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Original Article

Factors Affecting Prediction Accuracy of Postoperative FEV1 and $D_{L,CO}$ in Patients Undergoing Lung Resection

Anastas Chapkanov[1], Miroslava Todorova[2], Antoaneta Chirlova[3], Blagoi Marinov[4]

[1] *Department of Special Surgery, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria*

[2] *FAMA Medical Center, Plovdiv, Bulgaria*

[3] *Kaspela University Hospital, Plovdiv, Bulgaria*

[4] *Department of Pathophysiology, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria*

Corresponding author: Anastas Chapkanov, Department of Special Surgery, Faculty of Medicine, Medical University of Plovdiv, 15A Vassil Aprilov Blvd., 4002 Plovdiv, Bulgaria; Email: achapkanov909@gmail.com; Tel.: +359 888 312 287

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Abstract

Introduction: Despite significant development in systemic therapy and radiotherapy, surgery is still the cornerstone for curative lung cancer treatment. Although predicted postoperative function (ppo) somewhat exactly correlates with actual postoperative function bigger differences may be a cause of serious clinical outcome.

Aim: The aim of our study was to identify clinical factors affecting prediction accuracy of postoperative lung function for more careful selection of operable lung cancer patients.

Patients and methods: Seventy patients were studied prospectively. The preoperative lung function tests (FEV1 and $D_{L,CO}$) were performed within a week before surgery, and the follow-up tests were performed 4 to 6 weeks after surgery. Calculation of predicted postoperative values were calculated by three methods: two segment formulas and vibration response imaging (VRI). The correlation between each clinical parameter and accuracy of prediction was screened on univariate analysis of Pearson's correlation coefficient, and significant factors were confirmed by multivariate linear regression analysis applying backward stepwise elimination approach.

Results: Univariate linear regression analysis between the predicted and the actual postoperative values of FEV1% and $D_{L,CO}$ showed the highest prediction accuracy with acoustic mapping (VRI). Multivariate regression analysis showed that prediction accuracy of postoperative lung function is significantly affected by COPD ($p<0.001$) and volume of resection ($p<0.001$).

Conclusion: Vibration response imaging (VRI) is a more accurate method for predicting postoperative lung function than segment method formulas. Anatomical calculation significantly underestimates the postoperative values of FEV1% in patients with COPD. Prediction of FEV1% and $D_{L,CO}$ with segment counting is significantly influenced by the volume of resection.

Keywords

lung cancer, postoperative lung function, prediction accuracy, vibration response imaging

INTRODUCTION

Despite significant development in systemic therapy and radiotherapy, surgery is still the cornerstone for curative lung cancer treatment. Pulmonary lobectomy is the standard operative treatment for primary non-small cell lung cancer (NSCLC). Because of relatively high incidence of postoperative complications, the hospital mortality, as well as disappointing long-term survival after surgical resection of lung cancer, the appropriate selection of patients for pulmonary resection is a continuing challenge. Forced expiratory volume in one second (FEV1) and the diffusing capacity for carbon monoxide ($D_{L,CO}$) are the most commonly used predictors of postoperative outcome.[1-3] Postoperative values of FEV1 and $D_{L,CO}$ are the mainstay for assessing perioperative risk after lung resection. Although predicted postoperative function (ppo) somewhat exactly correlates with actual postoperative function, bigger differences may be a cause of serious clinical outcome, especially in patients with marginal postoperative lung function: someone may undergo life-threatening lung resection, and someone may lose the opportunity to be cured by surgery.

AIM

The aim of our study was to identify clinical factors affecting prediction accuracy of postoperative lung function for more careful selection of operable lung cancer patients.

PATIENTS AND METHODS

Patients

We conducted a prospective cohort study of patients undergoing anatomical lung resection in the Department of Special Surgery at St George University Hospital in Plovdiv and the Department of Thoracic Surgery at Kaspela University Hospital in Plovdiv.

Lung function tests

The preoperative lung function tests were performed within a week before surgery, and the follow-up tests were performed 4 to 6 weeks after surgery. Lung function tests were performed using the MasterScreen Body/Diffusion™ computerized spirometer (Jaeger, Wuerzburg, Germany) with real-time curve drawing and automatic correction (BTPS – body temperature pressure saturated). The postbronchodilator lung function values were used.

Calculation of predicted postoperative values (ppo) of FEV1 and $D_{L,CO}$

Predicted postoperative FEV1% and $D_{L,CO}$%, were calculated by three methods.

Anatomical calculation

SF1

The simple calculation method introduced by Juhl et al.[4] assumes that the right lung is composed of 10 segments (3 segments in the upper lobe, 2 segments in the middle lobe, and 5 segments in the lower lobe), the left lung of 9 segments (5 segments in the upper lobe, 4 segments in the lower lobe), and that all the segments contribute equally to lung function.

SF1–(Juhl & Frost, 1975; Zeiher et al., 1995).[4,5]

$$\text{Number of segments (S): ppoFEV1} = \text{preoperative FEV1} \times [1 - (\frac{\text{number of segments to be resected}}{19})]$$

SF2

Modified segment formula introduced by Bolliger that takes into account only functional (none obstructed) segments

SF2–(Bolliger et al. 2002)[6]

$$\text{Number of functional segments (FS): ppoFEV1} = \text{preoperative function} \times (1 - \frac{y}{z}),$$

where y is the number of functional segments to be removed and z is the total number of functional segments.

Vibration response imaging (VRI) and O-Plan software

The vibration response imaging system (VRIxp, Deep Breeze, Or-Akiva, Israel) quantifies breath sounds and displays the results as a dynamic image and numerical values. It measures the vibration energy of lung sounds generated during the respiratory cycle. Vibration response imaging (VRI) technology is harmless, non-invasive and does not require the addition of a tracer to the inhaled air or blood stream. The technology and the calculation were described in detail earlier.[7,8]

Clinical parameters affecting prediction accuracy of postoperative lung function

In the literature, we have identified clinical factors with potential impact on the accuracy of prediction of postoperative lung function: sex, body mass index, smoking, preoperative FEV1%, presence of COPD and type of operation.[9-12]

Patients were divided in groups according to the studied factor: male/female; smoker/ex-no smoker; patients with baseline FEV1% ≥ 80% and with FEV1% < 80%; with COPD and without COPD as defined by GOLD 2007 criteria; patients with COPD index ($COPD_I$) <1.5 and those with $COPD_I$ ≥1.5. To investigate the influence of operative intervention on the accuracy of prediction of the postoperative lung function, we performed a comparison between the results obtained in patients with upper and lower lobectomy, lobectomy and pulmonectomy and removal of >4 and ≤4 functioning lung segments. We compared the prediction accuracy of the three calculation methods. The influence of the clinical parameters on prediction was studied separately for each method.

Statistical analysis

The adjusted coefficient of determination (adjusted R^2) was used to compare the prognostic accuracy of the three methods.

To assess the influence of studied clinical factors on the prediction made by the three different methods used (SF1, SF2 and VRI), the value of relative deviation in percentages was introduced:

$$D\% = \frac{ppo - apo}{apo} . 100,$$

where ppo – predicted postoperative values of FEV1 and $D_{L,CO}$; and apo – actual postoperative values of FEV1 and $D_{L,CO}$.

Metric variables were checked for normality of distribution by the Kolmogorov-Smirnov test. An independent sample *t*-test was used to compare means of continuous variables. The Mann-Whitney *U*-test was used for variables not normally distributed. The correlation between each clinical parameter and accuracy of prediction was screened on univariate analysis of Pearson's correlation coefficient, and significant factors were confirmed by multivariate linear regression analysis applying backward stepwise elimination approach. A *p*-value less than 0.05 was considered to be significant in all statistical analyses.

The study design was approved by the Medical University of Plovdiv's institutional review board and is in accordance with the Declaration of Helsinki ethical standards.

RESULTS

Patient characteristics

The baseline characteristics of the patients are summarized in **Table 1**. One hundred and two patients were studied prospectively. Of these, five patients dropped out due to failure to appear for post-operative examination and 27 due to initiation of adjuvant therapy before post-operative examination. Seventy patients remained for the study. There were 52 (74.3%) men and 18 (25.7%) women. The mean age was 61.7±8.0 years in the range between 46 and 78 years.

Table 1. Patient characteristics of the studied population

Patient characteristics	n	(%)
BMI		
< 18.5	2	2.9
18.5-24.9	31	44.3
25-29.9	19	27.1
> 30	18	25.7
COPD index		
< 1.5	25	35.7
> 1.5	45	64.3
GOLD		
Without COPD	51	72.9
COPD	19	27.1
Type of surgery		
Pneumonectomy	17	24.3
Upper lobectomy	34	48.6
Lower lobectomy	19	27.1
Smoking status		
smoker	38	54.3
no+ex smoker	32	45.7
Number of resected functional segments		
≤ 4	30	42.9
> 4	40	57.1
Preoperative FEV1%		
> 80%	48	68.6
< 80%	22	31.4

Prediction accuracy of postoperative lung function

Univariate linear regression analysis between the predicted and the actual postoperative values of FEV1% and $D_{L,CO}$ showed the highest prediction accuracy with acoustic mapping (VRI). The adjusted coefficient of determination for FEV1% was R^2 adj=55.12% for VRI, R^2 adj=46.23% for SF1, and R^2 adj=31.29% for SF2. For $D_{L,CO}$%, VRI showed R^2 adj=64.00%. SF1-R^2 adj=47.85% and SF2-R^2 adj=45.11.

Clinical parameters affecting prediction accuracy of postoperative lung function

Univariate analysis of BMI and smoking status showed no statistically significant influence on prediction accuracy with all three methods.

When examining the influence of gender on the determination of ppo FEV1.0% and $D_{L,CO}$, a difference was found. In men, the values were negative, indicating that the predicted values were lower than those measured postoperatively. For women, the values were higher than actually measured. Statistically significant difference was found only for the prediction of ppo FEV1% with acoustic mapping. A similar trend was observed for $D_{L,CO}$(%), but the sex difference did not reach significance.

To investigate the influence of baseline preoperative FEV1 (%), patients were categorized into two groups: FEV1

(%) >80% and FEV1 (%) ≤80%. All three methods reported an overestimation of functional loss. When using the SF1 segment formula, we observed a significantly greater value of relative deviation (D%) of FEV1 (%) in the FEV1 (%) ≤80% group with a median of −25.58% compared to median −4.97% in patients with FEV1 (%) >80%, p=0.001. With the SF2 formula, a significantly higher D% value was also found in the FEV1 (%) ≤80% group with a median of −7.68% compared to a median of −3.03% in patients with FEV1 (%) >80%, p=0.012. D% showed no significant difference between the groups when calculated with VRI, p=0.256. No statistically significant difference was observed between the two groups in the calculation of $D_{L,CO}$% with all the three methods.

In patients with COPD, all methods reported an underestimation of postoperative FEV1 (%). Significantly greater values were found in patients with COPD predicted with SF1 formula – median −20.68% compared to median −5.69% in patients without COPD, p=0.002. The difference was significant with SF2 formula, with a median of −12.4% in the COPD group and 4.00% in the non-COPD group, p=0.005. The relative deviation for diffusion capacity (D%) $D_{L,CO}$% showed no significant differences between patients with and without COPD in all three prognostic methods.

In patients with $COPD_I$ ≥1.5 and $COPD_I$ <1.5, a significant difference was found in the prediction of FEV1 (%) with SF1 segment formula, with a significantly greater value in the group with $COPD_I$ <1.5 (-18.65±15.7%) compared to those with $COPD_I$ ≥1.5 (−2.81±18.8%), p=0.001.

Lobectomy was performed in 53 patients, in 34 of whom with upper lobectomy and in 19 with lower lobectomy. Pulmonectomy was performed in 17 patients. Comparative analysis of the relative deviation between lobectomy and pulmonectomy patients was preceded by an intergroup comparison between upper and lower lobectomy patients. Based on the intergroup analysis, upper and lower lobectomy patients were pooled into one lobectomy group, due to lack of significant difference between upper and lower lobectomy patients in all indices and methods

When predicting FEV1 (%), the D% values, predicted with either of the three methods, were negative as a result of the greater underestimation of postoperative FEV1 (%) in the pneumonectomy patients compared to the lobectomy patients. The difference was significant in patients with pulmonectomy calculated with the first variant of the segment method SF1 (p<0.001). Significantly higher negative D% $D_{L,CO}$% values were found in the pneumonectomy patients predicted with all three methods.

A significant difference was observed in the prediction of $D_{L,CO}$% with both segment formulas when comparing patients with more than 4 segments removed to patients with 4 or less removed segments. A significantly higher relative deviation of $D_{L,CO}$% was observed with SF1 method in the >4 segments removed group (−12.94±18.4%) compared to the ≤4 segments removed group (−2.14±16.3%), p=0.015. For SF2, the relative deviation D% $D_{L,CO}$% was (6.94±14.3%) in the ≤4 segments removed group, while in those with >4 segments removed, D% $D_{L,CO}$% had a negative value (−8.52±18.6), p<0.001. In SF2, the same dependence was observed in D% FEV1 (%), where in the group of patients with ≤4 segments removed, the relative deviation had a positive value (8.22±24.1%) and negative in the group with >4 segments removed (−6.31±17.8%), p<0.001.

Sex and operative intervention (pulmonectomy/lobectomy) were identified by univariate analysis as factors affecting the accuracy of VRI to predict postoperative FEV1 (%) and $D_{L,CO}$%. The results of the multivariate regression analysis showed that they do not contribute significantly to improvement of the prediction accuracy

For the first variant of the segment method (SF1), multivariate regression analysis found out that two of the six variables included in the prognostic model have a significant prognostic role: COPD (p=0.019), in the prediction of postoperative FEV1% and the type of operation (lobectomy/pulmonectomy) in the prediction of $D_{L,CO}$% (p<0.001).

For the second variant of the segment method (SF2), COPD (p=0.004) and number of removed segments (p=0.049) were found to be significant factors in prediction accuracy of FEV1%.

DISCUSSION

Medical operability of lung cancer has been frequently determined based on FEV1, D_{LCO}, and VO2max. Accurate prediction of postoperative residual lung function is mandatory to minimize postoperative morbidity and mortality. Although predicted postoperative function (ppo) somewhat exactly correlates with actual postoperative function bigger differences may be critical in the patients with marginal lung function after lung resection. We should consider that the accuracy can be affected not only by the technique to measure the regional lung function, but also several clinical factors

In our study, we found that VRI-based prediction was a more accurate method than anatomical calculation irrespective of the extent of resection. This result is in consistency with Berreta et al.[13], and Detterbeck et al.[14] The prediction accuracy of VRI was confirmed by the studies of Comce et al.[15], Jimenez et al.[16], Morice et al.[17], and Kim et al.[18] in comparison with perfusion scintigraphy, which is considered the gold standard in determining the predicted postoperative values of FEV1 and $D_{L,CO}$.

We observed a higher overestimation of functional loss in patients with FEV1%<80%, (postoperatively measured values were higher than predicted) in all three methods. Boushy et al.[19] first reported that the decrease in FEV1 after lung resection was inversely related to the preoperative FEV1% and that patients with better function had a greater decrease in FEV1. Pierce et al.[20] found a significant relationship between percent change in FEV1.0 after pulmonary resection and baseline FEV1%, indicating that functional loss was proportionally less in patients with worse baseline function. Santambrogio et al.[21] observed a consistent decrease in post-operative FEV1% in patients with FEV1% more than 80% and slight decrease in the post-operative FEV1% in patients with FEV1% less than 80% and the difference was highly statistically significant.

This smaller difference in the degree of functional loss in individuals with poor baseline lung function has also been observed by Baldi et al.[22], Bobbio et al.[23], and Edwards et al.[24] Current experience with lung volume reduction surgery suggests that predicted postoperative FEV1 may be underestimated in COPD patients undergoing lobectomy for lung cancer. In addition, COPD patients with lower FEV1 may have less loss of lung function after lobectomy.[22,25,26]

COPD is defined in several ways, and differences in definitions and diagnosis affect estimates of disease severity. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 defined the disease in degrees of clinical severity based on FEV1 and FEV1/FVC (forced vital capacity) from post-bronchodilator spirometry. To define airflow limitation, the fixed ratio FEV1/FVC <0.7, measured after the bronchodilator, is recommended, despite the risk of overdiagnosis.[27]

Using this definition, we found a significantly less volume loss in COPD patients when comparing predicted versus actual postoperative FEV1 (%) values calculated with the segmental (SF1 and SF2) formulas, and no significant differences in $D_{L,CO}$%. Sekine et al.[12] also found minimal change in postoperative pulmonary function in patients with COPD. The ratio of actual postoperative forced expiratory volume in one second to the predicted postoperative forced expiratory volume in one second (apo/ppo FEV1) was higher in the chronic obstructive pulmonary disease (COPD) group than in the non-COPD group.

A study by Pompili et al.[28] 2010 showed that patients with COPD had a lower reduction in FEV1 (6% vs. 13%, p=0.0002) compared to patients without COPD after lobectomy for lung cancer. The studies by Baldi et al.,[22] Kushibe et al.[29], and Liao et al.[30] confirm these results.

Another way to define and evaluate chronic obstructive pulmonary disease in the practice of thoracic surgery is the so-called "COPD index". To classify patients according to severity and purity of obstructive pulmonary disease, Korst et al.[25] defined a "COPD index" (COPDI) and calculated it for each patient as the sum of the preoperative FEV1 (% of predicted in decimal form) to the preoperative FEV1/FVC (forced vital capacity) ratio. For example, if a patient has an FEV1 of 60% and the FEV1/FVC ratio is 0.5, the COPD index would be 0.6 plus 0.5, or 1.1. The COPD index, defined in this way, is an attempt to identify those patients with the most severe and pure obstructive pulmonary disease. Therefore, the patients with the lowest COPD index were those with the purest and most severe obstructive disease.

We found underestimation of predicted postoperative FEV1 (%) and $D_{L,CO}$% in patients with COPD index <1.5. Baldi et al.[22] similarly observed a better than predicted postoperative FEV1% when the COPD index was less than 1.5. Santambrogio et al.[21], in their study, applied the Korst index and divided COPD patients into two groups. The authors found that in the subgroup with a strong decrease in FEV1 (%), the COPD index was 1.35, and in the other with a smaller decrease, it was 1.15 and the difference was statistically significant.

When examining the effect of the volume of resection (lobectomy/pulmonectomy) on the accuracy of prediction of ppo FEV1, we found greater underestimation in pneumonectomy patients compared with lobectomy patients. The difference was statistically significant only with the SF1 segment formula. This underestimation is statistically significant for $D_{L,CO}$% in all three methods. Similar to our results, Bolliger et al.[6] found that anatomical calculations had significantly reduced correlation coefficients after pulmonectomy, the lowest when using equation SF1 (segments), which did not take into account the function of the parenchyma to be removed (SF2). This formula is consistently worse than all other methods because it significantly overestimates functional loss, especially after pneumonectomy. The authors suggest that anatomically calculated scores should only be used for resections that do not exceed one lobe. Beccaria et al.[31] reported that a simple calculation of ppoFEV1 correlated well with the actual value of apoFEV1 six months after surgery in all patients who underwent lobectomy. However, this is not the case in patients who have undergone pneumonectomy; in fact, in these patients, ppoFEV1 consistently underestimated actual apoFEV1 by an average of 500 ml. These results are consistent with data previously presented by Zeiher et al.[5] They found that in individuals with atelectasis, hilar involvement, or endobronchial involvement with radiologic evidence of dysventilation, simple calculation of ppoFEV1 is not reliable. In this group of patients, ppoFEV1 did not correlate with the actual postoperative value in patients who underwent pulmonectomy. The bias was always in the direction of underestimation of the actual apoFEV1.[32]

Kim et al.[10] performed multivariate linear regression analysis to identify clinical parameters influencing the accuracy of prediction. They found the number of resected lung segments and the preoperative FEV1 to be significant factors. The smaller the preoperative FEV1 and the more lung segments resected, the more the postoperative FEV1 (apoFEV1) tends to be greater than the predicted ppoFEV1. Apo FEV1 was closest to ppoFEV1 when four segments were resected.

We found an underestimation of the postoperative indicators in the group of patients with more than 4 segments resected. This difference was significant when predicting $D_{L,CO}$(%) and FEV1 (%) with the SF2 formula and for $D_{L,CO}$ (%) calculated with the SF1 formula.

In our study, we found no influence of the type of lobectomy (upper/lower) on the accuracy of prediction of postoperative lung function. Accurate assessment of anatomic-functional loss after lung lobectomy is also complicated by the fact that damaged lung areas, especially emphysematous areas, are often distributed heterogeneously in the upper or lower lobe, changing the functional roles of these lobes. Data are conflicting in the literature. Kim et al. found no influence of the type of lobectomy on the prediction of ppoFEV1 (%) and $D_{L,CO}$ (%).[10] Kushibe et al.[26] studied 178 lobectomy patients and found that upper lobectomy resulted in less than predicted loss of FEV1 (%) and may have an effect similar to volume reduction surgery. Sekine et al.[12] reported that the presence of COPD and resection of the lower part of the lung (lower lobectomy or mid-inferior bilobectomy) were significantly associated with minimal deterioration of lung function after lobectomy. Minimal change in postoperative lung function was confirmed to be associated with COPD (vs. non-COPD) and lower lung resection (vs. upper lung) in multivariate analysis.

The theory of volume reduction surgery may explain the minimal change of apoFEV1 in patients with COPD. For patients without COPD, the authors speculated that accidental anatomical repositioning after upper lobectomy, which causes narrowing of the opening of the lower or middle lobe of the bronchi, and different movement and elevation of the diaphragm between upper lobectomy and lower lobectomy may be the potential reason for the minimal change in the cases of resection of the lower part of the lung.[12,33,34]

Sengul et al. found that in lower lobectomy, volume recovery is mainly due to expansion of the contralateral lung along with increase in the volume of ipsilateral remaining lung, especially after right lower lobectomy.[35]

CONCLUSION

We should consider that the accuracy of prediction can be affected not only by the technique to measure the regional lung function, but also several clinical factors such as preoperative FEV1%, the presence of obstructive lung disease, extent of lung volume resection

Vibration response imaging (VRI) is a more accurate method for predicting postoperative lung function than the segment method formulas.

Anatomical calculation significantly underestimates the postoperative values of FEV1% in patients with COPD.

Prediction of FEV1% and $D_{L,CO}$ with segment counting is significantly influenced by the volume of resection and should not be used alone to determine the postoperative values of FEV1% and $D_{L,CO}$% in patients scheduled for an operative intervention greater than lobectomy.

Author contributions

A.C.: design, collection of data, operative task completion and critical review of manuscript; M.T.: design, collection of lung function and VRI data and critical review of manuscript; N.C.: collection of data, statistical analysis, and critical review of manuscript; B.M.: design, collection of lung function and VRI data and critical review of manuscript. All authors have contributed to the tasks of the study and critically reviewed the final version of the manuscript.

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Competing Interests

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Факторы, влияющие на точность прогнозирования послеоперационного FEV1 и $D_{L,CO}$ у пациентов, перенёсших резекцию лёгкого

Анастас Чапканов[1], Мирослава Тодорова[2], Антоанета Чирлова[3], Благой Маринов[4]

[1] *Кафедра специализированной хирургии, Факультет медицины, Медицинский университет - Пловдив, Пловдив, Болгария*

[2] *Медицинский центр FAMA, Пловдив, Болгария*

[3] *Университетская больница „Каспела“, Пловдив, Болгария*

[4] *Кафедра патофизиологии, Факультет медицины, Медицинский университет - Пловдив, Пловдив, Болгария*

Адрес для корреспонденции: Анастас Чапканов, Кафедра специализированной хирургии, Факультет медицины, Медицинский университет - Пловдив, бул. “Васил Априлов“ № 15А, 4002 Пловдив, Болгария; Email: achapkanov909@gmail.com; тел.: +359888312287

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Резюме

Введение: Несмотря на значительное развитие системной терапии и лучевой терапии, хирургия по-прежнему остается краеугольным камнем радикального лечения рака лёгких. Хотя прогнозируемая послеоперационная функция (ППОФ) точно коррелирует с фактической послеоперационной функцией, большие различия могут быть причиной серьёзного клинического исхода.

Цель: Целью нашего исследования было выявление клинических факторов, влияющих на точность прогнозирования послеоперационной функции лёгких, для более тщательного отбора операбельных больных раком лёгких.

Пациенты и методы: Проспективно исследовано 70 пациентов. Предоперационные тесты функции лёгких (FEV1 и $D_{L,CO}$) проводились в течение недели до операции, а последующие тесты проводились через 4–6 недель после операции. Расчёт прогнозируемых послеоперационных значений осуществлялся тремя методами: двухсегментной формулой и визуализацией вибрационного отклика (VRI - Vibration Response Imaging). Корреляция между каждым клиническим параметром и точностью прогноза проверялась с помощью одномерного анализа коэффициента корреляции Pearson, а значимые факторы были подтверждены с помощью многомерного линейного регрессионного анализа с применением подхода обратного пошагового исключения.

Результаты: Одномерный линейный регрессионный анализ между прогнозируемыми и фактическими послеоперационными значениями FEV1% и $D_{L,CO}$ показал самую высокую точность прогнозирования с помощью акустического картирования (VRI). Многофакторный регрессионный анализ показал, что на точность прогнозирования послеоперационной функции лёгких существенное влияние оказывают ХОБЛ (p<0.001) и объём резекции (p<0.001).

Заключение: Визуализация вибрационного отклика (VRI) является более точным методом прогнозирования послеоперационной функции лёгких, чем формулы сегментного метода. Анатомический расчёт существенно занижает послеоперационные значения FEV1% у больных ХОБЛ. На прогноз FEV1% и $D_{L,CO}$ при подсчёте сегментов существенное влияние оказывает объём резекции.

Ключевые слова

рак лёгких, послеоперационная функция лёгких, точность прогнозирования, виброотдача