Prediction of Postoperative Lung Function

Seung Hun Jang
Division of Pulmonary, Allergy and Critical Care Medicine,
Hallym University Sacred Heart Hospital,
Republic of Korea

1. Introduction

Lung cancer is the leading cause of cancer death in many counties. Despite significant improvement in chemotherapy and radiotherapy, surgery is still the cornerstone of non-small cell lung cancer treatment. The lung cancer is categorized into non-small cell lung cancer or small cell lung cancer according to the histology. The patients with stage IA-IIB non-small cell lung cancer and stage I small cell lung cancer are good candidates for lung resection which can offer the best chance for cure. In a series of 407 individuals with resectable cancer, the 346 who went to thoracotomy had a median survival of 30.9 months compared with 15.6 months in the 57 who did not go to surgery (Loewen, et al. 2007). A part of individuals with stage IIIA non-small cell stage may also be the surgical candidates if they are adequately treated with chemotherapy and/or radiotherapy before and/or after surgery. The long term goals of lung cancer surgery include cancer control improving survival and quality of life of the patients.

Smoking is the important risk factor not only for lung cancer but also for other comorbid diseases such as chronic obstructive pulmonary disease (COPD) and coronary heart disease. The patients with lung cancer and COPD have reduced ability to tolerate further losses in lung function. 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. It was reported that only about 30% of individuals with lung cancer were determined to be candidates for lung resection because of the advanced stage (Damhuis & Schutte 1996). In addition, a report showed that 37% of individuals who present with anatomically resectable disease deemed not to be surgical candidates based on poor lung function alone (Baser, et al. 2006). If a patient is deemed a candidate for surgery, it must be realized that pulmonary function will be affected by the resection. The decline in lung function varies with the extent of the resection. Accordingly, it is important to be informed about the risk factors and how they affect postoperative morbidity, mortality, and long-term survival.

Pulmonary function measures such as the forced expiratory volume in one second (FEV1) and the diffusing capacity for carbon monoxide (DLco) are useful predictors of postoperative outcome (Bousamra, et al. 1996; Ferguson, et al. 1988; Markos, et al. 1989). Postoperative value of FEV1 is certainly the most widely used parameter for preoperative risk stratification. It has been shown to be an independent predictor of complications including mortality (Kearney, et al. 1994; Mitsudomi, et al. 1996; Ribas, et al. 1998). The assessment of regional lung function to predict postoperative function is integral to preoperative evaluation of pulmonary resection candidates who have impaired lung function. There are four validated ways to predict postoperative FEV1. However, all of them tend to underestimate the predicted value compared with the actual postoperative lung function. Although predicted postoperative FEV1 (ppoFEV1) somewhat exactly correlates with actual postoperative FEV1 (apoFEV1), the correlation can be affected by several clinical factors. If actual postoperative lung function quite differs from predicted value, it may be a cause of serious clinical outcome especially in the patients with marginal postoperative lung function; someone may undergo life-threatening lung resection, and someone may lose the opportunity to be cured by surgery. Therefore, we need to know clinical factors as many as possible which can affect the discrepancy between apoFEV1 and ppoFEV1. The aim of the chapter is to review the accuracy of the prediction methods for postoperative lung function, especially FEV1, and the clinical factors affecting the prediction accuracy. This will confer the ideas about the appropriate selection of patients for pulmonary resection and perioperative management for risk reduction.

2. The physiologic evaluation for the decision about operability

2.1 Lung function test

Among lung function measures, FEV1 and DLco are the most useful predictors of postoperative outcomes. Both absolute values and percent predicted normal values have been studied and proved as a predictors of postoperative complications including mortality (Licker, et al. 2006). The generally accepted lung function for minimal postoperative mortality is preoperative FEV1 > 1.5 L for a lobectomy, and > 2L for a pneumonectomy. Those who have lung function above this level can undergo surgery without further evaluation. There is little evidence that one cutoff absolute value of FEV1 should be used to permit resection of varying extent. Although the absolute value for ppoFEV1 that would allow resection has not been found, the previous studies suggested the values greater than 0.8-1 L for acceptable postoperative mortality (Boysen, et al. 1981; Wernly, et al. 1980). The values of pulmonary function expressed as percentage of normal are more convenient and useful because they are affected by individual's age, sex, height, and race. In terms of percentage of normal, ppoFEV1 less than 30% predicted would be very highly risky for perioperative death and ppoFEV1 greater than 40% has been suggested for tolerable resection up to calculated extent of resection (Beckles, et al. 2003; Colice, et al. 2007; Markos, et al. 1989). If ppoFEV1 is between 30% and 40%, the decision had better to incorporate the result of maximal oxygen consumptions (VO2max).

Cardiopulmonary exercise testing has been used as a means to access a patient's fitness for lung resection. Several studies have identified exercise capacity (VO2max) as a predictor of postoperative complications as well as of postoperative long term mortality (Bolliger, et al. 1995; Brutsche, et al. 2000). Risk for perioperative complications can generally be stratified by VO2max. Several studies demonstrated that preoperative VO2max > 20 mL/kg/min was not associated with increased risk of complications or death (Bolliger, et al. 1994; Richter Larsen, et al. 1997). Patients with VO2max of 15 to 20 mL/kg/min can undergo curative lung cancer surgery with an acceptably low mortality rate (Richter Larsen, et al. 1997; Win, et al. 2005). On the contrary, the risk of perioperative death sharply increases below the level of VO2max < 15 mL/kg/min (Bolliger, et al. 1995; Win, et al. 2005). VO2max < 10 mL/kg/min has been reported as a very high risk of postoperative death (Holden, et al. 1992; Olsen, et al. 1989).

Algorithmic approaches for the candidate selection have been developed in an effort to improve decision making (Colice, et al. 2007; Wyser, et al. 1999). Wyser et al. showed that algorithmic decision reduced the complications in half compared with the author's prior series. In summary, individuals with VO2max < 10 mL/kg/min, or < 15 mL/kg/min with both ppoFEV1 and ppoDLco < 40% predicted, are at high risk for perioperative death and complications. Both preoperative FEV1 and DLco ≥ 80% predicted normal or VO2max ≥ 20 mL/kg/min allow lobectomy or pneumonectomy without any further evaluation.

2.2 Stair climbing and walking test

If cardiopulmonary exercise test were not available, another simple exercise test could replace the test. Stair climbing has been investigated, and it was proven to correlate with FEV1 and VO2max very well (Bolton, et al. 1987; Pollock, et al. 1993). It is generally accepted that patient who can climb five flights of stairs has VO2max > 20 mL/kg/min, and conversely, patient who cannot climb one flight of stairs has VO2max < 10 mL/kg/min (Beckles, et al. 2003). The data about the shuttle walking or 6-minute walking test are limited, but they can also surrogate cardiopulmonary exercise test.

2.3 Arterial blood gas analysis

The results of arterial blood gas analysis reflect the cardiopulmonary functional status. Historically, hypercapnea (PaCO2 > 45 mmHg) has been regarded as an exclusion criterion for lung resection (Celli 1993). However, a few clinical studies suggested that hypercapnea did not increase perioperative complications (Harpole, et al. 1996; Kearney, et al. 1994). Hypercapnea is not an independent risk factor for increased perioperative complications, and the operability should be decided after further physiologic testing.

3. The methods for prediction of postoperative lung function

The surgical procedure depends on the stage of lung cancer and on the cardiopulmonary reserve of the patients. A prospective randomized trial comparing limited resection to lobectomy in patients with peripheral stage I lung cancers reported that the patients treated with limited resection had a three-fold increase in local recurrence, a 75% increase in combined local and distant recurrence, and a 50% increase in death with cancer (Ginsberg & Rubinstein 1995). Therefore, anatomic resection such as lobectomy or pneumonectomy should be done if physiologically feasible. Lung sparing anatomic resection like sleeve lobectomy is preferred over pneumonectomy, if anatomically appropriate and if margin-negative resection can be achieved. A study compared clinical outcomes of the elderly patients undergoing sleeve lobectomy or pneumonectomy due to non-small-cell lung cancer (Bolukbas, et al. 2011). The loss of FEV1 was 12.0% vs. 27.3% ($p = 0.001$), and 5 year survival rate was 59% vs. 0% favoring sleeve lobectomy although there was no statistical difference in postoperative mortality (6.5% in sleeve lobectomy vs. 10.3% in pneumonectomy). Sublobar resection, either segmentectomy (preferred) or wedge resection, is appropriate in selected patients if margin-negative resection can be achieved. The limited resection is appropriate especially for the patients with poor pulmonary reserve or other major co-morbidity that contraindicates lobectomy.

For the prediction of postoperative remnant lung function, the anatomy of the lung should be understood. The right lung consists of three lobes; upper, middle and lower lobe. The right upper lobe consists of 3 segments, the right middle lobe 2 segments, and the right lower lobe 5 segments. The left lung consists of two lobes; upper and lower lobe. The left upper lobe consists of 4 segments, the left lower lobe 4 segments. The anteromediobasal segment of the left lower lobe is the counterpart of anterobasal segment and mediobasal segment of the right lower lobe, but it has a common bronchial orifice. Although it is anatomically one segment, it contains two segments in volume. Therefore, the left lung is regarded to have 9 segments in terms of volume; 4 segments in the left upper lobe and 5 segments in the left lower lobe. Each segment is assumed to have same volume (1/19 of the lung function). The four validated methods to predict postoperative lung function are: 1) anatomic calculation, 2) split radionuclide perfusion scanning, 3) quantitative computed tomography (CT) scanning, and 4) dynamic perfusion magnetic resonance imaging (MRI). Using these techniques, the actual lung function was consistently underestimated, particularly if the starting value was lower (Giordano, et al. 1997; Zeiher, et al. 1995). The accuracy of prediction of anatomic calculation is slightly lower than the other methods, but the other methods effectively predict postoperative FEV1 with similar accuracy. Medical cost, local expertise and availability of equipments should be considered for the choice.

3.1 Anatomic calculation

Estimation of predicted postoperative lung function based on anatomical calculation is the simplest, but the accuracy is slightly lower than other methods. Predicted postoperative FEV1 can be calculated by simple subtraction of the FEV1 proportion of resected lung segments from the total preoperative FEV1 (Juhl & Frost 1975; Zeiher, et al. 1995).

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

For example, if a patient will undergo right upper lobectomy, the predicted postoperative FEV1 will be calculated to remain 16/19 (84.2%) of preoperative FEV1. This method is also applied to the other methods as a basic concept.

3.2 Split radionuclide perfusion scanning

In most clinical cases, the extent of pulmonary disease may be different in each side of the lung, which is leading cause of different regional lung function according to the disease status. This is a major violation of the assumption that each lung segment represents the same lung function. The general principle of the radionuclide scanning technique is same for the anatomic calculation method. The prediction of postoperative lung function can be calculated by the following two steps. The first step is determining the functional contribution of resected (right or left) lung by quantitative perfusion lung scan, and the second step is applying the principle of anatomical calculation to the resected lung. Postoperative lung function is then estimated to be the product of the preoperative function and the portion of lung function that will remain after resection as estimated by the scan.

$$\text{ppoFEV1} = \text{preoperative FEV1} \times [1 - \text{functional fraction of the resected lung}$$
$$\times (\text{number of segments to be resected}/\text{total segments of that lung})]$$

The accuracy of these techniques has been questioned. A recent study using technetium scanning calculated values of imprecision from 18%-21% despite showing reasonable correlation (Giordano, et al. 1997).

3.3 Quantitative CT scanning

Quantitative computed tomography scanning has been studied as a technique to estimate postresection lung function. The basic concept is similar to radionuclide perfusion scanning method. This measures the split lung function using the CT attenuation density instead of radionuclide signal intensity. The volume of lung with attenuation between -500 and -910 Hounsfield units was used to estimate functional lung volume. The portion of the lung remaining postresection was predicted by calculating lung volume in the area to be resected as a portion of total lung volume. With this, predicted postoperative function correlated as well as the method using radionuclide quantitative perfusion imaging (Wu, et al. 2002).

3.4 Dynamic perfusion magnetic resonance imaging (MRI)

A study showed that magnetic resonance (MR) perfusion imaging had almost the same sensitivity and specificity for diagnosis of pulmonary perfusion defects as conventional perfusion scintigraphy (Berthezene, et al. 1999). The regional lung function is calculated from the subtraction images for normal lung parenchyma using image analysis software. The accuracy of MR perfusion for the prediction of ppoFEV1 was validated in a study (Iwasawa, et al. 2002). This study demonstrated that the correlation between perfusion ratios derived from MR perfusion image and radionuclide perfusion scanning was excellent ($R = 0.92$). The correlation between ppoFEV1 and actual postoperative FEV1 was similar when the two methods were compared ($R = 0.682$ in MR perfusion and $R = 0.667$ in radionuclide perfusion).

4. Clinical parameters affecting prediction accuracy of postoperative lung function

Prediction accuracy of postoperative lung function is affected not only by the calculation technique, but also the clinical factors associated with the actual postoperative lung function. The actual lung function closely relates to the physiology of lung volume reduction, reversibility of airway obstruction, pharmacotherapy, and postoperative respiratory rehabilitation.

4.1 Chronic obstructive pulmonary sisease

Pulmonary function is affected by lung resection and the decline in lung function varies with the extent of the resection. The degree of functional loss appears to be less in individuals with poor baseline lung function uniformly across the studies (Bobbio, et al. 2005; Boushy, et al. 1971; Edwards, et al. 2001). In patients with severe emphysema, surgery performed to remove the most emphysematous portion of the lung may lead to improvements in lung function (Fishman, et al. 2003). A case-matched study demonstrated that the patients with COPD had a three-fold higher rate of cardiopulmonary morbidity (28% versus 10%, $p=0.04$), but lower reduction in FEV1 (6% versus 13%, $p=0.0002$) compared with non-COPD patients after lobectomy for lung cancer (Pompili, et al. 2010). Importantly, although the postoperative quality of life in both groups was reduced, there were no significant differences in quality of life between the groups. This suggests that the patients with lung cancer and COPD may be unexpectedly tolerable with the curative lung resection if the candidates are carefully selected. This is attributed to lung volume reduction effect which takes place very early. The risk-benefit should be balanced based on the negative physiologic effects of thoracotomy versus positive effects of lung volume reduction in the surgical decision for the patients with lung cancer and COPD. As most lung cancer patients have more or less emphysematous changes, adequate volume reduction may open small airways, expand or overinflate functional alveoli, improve diaphragmatic movement and consequently increase postoperative FEV1 than the expected. This is consistent with the basic principle of volume reduction surgery for severe emphysema that postoperative lung function can be improved by resection of relatively functionless emphysematous lung.

4.2 Resected lung portion

Besides preoperative lung function, a study has suggested that the prediction accuracy of postoperative lung function could be influenced by other clinical factor such as resected lung portion (Sekine, et al. 2003). Sekine et al. reported that the presence of COPD and resection of the lower lung portion (lower lobectomy or middle-lower bilobectomy) were significantly associated with minimal deterioration of pulmonary function after lobectomy. The authors retrospectively analyzed 521 patients who had undergone lobectomy for lung cancer. The ppoFEV1 was calculated by modified anatomic calculation by multiplying a specific coefficient according to the baseline FEV1 categories. The apoFEV1 was measured at 1 month after operation. Minimal alteration of postoperative lung function, defined as apoFEV1 $\geq 1.15 \times$ ppoFEV1, was confirmed to be associated with COPD (vs. non-COPD) and resection of the lower lung portion (vs. upper lung portion) in multivariate analysis. Lung volume reduction theory can explain minimal alteration of apoFEV1 in the patients with COPD. The authors speculated that occasional anatomic repositioning after upper lobectomy, which causes narrowing of the orifice of lower or middle lobe bronchus, and different movement and elevation of diaphragm between upper lobectomy and lower lobectomy might be the potential causes the minimal alteration in the cases of resection of the lower lung portion (Nonaka, et al. 2000; Van Leuven, et al. 1999).

4.3 Number of resected lung segment and bronchodilator response

The writer of this chapter and his colleagues (Kim, et al. 2008) investigated another clinical factors affecting prediction accuracy. Some of the findings would like to be introduced in detail, because those may help for the selection of candidates for surgery and perioperative management of the patients.

A total of 82 patients with non-small-cell lung cancer undergoing pulmonary resection were retrospectively analyzed in this study. Forty eight patients underwent lobectomy, 11 patients underwent bilobectomy, and the remaining 23 patients underwent pneumonectomy. The ppoFEV1 was dually estimated by anatomical calculation and split radionuclide perfusion scanning method. The mean time interval between surgery and apoFEV1 was 24 ± 7 days. The ppoFEV1 calculated by split radionuclide perfusion scanning method was more accurate than that by anatomic calculation method (apoFEV1/ppoFEV1 = 1.00 ± 0.19 vs. 1.07 ± 0.23, $p < 0.001$). Multivariate linear regression analysis was performed to identify clinical parameters affecting the prediction accuracy with the covariates of age, gender, preoperative FEV1, time interval between surgery and the day of measuring apoFEV1, preoperative bronchodilator response (% increase in FEV1 after inhalation of short acting beta-2 agonist), resected lung portion, and the number of resected lung segments. Among these clinical factors, the number of resected lung segments and preoperative FEV1 were significant clinical factors affecting the prediction accuracy ($p = 0.026$ and 0.002, respectively). As the preoperative FEV1 became smaller and the more lung segments were resected, apoFEV1 tended to be larger than ppoFEV1. It is noteworthy that the corresponding means of apoFEV1/ppoFEV1 for each number of resected lung segments gathered on a straight line of a constant slope. The apoFEV1 was closest to ppoFEV1 when four segments were resected. Contrary to the previous report, resected lung portion (upper or lower portion resection) was not related to the prediction accuracy ($p = 0.10$). However, more number of segments was resected in lower portion resection compared with upper portion resection (5.6 ± 1.1 vs. 3.7 ± 1.0, $p = 0.001$), which might be a confounding factor.

Lung functions of 46/82 patients were followed at 106 ± 30 days after surgery, which was reflecting plateau lung function of the patients undergoing lung resection. As expected, plateau apoFEV1 was increased by 13% compared with apoFEV1 measured at 24 days after surgery. In predicting plateau lung function, split radionuclide perfusion scanning method was also superior to anatomic calculation (plateau apoFEV1/ppoFEV1 = 1.11 ± 0.24 vs. 1.18 ± 0.30, $p < 0.001$). These data also indicate that the prediction methods are fitter for short-term postoperative value rather than long-term value. In general, postoperative lung function gradually improves with time (Brunelli, et al. 2007). However, the plateau apoFEV1 was lower than the apoFEV1 measured at 24 days in 9/46 (19%) patients. Their preoperative bronchodilator response values were higher than those of the others although it did not reach statistical significance ($11.2 \pm 8.4\%$ vs. $7.0 \pm 6.8\%$, $p = 0.11$). The study did not investigate prescription status of bronchodilator or the patients' adherence to the drugs. However, this finding suggests that adequate perioperative bronchodilator therapy is necessary for the patients with high bronchodilator response, especially for the patients with poor lung function. Bronchodilator response is a well known predictor of pulmonary function improvement after long term treatment with long acting beta-2 agonist. A study demonstrated that bronchodilator response, wheezing history positively correlated with improvement in FEV1 after three months inhalation treatment with salmeterol/fluticasone combination, conversely negative correlation with emphysema extent (Lee, et al. 2011). COPD is a complex and heterogeneous disorder of mixed chronic bronchitis and emphysema. Another study showed that three months inhalation treatment with long-acting beta-agonist and corticosteroid significantly improved the FEV1 of obstruction-dominant patients compared with the emphysema-dominant subgroup. Again, baseline bronchodilator response and DLco were the meaningful predictors associated with improvement of FEV1 after the treatment (Lee, et al. 2010). If the patients with high bronchodilator response do not receive regular bronchodilator treatment after surgery, the FEV1 should decrease and the prediction accuracy of postoperative lung function would be affected as a matter of course.

Preoperative FEV1 was significantly lower in the COPD group than in the non-COPD group ($67.1 \pm 8.3\%$ vs. $101.6 \pm 15.2\%$, $p < 0.001$). The apoFEV1 was about 14% larger than ppoFEV1 in the COPD group while apoFEV1 was very similar to ppoFEV1 in the non-COPD group (apoFEV1/ppoFEV1 = 1.1 ± 0.2 in COPD group and 1.0 ± 0.1 in non-COPD group, $p < 0.001$). These are the same results with the previous studies indicating that the prediction of postoperative lung function is more accurate in the non-COPD group than in the COPD group, and postoperative lung function of the COPD group may be less deteriorated than that of the non-COPD group.

5. Physiologic changes in the lung volume reduction surgery

Actual postoperative FEV1 is better than the predicted value in the patients with COPD, which is universally observed in many clinical studies. This phenomenon is explained by the physiology of lung volume reduction. In patients with COPD, inhaled air is trapped in the thorax as a result of decreased elastic recoil of the lung and early closure of the small airways during exhalation. This is manifested as hyperinflation of the chest, flattening of the diaphragm, increased intra-thoracic pressure, and reduced inspiratory capacity. These worsen during exercise and result in dyspnea and limitation of exercise capacity. After surgical volume reduction, there is expansion of the remaining lung in addition to reduction of the overall thoracic volume and pressure, and it is probable that some areas of relative compression have been reexpanded. Lung volume reduction surgery is associated with improvement in exercise capacity, lung function, quality of life, and dyspnea, but the changes after surgery are variable according to the individuals (Gelb, et al. 2001). The improvement of FEV1 and reduction in hyperinflation has been explained by the increase of lung parenchymal elastic recoil (Sciurba, et al. 1996). It is accompanied with subsequent repositioning of the diaphragm, recruitment of inspiratory muscles, and improvement of respiratory mechanics (Benditt, et al. 1997; Criner, et al. 1998).

Surgical treatment of emphysema had been tried with multiple wedge resections and plications technique which is no longer used (Brantigan & Mueller 1957), and then Cooper et al. reintroduced lung volume reduction surgery as a possible surgical therapy for selected patients with a heterogeneous form of emphysema (Cooper, et al. 1995). The most affected portions are excised about 20% to 35% of the volume of each lung for lung volume reduction. The surgical mortality rate ranges 4-15% and one-year mortality rates are as high as 17% (Argenziano, et al. 1996; Flaherty, et al. 2001; Gelb, et al. 2001). A large randomized controlled trial was conducted to compare lung volume reduction surgery with medical therapy for severe emphysema (Fishman, et al. 2003). The FEV1 of surgery arm was significantly better than that of medical treatment group after 6, 12, and 24 months follow-up. The rates of improvement versus deterioration of FEV1 compared with the baseline were 65% : 35% at 6 months follow-up, 56% : 44% at 12 months, and 43% : 57% at 24 months in the lung volume reduction surgery group. It is also observed in the bullectomy case series that FEV1 is initially improved after lung volume reduction surgery and then returns to the baseline lung function with time. The 90-day mortality was 7.9% (95% confidence interval, 5.9-10.3%) in surgery group, and 1.3% (95% confidence interval, 0.6-2.6%) in medical treatment group. The functional benefits of lung volume reduction surgery came at the price of increased short-term mortality. Overall mortality was similar in both treatment groups, but subgroup analysis showed that the survival benefit was observed in the patients with predominantly upper lobe emphysema and a low baseline exercise capacity. Patients with non–upper lobe emphysema and high baseline exercise capacity are poor candidates for lung volume reduction surgery, because of increased mortality and negligible functional gain.

The similar physiologic changes can be also expected in the giant bullae. If a giant bulla compresses the adjacent normal lung parenchyma and it is causing incapacitating dyspnea, it should be resected for the reexpansion of the normal lung. Bullectomy can produce immediate lung function improvement, but the benefit usually decline with time (Laros, et al. 1986; Schipper, et al. 2004). Giant bullae are frequently combined with emphysema.

6. COPD and lung cancer

COPD is characterized by chronic airflow limitation that is not fully reversible and usually progressive with time. The airflow limitation is usually associated with an abnormal inflammatory response of the lung to noxious particles or gases. COPD refers to patients with emphysema or chronic bronchitis, though these two disease entities are frequently mixed up to a varying ratio. It is accompanied with some significant extrapulmonary effects and comorbidities (Agusti 2005). COPD has been defined in several ways, and the differences in definitions and diagnosis affect the estimates of the burden of the disease. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines the disease in stages of clinical severity based on FEV1 and FEV1/FVC (forced vital capacity) from post-bronchodilator spirometry (Rabe, et al. 2007). The statement recommends to use the fixed ratio post-bronchodilator FEV1/FVC < 0.7 for definition of airflow limitation despite a problematic issue of overdiagnosis.

COPD are at risk for lung cancer due to common risk factors like aging, smoking, reactive oxygen species (Azad, et al. 2008; Soriano, et al. 2005; Young, et al. 2009). Tobacco smoking is considered to be the leading cause both of lung cancer and COPD. Smokers have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual decline rate in FEV1 and a greater COPD mortality rate than nonsmokers. Smoking accounts for more than 85-90% of all lung cancer related deaths (Doll & Peto 1976). Cancer cells proliferate in reactive oxygen species rich inflammatory environment which is promoting DNA damage, inactivation of apoptosis, upregulation of growth factors, cytokines, and activating growth supporting genes (Cook, et al. 2004). Reactive oxygen species and chronic inflammation are also important pathologic mechanisms of COPD. A meta-analysis demonstrated that overall relative risk of lung cancer for subjects with COPD was 2.22 (95% confidence interval, 1.66-2.97%). Besides COPD, previous history of pneumonia or tuberculosis also increased the lung cancer risk even in never-smoker population (Brenner, et al. 2011). Chronic inflammation has been proposed as a cause of cancer development.

An effective COPD management includes severity assessment, regular monitoring, risk factor elimination, pharmacotherapy, and rehabilitation. This multidimensional approach includes patient education, health advice, counseling about smoking cessation, instruction in exercise and nutrition. Almost all the same therapeutic approach and monitoring should be also applied to the patients with the patients undergoing lung resection. Pharmacotherapy is helpful to prevent and control respiratory symptoms, reduce the frequency and severity of exacerbation, and improve exercise capacity and quality of life. The existing medications for COPD do not modify the long-term decline in lung function, but regular treatment with long-acting anticholinergic bronchodilator (Tiotropium bromide), long-acting beta-2 agonists, inhaled glucocorticoid, and its combination can decrease the rate of decline of lung function (Celli, et al. 2008; Tashkin, et al. 2008). Bronchodilators acting on peripheral airways reduce air trapping, thereby reducing residual lung volume and improving respiratory symptoms and exercise capacity. Patient education is essential in COPD like any other chronic diseases. The component of education should include smoking cessation, disease information about pathophysiology and natural course, general approach to the therapy, and self management skill. The poor adherence of the patients with COPD to the inhaler medication has been pointed out (Bender, et al. 2006). However, it is essential to remind the patients of regular using inhaler medication, because adherence to inhaled medication has been shown to be significantly associated with reduced risk of death and admission to hospital due to exacerbation in COPD (Vestbo, et al. 2009).

COPD doubles the risk of postoperative pulmonary complications (Kroenke, et al. 1993). Strategies for reducing pulmonary complications are needed. Preoperatively, inhaled bronchodilators such as long-acting anticholinergics or beta-2 agonists are indicated for the patients with COPD. Adequate drug therapies can maximize the potential to tolerate lung resection, help us to offer potentially curative treatment to the patients as many as possible. Postoperatively, lung expansion maneuvers and pain control are the two most important methods for reducing the risk of pulmonary complications. Both the incentive spirometry and deep breathing exercise are proved to be effective for lung expansion and reducing pulmonary complications (Thomas & McIntosh 1994). A meta-analysis of randomized controlled trials of postoperative pain control and pulmonary complications demonstrated that epidural local anesthetics significantly reduce the risk of pneumonia and all postoperative pulmonary complications (Ballantyne, et al. 1998). Pulmonary function recovers up to 6 months after a lobectomy, and up to 3 months after a pneumonectomy (Bolliger, et al. 1996; Nezu, et al. 1998). There has been little research on long term postoperative optimized outcome in terms of lung function and quality of life. There is no direct evidence supporting an additional role of bronchodilators in the lung resection candidate beyond what would be standard use for COPD or asthma. A study showed that post-operative respiratory rehabilitation after lung resection for lung cancer was beneficial for the Borg dyspnea scale, exercise capacity represented by 6-minute walk distance, and maintenance of lung function (Cesario, et al. 2007). The inpatient rehabilitation program included supervised incremental exercise and educational sessions covering such topics as pulmonary physiopathology, pharmacology of patients' medications, dietary counseling, relaxation and stress management techniques, energy conservation principles, and breathing retraining. The individuals joining the rehabilitation program had the significantly improved exercise capacity and maintained FEV1, whereas the control group had the significantly decreased exercise capacity and decreased FEV1 compared with baseline values. Although the rehabilitation is not confined to pharmacotherapy, it should be kept in mind that multidimensional efforts to maintain exercise capacity and lung function should be required because they could be labile after lung resection.

7. Conclusion

Medical operability of lung cancer has been frequently determined based on preoperative FEV1, DLCO, and VO2max. Predicted postoperative FEV1 is still the most helpful indicator for the safe operation as it provides fundamental information about underlying lung function and disease status. As the concept of regional lung function is introduced to anatomic calculation, the prediction accuracy of postoperative lung function is improved. However, substantial gap is still present between ppoFEV1 and apoFEV1, which tends to be greater in COPD and large lung volume resection. This inaccuracy may be critical in the patients with marginal lung function after lung resection. We should consider that the the accuracy can be affected not only by the technique to measure the regional lung function, but also several clinical factors such as the presence of obstructive lung disease, resected lung portion, extent of lung volume resection, preoperative bronchodilator response, adherence to bronchodilator therapy, physical exercise, nutrition, postoperative pain control, patient education and so on.

The moderate to severe COPD should not hinder the curative resection of lung cancer which could increase the chance of cure, if the candidates of surgery would be properly selected, because the surgery could partly work as lung volume reduction, thereby minimizing the loss of pulmonary function in patients with COPD. Proper perioperative management regarding the aforementioned clinical factors is mandatory to improve lung function and reduce postoperative complication despite remarkable advances in anesthesia, surgery.

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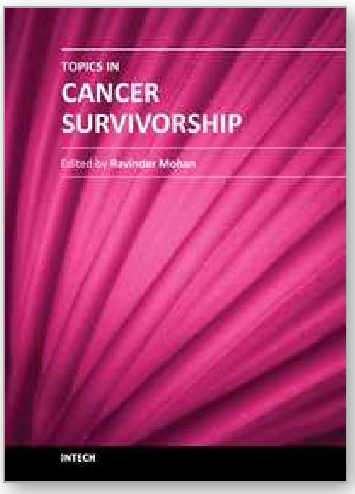

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821