



## Original Article

# Dosimetric predictors for postoperative pulmonary complications in esophageal cancer following neoadjuvant chemoradiotherapy and surgery



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## ABSTRACT

**Background and purpose:** In locally advanced esophageal cancer, the optimal dose constraints for neoadjuvant chemoradiotherapy (NACRT) have yet to be established. This study is carried out to identify the most reliable dosimetric predictors for pulmonary complications following NACRT and surgery for esophageal cancer.

**Materials and methods:** We retrospectively reviewed the medical records of 308 patients with esophageal cancer who received surgery following NACRT for locally advanced esophageal cancer from January 2005 to June 2017. Dose–volume histograms (DVH) of both lungs were computed for each patient along with total lung volume, mean lung dose (MLD),  $V_5$ ,  $V_{10}$ ,  $V_{20}$ , and  $V_{30}$ . The effect of each parameter on postoperative pulmonary complications was estimated in univariate and multivariate logistic regression analysis.

**Results:** Postoperative pulmonary complications occurred in 22.1% of all patients. Univariate analysis for pulmonary complications showed that location of tumor ( $P = 0.017$ ), pre-RT FEV1 ( $P = 0.003$ ), MLD ( $P = 0.002$ ),  $V_5$  ( $P < 0.001$ ),  $V_{10}$  ( $P < 0.001$ ), and  $V_{20}$  ( $P = 0.007$ ) were all significant risk factors. Significant factors for postoperative pulmonary complications in multivariate analysis were MLD (odds ratio (OR) 1.118, 95% confidence interval (CI) 1.025–1.219,  $P = 0.012$ ) and pre-RT FEV1 (OR 0.483, 95% CI 0.294–0.795,  $P = 0.004$ ).

**Conclusions:** In patients who received NACRT and surgery for esophageal cancer, MLD was the parameter most related to postoperative pulmonary complications. Further studies are needed to establish the optimal DVH constraints for NACRT in order to minimize the risk of postoperative pulmonary complications in esophageal cancer patients.

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Surgical resection is the mainstay treatment for resectable esophageal cancer. Following esophagectomy alone, postoperative morbidities and mortalities are reported to be 42–50% and 2.8–4.3%, respectively [1–4]. The most common postoperative complications include anastomotic leakage, wound complication, and pulmonary complication [1,5,6]. Among them, pulmonary

complications are reported to occur in 13–38% of patients following esophagectomy and are associated with poor survival [1,7–9].

Neoadjuvant chemoradiotherapy (NACRT) prior to esophagectomy improves loco-regional control and survival outcomes in locally advanced esophageal cancer [10–12]. However, the possible increased risk of postoperative pulmonary complications by adding NACRT is a major concern for surgeons. Although several studies have suggested that NACRT is not related to increased postoperative complications, other studies have shown that patients who received NACRT have higher postoperative mortalities than those treated with surgery alone [13,14]. A recent study suggested that NACRT does not increase the incidence, but rather the severity of postoperative complications [15]. The reported rates of postopera-

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tive pulmonary complications following NACRT and surgery are 33–46%, which seem to be slightly higher than those in surgery alone cases, reported at 13–38% [10,16,17].

Recently, intensity modulated radiation therapy (IMRT) enabled the application of NACRT to extensive esophageal cancer, which could not have been treated with three-dimensional conformal RT (3D-CRT) [18]. On the other hand, the growing use of IMRT has raised concerns about low dose irradiation of lungs [19]. Currently, as optimal lung dose constraints for esophageal cancer treatment have yet to be established, the constraint guidelines for esophageal cancer treatment are usually derived from lung cancer studies. The endpoints of lung toxicities in these lung cancer studies are usually symptomatic radiation pneumonitis (RP) [20]. Namely, the relationship between lung DVH parameters and postoperative pulmonary complications has yet to be clarified.

This study is carried out in order to determine the most relevant dosimetric predictors of postoperative pulmonary complications in patients who received NACRT and surgery for locally advanced esophageal cancer.

## Materials and methods

Following approval by our institutional review board (IRB No. 2016-01-042-002), we retrospectively reviewed the medical records of 308 patients with esophageal cancer who received surgery following NACRT for locally advanced esophageal cancer from January 2005 to June 2017. We excluded patients who received surgery with a palliative aim ( $N = 3$ ) or those with unavailable DVH information ( $N = 46$ ).

### Treatment

All patients underwent computed tomography (CT) simulation. During the early period of the current study, 3D-CRT was mainly used with three- or four-field techniques. IMRT was used in later part of this study using step-and-shoot techniques ( $N = 28$ ), volumetric modulated arc therapy ( $N = 27$ ), or helical tomotherapy ( $N = 1$ ). Gross tumor volume (GTV) encompassed the primary tumor and involved regional lymph nodes (LNs). The clinical target volume (CTV) of primary tumor was delineated by adding 2–3 cm margins in the craniocaudal directions and 0.5 cm margin in the circumferential direction to the primary GTV. The nodal CTV included a 1 cm margin in all directions from the nodal GTV. We did not routinely apply elective irradiation to the supraclavicular and/or celiac LN. The planning target volume (PTV) was CTV plus 0.5–0.7 cm margin in all directions. The RT dose was 43–45 Gy with 1.8–2.15 Gy daily per fraction. Median equivalent dose in 2 Gy fractions (EQD2) dose was 44 (range, 43.5–44.3) Gy. Dose constraints for normal organs were  $V_{20} < 35\%$ ,  $MLD < 20$  Gy, heart  $V_{40} < 40\%$ , and maximum dose of spinal cord  $< 45$  Gy. The regimen of concurrent chemotherapy was 5-fluorouracil (5-FU) 1,000 mg/m<sup>2</sup>/day for four consecutive days plus cisplatin 60 mg/m<sup>2</sup>/day on the first day at three weeks' interval in all patients, and the first cycle was planned to be on the first day of RT.

Following the completion of NACRT, all patients received transthoracic esophagectomy with either two-field or three-field lymphadenectomy. Two-field (thoracic and abdominal) LN dissection was mainly performed in the patients with lower thoracic esophageal cancer whereas three-field (cervical, thoracic, and abdominal) LN dissection was mainly done in those with upper or mid-thoracic esophageal cancer.

### Measurement of postoperative complications and DVH parameters

Postoperative pulmonary complications were defined as the occurrence of respiratory insufficiency requiring medication,

pneumonia, pleural effusion, or other respiratory events which require intervention within 30 days following surgery or during the same hospital stay after surgery. We scored the severity of the pulmonary complications according to the Clavien–Dindo classification (Supplementary Table 1) [21]. The DVHs of both lungs were computed for each patient and the total lung volume; mean lung dose (MLD); and relative and absolute lung volume receiving 5 Gy or higher ( $V_5$ ), receiving 10 Gy or higher ( $V_{10}$ ), receiving 20 Gy or higher ( $V_{20}$ ), and receiving 30 Gy or higher ( $V_{30}$ ) were generated.

### Statistical analysis

The clinical and DVH parameter characteristics according to the development of pulmonary complications were compared using Fisher's exact test for categorical variables and Mann–Whitney's  $U$  test for continuous variables. Logistic regression analysis was used in order to identify the significant dosimetric parameters obtained from the lung DVH that were relevant to the development of postoperative pulmonary complications. We used Pearson's correlation analysis to obtain Spearman's correlation coefficients in order to check the multiplicities between the factors. Multivariate logistic regression analysis was performed in order to evaluate the association between the postoperative complications and the DVH parameters, adjusting for other clinical variables. The goodness of fit of the logistic regression model was assessed by the Hosmer–Lemeshow test. The prediction was considered acceptable if the  $p$  value by the Hosmer–Lemeshow test is  $> 0.05$ , and in all other analyses, a  $p$  value  $< 0.05$  was considered to be statistically significant. We conducted all analyses using SPSS version 20 (IBM Corp., USA), Stata version 14 (StataCorp, USA), and SAS version 9.4 (SAS Institute Inc, USA).

## Results

### Patient characteristics

The median age was 63 (range, 41–80) and the median interval between NACRT and surgery was five weeks (1.6–36.4, Table 1). The majority of the patients (98.4%,  $N = 303$ ) had ECOG performance status 0–1 and 94.5% ( $N = 291$ ) were male. Among all patients, 51.3% ( $N = 158$ ) were current smokers, 34.1% ( $N = 105$ ) were former smokers, and 10.7% ( $N = 33$ ) had never been smokers. The pretreatment diffusing capacity for carbon monoxide (DLCO) was median 91.0% (range, 50.0–145.0) and the forced expiratory volume in the first second (FEV1) was 2.85 (0.87–4.50) L. The majority of patients (81.8%,  $N = 252$ ) received 3D-CRT. IMRT was applied in 56 patients (18.2%), in whom normal organ constraints were unmet by 3D-CRT plan. Median CTV volume was 201.6 (range, 35.1–793.5) cc and median MLD was 9.57 (1.23–30.5) Gy. Median relative  $V_5$ ,  $V_{10}$ ,  $V_{20}$ , and  $V_{30}$  were 54.0%, 37.2%, 15.2%, and 4.7%, respectively.

### Predictors of postoperative pulmonary complications

Postoperative pulmonary complications occurred in 22.1% of all patients ( $N = 68$ , Table 2). Among them, pneumonia was the most frequent complication, developed in 26 (8.4%) patients, followed by acute lung injury in 21 (6.8%), and pleural effusion in 20 (6.5%) patients. Grade 3B or more pulmonary complications were identified in 15 patients (4.9%) and the total 90-day mortality was 3.2%.

We divided the patients into two groups according to the development of pulmonary complications. The comparisons between the clinical and dosimetric characteristics of the groups are described in Table 3. In patients who developed pulmonary complications, middle thoracic esophageal cancers were more frequent

**Table 1**  
Characteristics of patients.

	N = 308
<i>Clinical factors</i>	
Age	63 (41–80)
Pre-RT DLCO	91.0 (50.0–145.0)
Pre-RT FEV1 (L)	2.85 (0.87–4.50)
Pre-RT FEV1 (%)	93.0 (42.0–129.0)
Pre-RT FEV1	
<70%	23 (7.5%)
≥70%	258 (83.8%)
Unknown	27 (8.8%)
Gender	
Male	291 (94.5%)
Female	17 (5.5%)
Smoking history	
Current	158 (51.3%)
Former	105 (34.1%)
Never	33 (10.7%)
Unknown	12 (3.9%)
Performance status (ECOG)	
0–1	303 (98.4%)
2–3	5 (1.6%)
Clinical stage	
II	91 (29.5%)
III	217 (70.5%)
Location	
Upper	95 (30.8%)
Middle	138 (44.8%)
Lower	75 (24.4%)
<i>Treatment factors</i>	
RT-surgery interval (weeks)	5.0 (1.6–36.4)
Lymphadenectomy	
2 field	129 (41.9%)
3 field	179 (58.1%)
Total dose (Gy)	44 (-50)
Daily dose (Gy)	2 (1.8–2.15)
RT modality	
3D-CRT	252 (81.8%)
IMRT	56 (18.2%)
<i>DVH factors</i>	
CTV volume	201.6 (35.1–793.5) cc
Median MLD (range)	9.57 (1.23–30.5) Gy
V <sub>5</sub> (cc)	1788.58 (174.84–4005.25)
V <sub>10</sub> (cc)	1259.53 (113.26–2963.02)
V <sub>20</sub> (cc)	499.85 (25.86–2286.91)
V <sub>30</sub> (cc)	159.39 (0–1785.19)
V <sub>5</sub> (%)	54.0 (4.4–97.5)
V <sub>10</sub> (%)	37.2 (3.2–87.1)
V <sub>20</sub> (%)	15.2 (1.1–64.0)
V <sub>30</sub> (%)	4.7 (0–50.0)

*Abbreviations:* RT, radiation therapy; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in the first second; 3D-CRT, 3-dimensional conformal radiation; IMRT, intensity modulated radiation therapy; DVH, dose–volume histogram; CTV, clinical target volume; MLD, mean lung dose; V<sub>5</sub>, lung volume receiving 5 Gy or higher; V<sub>10</sub>, lung volume receiving 10 Gy or higher; V<sub>20</sub>, lung volume receiving 20 Gy or higher; V<sub>30</sub>, lung volume receiving 30 Gy or higher.

than those without pulmonary complications (58.8% vs. 40.8%), while upper and lower thoracic esophageal cancers were more frequently observed in those who did not develop complications. Otherwise, there was no difference in clinical characteristics

**Table 2**  
Incidence of postoperative complications (N = 68).

	ALI	Pneumonia	Effusion	Others	Total
Grade*					
I–IIa	12 (3.9%)	21 (6.8%)	20 (6.5%)	0	53 (17.2%)
IIIb–IV	0	2 (0.6%)	0	1 (0.3%)	3 (1.0%)
V	9 (2.9%)	3 (1.0%)	0	0	12 (3.9%)
Total	21 (6.8%)	26 (8.4%)	20 (6.5%)	1 (0.3%)	68 (22.1%)
90-day mortality	8 (2.6%)	2 (0.6%)	0	0	10 (3.2%)

*Abbreviations:* ALI, acute lung injury.

\* Grading by the Clavien–Dindo classification.

between the patients who did or did not experience pulmonary complications. In regard to DVH parameters, all kinds of parameters including MLD and absolute and relative V<sub>5</sub>, V<sub>10</sub>, V<sub>20</sub>, and V<sub>30</sub> were higher in the complication groups than in those without complications (Fig. 1).

Univariate analysis for pulmonary complications showed that the location of tumor ( $P = 0.017$ ), pre-RT FEV1 ( $P = 0.003$ ), MLD ( $P = 0.002$ ), absolute V<sub>5</sub> ( $P = 0.012$ ), absolute V<sub>10</sub> ( $P = 0.011$ ), relative V<sub>5</sub> ( $P < 0.001$ ), relative V<sub>10</sub> ( $P < 0.001$ ), and relative V<sub>20</sub> ( $P = 0.007$ ) were all significant risk factors (Table 4). Multivariate analysis for pulmonary complications included the significant clinical factors, including the location of tumor and pre-RT FEV1, and MLD as a representative of DVH parameters. Significant factors for postoperative pulmonary complications according to multivariate analysis were FEV1 (OR 0.483, 95% CI 0.294–0.795,  $P = 0.004$ ) and MLD (OR 1.118, 95% CI 1.025–1.219,  $P = 0.012$ , Table 4).

Predictive probabilities of pulmonary complications by MLD were calculated by logistic regression model in two different risk groups by pre-RT FEV1 values. The patients with 4 Gy of MLD would have 10% probabilities of developing pulmonary complications in both groups. However, MLD having predicted 20% risk of pulmonary complications was 7 Gy in patients with FEV1 < 2L and 9.4 Gy in patients with FEV1 ≥ 2L (Fig. 2).

## Discussion

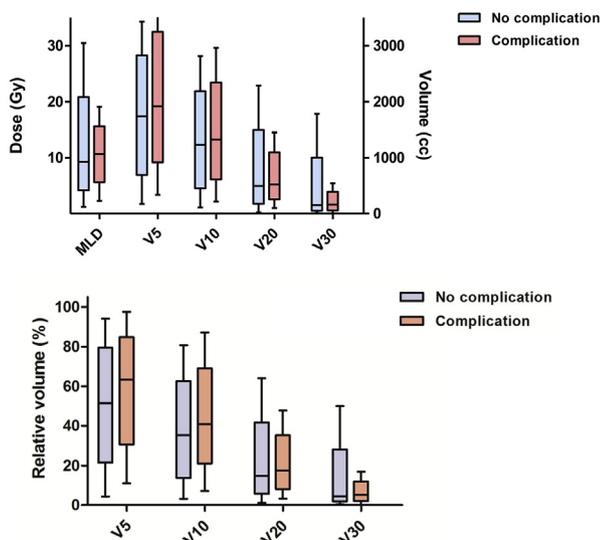
As the use of NACRT has been increasing in locally advanced esophageal cancer, optimal lung dose constraints for minimizing the risk of postoperative pulmonary complications need to be clarified. A number of lung cancer studies have established that if the lung DVH satisfy V<sub>20</sub> < 30–35% and MLD < 20 Gy, the probabilities of symptomatic radiation pneumonitis are less than 20% [22,23]. However, the irradiated lung dose in esophageal cancer patients is less than that of lung cancer patients. In this situation, the DVH parameters which we should prioritize to minimize the risk of postoperative pulmonary complications are yet to be clarified. In the current study, MLD, relative V<sub>5</sub>, and relative V<sub>10</sub> were the most relevant parameters for postoperative pulmonary complications.

Several other studies have shown the relationship between the MLD and postoperative pulmonary complications: Wang et al. from MDACC analyzed a large number of patients treated with NACRT and surgery for esophageal cancer [24,25]. They concluded that MLD was associated with pulmonary complication rates [24] and that IMRT diminished complication rates compared to 3D-CRT by reducing MLD. In this study, the MLD and pulmonary complication rates were 10.7 Gy and 30.3% in 3D-CRT, and 10.0 Gy and 23.8% in IMRT plan, respectively. In our study, the MLD was 9.6 Gy and the incidence of pulmonary complications was 22.1%. Although only 18% of the patients in the current study received IMRT, the median MLD was lower than that of IMRT cases from MDACC study. This was probably due to the lower total dose (median 44 Gy) of our study than that in the MDACC study (median 50.4 Gy). In line with the results of the previous study, IMRT cases

**Table 3**  
Characteristics of patients according to pulmonary complication.

	No Complication	Complication	P-value
<i>Clinical factors</i>			
Median Age	62 (42–80)	63 (41–79)	0.845
Median pre-RT DLCO	93 (50–145)	87 (56–140)	0.662
Median Pre-RT FEV1 (L)	2.94 (0.87–4.50)	2.63 (1.08–4.12)	0.001
Median Pre-RT FEV1 (%)	93.0 (44–129)	92.0 (42–125)	0.510
Gender			0.453
Male	228 (95.0%)	63 (92.6%)	
Female	12 (5.0%)	5 (7.4%)	
Smoking			0.710
Never	27 (11.3%)	6 (8.8%)	
Ex-smoker	84 (35.0%)	21 (30.9%)	
Current smoker	119 (49.6%)	39 (57.4%)	
Unknown	10 (4.2%)	2 (2.9%)	
Performance status (ECOG)			0.230
0–1	235 (97.9%)	68 (100.0%)	
2–3	5 (2.1%)	0	
Clinical stage			0.743
II	72 (30.0%)	19 (27.9%)	
III	168 (70.0%)	49 (72.1%)	
Location			0.014
Upper	76 (31.7%)	19 (27.9%)	
Middle	98 (40.8%)	40 (58.8%)	
Lower	66 (27.5%)	9 (13.2%)	
<i>Treatment factors</i>			
RT-Surgery interval	5.0 (1.6–36.4)	5.1 (2.9–10.9)	0.885
Lymphadenectomy			
2-Field	100 (41.7%)	29 (42.6%)	
3-Field	140 (58.3%)	39 (57.4%)	
RT modality			0.627
3D-CRT	195 (81.3%)	57 (83.8%)	
IMRT	45 (18.7%)	11 (16.2%)	
<i>DVH factors (median, range)</i>			
CTV volume (cc)	201.6 (35.1–793.5)	200.95 (41.6–377.1)	0.891
MLD (Gy)	9.27 (1.23–30.5)	10.66 (2.32–19.10)	0.004
V <sub>5</sub> (cc)	1740.8(174.8–3429.4)	1919.3 (338.6–4005.3)	0.074
V <sub>10</sub> (cc)	1230.4 (113.3–2812.4)	1321.8(216.2–2963.0)	0.131
V <sub>20</sub> (cc)	497.4 (25.9–2286.9)	523.3 (100.6–1449.9)	0.492
V <sub>30</sub> (cc)	157.4 (11.3–3045.9)	167.9 (0–540.7)	0.492
V <sub>5</sub> (%)	51.4 (4.4–94.1)	63.3 (11.1–97.5)	0.001
V <sub>10</sub> (%)	35.4 (3.2–80.7)	40.9 (7.1–87.1)	0.004
V <sub>20</sub> (%)	14.8 (1.1–64.0)	17.4 (3.3–47.7)	0.017
V <sub>30</sub> (%)	4.6 (0.5–50.0)	5.3 (0–16.9)	0.116

**Abbreviations:** RT, radiation therapy; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in the first second; 3D-CRT, 3-dimensional conformal radiation; IMRT, intensity modulated radiation therapy; DVH, dose-volume histogram; CTV, clinical target volume; MLD, mean lung dose; V<sub>5</sub>, lung volume receiving 5 Gy or higher; V<sub>10</sub>, lung volume receiving 10 Gy or higher; V<sub>20</sub>, lung volume receiving 20 Gy or higher; V<sub>30</sub>, lung volume receiving 30 Gy or higher.



**Fig. 1.** Dosimetric parameters of lung between those who did and did not experience pulmonary complications.

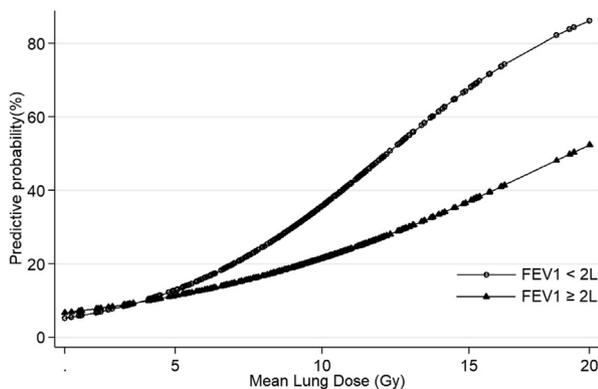
showed much lower MLD than 3D-CRT cases (8.9 Gy vs. 9.7 Gy), in spite of the larger target volume (median CTV 251.5 cc vs. 187.1 cc in IMRT vs. 3D-CRT) in the current study (Supplementary Table 2). Along with total RT dose and RT technique, MLD can be affected by various factors, including different priorities in normal organ constraints, beam arrangements, or treatment volume. Although detailed information regarding target delineation is not documented in other studies, the relatively small target volume of our institution without routine irradiation to supraclavicular or celiac area might contribute to low MLD.

Not only DVH factors, but also clinical factors, can affect the occurrence of pulmonary complications. Dhungel et al. [1] investigated the predictors of postoperative mortality with a large database of 1,032 patients. They found that age, diabetes mellitus, smoking, and alcohol consumption were all associated with respiratory complications. On the other hand, Yoshida et al. reported that obesity, chronic obstructive pulmonary disease, and diabetes mellitus did not affect the occurrence of pulmonary complications [14]. Wang et al. [25] reported that pre-RT DLCO and post-RT DLCO as well as post-RT FEV1 were associated with the risk of postoperative pulmonary complications while age, comorbidities, smoking history, pre-RT body mass index, stage, location, and type of surgery were not. The current study found that pre-RT FEV1 was a sig-

**Table 4**  
Univariate and multivariate analysis for pulmonary complications.

	Univariate			Multivariate		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age	1.023	0.988–1.059	0.194			
Gender (M vs F)	0.663	0.225–1.953	0.456			
Location of tumor (upper vs. lower) (middle vs. lower)	1.833	0.687–4.896	0.333	–	–	0.206
RT-surgery interval	2.993	1.216–7.367	0.013			
Pre-RT DLCO (%)	1.026	0.929–1.134	0.612			
Pre-RT FEV1(L)	0.994	0.977–1.012	0.528			
Smoking (ex vs. non) (current vs. non)	0.478	0.295–0.773	0.003	0.483	0.294–0.795	0.004
	1.125	0.412–3.075	0.561			
	1.475	0.567–3.835	0.818			
			0.426			
Lymphadenectomy (3-field vs. 2-field)	0.961	0.557–1.656	0.885			
IMRT vs. 3D-CRT	0.836	0.406–1.722	0.628			
CTV (cc)	0.881	0.640–1.214	0.439			
Mean lung dose	1.138	1.048–1.236	0.002	1.118	1.025–1.219	0.012
V <sub>5</sub> (cc)	1.049	1.010–1.089	0.012			
V <sub>10</sub> (cc)	1.064	1.015–1.117	0.011			
V <sub>20</sub> (cc)	1.094	0.997–1.199	0.058			
V <sub>30</sub> (cc)	1.450	0.716–2.936	0.302			
V <sub>5</sub> (%)	1.029	1.014–1.045	<0.001			
V <sub>10</sub> (%)	1.033	1.015–1.051	<0.001			
V <sub>20</sub> (%)	1.044	1.012–1.077	0.007			
V <sub>30</sub> (%)	1.028	0.969–1.092	0.360			

Abbreviations: CI, confidence interval; RT, radiation therapy; DLCO, diffusing capacity for carbon monoxide; FEV1, forced expiratory volume in the first second; 3D-CRT, 3-dimensional conformal radiation; IMRT, intensity modulated radiation therapy; DVH, dose–volume histogram; CTV, clinical target volume; MLD, mean lung dose; V<sub>5</sub>, lung volume receiving 5 Gy or higher; V<sub>10</sub>, lung volume receiving 10 Gy or higher; V<sub>20</sub>, lung volume receiving 20 Gy or higher; V<sub>30</sub>, lung volume receiving 30 Gy or higher.



**Fig. 2.** Relationship between mean lung dose and incidence of pulmonary complications in patients with the forced expiratory volume in the first second (FEV1) < 2L and those with FEV1 ≥ 2L.

nificant factor for pulmonary complications while other factors such as age, location, pre-RT DLCO, and smoking were not.

This study has several limitations: As we collected the data retrospectively, pulmonary function tests prior to and after RT are not thoroughly analyzed. Furthermore, the surgical factors including cervical anastomosis and operation time were not analyzed in this study. However, we included a large number of patients with squamous cell carcinoma of esophagus from the center that performs the highest volume of esophageal surgery in Korea. Despite the much lower range of MLD (median 9.6 Gy) in this study than that of usual lung cancer studies (~20 Gy), a relationship between lung dose and pulmonary complications was detected. The result implies that application of lung cancer DVH guidelines to esophageal cancer might be inappropriate. In line with other previous studies that showed the relationship between MLD and postoperative pulmonary complications, this study suggests that it is necessary to make efforts to reduce MLD as well as V<sub>5</sub> and V<sub>10</sub> of to lung as low as possible in planning NACRT for esophageal cancer, in order to lower postoperative pulmonary complications.

In summary, this study demonstrated that the MLD was associated with increased postoperative pulmonary complication rates. Further studies are needed to establish the optimal DVH constraints for NACRT in order to minimize the risk of postoperative pulmonary complications in esophageal cancer patients.

#### Conflicts of interest

There are no conflicts of interest relevant to this article to report.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.01.005>.

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