCLC patients. Therefore, to reduce the rate of RP after surgery, it is important to consider V20r and MLDr in the planning of radiotherapy. Newer technologies, such as intensity modulated radiation therapy, may make it easier to keep V20r and

MLDr as low as possible without sacrificing the tumor control and increasing adverse events other than RP after surgery

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