EVALUATION OF EMPHYSEMA USING THREE-DIMENSIONAL COMPUTED TOMOGRAPHY: ASSOCIATION WITH POSTOPERATIVE COMPLICATIONS IN LUNG CANCER PATIENTS

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ABSTRACT

Three-dimensional computed tomography (3D-CT) enables in vivo volumetry of total lung volume (TLV) and emphysematous low-attenuation volume (LAV) in patients with chronic obstructive pulmonary disease (COPD). We retrospectively investigated the correlation between preoperative 3D-CT volumetry and postoperative complications in lung cancer patients. We searched our institution’s surgical records from December 2006 to December 2009 and selected patients who had undergone pulmonary lobectomy for primary lung cancer. From 3D-CT data, TLV and LAV <–950 HU of thresholds were retrospectively measured. The LAV% was calculated as follows: LAV% = LAV/TLV×100. The associations between the seven independent variables (LAV%, age, gender, body mass index, smoking history, forced expiratory volume in 1 second as percent forced vital capacity [FEV1%], and resected lobe) and the two outcomes (postoperative complications and prolonged postoperative stay [PPS]) were compared using logistic regression analysis. A total of 309 patients (222 males, 87 females; mean age, 67 years; range, 40–87 years) were evaluated. On multivariate analysis, age and LAV% were significantly correlated with postoperative complications (p = 0.006 and p = 0.006, respectively), and LAV% was significantly correlated with PPS (p = 0.031). LAV% measured using 3D-CT is more sensitive for predicting complications after lobectomy for lung cancer than FEV1%.

Key Words: Chronic obstructive pulmonary disease; Lung cancer; Thoracic surgery; Postoperative complication; Computed tomography

Abbreviations

3D-CT Three-dimensional computed tomography
AUC area under the curve
BI Brinkman index
BMI body mass index
CAD computer-aided diagnosis
COPD chronic obstructive pulmonary disease
FEV1 forced expiratory volume in 1 second
FEV1% forced expiratory volume in 1 second as percent forced vital capacity

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) often occurs in lung cancer patients due to their smoking history. Surgery provides the best chance of prolonged survival for early-stage non-small cell lung cancer. However, postoperative pulmonary complications are among the most common sources of morbidity in patients undergoing major surgery. Notably, COPD is the main predictor of perioperative mortality and respiratory morbidity. Therefore, preoperative patient evaluation for COPD should be performed accurately.

Pulmonary function test (PFT) using a spirometer remains the standard screening test performed before pulmonary resection. However, PFT has a limited role and its results should not be the basis for denying surgery if the surgical indication is compelling, because the severity of COPD based on forced expiratory volume in 1 second (FEV1) by spirometry is imperfectly associated with the presence of symptoms in the individual patient.

Computed tomography (CT) is excellent for demonstrating pulmonary emphysema as a low-attenuation area. In addition, development of three-dimensional (3D) CT and computer-aided diagnosis (CAD) enables in vivo 3D volumetry of total lung volume and emphysematous lung volume. Several studies have shown that 3D-CT volumetry can accurately and objectively evaluate the severity of COPD. Ueda et al. reported that determination of the area of emphysema by quantitative CT is useful in predicting early postoperative oxygenation capacity. Therefore, we assume that preoperative 3D-CT volumetry of emphysematous lungs may precisely predict postoperative complications of lung cancer. Accordingly, in the present study we retrospectively investigated the correlation between preoperative 3D-CT volumetry and postoperative complications in lung cancer patients.

MATERIALS AND METHODS

Patient selection
We searched our institution’s surgical records from December 2006 to December 2009 and selected patients who had undergone a pulmonary lobectomy for primary lung cancer in our institution. We then obtained clinical records and preoperative CT images for these patients. For all selected cases, we recorded age, gender, body mass index (BMI), smoking history, forced expiratory volume in 1 second as percent forced vital capacity (FEV1%) measured by spirometry, resected lobe, postoperative complications, and postoperative duration of hospital stay.

Postoperative complications and prolonged postoperative stays
In this study, postoperative complications and prolonged postoperative stays (PPS) were
defined as follows based on the definitions used in previous studies.\textsuperscript{12, 13} Postoperative pulmonary complications included: (i) prolonged oxygen treatment (POT) (the need for oxygen therapy for >2 days or the restart of oxygen therapy); (ii) pneumonia (radiological evidence without bacteriological confirmation was reported as “pneumonia suspected”; radiological evidence including atelectasis and documentation of pathological organism by Gram stain or culture was reported as “pneumonia confirmed”); (iii) prolonged ventilation (PV) (unexpected extubation failure at the end of surgery or postoperative ventilator dependence for >48 hours); (iv) reintubation due to respiratory failure; and (v) prolonged air leakage (bronchial fistula or and pulmonary fistula). All postoperative pulmonary complications with more than the mild (grade1) described by Common Terminology Criteria for Adverse Events (version 4.0) were detected. Cardiac complications included myocardial infarction, supraventricular arrhythmias, and ventricular arrhythmias, for all of which treatment was needed. Combined cardiopulmonary complications included POT, pneumonia, PV, reintubation due to respiratory failure, prolonged air leakage, and supraventricular arrhythmias. When one patient had some postoperative pulmonary and cardiac complications, we counted one combined cardiopulmonary complication. We defined non-COPD patients as FEV\textsubscript{1}%≥70%. Mean postoperative stays in non-COPD patients was 11days, therefore, a PPS was defined as a hospital stay of ≥12 days based on the previous study of Matsuo et al.\textsuperscript{13}

**CT scan**
All preoperative CT examinations were performed using a 64-detector row scanner (Aquilion 64; Toshiba Medical Systems Corp., Tokyo, Japan). All scans were obtained from the lung apex to the diaphragm, during a breath-hold at deep inspiration, using the following parameters: x-ray tube voltage, 120 kVp; automatic tube-current maximum, 225 mAs; gantry rotation speed, 0.5 sec; and beam collimation, 64×0.5mm. CT images were reconstructed from 5-mm slices with intervals of 5 mm, using a standard algorithm. No intravenous contrast media was administered.

**3D-CT volumetry**
All CT data for each patient were transferred to a computer workstation (ZioStation; Ziosoft, Osaka, Japan), and 2 radiologists (with 18 and 3 years of experience in interpreting thoracic CT) reconstructed 3D models (Fig. 1). Threshold limits of –400 to –1,024 HU were automatically applied to exclude soft tissue surrounding the lung and large vessels within the lung. The 3D model was viewed as a volume-rendering display at multiple angles to ensure that the model was valid. The trachea, main-stem bronchi, and lobar to segmental bronchus were semi-automatically and selectively removed from the 3D model of the whole lung. First, the volume of voxels on these 3D images was calculated as total lung volume (TLV). Second, the volume of voxels with attenuation values <−950 HU of thresholds was measured as low-attenuation volume (LAV). Finally, the percentage of LAV per TLV (LAV%) was calculated as follows: LAV% = LAV/TLV*100.

**Statistical analysis**
The associations between the seven independent variables (LAV%, age, gender, BMI, smoking history, FEV\textsubscript{1}%, and resected lobe) and the two outcomes (postoperative complications and PPS) were compared using univariate and multivariate logistic regression analysis. For this analysis, patients were assigned to two groups based on the Brinkman index (BI) of 200 for smoking history. Next, we determined a cut-off level that would indicate postoperative complications and PPS for LAV% using receiver operating characteristic (ROC) curve analysis and Youden’s index. Excel 2007 (Microsoft Corp., Redmond, WA) and SPSS, version 21.0 (IBM Corp., Armonk, NY) were used to conduct statistical analyses. A \(p\)-value of <0.05 was considered significant.
RESULTS

Study cohort
A total of 309 patients (222 males and 87 females; mean age, 67 years; range, 40–87 years) were enrolled. Other patient characteristics are summarized in Table 1.

Two hundred forty patients (77.7%) had a smoking history and one hundred thirty-three patients (43.0%) demonstrated obstructive abnormality (FEV₁% < 70%). The global initiative for chronic obstructive lung disease (GOLD) stage distribution was as follows: stage I (n=98), stage II (n=32), and stage III (n=3). The mean ± standard deviation (SD) LA V% of non-COPD, GOLD stage I, II, and III group were 2.5 ± 4.9%, 5.4 ± 6.6%, 14.4 ± 14.4%, and 33.6 ± 16.7%, respectively. Resected lobes included the right upper lobe (n=105), right middle lobe (n=18), right lower lobe (n=51), right middle and lower lobe (n=9), left upper lobe (n=89), and left lower lobe (n=37). Pathological analysis of postoperative specimens confirmed 197 adenocarcinomas, 71 squamous cell carcinomas, 15 adenosquamous carcinomas, and 26 other.

Postoperative complications were observed in 120 patients (38.8%); these data are shown in Table 2. The mean ± standard deviation (SD) postoperative duration of hospitalization was 12.8 ± 17.4 days (range, 5–291 days), and 108 patients (35.0%) stayed for ≥12 days.

Table 3 shows the association between independent variables and postoperative complications using univariate and multivariate logistic analysis. On univariate analysis, gender, age, smoking history, LA V%, and FEV₁% were significantly correlated with postoperative complications (p = 0.001, p = 0.010, p = 0.003, p < 0.001, and p = 0.004, respectively), while BMI and resected lobe were not correlated with complications (p = 0.122 and p = 0.665, respectively). On multivariate analysis, only age and LA V% were significantly correlated with postoperative complications (p = 0.006 and p = 0.006, respectively).
Table 1  Patient characteristics

|                        | Mean ± SD | Range    |
|------------------------|-----------|----------|
| Age (years)            | 67 ± 8    | 40 – 87  |
| BMI (kg/m²)            | 22.2 ± 3.5| 13.4 – 38.3|

3D-CT volumetry

|                        |           |          |
|------------------------|-----------|----------|
| TLV (mL)               | 4494 ± 1092| 1507 – 7668|
| LAV (mL)               | 267 ± 509  | 0 – 3825  |
| LA V% (%)              | 5.0 ± 8.4  | 0 – 51.6  |

Spirometry

|                        |           |          |
|------------------------|-----------|----------|
| %VC (%)                | 108.0 ± 17.5| 62.6 – 199.0|
| FEV₁% (%)              | 71.0 ± 10.5| 25.6 – 98.0|
| %DLco/VA (%)           | 95.9 ± 27.9| 23.7 – 181.5|

BMI, body mass index; 3D-CT, three-dimensional computed tomography; TLV, total lung volume; LAV, low-attenuation volume; VC, vital capacity; FEV₁, forced expiratory volume in 1 second; DLco, carbon monoxide diffusing capacity; VA, alveolar ventilation

Table 2  Postoperative complications

|                                    | n   |
|------------------------------------|-----|
| Total                              | 120 |
| Prolonged oxygen treatment         | 84  |
| Cardiac complication               | 43  |
| Pneumonia                          | 19  |
| Prolonged air leakage              | 19  |
| Prolonged ventilation / Reintubation | 10  |

Association between independent variables and PPS

Table 4 shows the association between independent variables and postoperative complications using univariate and multivariate logistic analysis. On univariate analysis, gender, smoking history, LA V%, and FEV₁% were significantly correlated with PPS \((p = 0.0027, p = 0.005, p < 0.001, \text{ and } p = 0.007, \text{ respectively})\), while age, BMI, and resected lobe were not \((p = 0.330, p = 0.326, \text{ and } p = 0.547, \text{ respectively})\). On multivariate analysis, only LA V% was significantly correlated with PPS \((p = 0.031)\).

Determination of suitable cut-off values for predicting postoperative outcomes

In the analysis of postoperative complications the results of the ROC analysis for LA V% showed an area under the curve (AUC) of 0.668 (Fig. 2). A suitable cut-off value for determining complications was estimated to be 2.2%. This value yielded a sensitivity and specificity for postoperative complications of 60.8% and 70.4%, respectively. Of 129 patients who demonstrated an

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**Table 2**  Postoperative complications

|                                    | n   |
|------------------------------------|-----|
| Total                              | 120 |
| Prolonged oxygen treatment         | 84  |
| Cardiac complication               | 43  |
| Pneumonia                          | 19  |
| Prolonged air leakage              | 19  |
| Prolonged ventilation / Reintubation | 10  |
LA V% >2.2% on 3D-CT, 44 patients demonstrated normal FEV1% values (≥70%) on spirometry. In the PPS analysis, the results of the ROC analysis for LA V% showed an AUC of 0.621 (Fig. 3). A suitable cut-off value for determining PPS was estimated to be 4.6%. This value yielded a sensitivity and specificity for PPS of 43.5% and 77.6%, respectively. Of 90 patients who demonstrated an LA V% >4.6% on 3D-CT, 29 patients demonstrated normal FEV1% values on spirometry.

### DISCUSSION

In this study, we retrospectively investigated the association between preoperative 3D-CT
Fig. 2 The ROC curve for the percentage of low-attenuation volume (LAV%) in the postoperative complications analysis. The area under the curve (AUC) of 0.668. A suitable cut-off value for determining complications was estimated to be 2.2%.

Fig. 3 The ROC curve for the percentage of low-attenuation volume (LAV%) in the prolonged postoperative stay (PPS) analysis. The area under the curve (AUC) of 0.621. A suitable cut-off value for determining complications was estimated to be 4.6%.
volumetry and postoperative complications in lung cancer patients. The LA V% calculated from 3D-CT volumetry was significantly correlated with complications after lobectomy, as well as with PPS by multivariate logistic regression analysis. Preoperative FEV1% on spirometry was also correlated with postoperative complications by univariate analysis, while it was not significantly correlated with postoperative complications by multivariate analysis. These results suggest that the LA V% might be more sensitive for predicting complications than the FEV1%.

High-resolution CT is used to assess visually obstructive disease; low-attenuation areas on CT reflect emphysema or air trapping in COPD patients. Recently, CAD has enabled volumetry of low-attenuation areas from pulmonary 3D-CT data, and LA V% is frequently used to objectively evaluate the severity of emphysema. Moreover, the present results demonstrated that the LA V% could be used as an imaging biomarker to predict postoperative complications. However, FEV1% has always been used to evaluate preoperative pulmonary function as a simple index of obstructive pulmonary disorder, even though it is affected not only by simple pulmonary function but also by other factors, including patient effort, age, and breathing muscle function, as well as the examiner’s skill. Mild obstructive pulmonary disorder might also play a role. In fact, one-third of the patients with an LA V% >2.2% in this study showed normal FEV1% values.

We also evaluated suitable cut-off values for determining postoperative complications and PPS by ROC analysis, which were 2.2% and 4.6%, respectively. These values were unexpectedly low, primarily due to the fact that we used 5-mm–thick CT images and therefore may have underestimated partial volume effects. However, even if emphysema is mild, it has the potential to influence pulmonary function, particularly in the perioperative period since pulmonary volume reduction and inflammation occur after lobectomy.

Patient age was also a significant factor for postoperative complications. Male gender and smoking history, which are known to be associated with COPD, were significantly correlated with postoperative complications in univariate analysis, but not in multivariate analysis. LA V% was more closely correlated with respiratory function. Neither BMI nor the resected lobe were significantly correlated with postoperative complications or PPS. The present results are consistent with the reports of Smith et al. and Dhakal et al., which stated that obesity does not increase the incidence of perioperative complications or length of stay following anatomic resection for non-small cell lung cancer.

Several studies have shown that preoperative respiratory rehabilitation programs and use of inhaled bronchodilators in lung cancer patients with COPD can effectively reduce postoperative complications. Traditionally, COPD is diagnosed based on FEV1% values measured by spirometry. However, the present results showed that LA V% values calculated by 3D-CT could more correctly predict COPD compared to FEV1%. Therefore, preoperative affirmative intervention based on LA V% in lung cancer patients might be more effective for preventing postoperative complications.

This study has four limitations. First, it is a retrospective and single-center study. Second, we used 5-mm–thick images to reconstruct 3D-CT, which caused some inaccuracies in the calculation of LA V, as noted above. We suggest that recently developed high-speed CT scanners that can acquire sequential sub-millimeter images and thus more correctly calculate LA V be used in future analyses. Third, we could not evaluate wall thickness of bronchi, which represents airway inflammation, due to the low resolution of the 5-mm–thick CT images. COPD consists of emphysema and obstructive bronchitis, and bronchial wall thickness is significantly correlated with airway obstruction. To predict postoperative complications more accurately, additional analysis of the bronchial wall is needed. Fourth, we could not evaluate the difference of LA V distribution between upper and lower lobes because the interlobar fissure was fuzzy on 5-mm thickness CT images. Recent studies show that pulmonary function seem to be different between
the upper and lower lobes in COPD patients.\textsuperscript{7, 27} Further investigation is needed.

In conclusion, we have demonstrated that LAV\% on preoperative chest 3D-CT is significantly associated with postoperative complications and PPS. Multivariate analysis showed that age and LAV\% were significantly correlated with postoperative complications, and that LAV\% was significantly correlated with PPS. A suitable LAV\% cut-off value for determining postoperative complications and PPS were estimated to be 2.2\% and 4.6\%, respectively. LAV\% was more sensitive for predicting complications after lobectomy for lung cancer than FEV\textsubscript{1}\%, and could potentially be used as a biomarker in the implementation of preoperative respiratory rehabilitation programs.

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