Prediction of postoperative lung function after major lung resection for lung cancer using volumetric computed tomography

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ABSTRACT

Objectives: The study objectives were to assess the accuracy of volumetric computed tomography to predict postoperative lung function in patients with lung cancer in relation to anatomic segments counting and perfusion scintigraphy, to generate specific predictive equations for each functional parameter, and to evaluate accuracy and precision of these in a validation cohort.

Methods: We assessed pulmonary functions preoperatively and 3 to 4 months postoperatively after lung resection for lung cancer (n = 114). Absolute and relative lung volumes (total and upper/middle/lower) were determined using volumetric software analysis for staging thoracic computed tomography scans. Predicted postoperative function was calculated by segments counting, scintigraphy, and volumetric computed tomography.

Results: Volumetric computed tomography achieves a higher correlation and precision with measured postoperative lung function than segments counting or scintigraphy (correlation and intraclass correlation coefficients, 0.779-0.969 and 0.776-0.969; 0.573-0.887 and 0.552-0.882; and 0.578-0.834 and 0.532-0.815, respectively), as well as greater accuracy, determined by narrower agreement coefficients for forced vital capacity, forced expiratory volume in 1 second, lung diffusing capacity, and peak oxygen uptake. After validation in an independent cohort (n = 43), adjusted linear regression including volumetric estimation of decreased postoperative ventilation for postoperative lung function parameters explains 98% to 99% of variance.

Conclusions: Volumetric computed tomography is a reliable and accurate method to predict postoperative lung function in patients undergoing lung resection that provides better accuracy than conventional procedures. Because lung computed tomography is systematically performed in the staging of patients with suspected lung cancer, this volumetric analysis might simultaneously provide the information necessary to evaluate operability. (J Thorac Cardiovasc Surg 2018;156:2297-308)

Segmentation of the thorax in a CT scan with a volumetric representation of the lung areas.

Central Message

Volumetric CT is an accurate and precise method to predict postoperative lung function in patients undergoing lung resection, with better accuracy than conventional procedures.

Perspective

Preoperative evaluation is essential to define the immediate perioperative and the long-term risks of pulmonary disability associated with surgical loss of lung parenchyma. Recent advances in technology, multidetector row CT, and simulation software allow for 3-dimensional lung models to be reconstructed, providing more accurate estimations of the different lung volumes than conventional methods.

See Editorial Commentary page 2309.

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Lung resection is the primary treatment option for patients with early-stage non–small cell lung cancer.¹ According to current guidelines, preoperative physiologic assessment should include the measurement of forced expiratory volume in 1 second (FEV₁) and diffusing capacity for

Scanning this QR code will take you to the article title page to access supplementary information.

Abbreviations and Acronyms

ASC	= anatomic segments counting
CT	= computed tomography
DLCO	= diffusing capacity for carbon monoxide
FEV ₁	= forced expiratory volume in 1 second
FVC	= forced vital capacity
ppo	= predicted postoperative
PS	= perfusion scintigraphy
VO ₂	= oxygen uptake

carbon monoxide (DLCO), as well as peak oxygen uptake (VO₂) when FEV₁ or DLCO is lower than 80% predicted.² Moreover, it is recommended that predicted postoperative (ppo) lung function be calculated, because it is a standard measure for assessing the potential risks of major lung resection²⁻⁴ and is a more powerful predictor than preoperative values.⁵

Commonly used methods for predicting postlung resection function include conventional lung perfusion scintigraphy (PS) and an anatomic method based on counting the number of functional segments to be removed before lobectomy.^{2,6,7} However, the accuracy of these methods varies according to the type of resection performed.^{2,8} Among the different alternatives proposed,⁹⁻¹⁷ chest computed tomography (CT) is particularly interesting, because it is mandatory for the staging of any patient with lung cancer and therefore might provide simultaneous evaluation of operability. With recent advances in technology, multidetector row CT and simulation software (which complete the densitometry analysis with a volumetric analysis) allow for 3-dimensional lung models to be reconstructed, providing more accurate estimations of the different lung volumes.^{18,19}

The aims of this study were (1) to compare volumetric CT with traditional methods to predict several postoperative lung parameters; (2) to develop new equations for predicting these using volumetric CT, based on measured pulmonary function and pre- and postpulmonary resection variables; and (3) to evaluate the accuracy and precision of these equations in a validation cohort operated on subsequent to the equation development cohort.

MATERIAL AND METHODS

Study Subjects

Patients with lung cancer or other intrathoracic malignancies, considered candidates for lung resection and referred to estimate postoperative lung function, were recruited from La Paz Hospital between 2009 and 2014. Operability assessment was performed by applying the Wyser algorithm,²⁰ which has been validated in our setting.²¹ For each patient, the most favorable postoperative lung function predicted by anatomic segment counting or PS was considered. Excluded from the study were patients who had undergone any type of prior thoracic surgery, those with contraindications for lung function

testing, or those who had died within 3 months after lung resection. Patients operated on between 2009 and 2013 were considered the cohort to generate multivariable regression equations for ppo lung function values, and patients operated on in 2014 constituted the validation cohort of said equations. Bronchial tumors were staged according to the seventh edition of the International System for Staging Lung Cancer.²² Patients of the development cohort underwent preoperative lung CT and PS, as well as pulmonary function tests before and 3 to 4 months after surgery. In the validation cohort, only lung CT and pulmonary function tests were performed. All subjects provided informed consent, and the study was approved by the local Human Research Ethics Committee (PI-1266).

Computed Tomography Image Acquisition and Postprocessing

CT performed in the lung cancer diagnosis and staging process was used. Subjects were scanned in the supine position from the lung apex to the base of the chest at withheld full inspiration. All image data were obtained with a 16-row multidetector CT scanner (Somatom Emotion 16, Siemens, Erlangen, Germany) with the following parameters: slice width, 0.3 mm; reconstruction increment, 0.5 mm; collimation, 16 × 0.75 mm; pitch, 0.8; slice collimation, 0.6 mm; voltage, 120 kVp; reference tube current-time, 160 mAs; and rotation time, 0.6 seconds. Routine matrix clinical images were reconstructed with B41 kernel to assessment of soft tissues and high-resolution B90 kernel to assessment of lung parenchyma.

Postprocessing was performed in an independent reconstruction console (Leonardo, Siemens) using a semiautomatic analysis program (syngo InSpace4D, Siemens), which performs a quantitative evaluation of the attenuation of lung parenchyma. The software automatically performs a 3-dimensional segmentation of the lung and, based on the pulmonary reference points and the attenuation thresholds, allows the automatic 3-dimensional quantification of the volume and relative volume percentages of each lung, stratifying the results by lung thirds (upper, middle, and lower) (Figure E1).

Lung Function Tests

Evaluations were performed before and 3 to 4 months after lung resection surgery using the same procedures and equipment. Spirometry and carbon monoxide diffusion tests were performed according to American Thoracic Society/European Respiratory Society guidelines by means of a MasterLab Pro system (Vyasis Healthcare, Hoechst, Germany). Spirometric parameters used for the preoperative evaluation were obtained 20 minutes after inhalation of 400 µg of salbutamol, whereas DLCO was corrected for the patients' hemoglobin values (obtained within a maximum period of 72 hours). Reference values of Quanjer and Cotes were used.^{23,24}

In patients with a FEV₁ or DLCO less than 80% predicted, a symptom-limited incremental exercise test was performed on an electromagnetically braked cycle-ergometer, using a 1-minute step protocol at 15 W/min according to American Thoracic Society/American College of Chest Physicians guidelines. Ventilation and pulmonary gas exchange were measured breath by breath with an Oxycon Alpha exercise system (Vyasis Healthcare, Conshohocken, Pa). Data were averaged every 10 seconds to obtain VO₂ peak. The predicted values of Jones were used for the exercise measurements.²⁵

Lung Perfusion Scintigraphy

Patients received an intravenous injection of 185 MBq (5 mCi) macroaggregated albumin labeled with technetium-99 in the supine position, and a double-head Axis 2 gamma camera (Picker, Fort Myers, Fla) was used with a low-energy high-resolution collimator, 256 × 256 matrix, 140 keV, and a 15% energy window. Five minutes after radiotracer injection, static images of the lungs with 500,000 counts were obtained in

FIGURE 1. CONSORT diagram of the selection process of the development cohort. *DLCO*, Lung diffusion capacity for carbon monoxide; *FEV₁*, forced expiratory volume in 1 second; *ppo*, predicted postoperative; *VO₂*, oxygen uptake.

the anterior, posterior, both posterior oblique, and both anterior oblique projections. Semiquantitative analyses of planar and tomographic images were performed with the Odyssey FX 810 workstation (Marconi Medical System, Cleveland, Ohio). Regions of interest were drawn in the anterior and posterior projections around the entire lung, and each lung was divided into thirds to create superior, middle, and inferior regions of interest. The percentages of the function for each region were calculated by the geometric mean of the anterior and posterior counts.

Prediction of Postoperative Lung Function

The ppo lung function was computed by 3 methods: anatomic functional segments counting (ASC), PS, and volumetric CT. Predictions of postoperative lung function based on functional segments were based on the following equation: ppo value = preoperative value $\times [1 - (S - N)/(19 - N)]$, where *S* is the number of resected segments, *N* is the number of obstructed or consolidated segments resected, and 19 indicates the total number of segments in both lungs. On the basis of the findings of lung CT and bronchoscopy, *N* was counted as 1 for a segment with a narrowing greater than 75% or as 0.5 for a segment with 50% to 75% stenosis.²⁶ The number of segments resected was assigned as 3 for right upper lobectomy, 2 for middle lobectomy, 5 for right lower lobectomy, 5 for left upper lobectomy, 4 for left lower lobectomy, and the sum corresponding for each type of bilobectomy or pneumonectomy.² In the methods based on PS or volumetric CT, the percentage of perfusion or the percentage of volume in each zone/lobe was determined in relation to the perfusion or volume of both lungs. Thus, the following equation was used: ppo value = preoperative value $\times (1 - \text{functional contribution of perfusion or ventilation of the region to be resected})$.¹⁶ Calculations were made for both absolute and percent predicted values of ppo-FEV₁, ppo-forced vital capacity (FVC), ppo-DLCO, and ppo-VO₂ peak.

Statistical Analysis

Sample size calculation was based on an agreement coefficient between the measured postoperative FEV₁, and the ppo-FEV₁ determined by PS of 0.04 ± 0.23 l.¹⁶ On the basis of a 2-tailed test with an $\alpha = 0.05$ and $\beta = 0.20$, the sample size necessary to detect a difference of at least 0.06l using the volumetric CT method was 114 participants.

Data are summarized as mean $\pm$ standard deviation for continuous variables, and frequencies (percentages) are used for categoric variables. The normality of the distribution of variables was tested using the Kolmogorov-Smirnov test. Relationships between predicted and measured

TABLE 1. Patient characteristics*

Parameter	Development cohort	Validation cohort
n	114	43
Men, n (%)	87 (72%)	30 (70%)
Age, y	63 $\pm$ 12	66 $\pm$ 11
BMI, kg/m ²	26.5 $\pm$ 4.3	26.0 $\pm$ 3.6
Current smokers, n (%)	33 (32%)	15 (35%)
COPD diagnosis, n (%)	45 (40%)	20 (47%)
Histology		
Adenocarcinoma	59 (52%)	26 (61%)
Squamous	24 (21%)	10 (23%)
NSCLC, not specified	11 (10%)	3 (7%)
Other neoplasms	20 (18%)	4 (9%)
Final pathologic stage		
O, I	53 (46%)	28 (65%)
II	24 (21%)	9 (21%)
III	20 (18%)	3 (7%)
Pulmonary resection		
Pneumonectomy	17 (15%)	3 (7%)
Bilobectomy	13 (11%)	5 (12%)
Lobectomy	84 (74%)	35 (81%)
Baseline lung function		
FVC, l	3.32 $\pm$ 0.92	3.39 $\pm$ 0.85
FVC, % predicted	97 $\pm$ 19	118 $\pm$ 29
FEV ₁ , l	2.33 $\pm$ 0.73	2.35 $\pm$ 0.69
FEV ₁ , % predicted	86 $\pm$ 19	98 $\pm$ 22
FEV ₁ /FVC	0.70 $\pm$ 0.11	0.70 $\pm$ 0.14
DLCO, mm/min/kPa	6.79 $\pm$ 0.70	6.66 $\pm$ 1.62
DLCO, % predicted	83 $\pm$ 17	84 $\pm$ 17
VO ₂ peak, mL/kg/min†	18.8 $\pm$ 2.6	17.0 $\pm$ 3.1
VO ₂ peak, % predicted†	80 $\pm$ 29	83 $\pm$ 27
Postoperative lung function		
FVC, l	2.59 $\pm$ 0.78	2.96 $\pm$ 0.98
FVC, % predicted	76 $\pm$ 18	89 $\pm$ 20
FEV ₁ , l	1.80 $\pm$ 0.60	1.92 $\pm$ 0.71
FEV ₁ , % predicted	66 $\pm$ 17	74 $\pm$ 18
FEV ₁ /FVC	0.70 $\pm$ 0.10	0.67 $\pm$ 0.15
DLCO, mm/min/kPa	5.26 $\pm$ 1.55	5.26 $\pm$ 1.44
DLCO, % predicted	64 $\pm$ 17	67 $\pm$ 15
VO ₂ peak, mL/kg/min†	14.8 $\pm$ 2.7	12.9 $\pm$ 2.4
VO ₂ peak, % predicted†	63 $\pm$ 24	64 $\pm$ 24

BMI, Body mass index; COPD, chronic obstructive pulmonary disease; NSCLC, non-small cell lung cancer; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusion capacity for carbon monoxide; VO₂, oxygen uptake. *Values are mean $\pm$ standard deviation or percentage. †VO₂ peak was determined in 58 patients in the development cohort and in 21 patients in the validation cohort.

postoperative values for each lung function parameter were calculated with Pearson's correlation, and reliability was assessed through intraclass correlation coefficients for single measures, using a 2-way mixed model and absolute agreement. Limits of agreement between measured and ppo lung function values were analyzed by means of Bland-Altman analysis.²⁷

In the development of multivariable predictive equations for postoperative lung function, sex, age, height, weight, body mass index, and body surface area were included as independent variables, along with the preoperative lung function, the time since surgery to measurement

TABLE 2. Comparison of measured postoperative lung function values with the estimated values by the 3 evaluated methods*

Parameter	Measured	Anatomic segments counting	PS	Volumetric CT	P value
FVC, l	2.59 ± 0.78	2.49 ± 0.81	2.44 ± 0.87	2.56 ± 0.77	.475
FVC, % predicted	76 ± 18	73 ± 18	71 ± 21	75 ± 17	.234
FEV ₁ , l	1.80 ± 0.60	1.75 ± 0.63	1.70 ± 0.64	1.79 ± 0.61	.616
FEV ₁ , % predicted	66 ± 17	64 ± 17	63 ± 19	66 ± 17	.359
FEV ₁ /FVC	0.70 ± 0.11	0.71 ± 0.11	0.70 ± 0.11	0.70 ± 0.11	.989
DLCO, mmol/min/kPa	5.26 ± 1.55	5.07 ± 1.48	4.99 ± 1.66	5.23 ± 1.48	.489
DLCO, % predicted	64 ± 17	62 ± 15	61 ± 19	64 ± 16	.348
VO ₂ peak, mL/kg/min	14.8 ± 2.7	14.1 ± 2.3	13.7 ± 3.4	14.4 ± 2.7	.213
VO ₂ peak, % predicted	63 ± 24	60 ± 23	58 ± 23	61 ± 23	.679

Comparisons between groups by analysis of variance. PS, Perfusion scintigraphy; CT, computed tomography; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusing capacity of carbon monoxide; VO₂, oxygen uptake. *Data are mean ± standard deviation.

of postoperative lung function, and the conversion factor previously described for each evaluation method (ASC, PS, and volumetric CT). The effect of logarithmic and square root transformations of pulmonary function parameters before modeling was also examined. Various regression models (linear, logarithmic, inverse, quadratic, cubic, growth, and exponential) were applied to the series to explain the postoperative lung function values. In the end, we selected a low-order polynomial model because the other tested models did not appear to offer any further significant statistical advantages. In the multiple linear regression analysis, the stepwise method was used to include or remove 1 independent variable at each step, based on the probability of F (entry: 0.05; removal: 0.10). Other aspects explored included the residual standard deviation, changes in the distribution of the residuals, and homogeneity of the variance over the predictors. The assumptions of linearity and distributional normality were confirmed for all variables. Histogram of residuals and normal probability plot of residuals were used to test for normality. Homoscedasticity was explored by scatter plots of the standardized residuals on the standardized predicted values and by Levene's test for equality of variances. When heteroscedasticity was suspected, regression coefficients were computed using weighted least squares. In all regression models, multicollinearity was checked by the determination of the variance inflation factor less than 3 for each predictor. All analyses were performed using SPSS 13.0 software (SPSS Inc, Chicago, Ill).

RESULTS

A total of 114 patients were included in the development cohort (Figure 1) and 43 patients in the validation cohort. All patients were available for the analysis, and postoperative lung function was examined 13 ± 3 weeks after surgery. General patient characteristics are presented in Table 1.

Relationships between the predicted and measured postoperative values (Table 2) are shown in Figure 2, as well as the reliability of the 3 methods for predicting postoperative lung function. For all lung function parameters, correlation coefficients for the ASC and PS were relatively similar, although lower than for the volumetric CT (Table E1). Intraclass correlation coefficients showed a similar tendency. Given that its intraclass correlation coefficient is greater than 0.90, volumetric CT reaches excellent reliability levels to predict postoperative FVC, FEV₁, DLCO, and VO₂ peak and is clearly superior to the other 2 methods.

Agreement between measured and ppo values by the 3 methods is shown in Figures 3 and E2. Volumetric CT reaches better agreement with measured postoperative lung function than ASC or PS for FVC (agreement limits: −0.42 to 0.35 vs −1.05 to 0.85 vs −1.21 to 0.90 l, respectively), FEV₁ (−0.34 to 0.32 vs −0.75 to 0.65 vs −0.88 to 0.68 l), DLCO (−1.25 to 1.18 vs −2.41 to 2.02 vs −2.77 to 2.23 mmol/min/kPa), or VO₂ peak (−0.4 to 3.2 vs −5.3 to 4.0 vs −6.9 to 4.7 mL/kg/min). When analyzed according to the extent of resection, limits of agreement showed a similar trend, both for pneumonectomies or bilobectomies and for lobectomies, and were always narrower for the estimates made by volumetric CT than by ASC or PS (Table E2). Likewise, no significant differences were detected in the agreement limits between patients with normal spirometry or airflow limitation (FEV₁/FVC <0.7), although they were also narrower when the ppo values were determined by volumetric CT than by the other 2 methods (Table E3).

Table 3 shows the parameters related with the postoperative lung function in the univariable regression and the output for each variable included in the final multivariable regression model. The multivariable regression equations developed to calculate the ppo lung function are presented in Table 4. Of the 3 evaluated methods, the models only retained the correction factor provided by the volumetric CT. It is interesting to note that the models generated for the 4 pulmonary function parameters evaluated account for more than 97% of the explained variance in each variable.

Finally, the multivariable equations for the prediction of postoperative lung function were tested in the validation cohort (Figure 4). As shown in Figure 5 and Table E4, Pearson correlation coefficients, intraclass correlation coefficients, and limits of agreement were similar to those reached in the development cohort, which confirms the validation of these equations in a new group of patients.

FIGURE 2. Relation between the absolute values of the measured and ppo lung function determined by ASC (left), PS (middle), or volumetric CT (right). Pneumonectomy (○), bilobectomy (Δ), or lobectomy (●). FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusion capacity for carbon monoxide; VO₂, oxygen uptake; ASC, anatomic segments counting; PS, perfusion scintigraphy; VCT, volumetric computed tomography.

DISCUSSION

Our results show that volumetric CT provides a better estimation for ppo lung function than conventional methods, such as ASC or pulmonary scintigraphy. With respect to the measured postoperative lung function, predicted values determined by volumetric CT reach a higher correlation, precision, and agreement than the other methods. Moreover, we have developed and validated a set of multivariable regression equations to predict

postoperative lung function parameters from volumetric CT, including other anthropometric variables and increasing prediction capacity (Video 1).

The prediction equations generated are applicable to patients considered for lung resection, regardless of the resection planned and the presence or lack of airflow limitation. However, caution should be exercised in patients with severe airflow limitation. In addition, they are specific for each functional parameter, without using a common

FIGURE 3. Agreement between the absolute values of the measured and ppo lung function determined by ASC (left), PS (middle), or volumetric CT (right). The continuous lines represent the mean difference, and the dashed lines represent 2 standard deviations around the mean. Pneumonectomy (○), bilobectomy (Δ), or lobectomy (●). FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusion capacity for carbon monoxide; VO₂, oxygen uptake.

adjustment percentage for the different functional values. This is particularly important when we consider that lung resection affects the different functional parameters differently. Thus, it has been described that the decreases from preoperative values for FVC, FEV₁, DLCO, and VO₂ peak are 30%, 28%, 39%, and 28%, respectively, after pneumonectomy, and 13%, 8%, 20%, and 12%, respectively, after lobectomy.²⁸ Similar differences have been reported by other authors. In fact, postoperative

decreases in FEV₁ of 23% after pneumonectomy and 8% after lobectomy have been described, whereas exercise capacity decreased by 16% after pneumonectomy and 13% after lobectomy.²⁹ Along the same line, Bolliger and colleagues³⁰ reported decreases in FVC of 36% after pneumonectomy and 6% after lobectomy, whereas the decreases in VO₂max were 20% and 1%, respectively. Furthermore, the equations generated also allow one to incorporate the calculation of the upper and lower limits

TABLE 3. Parameters related with the postoperative lung function in the univariate and multivariable analyses

Parameter				Multivariable regression analysis			
	Correlation analysis			Nonstandardized		Standardized	P
	r	95% CI	P value	coefficients	coefficients		
	B	95% CI					value
ppo-FVC, % predicted							
Sex	0.027	−0.158-0.210	.779	−0.031	-	-	.474
Age, y	0.067	−0.118-0.248	.479	−0.004	-	-	.911
Height, cm	−0.181	−0.353-0.003	.037	0.067	0.043-0.091	0.039	.027
Weight, kg	0.009	−0.175-0.193	.921	0.038	-	-	.349
BMI, kg/m ²	0.116	−0.069-0.294	.218	0.036	-	-	.309
Time since surgery, mo	0.060	−0.125-0.241	<.001	0.012	-	-	.457
Preoperative FVC, % predicted	0.746	0.651-0.818	.711	0.731	0.658-0.803	0.702	<.001
CF by ASC	0.113	−0.072-0.291	.232	−0.025	-	-	.479
CF by PS	0.288	0.110-0.448	.002	−0.045	-	-	.269
CF by volumetric CT	0.568	0.429-0.681	<.001	91.931	80.966-102.902	0.567	<.001
ppo-FEV ₁ , % predicted							
Sex	−0.402	−0.546-0.235	<.001	−0.018	-	-	.808
Age, y	−0.459	−0.593-0.300	<.001	−0.018	-	-	.807
Height, cm	0.444	0.283-0.581	<.001	−0.081	-	-	.282
Weight, kg	0.258	0.078-0.422	.006	0.097	-	-	.235
BMI, kg/m ²	0.053	−0.132-0.235	.576	0.063	-	-	.340
Time since surgery, mo	0.157	−0.028-0.331	.328	−0.097	-	-	.188
Preoperative FEV ₁ , % predicted	0.362	0.191-0.512	<.001	0.755	0.616-0.894	0.764	<.001
CF by ASC	0.144	−0.041-0.319	.127	−0.129	-	-	.128
CF by PS	0.121	−0.064-0.298	.198	0.038	-	-	.634
CF by volumetric CT	0.385	0.216-0.531	<.001	80.234	53.686-106.782	0.462	<.001
ppo-DLCO, % predicted							
Sex	−0.014	−0.197-0.170	.881	0.032	-	-	.521
Age, y	0.277	0.098-0.439	.003	0.054	0.050-0.058	0.018	.036
Height, cm	−0.213	−0.382-0.030	.027	−0.135	−0.181-0.079	0.021	.012
Weight, kg	0.184	0.000-0.356	.045	0.045	0.021-0.069	0.007	.044
BMI, kg/m ²	0.088	−0.097-0.268	.353	0.050	-	-	.287
Time since surgery, mo	0.116	−0.069-0.294	.469	−0.044	-	-	.348
Preoperative DLCO, % predicted	0.748	0.654-0.819	<.001	0.728	0.636-0.820	0.723	<.001
CF by ASC	0.032	−0.153-0.215	.739	0.024	-	-	.467
CF by PS	0.195	0.011-0.366	.038	−0.016	-	-	.521
CF by volumetric CT	0.504	0.353-0.630	<.001	75.441	60.135-90.747	0.465	<.001
ppo-VO ₂ peak, L/kg/min							
Sex	−0.004	−0.262-0.255	.976	0.084	-	-	.589
Age, y	0.075	−0.187-0.327	.574	0.028	-	-	.861
Height, cm	0.012	−0.247-0.269	.930	−0.189	-	-	.202
Weight, kg	−0.103	−0.352-0.160	.443	−0.072	-	-	.664
BMI, kg/m ²	0.316	0.063-0.531	.024	0.019	0.007-0.031	0.008	.043
Time since surgery, mo	0.204	−0.057-0.439	.318	0.196	-	-	.169
Preoperative VO ₂ peak, mL/kg/min	0.673	0.502-0.793	<.001	0.769	0.461-1.077	0.726	<.001
CF by ASC	0.038	−0.222-0.293	.779	0.085	-	-	.486
CF by PS	0.244	−0.015-0.473	.065	−0.090	-	-	.558
CF by volumetric CT	0.341	0.091-0.551	.009	19.294	5.944-32.644	0.388	.014

r, Pearson correlation coefficient; CI, confidence interval; B, regression coefficient; ppo, predicted postoperative; FVC, forced vital capacity; Sex, 0 = male, 1 = female; BMI, body mass index; CF, correction factor; ASC, anatomic segments count; PS, pulmonary scintigraphy; CT, computed tomography; FEV₁, forced expiratory volume at 1 second; DLCO, lung diffusing capacity for carbon monoxide; VO₂, oxygen uptake.

of normal for each prediction, which facilitates interpretation of the margin of variation in the estimation of postoperative lung function.

As for the conventional prediction methods, ASC and PS in our patients have reached an efficacy that is similar to reports in previous studies, with a correlation coefficient

TABLE 4. Multivariable regression equations to determine postoperative lung function parameters

Parameter	Predictive equation	R ²	RSD
ppo-FVC, % predicted	$0.731 \cdot \text{FVC} + 91.931 \cdot (1 - \text{FCVRR}) - 0.06714 \cdot \text{H} - 55.776$	0.980	2.4422
ppo-FEV ₁ , % predicted	$0.755 \cdot \text{FEV}_1 + 80.234 \cdot (1 - \text{FCVRR}) - 60.440$	0.982	2.3155
ppo-DLCO, % predicted	$0.728 \cdot \text{DLCO} + 75.441 \cdot (1 - \text{FCVRR}) - 0.135 \cdot \text{H} - 0.05417 \cdot \text{A} + 0.04488 \cdot \text{W} - 31.699$	0.977	2.3864
ppo-VO ₂ peak, mL/kg/min	$0.769 \cdot \text{VO}_2 \text{ peak} + 19.294 \cdot (1 - \text{FCVRR}) + 0.01925 \cdot \text{BMI} - 15.386$	0.991	0.2572

The lower limit of normal is computed as ppo value $- 1.645 \times \text{RSD}$. The upper limit of normal is computed as ppo value $+ 1.645 \times \text{RSD}$. R², Adjusted coefficient of determination; RSD, residual standard deviation; ppo, predicted postoperative; FVC, forced vital capacity; FCVRR, functional contribution of ventilation of the region to be resected measured by volumetric computed tomography; H, height in cm; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusing capacity of carbon monoxide; A, age in years; W, weight in kg; VO₂, oxygen uptake; BMI, body mass index in kg/m².

ranging from 0.70 to 0.87 for most parameters^{5,31,32} and limits of agreement similar to those obtained in our study.¹⁶ However, as previously mentioned, the PS, which estimates the functional contribution of a lobe or an entire lung by drawing regions-of-interest on planar perfusion images acquired with a gamma camera after injection of technetium-99m-labeled macroaggregate of albumin,³³ is not available in all centers, probably because of the costs of the equipment and the procedure. In addition, this technique generates an additional dose of radiation and causes more delay in the patient evaluation.

In contrast, CT is an interesting alternative. The first predictions of approximate postoperative lung function from CT were done with densitometry analysis. Lung volume was estimated by multiplying the area of each functionally relevant lung tissue by the slice thickness, and ppo lung function was calculated by subtracting the volume of the area to be resected from the total functional lung volume.¹³ In a small group of patients, it was reported that spirometric values predicted with this approximation correlated well with postoperative FEV₁ and FVC measurements.¹³ In comparison with PS, both methods

FIGURE 4. Relation between the absolute values of the measured and ppo lung function using the multivariable regression equations in the validation cohort. Pneumonectomy (○), bilobectomy (Δ), or lobectomy (●). FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusing capacity for carbon monoxide; VO₂, oxygen uptake.

FIGURE 5. Agreement between the measured and ppo lung function using the multivariate regression equations in the validation cohort, expressed as absolute value (left) or percentage of predicted (right). The continuous lines represent the mean difference, and the dashed lines represent 2 standard deviations around the mean. Pneumonectomy (○), bilobectomy (Δ), or lobectomy (●). FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusion capacity for carbon monoxide; VO₂, oxygen uptake.

VIDEO 1. Relevance of volumetric CT analysis to operability study of patients with lung cancer. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32018-X/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32018-X/fulltext).

reach a good correlation with measured postoperative FEV₁ in patients who underwent pneumonectomy or lobectomy.^{12,14,15} However, in patients with normal or only mildly decreased lung function, perfusion lung scanning was slightly superior to quantitative CT, mainly in the prediction of FVC, DLCO, and VO₂ peak.¹⁶ Moreover, the available information on the accuracy of the estimation of postoperative function by CT in patients with airflow limitation is limited.¹⁷

The information available about the accuracy of the 3-dimensional CT for predicting postoperative lung function is still scarce and, to our knowledge, limited to the description of a good correlation between ppo-FEV₁ and measured postoperative FEV₁ in a small group of patients.¹⁹ However, our results show that volumetric CT has a greater capacity for predicting postoperative lung function than the classic methods and far surpasses the degree of precision obtained with the estimation of lung volumes based on classic densitometry CT.¹²⁻¹⁷ These results, together with the relative accessibility of this type of analysis (software available for almost all CT equipment at an additional cost of ~\$17,000), make it an ideal procedure for the evaluation of operability. Likewise, the accuracy in the prediction of postoperative functional values by means of volumetric CT is also greater than that reported for alternative low-cost procedures, such as quantitative breath sound measurement using vibration response imaging.^{11,34}

In recent years, it has also been proposed to predict postoperative lung function using single-photon emission CT,¹⁰ 4-dimensional CT ventilation,^{9,35} positron emission tomography/CT,³⁶ or dynamic contrast-enhanced perfusion magnetic resonance imaging.^{12,37} The correlation coefficients between measured postoperative FEV₁ and that determined by these procedures range from

0.81 to 0.99,^{9,10,12,38,39} which do not surpass those obtained by volumetric CT, despite requiring more expensive and less-accessible procedures that, in some cases, involve additional radiation for the patient. In comparison, the evaluation of operability by means of volumetric CT uses an examination that is required in all patients with suspected lung cancer, without causing discomfort or additional risk for the patient. At the same time, its cost is low and limited to the acquisition of semiautomatic analysis software, and the estimated image postprocessing time is 10 to 15 minutes.

Study Limitations

Our study has several limitations. First, it is a single-center study analyzing a sample of patients operated on by a single surgical team. A *P* value of .05 was used to establish significance without adjustment for multiplicity, and the sample size was small for predictive modeling. Second, we did not analyze the impact on lung function of the surgical approach used, because patients who had been treated by thoracotomy or by video-assisted thoracoscopic surgery were analyzed together. Third, arbitrarily and in accordance with most of the previous literature, it was decided to evaluate the postoperative lung function 3 to 4 months after lung resection surgery. However, this period might not be sufficient in all cases to determine the definitive postoperative function. In fact, although the loss of lung function caused by pneumonectomy seems to remain stable over time, it has been described that some patients who undergo lobectomy experience a mild recovery of FEV₁ and peak VO₂ between 3 and 6 months after surgery.¹² Fourth, similarly to scintigraphy, the segmentation of the lung on the CT divides the lung into thirds, rather than actual anatomic segments. Fifth, only 6 of the 45 patients with airflow limitation in our study had severe obstruction. Therefore, precaution must be taken when applying the equations generated in patients with very severe chronic obstructive pulmonary disease, especially those with emphysema. This is particularly important for the so-called lobar volume reduction effect, which suggests that in patients with lung cancer and severe chronic obstructive pulmonary disease, the resection of the most affected parenchyma may determine an improvement in respiratory mechanics and elastic recoil, even originating an improvement in respiratory function 3 to 6 months after lobectomy.^{31,38,39}

CONCLUSIONS

Our study shows that volumetric CT is an accurate and precise method for predicting postoperative lung function in patients undergoing lung resection, achieving better performance than conventionally used procedures, such as ASC or PS. Therefore, and given that CT is done systematically in the staging of all patients with suspected

lung cancer, the volumetric analysis could simultaneously provide the information necessary for the evaluation of operability. To generalize this procedure, more studies are needed to evaluate its accuracy in other centers, with several surgical procedures and on large patient samples including more ethnic groups and a broad spectrum of comorbidities.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: computed tomography, lung cancer, lung function, operability, surgery

FIGURE E1. An example patient showing the segmentation of the thorax in the axial (A) and coronal (B) views to obtain a volumetric representation of both lungs with the division of lung areas (C). The software provides values for absolute and relative lung volumes (Vol. and Vol.rel., respectively), as well as mean lung density (*MLD*), standard deviation (*DE*), full width at half maximum (*FWHM*), low attenuation volume (*LAV*), and high attenuation volume (*HAV*) (D).

FIGURE E2. Agreement between the percentage of predicted of the measured and ppo lung function determined by anatomic segments counting (*left*), PS (*middle*), or volumetric CT (*right*). The continuous lines represent the mean difference, and the *dashed lines* represent 2 standard deviations around the mean. Pneumonectomy (○), bilobectomy (Δ), or lobectomy (●). FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusing capacity of carbon monoxide; VO₂, oxygen uptake.

TABLE E1. Relation and reliability of the 3 evaluated methods to predict postoperative lung function with respect to the measured postoperative lung function

Parameter	Pearson correlation coefficient (95% CI)			Intraclass correlation coefficient (95% CI)		
	Anatomic segments counting	PS	Volumetric CT	Anatomic segments counting	PS	Volumetric CT
FVC, l	0.820 (0.749-0.872)	0.801 (0.724-0.858)	0.969 (0.948-0.982)	0.814 (0.739-0.869)	0.783 (0.689-0.849)	0.969 (0.955-0.978)
FVC, % predicted	0.673 (0.558-0.763)	0.706 (0.600-0.788)	0.941 (0.902-0.965)	0.663 (0.543-0.756)	0.678 (0.553-0.771)	0.939 (0.912-0.958)
FEV ₁ , l	0.873 (0.821-0.911)	0.806 (0.730-0.862)	0.964 (0.940-0.979)	0.835 (0.770-0.883)	0.795 (0.711-0.856)	0.964 (0.948-0.975)
FEV ₁ , % predicted	0.718 (0.615-0.797)	0.713 (0.609-0.793)	0.936 (0.894-0.962)	0.715 (0.612-0.794)	0.695 (0.571-0.782)	0.936 (0.909-0.956)
DLCO, mmol/min/kPa	0.734 (0.636-0.809)	0.700 (0.592-0.783)	0.921 (0.870-0.953)	0.729 (0.630-0.805)	0.690 (0.578-0.776)	0.920 (0.886-0.944)
DLCO, % predicted	0.659 (0.541-0.752)	0.650 (0.529-0.745)	0.897 (0.831-0.938)	0.649 (0.529-0.744)	0.637 (0.511-0.736)	0.894 (0.850-0.926)
VO ₂ peak, mL/kg/min	0.573 (0.435-0.685)	0.578 (0.441-0.689)	0.779 (0.652-0.864)	0.552 (0.346-0.708)	0.532 (0.311-0.697)	0.776 (0.649-0.861)
VO ₂ peak, % predicted	0.887 (0.840-0.921)	0.834 (0.768-0.883)	0.940 (0.900-0.964)	0.882 (0.808-0.929)	0.815 (0.686-0.891)	0.939 (0.899-0.963)

CI, Confidence interval; PS, pulmonary scintigraphy; CT, computed tomography; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusing capacity of carbon monoxide; VO₂, oxygen uptake.

TABLE E2. Limits of agreement between the measured and the predicted postoperative lung function according to the type of resection performed

Parameter	Pneumonectomy or bilobectomy (n = 30)	Lobectomy (n = 84)	Overall (n = 114)
FVC, l			
Anatomic segments counting	−0.98 to 1.28	−1.01 to 0.62	−1.05 to 0.85
PS	−1.04 to 0.87	−1.26 to 0.90	−1.21 to 0.90
Volumetric CT	−0.56 to 0.43	−0.36 to 0.31	−0.42 to 0.35
FVC, % predicted			
Anatomic segments counting	−28 to 36	−31 to 20	−32 to 25
PS	−32 to 27	−36 to 25	−35 to 26
Volumetric CT	−16 to 13	−12 to 10	−13 to 11
FEV ₁ , l			
Anatomic segments counting	−0.77 to 1.01	−0.69 to 0.47	−0.75 to 0.65
PS	−0.79 to 0.67	−0.91 to 0.68	−0.88 to 0.68
Volumetric CT	−0.49 to 0.42	−0.27 to 0.27	−0.34 to 0.32
FEV ₁ , % predicted			
Anatomic segments counting	−27 to 35	−27 to 18	−28 to 24
PS	−30 to 25	−32 to 23	−32 to 24
Volumetric CT	−18 to 15	−11 to 10	−13 to 12
DLCO, mmol/min/kPa			
Anatomic segments counting	−2.41 to 3.10	−2.24 to 1.48	−2.41 to 2.02
PS	−2.35 to 2.21	−2.92 to 2.23	−2.77 to 2.23
Volumetric CT	−1.41 to 1.37	−1.19 to 1.12	−1.25 to 1.18
DLCO, % predicted			
Anatomic segments counting	−29 to 35	−28 to 19	−29 to 24
PS	−30 to 28	−34 to 26	−33 to 26
Volumetric CT	−18 to 17	−15 to 14	−15 to 15
VO ₂ peak, mL/kg/min			
Anatomic segments counting	−6.55 to 5.69	−4.74 to 3.29	−5.29 to 4.00
PS	−8.38 to 7.01	−6.18 to 3.76	−6.86 to 4.73
Volumetric CT	−5.75 to 3.75	−2.97 to 2.78	−3.89 to 3.20
VO ₂ peak, % predicted			
Anatomic segments counting	−35 to 31	−20 to 15	−25 to 20
PS	−40 to 32	−29 to 18	−32 to 22
Volumetric CT	−28 to 19	−13 to 12	−18 to 15

FVC, Forced vital capacity; PS, pulmonary scintigraphy; CT, computed tomography; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusing capacity of carbon monoxide; VO₂, oxygen uptake.

TABLE E3. Limits of agreement between the measured and the predicted postoperative lung function according to the presence or absence of airflow limitation

Parameter	Normal spirometry (n = 69)	Airflow limitation (n = 45)
FVC, l		
Anatomic segments counting	−1.02 to 0.92	−1.10 to 0.72
PS	−1.18 to 0.90	−1.26 to 0.89
Volumetric CT	−0.42 to 0.37	−0.42 to 0.32
FVC, % predicted		
Anatomic segments counting	−31 to 28	−32 to 20
PS	−32 to 25	−39 to 27
Volumetric CT	−13 to 11	−14 to 10
FEV ₁ , l		
Anatomic segments counting	−0.79 to 0.76	−0.65 to 0.45
PS	−0.93 to 0.77	−0.78 to 0.53
Volumetric CT	−0.37 to 0.39	−0.25 to 0.18
FEV ₁ , % predicted		
Anatomic segments counting	−30 to 28	−24 to 16
PS	−32 to 26	−31 to 20
Volumetric CT	−14 to 14	−10 to 7
DLCO, mmol/min/kPa		
Anatomic segments counting	−2.61 to 2.31	−2.04 to 1.53
PS	−2.96 to 2.38	−2.50 to 2.00
Volumetric CT	−1.38 to 1.26	−1.02 to 1.05
DLCO, % predicted		
Anatomic segments counting	−31 to 27	−26 to 19
PS	−34 to 27	−32 to 25
Volumetric CT	−17 to 15	−13 to 13
VO ₂ peak, mL/kg/min		
Anatomic segments counting	−4.74 to 5.27	−5.21 to 2.54
PS	−6.96 to 5.80	−6.72 to 3.86
Volumetric CT	−4.29 to 4.59	−3.21 to 1.78
VO ₂ peak, % predicted		
Anatomic segments counting	−27 to 29	−20 to 9
PS	−32 to 26	−32 to 18
Volumetric CT	−21 to 22	−14 to 8

FVC, Forced vital capacity; PS, pulmonary scintigraphy; CT, computed tomography; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusing capacity of carbon monoxide; VO₂, oxygen uptake.

TABLE E4. Evaluation of the volumetric computed tomography–derived multivariable regression equations to predict postoperative lung function values with respect to the measured postoperative function in patients from the validation cohort

Parameter	Pearson correlation coefficient (95% CI)	Intraclass correlation coefficient (95% CI)	Limits of agreement
FVC, l	0.955 (0.918–0.976)	0.949 (0.908–0.972)	−0.46 to 0.62
FVC, % predicted	0.905 (0.830–0.948)	0.895 (0.815–0.942)	−14 to 18
FEV ₁ , l	0.953 (0.914–0.974)	0.952 (0.913–0.974)	−0.29 to 0.45
FEV ₁ , % predicted	0.909 (0.837–0.950)	0.908 (0.836–0.949)	−11 to 15
DLCO, mmol/min/kPa	0.859 (0.753–0.922)	0.859 (0.754–0.921)	−1.27 to 1.19
DLCO, % predicted	0.812 (0.677–0.894)	0.812 (0.678–0.894)	−16 to 16
VO ₂ peak, mL/kg/min	0.875 (0.712–0.948)	0.874 (0.718–0.947)	−2.8 to 2.4
VO ₂ peak, % predicted	0.962 (0.907–0.985)	0.963 (0.912–0.985)	−14 to 12

CI, Confidence interval; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; DLCO, lung diffusing capacity of carbon monoxide; VO₂, oxygen uptake.