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Association of Clinical and Dosimetric Factors with Postoperative Pulmonary Complications in Esophageal Cancer Patients Receiving Intensity-Modulated Radiation Therapy and Concurrent Chemotherapy Followed by Thoracic Esophagectomy

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ABSTRACT

Background. To investigate the association between clinical/dosimetric factors and postoperative pulmonary complications (PPC) in esophageal cancer patients undergoing neoadjuvant chemotherapy and intensity-modulated radiation therapy (IMRT) followed by thoracic esophagectomy.

Methods. The data from 52 patients receiving combined modality treatment were analyzed. Chemotherapy was taxane-based in 43 and 5-fluorouracil-based in 9 patients. IMRT (40–45 Gy, median 40 Gy, at 1.8–2 Gy per fraction) was given using a 3–5-beam arrangement. Surgery consisted of open or minimally invasive esophagectomy. The dosimetric parameters were generated from lung dose-volume histogram computed by the treatment planning software. PPC was defined as pneumonia or respiratory insufficiency within 30 days after surgery. Statistical correlations were analyzed between clinical/dosimetric factors and PPC.

Results. The incidence of PPC was 34.6%. No patients died of PPC. Two patients (3.8%) became ventilator dependent. In univariate analyses, preoperative forced expiratory volume in 1 s (FEV1) and forced vital capacity before surgery were significantly associated with PPC ($P =$ 0.02 and 0.04, respectively). None of the dosimetric factors predicted development of PPC. For the 51 patients undergoing right transthoracic surgery, higher absolute spared volume of the right lung receiving 15 Gy was significantly associated with PPC ($P =$ 0.03). In multivariate analysis, preoperative FEV1 was the only independent factor associated with PPC ($P =$ 0.002).

Conclusions. Preoperative rather than prechemoradiation FEV1 predicts development of PPC. Reducing the absolute volume of the right lung that is irradiated might decrease the risk of PPC for patients receiving right transthoracic surgery.

Combined neoadjuvant chemoradiotherapy followed by surgery improved overall survival in recent meta-analyses, and is considered as the standard of care for resectable locally advanced esophageal cancer.[1] Whether the addition of neoadjuvant chemoradiotherapy increases the risk of perioperative mortality remains controversial. Two meta-analyses showed neoadjuvant chemoradiotherapy might increase the risk of postoperative mortality.[2,3] However, retrospective reviews and recent prospective randomized trials did not find any significant difference in postoperative morbidity and mortality.[4–6] The perioperative mortality rate was 5–10% with modern surgical techniques.[4,7]

Postoperative pulmonary complications develop in 16–36% of patients receiving esophagectomy and are the leading cause of postoperative mortality.[4–6,8,9] Risk factors related to the development of postoperative pulmonary complications after esophagectomy include advanced age, poor nutrition status, poor performance status, poor lung function, and host inflammatory response.[5,6,8–12]

It has been well recognized that thoracic radiation induces pneumonitis through an inflammatory process.[13] However, the relationship between radiation injury and

postoperative pulmonary complication is barely understood. Some authors found that neoadjuvant chemoradiotherapy seems to increase the risk of postoperative pulmonary complications, while others did not.[5,6,8,14] The MD Anderson Cancer Center reported that absolute volume of lung spared from 5 Gy is an independent factor associated with the postoperative pulmonary complications.[15] It was hypothesized that the physiologic strain of surgery might trigger pulmonary complications that otherwise would remain subclinical damage after chemoradiotherapy.

The development of intensity-modulated radiation therapy (IMRT) has improved the conformity of tumor dose distribution and sparing of normal tissue. IMRT offers the potential benefit of reducing toxicity at the cost of spreading low dose to a larger region. Dosimetric comparison studies have shown that IMRT plans using four beam fields reduce total lung volume treated above 5, 10, and 20 Gy, and mean lung dose.[16] IMRT plans using seven or nine beam fields improved conformity index but did not reduce total lung volume treated above 5 Gy.

In this pilot work, we investigated the relationship between clinical/dosimetric factors and the postoperative pulmonary complications of esophageal cancer patients undergoing neoadjuvant chemoradiotherapy using IMRT followed by thoracic esophagectomy.

PATIENTS AND METHODS

We performed a retrospective analysis of consecutive patients with biopsy-proved esophageal cancer treated with neoadjuvant chemoradiotherapy using IMRT, followed by en bloc esophagectomy at National Taiwan University Hospital from June 2006 to June 2008. All patients had resectable stage III or IVA diseases according to the sixth edition of the cancer staging manual published by the American Joint Committee on Cancer. The pretreatment evaluations included complete medical history and physical examination; complete blood count and biochemistry survey; esophagogram; computed tomography (CT) of chest and abdomen; endoscopic ultrasonography (EUS); and screening pulmonary function tests including forced vital capacity (FVC) and force expiratory volume in 1 s (FEV1). Positron emission tomography (PET) scan was also performed in some patients.

All patients underwent CT simulation with images taken at 5-mm thickness throughout the entire neck, thorax, and abdomen. Patients were immobilized with a thermoplastic mask for head and neck treatment or a vacuum-locked alpha cradle according to the location of the primaries. The gross tumor volume (GTV) was defined as all macroscopically identifiable tumor determined by CT scan, EUS, esophagogram, and PET scan. The clinical target volume

(CTV) was defined as 3–4 cm proximal and distal as well as 1 cm lateral beyond GTV. Uninvolved bony structures and lung parenchyma were excluded from the CTV. The CTV included the supraclavicular nodes for upper-third primaries and celiac nodes for distal-third primaries. The planning target volume (PTV) was defined as the CTV plus 0.5- to 1-cm margins. The normal structures, including spinal cord, lung parenchyma, heart, liver, and kidney, were delineated on each planning CT image. The lung volume was defined as total lung volume minus CTV. A 0.5-cm margin around spinal cord was added for the planning organ-at-risk volume. The inverse IMRT plans were generated using a commercial treatment planning system (Pinnavle3, v7.6, ADAC Laboratories, Milpitas, CA). A representative sample of isodose distribution and dose–volume histogram is shown in Fig. 1. The CTV was irradiated with a total dose of 36–45 Gy (median 40 Gy) at 1.8–2 Gy (median 2 Gy) per fraction. Heterogeneity correction was applied to all dose calculations. The treatment was delivered with 6- and/or 10-MV photons using 3–5 beam fields (median 4 beams). The typical beam orientation was similar to the conventional four-beam arrangement with anteroposterior, posteroanterior, and two posterior oblique fields. Typical oblique beam angles were 140–200° from the posterior side. One patient was treated with a noncoplanar beam arrangement. The goals of inverse IMRT planning were to ensure that ≥99% of the PTV received ≥93% of the prescribed dose while keeping the exposure of normal structures including lung, heart, spinal cord, liver, and kidney to within normally acceptable tolerances. The total lung dose–volume histogram (DVH) was considered acceptable if one of the following constraints was met: ≤45% of total lung volume receiving ≥10 Gy; ≤35% of total lung volume receiving ≥15 Gy; ≤30% of total lung volume receiving ≥20 Gy. The dosimetric parameters, including lung volume, mean lung dose, absolute and relative volumes of lung receiving more than a threshold dose (V_{dose}), absolute volumes of lung spared from a threshold dose (VS_{dose}) of the total lung, right lung, and left lung, were generated from the DVH of lung computed by the treatment planning software. Biological equivalent dose conversion was not applied.

All patients received concurrent chemoradiotherapy with cisplatin-based regimens. The concurrent chemotherapy regimens consisted of paclitaxel (35 mg/m^2) on days 1 and 4 of each week and cisplatin (15 mg/m^2) on days 2 and 5 of each week ($n = 32$); docetaxel (20 mg/m^2) and cisplatin (20 mg/m^2) once weekly ($n = 11$); cisplatin (30 mg/m^2) and fluorouracil (425 mg/m^2) once weekly ($n = 5$); cisplatin (75 mg/m^2) on day 1 and fluorouracil (1,000 mg/m^2) on days 1–4 every 4 weeks ($n = 2$); or cisplatin (30 mg/m^2) once weekly ($n = 2$). The use of induction chemotherapy before concurrent chemoradiotherapy
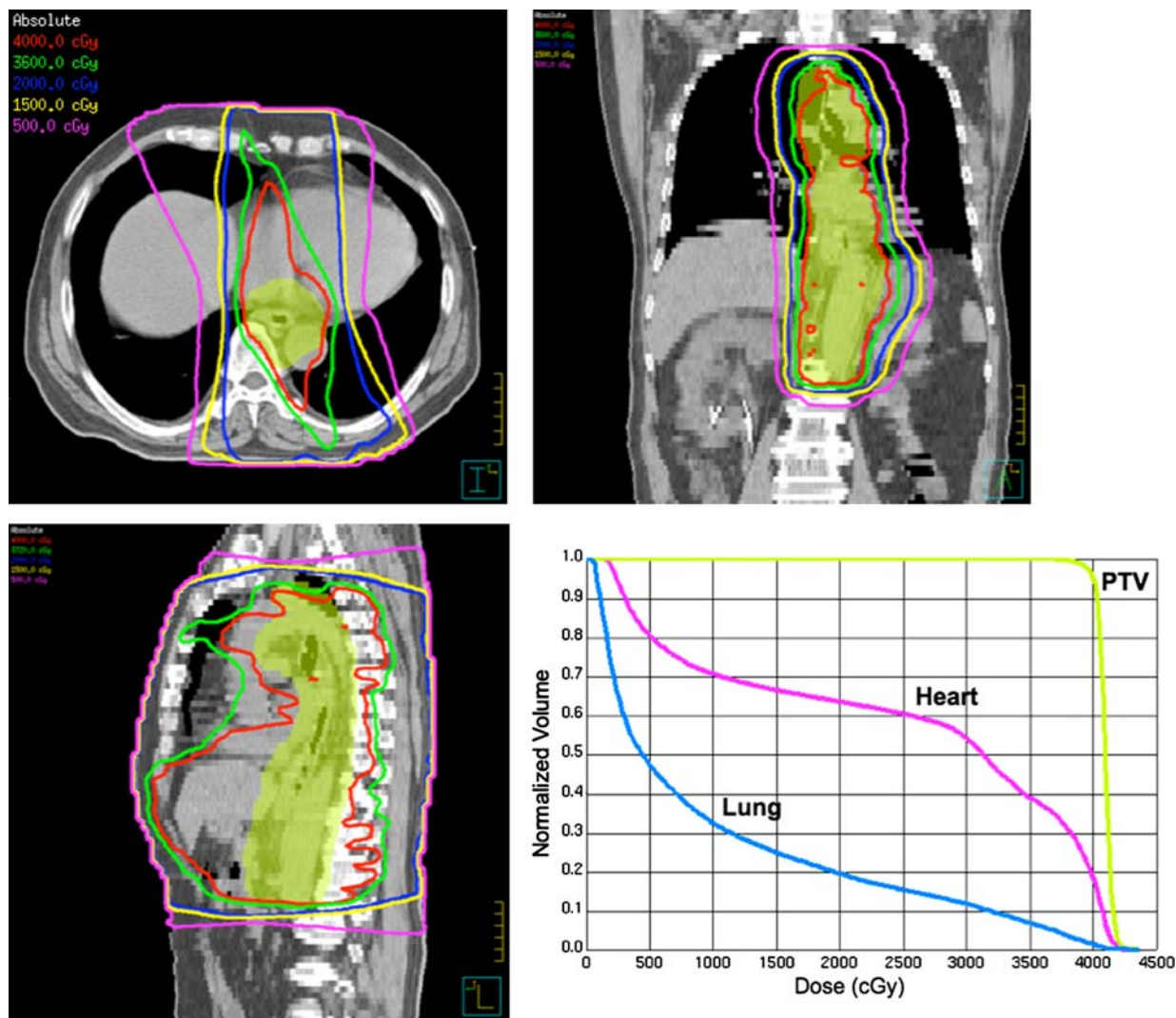
FIG. 1 The dose distributions of transverse, coronal, sagittal views and dose–volume histogram of one representative esophageal cancer patient treated with 40 Gy of intensity-modulated radiation therapy

was part of an institutional prospective phase II protocol. The induction chemotherapy regimens consisted of paclitaxel (80 mg/m^2) on days 1 and 8, cisplatin (35 mg/m^2) on days 2 and 9, and fluorouracil (2,000 mg/m^2) and leucovorin (300 mg/m^2) on days 2 and 9.

Surgery was performed 20–132 days (median 52 days) after completion of neoadjuvant chemoradiotherapy. In all except one patient, the procedure involved a right transthoracic approach with open transthoracic esophagectomy or video-assisted thoracoscopic (VATS) esophagectomy. Cervical, mediastinal, and abdominal lymph node dissections were routinely performed except for the only patient receiving left thoracoabdominal incision, whose lymph node dissection was confined to the mediastinum and abdomen. All patients remained ventilated postoperatively and were transferred to intensive care unit (ICU) for postoperative care. Patients tried weaning from mechanical ventilator on the first day after operation and were extubated if they met the criteria of weaning protocol.

Postoperative pulmonary complications were defined as pneumonia or respiratory insufficiency developing within 30 days after surgery during postoperative hospital stay. The clinical diagnosis of pneumonia met the Centers for Disease Control and Prevention definition if at least three of the following criteria were present: leukocytosis, fever, purulent sputum, persistent infiltrate on chest X-ray, pathogenic bacteria from endotracheal aspirate. The clinical diagnosis of respiratory insufficiency was defined as pulmonary infiltrate requiring reintubation for ventilatory support, steroid therapy or PaO$_2$/FiO$_2 \leq 200$ for more than 24 h. Perioperative mortality was defined as death occurring within 30 days after surgery. Hospital mortality was

defined as any death occurring during convalescence before discharge.

The correlation between categorical clinical factors and the postoperative pulmonary complications was evaluated by the Fisher's exact test or Pearson chi-squared test. The relationship between continuous clinical factors or dosimetric parameters of the lung and the incidence of postoperative pulmonary complications was assessed using logistic regression analysis. Mann–Whitney U-test was also used to compare the distribution of duration of mechanical ventilation and length of ICU stay between patients with and without postoperative pulmonary complications. Two-tailed P value of less than 0.05 was considered to be statistically significant. Factors with statistical significance in univariate analysis were evaluated in multivariate analysis with forward-stepwise logistic regression. All analyses were performed using SPSS version 12 (SPSS Inc., Chicago, IL).

RESULTS

Patient Characteristics

Fifty-two consecutive patients with esophageal cancer receiving neoadjuvant chemoradiotherapy plus en bloc esophagectomy were enrolled for analysis. Their clinical characteristics are summarized in Tables 1 and 2.

Incidence of Postoperative Pulmonary Complication and Surgical Mortality

Eighteen (34.6%) patients developed postoperative pulmonary complications. Thirteen patients had pneumonia and five patients had respiratory distress. Two (3.8%) patients required tracheostomy and became ventilator dependent. One patient (1.9%) died perioperatively. There were four (7.7%) hospital mortalities, including two due to profound soft tissue infection requiring surgical drainage, one due to systemic fungal infection, and one due to rapid progression of systemic metastasis. Three of these four patients also had postoperative pulmonary complications. The development of postoperative pulmonary complications was not associated with hospital mortality ($P = 0.11$).

Length of mechanical ventilation duration and length of ICU stay were significantly longer for patients with postoperative mortality ($P < 0.001$ for both). The median lengths of overall and initial mechanical ventilation duration were 7 days (range 1–32 days) and 13.5 days (range 1–283 days) for patients with pulmonary complications versus 2 days (range 1–11 days) for patients without pulmonary complications. Median length of ICU stay was 16.5 days (range 3–80 days) for patients with pulmonary

TABLE 1 Categorical characteristics and presence of postoperative pulmonary complications ($n = 52$)

Characteristics	Number of patients	Incidence of pulmonary complications (%)	P-Value
Gender			
Male	49	33	0.272
Female	3	67	
Diabetes mellitus			
No	45	38	0.221
Yes	7	14	
COPD			
No	49	33	0.272
Yes	3	67	
Smoking history			
Smoker	47	34	0.572
Nonsmoker	5	40	
Body weight loss >10%			
No	34	32	0.431
Yes	18	39	
ECOG performance status			
0 or 1	39	33	0.736
2	13	39	
Histology			
Squamous cell carcinoma	50	34	0.577
Adenocarcinoma	2	50	
Tumor location			
Upper	10	40	0.621
Middle	26	39	
Lower/GEJ	16	25	
AJCC stage			
III	35	40	0.196
IVA	17	24	
Induction chemotherapy			
No	33	32	0.546
Yes	19	44	
Concurrent chemotherapy regimens			
5-Fluorouracil + cisplatin	9	22	0.690
Paclitaxel + cisplatin	32	38	
Docetaxel + cisplatin	11	36	
Radiation dose			
36 Gy	1	100	0.271
40 Gy	48	35	
45 Gy	3	0	
Beam numbers			
3 fields	17	35	0.865
4 fields	28	32	
5 fields	7	43	

TABLE 1 continued

Characteristics	Number of patients	Incidence of pulmonary complications (%)	P-Value
Types of surgery			
Right open thoracotomy	20	35	0.557
VATS	31	36	
Left thoracoabdominal incision	1	0	
Intraoperative blood transfusion			
No	21	43	0.232
Yes	31	29	

COPD chronic obstructive pulmonary disease, according to the American thoracic society guidelines, *GEJ* gastroesophageal junction, *AJCC* American joint committee on cancer, *VATS* video-assisted thoracoscopic surgery

complications versus 4.5 days (range 1–14 days) for patients without pulmonary complications.

Clinical Factors Associated with Postoperative Pulmonary Complications

The univariate analyses of dichotomous and continuous clinical factors and their association with postoperative pulmonary complications are summarized in Tables 1 and 2, respectively. Various clinical factors including gender, age, history of chronic obstructive pulmonary disease, diabetes mellitus, smoking history, presence of extensive body weight loss at diagnosis, performance status, tumor histology, tumor location, clinical stage, use of induction chemotherapy, concurrent chemotherapy regimen, radiation dose, IMRT beam number, type of surgery, intraoperative blood transfusion, intraoperative blood loss, operation duration, interval between completion of radiotherapy and surgery, preoperative serum albumin levels, and hemoglobin levels were not significantly associated with postoperative pulmonary complications. Patients with higher preoperative body weight tended to have lower risk of pulmonary complications ($P = 0.063$). The spirometric factors including FEV1 and FVC were evaluated as continuous factors. The observed volume of pulmonary function test before surgery was significantly associated with postoperative pulmonary complications. Patients with higher observed FEV1 or FVC had significantly lower risk of pulmonary complications ($P = 0.02$ and 0.04, respectively). The percentage of FEV1 or FVC predicted before chemoradiotherapy, or change in the percentage after chemoradiotherapy, was not associated with complications.

Dosimetric Factors for Lung Associated with Postoperative Pulmonary Complications

The univariate analyses of dosimetric parameters derived from the DVH of lung were evaluated as continuous variables. None of the dosimetric factors including

TABLE 2 Continuous characteristics and presence of postoperative pulmonary complications (n = 52)

Characteristics	Without pulmonary complications		With pulmonary complications		P-Value
	Median	Range	Median	Range	
Age (years)	54	39–79	53	46–75	0.569
Interval between RT and surgery (days)	49	20–132	54	31–99	0.375
Preop. body weight (kg)	61	44–91	56	39–73	0.063
Preop. serum albumin (g/dL) (n = 50)	4.4	3.3–4.8	4.3	3.5–4.7	0.734
Preop. serum hemoglobulin (g/dL)	12	9–14	12	9–13	0.386
Pre-RT FEV1 (L) (n = 34)	2.9	1.5–3.8	2.7	1.1–3.3	0.282
Pre-RT FEV1 (% of prediction) (n = 34)	104	71–119	107	81–134	0.280
Pre-RT FVC (L) (n = 34)	3.7	1.6–5.4	3.4	1.5–4.4	0.225
Pre-RT FVC (% of prediction) (n = 34)	106	85–120	108	85–128	0.405
Preop. FEV1 (L) (n = 48)	2.9	1.4–3.9	2.6	1.2–3.0	0.022
Preop. FEV1 (% of prediction) (n = 48)	107	66–126	97	63–131	0.246
Preop. FVC (L) (n = 48)	3.7	1.8–5.0	3.2	1.7–4.6	0.041
Preop. FVC (% of prediction) (n = 48)	107	82–144	105	64–133	0.350
Preop./Pre–RT FEV1 (n = 31)	0.98	0.83–1.18	0.97	0.84–1.16	0.767
Preop./Pre–RT FVC (n = 31)	0.96	0.84–1.14	1.02	0.84–1.16	0.617
Intraop. blood loss (mL) (n = 51)	400	150–1300	450	50–1750	0.811
Operation duration (h)	9	5–12	8	5–15	0.927

RT radiotherapy, *Preop.* preoperative, *Intraop.* Intraoperative, *FEV1* force expiratory volume in 1 s, *FVC* forced vital capacity

lung volume, mean lung dose, relative and absolute lung volume irradiated above 5–30 Gy, or absolute lung volume spared from 5–30 Gy was associated with postoperative pulmonary complications if both lungs were considered as a single organ. Patients with higher right lung volume spared from the dose of 15 Gy or more tended to have lower risk of pulmonary complications ($P = 0.05$).

When the only patient who received left thoracoabdominal incision instead of right transthoracic surgery was excluded from the analysis, the dosimetric parameters derived from the DVH of right lung became significantly associated with postoperative pulmonary complications. The results of univariate analyses are shown in Table 3. Patients with smaller right lung volume ($P = 0.09$) and larger right lung volume spared from the doses of 10 Gy ($P = 0.09$) and 20 Gy ($P = 0.09$) had borderline lower risk of pulmonary complications. The volume of the right lung spared from the 15-Gy dose was the only significant dosimetric factor associated with postoperative pulmonary complications ($P = 0.03$).

Preoperative observed volumes of FEV1, FVC, body weight, and VS15 of the right lung (VSR15) were used in multivariate analysis. Preoperative FEV1 was the only independent predictive factor for postoperative pulmonary complications both in the entire study cohort and in patients treated using a right-sided transthoracic approach ($P = 0.02$ and 0.01, respectively).

DISCUSSION

In this study, we identified preoperative FEV1 as the only independent factor associated with postoperative pulmonary complications in patients receiving neoadjuvant IMRT and concurrent chemotherapy followed by thoracic esophagectomy. Dosimetric parameters failed to predict the risk of postoperative pulmonary complications. On the other hand, the absolute volume of the unirradiated right lung rather than the entire lung or left lung might predict the development of postoperative pulmonary complications, especially in patients receiving right transthoracic resection. Wang and colleagues studied the association between dosimetric parameters of lung and the incidence of postoperative pulmonary complications in patients treated with neoadjuvant chemoradiotherapy followed by surgery.[15] All spared

TABLE 3 Dosimetric parameters from dose–volume histogram of lung and presence of postoperative pulmonary complications for patients with right transthoracic surgery ($n = 51$)

Parameters	Without pulmonary complications		With pulmonary complications		P-Value
	Median	Range	Median	Range	
Total lung volume (cm^3)	3491	2353–4856	3082	2011–4947	0.180
Right lung volume (cm^3)	2029	1281–2671	1668	1115–2647	0.092
Left lung volume (cm^3)	1456	1071–2332	1414	851–2299	0.377
Mean dose to total lung (Gy)	10.3	6.7–15.1	10.3	8.7–13.6	0.492
Mean dose to right lung (Gy)	9.0	5.8–13.7	8.9	7.4–12.1	0.477
Mean dose to left lung (Gy)	12.8	7.7–19	11.9	10.0–16.5	0.608
Absolute total lung volume spared (cm^3)					
VS5	1780	999–3320	1799	829–3094	0.586
VS10	2356	1363–3828	2179	1137–3510	0.271
VS15	2553	1612–4047	2351	1341–3766	0.228
VS20	2825	1767–4194	2486	1544–3927	0.174
VS30	3050	2032–4514	2712	1701–4298	0.206
Absolute right lung volume spared (cm^3)					
VS5	1097	625–1909	1057	510–1693	0.328
VS10	1438	865–2178	1274	720–1931	0.091
VS15	1609	970–2299	1299	832–2097	0.034
VS20	1694	1015–2367	1398	910–2173	0.094
VS30	1815	1099–2472	1502	1020–2299	0.100
Absolute left lung volume spared (cm^3)					
VS5	680	324–1411	675	238–1401	0.986
VS10	865	493–1649	882	387–1579	0.761
VS15	980	603–1748	1007	478–1669	0.607
VS20	1104	695–1827	1066	579–1754	0.378
VS30	1236	882–2042	1202	674–1999	0.453

volumes corresponding to the dose range 5–30 Gy were significantly associated with the incidence of postoperative pulmonary complications, but VS5 was the only independent predictor. Both studies showed that absolute volume of spared lung rather than relative or absolute irradiated volumes determined the development of postoperative pulmonary complications. Absolute FEV1 and FVC rather than percentage FEV1 and FVC were found to be significant predictors, supporting the hypothesis of Wang et al. that patients with smaller lung volumes and less functional reserve might be more susceptible to postoperative pulmonary complications.

Most published data on the endpoint of radiation pneumonitis indicate that dosimetric parameters (e.g., lung mean dose, relative V20, and V30) are predictive in patients receiving thoracic irradiation.[17] In terms of postoperative pulmonary complications, low-dose lung volume was more predictive than high-dose lung volume. Our work showed that VSR15 was the only dosimetric parameter significantly associated with pulmonary complications. This dose level was similar to the level found in the initial analysis by Lee et al.[18] They found that relative V10 and V15 were significant predictors. In one study, diffusion capacity of carbon monoxide (DLCO) correlated with local radiation dose to lung, and local DLCO decreased sharply when the local dose exceeded 13 Gy.[19] Surgical stress may account for subclinical pulmonary damage after low radiation doses (10–20 Gy) of thoracic chemoradiotherapy and may explain why low radiation doses are more predictive. Surgical stress might trigger an inflammatory response to subclinical pulmonary damage after neoadjuvant chemoradiotherapy and thereby provoke postoperative pulmonary complications.

Indeed, the inflammatory response has been associated with postoperative pulmonary complications. The bronchoalveolar lavage fluids of patients with pulmonary complications after esophagectomy have more interleukin-8 and higher granulocyte elastase activity.[20] In addition, Lee et al. identified genetic factors that were associated with postoperative pulmonary complications.[11] In their report, an angiotensin-converting enzyme (ACE) insertion/deletion polymorphism was a predisposing factor affecting individual susceptibility to pulmonary complications. Patients with ACE D/D genotype had a significantly higher risk of developing pulmonary complications. Patients with ACE D allele also had higher circulating ACE level, which was found to be associated with radiation pneumonitis as well.[21] Lower circulating ACE level, either before or after radiotherapy, was significantly associated with lower risk of radiation pneumonitis. Further pharmacogenetic studies are required to clarify these associations.

One unique finding of our study was that spared volume of the right lung was more predictive than that of both lungs or the left lung, especially for patients undergoing right transthoracic surgery. One possible explanation was that perioperative injury to the right lung is greater during one-lung ventilation. One-lung ventilation during esophagectomy has been shown to trigger a systemic inflammatory response and increase the risk of postoperative pulmonary complications.[22,23] Patients with right lung collapsed during one-lung ventilation had lower arterial oxygen tension and higher incidence of perioperative hypoxemia.[24] These perioperative events may eventually result in increased systemic inflammatory response and acute lung injury. Of note, minimally invasive thoracoscopic esophagectomy did not reduce the incidence of postoperative pulmonary complications. All patients required one-lung ventilation during the operation regardless of the esophagectomy technique used (open versus minimally invasive). The impact of surgical stress on the collapsed lung may trigger a similar systemic inflammatory response. In a randomized trial, Michelet et al. found protective ventilation during esophagectomy significantly decreased the plasma levels of inflammatory cytokines and reduced the postoperative ventilation duration.[25] Our study suggests that the spared volume in this collapsed right lung during one-lung ventilation might be critical in reducing postoperative pulmonary complications and supports the two-event hypothesis.[26] Given that VSR15 was not an independent predictor in multivariate analysis, our results based on a limited number of patients and complication events should be interpreted carefully and require further analyses.

IMRT with inverse treatment planning potentially improves dose conformity and normal organ sparing. The clinical use of IMRT for thoracic malignancies (unlike cancer of the prostate and head and neck) is limited. One of the concerns was that IMRT might spread low doses of radiation to large volumes of radiosensitive lung tissue. Using standard radiation dose of 40–50 Gy for esophageal cancer, spinal cord, liver, and kidney are well tolerated even using conventional three-dimensional conformal radiotherapy. The interest in using IMRT in esophageal cancer is based on its potential to spare lung and heart tissue. Until now only two plan studies have been published to investigate the potential benefit of definitive IMRT with no additional surgery.[16,27] Nutting et al. carried out IMRT plans using nine equi-spaced beam fields (9B) or four beam fields (4B).[27] They found that 9B-IMRT provided no dosimetric advantages in dose homogeneity and mean lung dose, but that 4B-IMRT increased dose homogeneity with the reduction of mean lung dose and relative V18. Chandra et al. compared IMRT plans using four, seven, and nine beam fields for distal esophageal cancer.[16] IMRT plans improved heterogeneity and conformity indexes, but the differences between them were small and

their clinical impact was uncertain. Regarding lung sparing, 4B-IMRT significantly reduced mean lung dose, V5, V10, and V20. The 7B- and 9B-IMRT plans had the significant reduction in mean lung dose, V10, and V20. In our study, we designed IMRT plans using 3–5 beam fields with carefully chosen beam angles to reduce radiation exposure to normal lung. With 40–45 Gy neoadjuvant chemoradiotherapy, IMRT improved dose homogeneity, conformity, and reduced heart dose compared with traditional antero-posterior-posteroanterior fields.

To our knowledge, this is the first report of use of IMRT for esophageal cancer in neoadjuvant chemoradiotherapy. The incidence of postoperative pulmonary complications was 34.5%, comparable to the historical series. Avendano et al. reported that 36.1% of their patients had significant pulmonary complications, with pneumonia in 32.8% and acute respiratory distress syndrome in 9.8% of patients.[8] Lin et al. reported that 30.1% of patients treated with induction therapy had pulmonary complications.[6] Among the 18 patients developing pulmonary complications, 2 became ventilator dependent and required tracheostomy. Both patients had VSR15 less than the median of 1,500 cm³. In addition, one patient had preoperative FEV1 of 1.23 liters (95%), while the other patient might have had upregulated systemic inflammatory response from significant blood loss and blood transfusion during operation. These predisposing factors might induce the mechanism similar to the two-event hypothesis in trauma. None of our patients died of progressive pulmonary complications, but three of the four hospital mortalities had pulmonary complications. The perioperative death and hospital mortality rates in our cohort were consistent with modern surgical series. Our preliminary results suggest that integration of IMRT into neoadjuvant chemoradiotherapy for esophageal cancer patients seem feasible with acceptable toxicities.

The development of postoperative pulmonary complications may be multifactorial and have complex interactions between different predisposing factors. We found that preoperative observed volume of FEV1 was the most important factor predicting postoperative pulmonary complications in esophageal cancer patients receiving IMRT and concurrent chemotherapy followed by thoracic esophagectomy. Patients with larger VSR15 may have lower risk of pulmonary complications. The radiation doses of 10–20 Gy to the right lung (i.e., the collapsed lung during one-lung ventilation) might be taken into consideration during radiation treatment planning. Further study is needed to investigate the long-term outcomes of IMRT in esophageal cancer and the individualized risk of postoperative pulmonary complication based on dosimetric factors, pharmacogenetics, and pulmonary functional reserve.

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