Guidelines for the Evaluation of Surgical Risk in Bronchogenic Carcinoma

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Introduction

Lung resection continues to be the treatment of choice for localized bronchogenic carcinoma. Since many affected patients also present significant comorbidity, lung resection is associated with an appreciable risk of operative complications and death. Consequently, it is desirable for there to be a broad consensus among professionals regarding the main variables associated with surgical risk and the preoperative analysis that is recommendable in each case.

These guidelines address some aspects of operability[1] or functional operability[2] of the patient, defined as the capacity to tolerate surgical resection of the lung without the procedure presenting a high risk of death or incapacitating sequelae. Resectability[1] or oncologic operability[3] is the preoperatively assessed capacity to fully resect all of the bronchogenic tumor with a favorable prognosis, whether demonstrated or presumptive.

These guidelines have been prepared based on expert consensus, since most of the recommendations cannot be based on clinical trials or other research methods that result in a higher level of scientific evidence.

Patient Variables That Affect Surgical Risk

General Aspects

Age is considered an independent predictor of mortality following lung resection.[4] In a series of cases published in 1986 it was found that 26% of patients with diagnosed bronchogenic carcinoma were at least 70 years of age[5]; furthermore, in that study, inoperability and rejection of the patient for surgery was more common in the older group (5% in patients older than 70 years compared with 1.6% in those younger than 70). The probability of death associated with pneumonectomy in patients at least 70 years old (14%) is twice that of patients younger than 60 (6.5%).[6]

Currently, albeit with a low evidence level, surgery is considered to be indicated or inadvisable on the basis of a combination of variables: age, type of resection, and tumor stage.[1,7] Surgery is considered in patients more than 70 years old when the tumor stage is IIC or below. A negative factor is the requirement for pneumonectomy, particularly if it is right sided. Patients more than 80 years old are considered operable when the tumor stage is IC and lobectomy is indicated.

The presence or absence of comorbidity, tumor size (in T2 tumors), and the opinion of the patient are some of the factors that should be taken into account to reach a final decision. For instance, a patient aged more than 70 years can be considered a candidate for surgery when classified as having stage cIIIA cancer on the basis of a 4 cm T3 (involvement of a rib through direct invasion) N1 M0 tumor, without comorbidity and treatable by lobectomy.

The performance status measures the degree of general autonomy of the patient. An Eastern Cooperative Oncology Group (ECOG) or World Health Organization (WHO) score of 2 or more ("needs to be in bed for more than 50% of normal daytime"),[7] which is equivalent to a Karnofsky index of 50%,[1] is a cutoff point, if autonomy is not recoverable, for the assessment of patient operability.

Comorbidity

Frequency and impact of comorbidity. Diseases associated with bronchogenic carcinoma can influence decisions made regarding the cancer itself in various ways: the prognostic prediction,[8] contraindication for chemotherapy or radiotherapy, or in assessing the risk of complications or death as a result of lung resection.[9]

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In these guidelines, comorbidity with bronchogenic carcinoma is only considered in terms of its capacity to influence the operability of the patient.

The frequency of significant comorbidity in bronchogenic carcinoma (lung or heart disease, or diabetes) is directly correlated with age: between 45 and 64 years, comorbid conditions are present in 26.6% of cases; between 65 and 74 years, in 39% of patients; and between 75 and 90 years, in 46% of patients.[10] Thus, the probability of comorbidity increases with age.

At the same time, the mean age of patients diagnosed with bronchogenic carcinoma in Spain has increased in the last 25 years. In a multicenter study of cases diagnosed in the 1970s, the mean (SD) age was 60 (9.12) years[11]; in another Spanish cooperative study of surgical cases between 1993 and 1997 the mean age was 64 (10) years.[12]

Thus, comorbidity, as a possible determining factor in the assessment of operability, will continue to be of increasing importance in years to come.

In a study of 3516 patients who underwent lung resection in United States Veterans Affairs Medical Centers (88% of those resections were for treatment of bronchogenic carcinoma), 39% also had chronic obstructive pulmonary disease (COPD), 38% had arterial hypertension, and 11% had diabetes mellitus.[4] In Spain, a study of the incidence of bronchogenic carcinoma in the autonomous community of Castile-León in 1997 found that the disease occurred alongside COPD in 50% of patients.[13] In that study, heart disease was present in 14% of patients diagnosed with lung cancer, peripheral vascular disease in 9%, hypertension in 11%, and diabetes mellitus in 7%.

In another Spanish study with close to 3000 lung cancer patients who underwent surgery in 19 hospitals between 1993 and 1997, 73% (n=2189) presented at least 1 comorbid condition.[3] COPD was associated with bronchogenic carcinoma in 50% of patients (n=1504), and of those, 32% had a forced expiratory volume in the first second (FEV_1) of less than 70% of the predicted value. A direct relationship between age and probability of comorbidity was also observed in that study.

When comorbidity in general is used in the assessment of operability, a patient is considered inoperable when they have "severe, uncontrolled associated disease, such as mental illness or any other disease that seriously limits, permanently or for an extended period, the most basic psychological and physical capacities of the patient or has an intrinsic prognosis that is fatal in the short term."[1]

Systemic comorbidity. A recent review considered the following factors to be predictive of complications associated with lung surgery: hypertension, hypoalbuminemia, obesity, diabetes mellitus, kidney failure, and the presence of neuromuscular disease or deforming disease of the chest wall.[9] However, peripheral vascular disease, cerebrovascular disease, or the presence of carotid bruit were not considered to be risk factors. In a Spanish assessment of predictors of operative morbidity and mortality in bronchogenic carcinoma, peripheral vascular disease was identified in univariate and multivariate analyses as an independent factor in postoperative morbidity and mortality.[14]

The guidelines recently published by the British Thoracic Society indicate that patients with a history of cerebrovascular accident or transient ischemia, or of carotid bruit, require assessment by echo-Doppler and if the obstruction is greater than 70% vascular surgery may be considered prior to thoracotomy.[7]

Numerous correlations exist between weight and operability. Low body weight index appears to function as a risk factor for complications,[7] while obesity is considered to be a risk factor for any surgery, including thoracic, due to the greater likelihood of atelectasis or associated ischemic heart disease (more common in women).[15] Significant involuntary weight loss (more than 10% of normal weight) is also considered a risk factor for complications following lung surgery.[16]

Various studies have considered hypoalbuminemia to be a consistent risk factor for complications.[4,7,16] The correction, where possible, of those parameters linked to weight and nutrition can reduce the risk, and nutritional treatment is advised for 7 to 10 days prior to surgery in cases of recent weight loss of more than 10% or serum albumin of less than 2.5 g/dL.[16]

Significant arterial hypertension (diastolic pressure >110 mm Hg)[15] and the presence of diabetes mellitus (strong correlation with ischemic heart disease, frequently silent)[14,15] are also factors that increase risk due to systemic disease.

It has recently been observed that the serum concentration of lactate dehydrogenase can be a predictive factor for pulmonary complications following lobectomy for treatment of lung cancer.[17]

Heart disease. Ischemic heart disease, like COPD, is assumed to be common in patients with lung cancer since it shares a common etiologic factor, namely tobacco. Furthermore, lung resection surgery can be considered to represent a risk in patients with ischemic heart disease since a substantial amount of pulmonary vasculature is removed.

In a recent Spanish study, operative mortality in the presence of heart disease (ischemic in the majority of cases) was twice that in its absence, a finding that was valid for both pneumonectomy (25% compared with 12%) and other pulmonary resections (7.6% compared with 4.6%).[18]

In the assessment of patients with heart disease, some guidelines recommend an electrocardiogram in all lung cancer patients in whom surgery is anticipated and an echocardiogram if they present cardiac murmur.[7] In the guidelines presented here, cardiac assessment will not be considered in depth. Readers are directed towards the publications of the Spanish Society of Cardiology and the professional associations for cardiology in the USA.[19,20]

Lung disease. Patients with COPD, cryptogenic fibrosing alveolitis, or silicosis are at increased risk of developing bronchogenic carcinoma independently of smoking habit.[21-23] In addition, to be oncologically valid, surgical treatment of bronchogenic carcinoma generally requires resection of nontumorous lung tissue. The combination of these factors can lead to uncertainty regarding the operability of the patient.

SEPAR has recently published guidelines on COPD that include considerations regarding surgery.[24] The guidelines include both perioperative measures and the description of an algorithm for use in making decisions on COPD patients who are candidates for lung resection. The British Thoracic Society has also produced an algorithm for the same purpose.[7] Both consider COPD as a uniform disease and the calculation of postoperative FEV_1 as fundamental to assessment. However, postoperative FEV_1 following lung resection has been found to increase or remain unchanged compared with the preoperative value in up to 18% of cases of bronchogenic carcinoma with a preoperative FEV_1 of less than 2.5 L[25]; in the cases that have been described, this response is significantly more frequent in cases of lobectomy and where lung function is more substantially reduced. This observation, which has been reported previously,[26] increases the uncertainty associated with decisions. In the guidelines presented here, other more precise assessments are described that improve the accuracy of risk predictions in the presence of comorbid pulmonary conditions.

Multiparameter methods. In a study addressing postoperative morbidity following surgery for bronchogenic carcinoma, the best associative model combined functional variables (carbon monoxide diffusing capacity of the lung [DLCO] and predicted FEV_1), endoscopic variables (obstructed segments to be resected), clinical variables relating to comorbidity (COPD and systemic arterial hypertension), and a pathologic TNM classification variable (pN).[27]

In another recent study of cardiorespiratory morbidity, the associated variables included, along with functional and therapeutic variables, the presence of comorbid conditions (ischemic heart disease, arrhythmias, and diabetes) and tumor staging.[28]

Multiparameter risk indices for lung resection surgery have included the assessment of nonfunctional cardiorespiratory variables, among others. One of these systems combines variables such as sex, history of smoking, serum albumin, lymphocyte count, and the presence of diabetes for the prediction of postoperative morbidity.[29]

The comorbidity index described by Romano et al[30] includes a mixture of diseases in which each one has a particular score. The following diseases are considered: ischemic heart disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic renal failure, diabetes mellitus, severe liver disease, and presence of COPD and/or malignancy. This index has been used in combination with other factors to predict risk groups for lung resection.[31] The most significant risk group, according to that study, is the group in which resection for bronchogenic carcinoma is combined with an FEV_1 of 80% or less of predicted and a comorbidity index of at least 4. With that combination, the probability of operative mortality is 24%. A comorbidity index of 4 is reached with the presence of COPD and diabetes mellitus.

Another study evaluated the risk of cardiac complications in stable patients undergoing elective major noncardiac surgery.[32] The simple index derived in that study would allow a wide range of probabilities of cardiac complications to be predicted: from 0.4% to 11%. The variables considered were type of surgery and history of ischemic heart disease, congestive heart failure, or cerebrovascular disease. Although the simplicity of this index makes it useful, it may be that it is not applicable to all surgical areas; such indices are valid as general guides more than for the accurate calculation of risk.[33] When different indices for the prediction of cardiac risk have been compared (American Society of Anesthesia index, Goldman index, etc), all have been observed to have a similar area under the receiver operating characteristics (ROC) curve of around 0.6 to 0.7.[34] Although such values suggest that those systems perform better than chance in their capacity to predict risk, they are still far from sufficient. There is still a high probability of uncontrolled variability in the proposed indices.

Preoperative Assessment of Lung Function

Arterial Blood Gas Analysis

Although arterial blood gas analysis has little value for the prediction of inoperability in patients who are candidates for lung resection, it is nevertheless an obligatory and routine analysis for the assessment of those patients.

A PaO_2 of less than 50 to 60 mm Hg is considered a risk factor for lung resection and a contraindication for surgery.[35-38] However, before ruling out surgery for a patient, assessment of the PaO_2 response during exercise is recommended.[7] Further reduction in PaO_2 is considered a contraindication for surgery. In contrast, if PaO_2 remains stable or increases, the patient is considered operable, albeit with high surgical risk.

$PaCO_2$ functions as an indicator of alveolar ventilation. Patients with persistently increased $PaCO_2$—more than 45 mm Hg—in whom neuromuscular disease and drug-induced hypoventilation have been ruled out are at high surgical risk.[39,40] Sustained hypercapnia implies chronic respiratory failure and increased surgical risk, and surgery should be ruled out in such patients. Nevertheless, some authors have failed to detect an increased risk of morbidity or mortality,[40-42] meaning that, of itself, hypercapnia is not a criterion for exclusion but, rather, can be decisive when considered alongside other preoperative assessment tests. It can be of interest to determine whether patients are able to adequately perform an exercise test.[7,43]

Spirometry

Abnormal respiratory function is a risk factor for postoperative morbidity and mortality, as well as for possible long-term incapacity and poor quality of life as a result of respiratory failure. That risk depends on both preoperative lung function and the extent of the surgery to be performed.

Just as FEV_1 is the main prognostic factor in COPD, it is also the main and most reliable factor in the identification of patients at high surgical risk.[7]

All patients for whom lung resection is planned should therefore undergo spirometry, which should be performed when the patient is clinically stable and receiving maximum medical treatment. Thus, the values that will be taken into account are measured following bronchodilation, and in patients with obstruction of respiratory flow, spirometry can be repeated after 1 or 2 weeks of intensive bronchodilator treatment.

Recommendations regarding the minimum acceptable value of FEV_1 vary from one study to another and none of them establish a clear, definitive limit.[41,44,45]

In some recent studies, an FEV_1 of more than 2 L for pneumonectomy and greater than 1.5 L for lobectomy has been considered to be indicative of a mortality rate of less than 5%,[7] suggesting that those values are safe for their respective types of lung resection so long as the patient does not present signs of interstitial lung disease—in that case, other functional tests, such as analysis of DLCO, are required because they allow better assessment of a patient's respiratory capacity. However, it is more appropriate to use percentages of the theoretical value rather than absolute values. Some authors define the safety limit for resection as an FEV_1 of more than 80% of the theoretical value.[41,46] Below this level it would be recommendable to perform other screening tests; however, the level of scientific evidence is insufficient to recommend a specific cutoff point.

For those authors who continue to use absolute values, if the FEV_1 is between 0.8 and 2.0 L, more tests are required before a decision is made; such tests include calculation of the postoperative FEV_1 or others that will be described below. An FEV_1 of less than 800 mL would be considered a criterion for directly ruling out surgery, since such a value would be associated with a greater likelihood of hypercapnia, lower exercise tolerance, and increased mortality due to respiratory failure. However, as the absolute value of FEV_1 does not have the same significance in different individuals due to variations according to age, sex, height, and race, the use of 30% of the theoretical FEV_1 in place of the classic value of 800 mL is recommended as an indicator of inoperability.

DLCO

Studies have shown that DLCO is a good indicator of pulmonary complications following lung resection and it has been suggested that this predictive capacity can also be extended to mortality.[47,48] In light of this, although DLCO is not routinely analyzed in the preoperative assessment of lung cancer, it is recommended when interstitial lung disease is suspected that may not be apparent with spirometry,[7] in patients with dyspnea that cannot be accounted for by lung volumes and cardiac dysfunction, and in patients who have received induction chemotherapy (as will be discussed below).

A value for DLCO of less than 60% is indicative of inoperability for pneumonectomy and when less than 50% for lobectomy; this would indicate that further tests should be performed prior to rejecting the patient for surgery.

Estimation of Postsurgical Lung Function

Assessment of Unilateral Function

Studies using radioactive isotopes facilitate assessment of the regional distribution of ventilation (using ^{133}Xe) or perfusion (using ^{99}Tc-labelled albumin macroaggregates). Ventilation-perfusion scintigraphy is currently the most widely used technique for the estimation of postsurgical lung function due to its ease of use and widespread availability.

Calculation of Postsurgical Lung Function

1. Through measurements of unilateral function. Calculations are performed through simple equations using information derived from a technique for the measurement of unilateral function, usually quantitative lung scintigraphy. Quantification of the distribution of perfusion is performed based on the signal emitted by the radioisotope in each hemithorax, the value of which is divided by the sum of the counts emitted in the 2 hemithoraxes.

Although the counts are normally analyzed in the posterior plane,[37] some authors average the results obtained in the anterior and posterior planes.[49]

The following formula is normally used to estimate the predicted postoperative FEV_1 (FEV_1-ppo) in the case of pneumonectomy:

$$FEV_1\text{-ppo} = FEV_1\text{-pre} \times \left(1 - \frac{\text{\% perfusion of lung to be resected}}{100}\right)$$

While the following is used in the case of lobectomy:

$$FEV_1\text{-ppo} = FEV_1\text{-pre} \times \left[1 - \left(\frac{\text{\% perfusion of lung to be resected}}{100} \times \frac{\text{number of segments in lung to be resected}}{\text{number of segments in lung}}\right)\right]$$

where FEV_1-pre indicates preoperative FEV_1 (usually the value obtained following administration of a bronchodilator).

Numerous studies have demonstrated a good correlation between the value of FEV_1-ppo calculated from the results of quantitative lung perfusion scintigraphy and the value measured following the intervention.[41] Nevertheless, there are certain limitations to the prediction when the degree of perfusion in a tumor-containing lung is low, since there is a tendency to overestimate the predicted postoperative value.[50] In addition, the correlation between the surgery that is programmed and that which is performed is not perfect, thereby increasing the inaccuracy of the calculated FEV_1-ppo.[51]

As with FEV_1-ppo, it is possible to estimate the postoperative value of the DLCO (DLCO-ppo)[49,52] and that of the maximum oxygen consumption during exercise ($\dot{V}O_2$max-ppo).[52-54]

2. Based on the number of resected segments. Some authors have employed a simple alternative for the calculation of postsurgical lung function—without performing studies of unilateral function—based only on the number of segments removed during surgery.[55] The following formula is used to calculate the FEV_1-ppo:

$$FEV_1\text{-ppo} = FEV_1\text{-pre} \times \frac{19 - n}{19}$$

where n is the number of segments to be resected and 19 is the total number of segments in both lungs.

Using this method, a group observed good correlations with the value measured following the intervention when the preoperative value for FEV_1 was greater than 55% of the predicted value.[55] In the same study, the formula was also applied to the calculation of DLCO-ppo and a good correlation was obtained with the value measured following the intervention.

Expression of the results. Although the results of FEV_1-ppo can be expressed in units of volume (L or mL), as mentioned, expressing the value in absolute terms is of little use, since FEV_1 depends on the sex, age, and height of the individual. Consequently, it is always preferable to express FEV_1-ppo as a percentage of the reference value.

DLCO-ppo is usually expressed as a percentage of the reference value.

$\dot{V}O_2$max-ppo has been expressed in mL/min/kg[56]; however, for the reasons mentioned, it is more appropriate to express it as a percentage of the reference value.

Multifactorial parameters. Recently, the concept of predicted postoperative product has been developed[55]; this variable is the product of FEV_1-ppo multiplied by DLCO-ppo, both expressed as percentages of the reference value.

Clinical implications. Numerous studies have demonstrated that the parameters obtained in the estimation of postsurgical lung function are good predictors of the possibility of postoperative complications. The most widely evaluated parameter is FEV_1-ppo, which has been demonstrated to have predictive value for postoperative complications in both unselected populations[41] and in populations selected on the basis of increased risk.[57] Low values for DLCO-ppo[49] and $\dot{V}O_2$max-ppo[56] have also been linked to an increased risk of developing postoperative complications.

A low value for the predicted postoperative product (<1650) has been correlated with an increased risk of postoperative death.[55,57] Despite the numerous studies performed in this field, it has not been possible to establish clear limits for the parameters derived from estimation of postsurgical lung function to allow a contraindication for surgery to be accurately established.

Exercise Testing

The pathophysiologic process that links the results of measurements made during exercise with surgical complications is not clear. In theory, when functional demands on the respiratory, circulatory, and oxygen-transport systems are increased, dysfunction that is not appreciable in tests performed at rest will be revealed, and in the case of chest surgery, it will become apparent whether or not the patient has sufficient reserves to tolerate the intervention.

Studies that have analyzed the value of exercise tests in the prediction of surgical risk can be grouped into 2 categories: those that evaluate exercise tolerance—the ability to perform a certain task such as climb stairs—and those that analyze the predictive capacity of certain variables obtained during exercise testing.

Analysis of Exercise Tolerance

Various studies have analyzed the predictive value of assessing the ability to perform a specific task such as walk a certain distance in a set period of time[58,59] or climb a set number of stairs.[60] Patients who are able to complete those tasks, which in most cases require vigorous effort, can be considered to be at low perioperative risk. However, the results of those studies have not led to the definition of a precise relationship between tolerance and risk or the association of a tolerance criterion with an unacceptable risk of death. To date, comparisons of the predictive capacity of exercise tolerance tests with that of testing baseline function have failed to yield a clear conclusion regarding morbidity and none has analyzed a sufficiently large sample to allow a conclusion to be drawn regarding the superiority or inferiority of exercise tolerance compared with baseline function in the prediction of perioperative mortality.

Maximum Oxygen Consumption

The relationship between maximum oxygen consumption during exercise ($\dot{V}O_2$max) and perioperative risk has been the subject of numerous studies since the 1980s. Due to space limitations, we will only refer to a small number of the studies that we consider most relevant. Assessment of $\dot{V}O_2$max has been proposed as a second step in the evaluation of operative risk—in other words, prior to undertaking quantitative scintigraphy to estimate postoperative function.[46] In the light of available information, this is a reasonable alternative if the necessary equipment is available. Various studies have shown a correlation between $\dot{V}O_2$max and death following resection.[56,61] Bolliger et al[56] reported that none of the surviving patients in their study had a $\dot{V}O_2$max-ppo of less than 10 mL/min/kg, while in the article of Larson et al[61] a $\dot{V}O_2$max of less than 50% separated the patients who died from cardiopulmonary causes from those who did not.

$\dot{V}O_2$max has also been correlated with postoperative cardiorespiratory morbidity with a cutoff point of 20 mL/min/kg for $\dot{V}O_2$max and 15 mL/min/kg for oxygen uptake corresponding to the lactate threshold ($\dot{V}O_2$LT).[62,63]

Puente et al,[64] studying patients with chronic airflow limitation and FEV_1 between 0.8 and 2 L, observed correlations between cardiorespiratory complications and size of resection, ratio of residual volume to total lung capacity (RV/TLC), DLCO-ppo (but not FEV_1-ppo), $\dot{V}O_2$max, and $\dot{V}O_2$max-ppo. Both $\dot{V}O_2$max and $\dot{V}O_2$max-ppo showed a significantly stronger correlation than baseline functional parameters. The best cutoff points were 13 mL/min/kg for $\dot{V}O_2$max-ppo and 17 mL/min/kg for $\dot{V}O_2$max. These cutoff points had high negative predictive values (90%) but the positive predictive values were low (75% and 60% for $\dot{V}O_2$max-ppo and $\dot{V}O_2$max, respectively). Multivariable models did not improve the predictive capacity. In contrast, other authors did not observe a correlation between postoperative complications and preoperative exercise capacity[65]; however, those authors included technical problems such as persistent air leaks, excessive blood loss, wound infection, and empyemas among the complications. Boysen et al[66] studied 17 patients with excellent function. They did not observe a correlation between $\dot{V}O_2$max, maximum minute ventilation during exercise limited by symptoms $\dot{V}$Emax), or maximum O_2 pulse obtained during a maximal treadmill exercise tolerance test and the incidence of postoperative cardiopulmonary complications. The ratio of $\dot{V}$Emax or heart rate to their theoretical values was correlated with the overall occurrence of complications but not specifically with cardiopulmonary complications. In the study of Markos et al,[49] $\dot{V}O_2$max did not differ between patients according to the presence or absence of complications. However, FEV_1-ppo, DLCO, DLCO-ppo, and desaturation during exercise did vary between patients with or without complications. In that study, half of the patients had an FEV_1 of more than 2 L and only 6% had an FEV_1 of less than 50%. Ribas et al[57] obtained comparable results using spirometric criteria to assess high-risk patients.

Some studies have obtained satisfactory results in efforts to describe the rate of mortality and morbidity in small samples of patients considered inoperable on the basis of predicted postoperative function but whose $\dot{V}O_2$max was greater than 10 mL/min/kg or 15 mL/min/kg.[67-69]

The reason for the discrepancies between studies that have attempted to correlate $\dot{V}O_{2max}$ with postoperative morbidity and mortality is not clear. In some cases it may be due to variations in patient selection leading to differences in the heart or lung function of the sample used. There are also differences between the type of complications considered, the complications presented by the patients studied, and the diagnostic criteria employed. There may have been differences in the methods used in exercise testing or in the cooperation of the subjects. Finally, differences may have been present in the measures employed to prevent and treat complications.

Lactate Threshold

In a study by Miyoshi et al[70] the $\dot{V}O_2$ per m^2 of body surface in which a specific concentration of lactate was found (20 mg/dL) predicted mortality but not morbidity. In a study of 31 patients, the same group reported that the best index with which to predict mortality was the oxygen delivery when lactate was at a level of 20 mg/dL. Another study found that patients with a $\dot{V}O_2$LT of more than 15 mL/min/kg did not present complications.[63]

Hemodynamic Studies During Exercise

Analysis of pulmonary artery occlusion during exercise has been employed for many years without clearly demonstrated utility. Although variations in the left ventricular ejection fraction during exercise have been reported to correlate with postoperative morbidity following lung resection,[71] a review of numerous recent studies reveals no evidence that any hemodynamic study during exercise improves upon less invasive studies for the prediction of risk, and consequently, such studies are not recommended.[57,67,72,73]

Desaturation During Exercise

Although numerous studies have observed a correlation between desaturation during exercise and postoperative risk,[74] some other authors found that while FEV_1-ppo was a predictor of complications, desaturation was not.[42,75]

Desaturation during exercise appears to be linked to a high risk of cardiorespiratory complications. However, there is insufficient evidence to determine whether it is a better criterion than others based on a $\dot{V}O_{2max}$ of more than 15 mL/min/kg or on estimates of FEV_1-ppo or DLCO-ppo.

Surgical Risk According to Type of Intervention

Anesthetic Technique

The use of an appropriate anesthetic technique during lung resection is sufficiently important to significantly affect the risk associated with the procedure. Patients considered to be at very high risk can undergo lung resection if the anesthetist is an expert in working with that type of surgery. Furthermore, various technical innovations that fall outside the remit of these recommendations also have a decisive influence.[76]

Pathophysiology. Various physiologic changes that occur during thoracotomy can aggravate existing respiratory function problems.

1. Changes in the ventilation-perfusion ratio. In lateral decubitus, gravity causes the uppermost lung to be the best ventilated and the lower lung the best perfused. Furthermore, general anesthesia causes a loss of diaphragmatic tone that, combined with the position in decubitus, leads to a reduction in lung volumes as a result of the more elevated position of the diaphragm. This leads to a reduction of between 16% and 20% in the residual functional capacity (FC), irrespective of the anesthetic used, and reduces both the expiratory reserve volume and the lung compliance. The closing capacity reduces in line with the residual FC, meaning that the risk of intrapulmonary shunt is similar.

The reduction in residual FC places the upper lung in the favorable zone of the pressure-volume curve—in other words, it is more elastic—and, therefore, the positive pressure that is produced during mechanical ventilation facilitates improved distension.

2. Single-lung ventilation. Thoracic surgery requires collapse of the uppermost lung, meaning that, initially, that lung is no longer ventilated while unoxygenated blood flow is maintained. Consequently, the alveolar-arterial oxygen gradient increases and there is a 20% to 30% increase in right-left shunt and, with it, hypoxemia.[77] Faced with this situation, the body initiates a compensatory mechanism—hypoxic pulmonary vasoconstriction[78]—that diverts flow from the uppermost, unventilated lung to the lower, ventilated lung, the shunt is reduced, and gas exchange is improved. Intolerance of lung collapse can be suspected and assessed preoperatively. However, anesthetists can use various different techniques to improve oxygenation. Among the most effective are an increase in the fraction of inspired oxygen (FiO_2), periodic inflation of the collapsed lung, and a continuous positive pressure of 5 to 10 cm H_2O in the collapsed lung, although this can interfere with surgery.[79]

Surgical Approach

Surgical resection of the lung can currently be performed using 3 different procedures: standard thoracotomy, muscle-sparing thoracotomy, and video-assisted thoracoscopic surgery (VATS).

Although the clinical implications are not known, there is evidence in the literature that the use of VATS procedures reduces the reactive response in the acute phase of the immediate postoperative period compared with other more aggressive procedures.[80-82]

In terms of the relationship between surgical approach and surgical risk, some authors claim that VATS reduces the adverse effects of lung resection.[81,83,84] However, it has not been possible to demonstrate such an advantage in randomized clinical trials,[85] and evidence is even lacking for a correlation between the use of muscle-sparing rather than standard thoracotomy and favorable postoperative evolution.[86]

Type of Surgery Performed

There is a direct relationship between the extent of surgery and the rates of morbidity and mortality.[87] However, this variable is not independent of the respiratory function or exercise capacity of the patient. Furthermore, the extent of resection is directly related to tumor stage.

Segmental resection, especially atypical segmentectomy, is recommended in patients with small, peripheral tumors who cannot tolerate lobectomy. However, the well-known clinical trial reported by the Lung Cancer Study Group[88] demonstrated that the advantages of segmentectomy over lobectomy in terms of reduced lung volumes disappeared a year after surgery. Furthermore, there is evidence suggesting that the effect of lobectomy on lung volumes is limited in COPD patients.[89] Keenan et al[90] concluded that segmental resection leads to less reduction of lung function; however, their study involved 2 case series that were not comparable.

If the risk of surgery is extreme and the tumor small, comorbid conditions probably have a worse prognosis than that of the cancer, meaning that resection of the tumor is not indicated.

Pneumonectomy appears as a significant risk factor in the majority of multivariate analyses performed to identify factors that determine morbidity and mortality.[14,36,87,91-93] Interestingly, mortality following right pneumonectomy is higher than following left.[87,92,94,95] For instance, Wahi et al[96] reported a mortality rate of 12% following right pneumonectomy compared with only 1% for left pneumonectomy. The explanation for this finding is not completely clear but appears to be linked to greater reduction in lung function and increased risk of developing a bronchial fistula, empyema, and pulmonary edema following resection.[97]

According to one study, the appearance of a postoperative bronchial fistula is fatal in 70% of patients that present it.[98] Furthermore, the following factors are significantly associated with the development of a bronchial fistula: presence of a tumor in the bronchial stump, requirement for prolonged postoperative mechanical ventilation, and mediastinal lymph node dissection.[99] Once again, we find that the risk of pneumonectomy is associated with other variables such as tumor extension.

The use of bronchoplastic procedures is a valid alternative to pneumonectomy for the treatment of benign or malignant central bronchial lesions, particularly if the patient has limiting lung function.

Survival of patients with bronchogenic carcinoma treated by bronchoplastic resection has been shown to be similar to those treated by standard resection.[73,100-103] Although a 10.3% local recurrence rate has been reported following bronchoplastic resection,[104] the rate of morbidity and mortality is similar[102,104] or lower[103] than that registered for pneumonectomy; as such, the technique offers clear advantages.[101] Of course, the incidence of postoperative respiratory failure is significantly higher in patients who have undergone pneumonectomy (7% vs 1.7%).[102]

Compared with standard resections, an increase in major respiratory complications has been observed when resection is extended to organs or chest structures other than the lungs that also leads to a significant increase in mortality.[105,106] For instance, in the series published in 1994 by Busch et al[107] there was no significant difference in mortality according to the procedure except when considering extended resections, in which case mortality associated with lobectomies increased up to 25%. In addition, respiratory complications were directly responsible for 33% of deaths and contributed in some way to the deaths of 50% of patients who died following extended resection.

Postoperative Care

As mentioned in relation to anesthetists, nursing staff and respiratory physiotherapists can have a significant impact on operative mortality and morbidity.

Prevention of ventilatory problems. Early extubation contributes to a reduction in barotrauma and the possibility of infection. When this is not possible, the double-lumen tube should be replaced with a standard tube that allows better bronchial cleaning.

Respiratory work is increased in the immediate postoperative period in the same way that lung elasticity is reduced according to the amount of tissue resected. Accumulation of bronchial secretions, microatelectases, increased lung fluid, and reduced surfactant activity aggravate this situation.[108-110] In addition, the maximum force that can be generated by the diaphragm is reduced and posterolateral thoracotomy leads to a greater postoperative reduction in respiratory muscle force, especially in older patients, in whom postoperative recovery of respiratory muscle force is slower.[109,111]

Hypoxemia and respiratory acidosis are, therefore, frequent findings in the first 3 days following chest surgery and are usually due to atelectasis, superficial breathing due to pain, and transudation of liquid with pulmonary edema following reinflation of the collapsed lung. As pointed out by Watkins and Lumb,[112] these factors mean that a series of general measures should be considered, such as maintaining the patient in a semiupright position and with supplementary oxygen (FiO_2, 0.4-0.5), with respiratory and hemodynamic monitoring, monitoring of hypothermia for at least 24 hours, and provision of adequate analgesia. However, these changes usually return to normal within the first week; although 50% of patients can remain hypoxemic on the 5th day. Nevertheless, there is a poor correlation between the extent to which gas exchange is compromised and the presence of detectable pulmonary complications.[113,114]

The literature does not contain evidence that either postoperative respiratory physiotherapy or incentive spirometry reduce the risk of complications following lung resection,[115] probably because it has yet to be studied in this particular type of surgery. However, it has been demonstrated that preoperative muscular training improves lung function in high-risk patients who are going to undergo resection.[116]

Circulatory alterations and transfusion of blood and blood derivatives. Although water balance must be monitored particularly carefully in patients subjected to pneumonectomy, mainly right sided, to prevent pulmonary edema, the appearance of this complication also seems to be affected by other factors such as prolonged surgery, hyperinflation and distention of the parenchyma, and transfusions, particular when they are cold.[117]

The requirement for blood transfusion in chest surgery patients is usually associated with perioperative vascular problems or, more frequently, complex and highly hemorrhagic techniques. Some authors have stated that the prevalence of hemorrhage in thoracic surgery is 16%.[118] Nevertheless, it is necessary in programmed chest surgery to initially type and cross match blood, and later assess whether there are risk factors that necessitate administration of platelets to improve oxygen delivery, along with the various possibilities for their administration. It is recommendable to maintain a cannula in a large vessel during the postoperative period and keep a blood warmer and a rapid infusion system available. Since there is no evidence to indicate that light or moderate anemia increases perioperative morbidity, most clinics decide to transfuse when the hemoglobin level falls below 7 to 8 g/dL,[119] except in patients with myocardial infarction or unstable angina, in whom a minimum hemoglobin level of 10 g/dL is usually preferred.[120]

Analgesia. Analgesia not only improves the comfort of the patient, it also allows respiratory physiotherapy to be undertaken, thereby preventing accumulation of secretions and, therefore, reducing the likelihood of atelectasis and secondary infection. In general, regional techniques appear to be better than intravenous analgesia, since they avoid respiratory depression, particularly in patients with reduced lung function. Epidural or paravertebral analgesia can be used with both local anesthetics and opiates. In principle, the paravertebral route[121] is more indicated because, in addition to presenting a reduced likelihood of peridural hematoma by virtue of the fact that it does not act on the midline, it localizes the analgesia to the treated hemithorax. Given the proven efficacy of multimodal therapies, both should be combined with intravenous

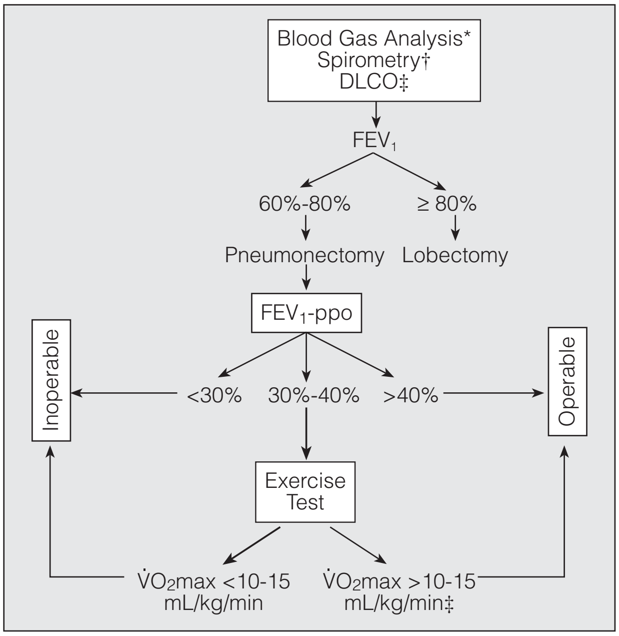

Figure. Algorithm for the assessment of surgical risk in patients who are candidates for lung resection surgery. (The criteria summarized in this algorithm should not be considered indisputable. There are no absolute limits and doubtful cases should be assessed by a multidisciplinary team.) DLCO indicates carbon monoxide diffusing capacity of the lung; FEV_1, forced expiratory volume in the first second; FEV_1-ppo, predicted postoperative FEV_1; $\dot{V}O_2max$, maximum oxygen consumption during exercise.
***Blood gas values do not constitute absolute criteria for operability.**
†Calculation of DLCO is recommended in all cases and is obligatory in patients with dyspnea that cannot be accounted for by lung volumes, interstitial disease, or in those receiving induction chemotherapy.
‡Although the patient may be considered operable, it is not without substantial risk.

nonsteroidal antiinflammatory drugs. Another option is intercostal nerve block performed by the surgeon at the end, or better, at the beginning of the procedure, since it provides excellent analgesia during the most immediate postoperative period. In contrast, intrapleural anesthesia[122] does not enjoy a good reputation, since no studies have successfully demonstrated its benefits.

Adverse effects of other drugs. In addition to opiates and sedatives, there are other drugs that can have adverse effects on the central nervous system.[123] Examples of such adverse effects include the following:

– H_2 antihistamines, cimetidine, and lidocaine can cause respiratory depression.
– Drugs that cause respiratory alkalosis (bicarbonates and diuretics) can also reduce respiratory stimulation.
– Some other drugs, such as captopril and amiodarone, can trigger neuropathy. As pointed out by Aldrich and Prezant,[123] numerous drugs can have the side effect of triggering neuromuscular blockade. Notable among these are the following: antibiotics (aminoglycosides, penicillins, macrolides, and tetracycline), calcium channel blockers (mainly affecting the diaphragm), steroids (by postsynaptic inhibition of neuromuscular transmission), and, logically, muscle relaxants.

Influence of Induction Chemotherapy

The increasingly common use of multimodal therapies in patients with bronchogenic carcinoma and, in particular, the use of induction chemotherapy[124] make it necessary for them to be considered in relation to morbidity and mortality, since they can influence surgical risk. In some publications, induction chemotherapy has been suggested to cause an increase in morbidity and mortality,[31,125] particularly of an infectious or cardiovascular nature, mainly in patients who have undergone pneumonectomy. However, that finding has not been confirmed in other studies.[126]

Recent findings suggest that lung volumes are not good indicators of surgical risk in patients receiving induction chemotherapy and it has been recommended that DLCO be measured in all cases.[127]

Recommendations

General Considerations

The considerations that figure in these recommendations cannot be taken as absolute criteria. There are no indisputable limits for the operability of a patient with lung cancer and any doubtful case should be discussed individually by an interdisciplinary team that includes all professionals involved in the process (thoracic surgeons, anesthetists, intensive care physicians, pulmonologists, oncologists, and others).

General Condition and Comorbidity

– Patient age alone is not a variable that allows decisions to be made on operability.
– Pneumonectomy and extended lobectomy are not recommended in individuals more than 80 years of age.
– Lung resection of any type is not recommended in patients with an ECOG or WHO score of 2 or more, or a Karnofsky score of 50% or less.
– Any comorbid condition with a prognosis demonstrated to be worse than that of bronchogenic carcinoma without surgical treatment should be considered a criterion for inoperability.
– In the presence of carotid or coronary stenosis with an indication for surgery, that surgery should be performed prior to lung resection.

Assessment of Lung Function (Figure)

– All patients in whom lung resection is indicated for treatment of bronchogenic carcinoma should be assessed by arterial blood gas analysis and forced spirometry.
– Assessment of DLCO is recommendable in all cases and is obligatory in patients with interstitial lung disease, unexplained dyspnea, and/or receiving induction chemotherapy, independently of lung volumes.
– Lung function should be assessed when patients are clinically stable and with maximal bronchodilation,

following a period of abstinence from smoking. Optimization of drug treatment is obligatory prior to surgery.

– If FEV_1 is greater than 80% of the theoretical value then no further tests are required. Otherwise, FEV_1-ppo should be calculated for the proposed resection.

– Lung perfusion scintigraphy with ^{99}Tc in the posteroanterior and anteroposterior planes is recommended for the calculation of postoperative lung function. Where this is not possible, it is acceptable to perform a calculation based on the number of functional segments that are to be resected.

– If DLCO is less than 60% of the theoretical value (50% for lobectomy), other tests are necessary in order to calculate postoperative lung function.

– Surgery is not advised when FEV_1-ppo is less then 30% of the theoretical value.

Exercise Tests

– Oxygen consumption during exercise should be tested in patients with FEV_1-ppo and/or DLCO less than 40%.

– $\dot{V}O_2$max of at least 10-15 mL/min/kg identifies operable patients, albeit with a significant operative risk.

– $\dot{V}O_2$max of less than 10-15 mL/min/kg is a contraindication for lung resection.

– Invasive hemodynamic studies are not recommended in the assessment of risk associated with lung resection.

Techniques and Perioperative Treatment

– No scientific evidence exists that wedge resection of the lung offers an appropriate balance between risk and effectiveness for the treatment of bronchogenic carcinoma.

– There is no scientific evidence to support minimally invasive surgery as a technique that reduces either morbidity or mortality in the general population following lung resection. However, on the basis of its reduced influence on the serum concentration of reactants during the acute phase, its use is recommended in patients at high risk.

– Bronchoplastic procedures should be used in place of pneumonectomy whenever it is considered technically feasible and oncologically appropriate.

– Lung resection for bronchogenic carcinoma is not recommended in surgical teams that do not contain surgeons, anesthetists, and nursing and physiotherapy staff who are specifically trained in this area.

REFERENCES

1. Grupo Cooperativo Médico-Quirúrgico del Carcinoma Bronocogénico del Hospital Universitario 12 de Octubre. Carcinoma broncogénico: algoritmo diagnóstico-terapéutico 2001. Available from: http://www.mbeneumología.org
2. López Encuentra A. The Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). Criteria of functional and oncological operability in surgery for lung cancer: a multicenter study. Lung Cancer. 1998;20: 161-8.
3. López Encuentra A, and Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). Comorbidity in lung cancer. A multicenter descriptive study of 2,992 patients. Lung Cancer. 2002;35:263-9.
4. Harpole DH, deCamp MM, Hur K, et al. Prognostic models of thirty-day mortality and morbidity after major pulmonary resection. J Thorac Cardiovasc Surg. 1999;117:969-79.
5. Varela G, Toledo J. Pulmonary resection for lung cancer in the elderly. In: Peters RM, Toledo J, editors. Perioperative care. Currents topics in general thoracic surgery. An international series. Amsterdam: Elsevier; 1992. p. 160-3.
6. de Perrot M, Licker M, Reymond MA, Robert J, Spiliopoulos A. Influence of age on operative mortality and long-term survival after lung resection for bronchogenic carcinoma. Eur Respir J. 1999;14:419-22.
7. British Thoracic Society and Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party. Guidelines on the selection of patients with lung cancer for surgery. Thorax. 2001;56:89-108.
8. Battafarano R, Piccirillo JF, Meyers B, et al. Impact of comorbidity on survival after surgical resection in patients with stage I non-small cell lung cancer. J Thorac Cardiovasc Surg. 2002;123:280-7.
9. Wernly JA, DeMeester TR. Preoperative assessment of patients undergoing lung resection for cancer. In: Roth JA, Ruckdeschel JC, Weisenburger TH, editors. Thoracic oncology. 2nd ed. Philadelphia: W.B. Saunders; 1995. p. 104-24.
10. Guadagnoli E, Weitberg A, Mor V, Silliman RA, Glicksman AS, Cummings FJ. The influence of patient age on the diagnosis and treatment of lung and colorectal cancer. Arch Intern Med. 1990;150:1485-90.
11. López Encuentra A, Martínez González del Río J, Pérez Rodríguez E. Datos epidemiológicos en carcinoma broncogénico. Med Clin (Barc). 1979;72:361-8.
12. Grupo Cooperativo de Carcinoma Broncogénico de la Sociedad Española de Neumología y Cirugía Torácica (GCCB-S). La cirugía del carcinoma broncogénico en España. Estudio descriptivo. Arch Bronconeumol. 1995;31:303-9.
13. Aller Álvarez JL, de Frutos Arribas JF, Díez Herranz A, et al. Comorbilidad. In: Grupo de Estudio del Carcinoma Broncopulmonar de SOCALPAR, editors. El carcinoma broncopulmonar en la Comunidad de Castilla y León. Año 1997. Madrid: FAES; 2000. p. 81-8.
14. Duque JL, Ramos G, Castrodeza J, Cerezal J, Castanedo M, Yuste MG, et al. Early complications in surgical treatment of lung cancer: a prospective, multicenter study. Grupo Cooperativo de Carcinoma Broncogénico de la Sociedad Española de Neumología y Cirugía Torácica. Ann Thorac Surg. 1997;63:944-50.
15. Belzberg H, Rivkind AI. Preoperative cardiac preparation. Chest. 1999;115 Suppl 5:S82-95.
16. McClave SA, Snider HL, Spain DA. Preoperative issues in clinical nutrition. Chest. 1999;115 Suppl 5:S64-70.
17. Uramato H, Kakahishi R, Fujino Y, et al. Prediction of pulmonary complications after a lobectomy in patients with non-small cell lung cancer. Thorax. 2001;56:59-61.
18. Duque JL, and Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). Mortality after pneumonectomy in patients with lung cancer and know cardiac disease. Lung Cancer. 2000;29 Suppl 1:135.
19. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation. 2002;105:1257-67.
20. Pastor Torres LF, Antiago Ramírez R, Honorato Pérez JM, Junquera Planas CM, Navarro Salas E, Ortiguera Aso FJ, et al. Guías de práctica clínica de la Sociedad Española de Cardiología en la valoración del riesgo quirúrgico del paciente cardiópata sometido a cirugía no cardíaca. Rev Esp Cardiol. 2001;54:186-93.
21. Hubbard R, Venn A, Lewis S, Britton J. Lung cancer and cryptogenic fibrosing alveolitis. A population-based cohort study. Am J Respir Crit Care Med. 2000;161:5-8.
22. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease. A prospective, matched, controlled study. Ann Intern Med. 1986;105:503-7.
23. Steenland K, Sanderson W. Lung cancer among industrial sand workers exposed to crystalline silica. Am J Epidemiol. 2001;153:695-703.
24. Grupo de Trabajo SEPAR. Guía clínica para el diagnóstico y el tratamiento de la enfermedad pulmonar obstructiva crónica. Barcelona: Doyma; 2001.
25. Díaz Cambriles T, López Encuentra A, Martín de Nicólas JL, Rey Terrón L, Valeri Busto MV, Martín Escribano P. ¿Puede mejorar o no

modificarse el FEV_1 tras resección pulmonar por carcinoma broncogénico? Arch Bronconeumol. 2001;37 Supl 1:73-4.
26. Korst RJ, Ginsberg RJ, Ailawadi M, et al. Lobectomy improves ventilatory function in selected patients with severe COPD. Ann Thorac Surg. 1998;66:898-902.
27. López Encuentra A, Pozo Rodríguez F, Martín Escribano P, et al. Surgical lung cancer. Risk operative analysis. Lung Cancer. 2004;43:361-2.
28. Santos-García G, Varela G, Novoa N, Jiménez MF. Prediction of postoperative morbidity after lung resection using an artificial neural network ensemble. Artif Intell Med. 2004;30:61-9.
29. Brunelli A, Fianchini A, Gesuita R, Carle F. POSSUM scoring system as an instrument of audit in lung resection surgery. Physiological and operative severity score for the enumeration of mortality and morbidity. Ann Thorac Surg. 1999;67:329-31.
30. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol. 1993;46:1075-9.
31. Bernard A, Ferrand L, Hagry O, Benoit L, Cheynel N, Favre JP. Identification of prognostic factors determining risk groups for lung resection. Ann Thorac Surg. 2000;70:1161-7.
32. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100:1043-9.
33. Locke KA. Clinical prediction guide. A simple index predicted cardiac complications in elective major noncardiac surgery. ACP Journal Club; March-April 2000.
34. Gilbert K, Larocque BJ, Patrick LT. Prospective evaluation of cardiac risk indices for patients undergoing noncardiac surgery. Ann Intern Med. 2000;133:356-9.
35. Mittman C. Assessment of operative risk in thoracic surgery. Am Rev Respir Dis. 1961;84:197-207.
36. Nagasaki F, Flehinger BJ, Martini N. Complications of surgery in the treatment of carcinoma of the lung. Chest. 1982;82:25-9.
37. Olsen GN, Block AJ, Swenson EW, Castle JR, Wynne JW. Pulmonary function evaluation of the lung resection candidate: a prospective study. Am Rev Respir Dis. 1975;111:379-87.
38. Reilly J. Evidence-based preoperative evaluation of candidates for thoracotomy. Chest. 1999;116:S474-6.
39. American College of Chest Physicians. Preoperative pulmonary function testing. Ann Intern Med. 1990;112:793-4.
40. Morice RC, Peters EJ, Ryan MB, Putnam JD, Ali MK, Roth JA. Exercise testing in the evaluation of patients at high risk for complications from lung resection. Chest. 1992;101:356-61.
41. Bolliger CT, Perruchoud AP. Functional evaluation of the lung resection candidate. Eur Respir J. 1998;11:198-212.
42. Kearney DJ, Lee TH, Reilly JJ, deCamp MM, Sugarbaker DJ. Assessment of operative risk in patients undergoing lung resection. Chest. 1994;105:753-9.
43. Ribas J. Aplicabilidad de las pruebas de esfuerzo en Neumología. Arch Bronconeumol. 2000;36:44-51.
44. Meléndez JA, Fischer ME. Preoperative pulmonary evaluation of the thoracic surgical patient. Chest Surg Clin North Am. 1997;7:641-54.
45. Miller JI. Physiologic evaluation of pulmonary function in the candidate for lung resection. J Thorac Cardiovasc Surg. 1993;105:347-52.
46. Wyser C, Stulz P, Soler M, Tamm M, Muller-Brand J, Habicht J, et al. Prospective evaluation of an algorithm for the functional assessment of lung resection candidates. Am J Respir Crit Care Med. 1999;159:1450-6.
47. Bousamra M II, Presberg KW, Chammas JH, Tweddell JS, Winton BL, Bielefeld MR, et al. Early and late morbidity in patients undergoing pulmonary resection with low diffusion capacity. Ann Thorac Surg. 1996;62:968-75.
48. Ferguson MK, Little L, Rizzo L, et al. Diffusing capacity predicts morbidity and mortality after pulmonary resection. J Thorac Cardiovasc Surg. 1988;96:894-900.
49. Markos J, Mullan BP, Hillman DR, Musk AW, Antico VF, Lovegrove FT, et al. Preoperative assessment as a predictor of mortality and morbidity after lung resection. Am Rev Respir Dis. 1989;139:902-10.
50. Ladurie MLR, Ranson-Bitker B. Uncertainties in the expected value for forced expiratory volume in one second after surgery. Chest. 1986;90:222-8.
51. Varela G, Jiménez MF, Novoa N, Aranda JL. Concordancia entre el tipo de resección programada y la efectuada en pacientes con carcinoma pulmonar. Arch Bronconeumol. 2005;41:84-7.
52. Corris PA, Ellis DA, Hawkins T, Gibson GJ. Use of radionuclide scanning in the preoperative estimation of pulmonary function after pneumonectomy. Thorax. 1987;42:285-91.
53. Bolliger CT, Jordan P, Soler M, Stulz P, Gradel E, Skarvan K, et al. Exercise capacity as a predictor of postoperative complications in lung resection candidates. Am J Respir Crit Care Med. 1995;151:1472-80.
54. Puente-Maestu L, Ruiz de Ona JM, Rodríguez-Hermosa JL, Santa-Cruz SA, Tatay E, Cubillo JM. Predicción de la capacidad de esfuerzo tras la resección pulmonar en pacientes con limitación crónica al flujo aéreo. Arch Bronconeumol. 1998;34:473-8.
55. Pierce RJ, Copland JM, Sharpe K, Barter CE. Preoperative risk evaluation for lung cancer resection: predicted postoperative product as a predictor of surgical mortality. Am J Respir Crit Care Med. 1994;947-55.
56. Bolliger CT, Wyser C, Roser H, Soler M, Perruchoud AP. Lung scanning and exercise testing for the prediction of postoperative performance in lung resection candidates at increased risk for complications. Chest. 1995;108:341-8.
57. Ribas J, Díaz O, Barberà JA, Mateu M, Canalis E, Jover L, et al. Invasive exercise testing in the evaluation of patients at high-risk for lung resection. Eur Respir J. 1998;12:1429-35.
58. Holden DA, Rice TW, Stelmach K, Meeker DP. Exercise testing, 6-min walk, and stair climb in the evaluation of patients at high risk for pulmonary resection. Chest. 1992;102:1774-9.
59. Tsubota N, Yanagawa M, Yoshimura M, Murotani A, Hatta T. The superiority of exercise testing over spirometry in the evaluation of postoperative lung function for patients with pulmonary disease. Surg Today. 1994;24:103-5.
60. Olsen GN, Bolton JWR, Weiman DS, Haynes JL, Hornung CA, Almond CH. Stair climbing as an exercise test to predict the postoperative complications of lung resection. Chest. 1991;99:587-90.
61. Larsen RK, Svendsen UG, Milman N, Brenoe J, Petersen BN. Exercise testing in the preoperative evaluation of patients with bronchogenic carcinoma. Eur Respir J. 1997;10:1559-65.
62. Smith TP, Kinasewitz GT, Tucker WY, Spillers WP, George RB. Exercise capacity as predictor of post-thoracotomy morbidity. Am Rev Respir Dis. 1984;129:730-4.
63. Torchio R, Gulotta C, Parvis M, Pozzi R, Giardino R, Borasio P, et al. Gas exchange threshold as a predictor of severe postoperative complications after lung resection in mild-to-moderate chronic obstructive pulmonary disease. Monaldi Arch Chest Dis. 1998;53:127-33.
64. Puente Maestu L, Rodríguez Hermosa JL, Ruiz de Ona JM, Santa-Cruz Seminiani A, de Lucas Ramos P, García de Pedro J, et al. Papel de la estimación preoperatoria de la captación máxima de oxígeno en la predicción de insuficiencia cardiorrespiratoria en el período postoperatorio inmediato en la cirugía torácica. Arch Bronconeumol. 1998;34:127-32.
65. Colman NC, Schraufnagel DE, Rivington RN, Pardy RL. Exercise testing in the evaluation of patients for lung resection. Ann Thorac Surg. 1987;44:344-9.
66. Boysen PG, Clark CA, Block AJ. Graded exercise testing and post-thoracotomy complications. J Cardiothorac Anesth. 1990;4:68-72.
67. Bolliger CT, Soler M, Stulz P, Gradel E, Muller-Brand J, Elsasser S, et al. Evaluation of high-risk lung resection candidates: pulmonary haemodynamics versus exercise testing. A series of five patients. Respiration. 1994;61:181-6.
68. Pate P, Tenholder MF, Griffin JP, Eastridge CE, Weiman DS. Preoperative assessment of the high-risk patient for lung resection. Ann Thorac Surg. 1996;61:1494-500.
69. Walsh GL, Morice RC, Putnam JB, Nesbitt JC, McMurtrey MJ, Ryan B, et al. Resection of lung cancer is justified in high risk patients selected by exercise oxygen consumption. Ann Thorac Surg. 1994;58:704-11.
70. Miyoshi S, Nakahara K, Ohno K, Monden Y, Kawashima Y. Exercise tolerance test in lung cancer patients: the relationship between exercise capacity and posthoracotomy hospital mortality. Ann Thorax Surg. 1987;44:487-90.
71. Okada M, Okada M, Ishii N, Yamashita C, Sugimoto T, Okada K, et al. Right ventricular ejection fraction in the preoperative risk evaluation of candidates for pulmonary resection. J Thorac Cardiovasc Surg. 1996;112:364-70.
72. Nakagawa K, Nakahara K, Miyoshi S, Kawashima Y. Oxygen transport during incremental exercise load as predictor of operative risk in lung cancer patients. Chest. 1992;101:1369-75.
73. Rendina EA, de Giacomo T, Venuta F, Ciccone AM, Coloni GF. Lung conservation techniques: bronchial sleeve resection and reconstruction of the pulmonary artery. Semin Surg Oncol. 2000;18:165-72.
74. Olsen GN, Wiman DS, Bolton JWR, Gass D, McLain WC, Schoonover GA, et al. Submaximal invasive exercise testing and quantitative lung scanning in the evaluation of tolerance to lung resection. Chest. 1989;95:267-73.
75. Varela G, Cordovilla R, Jiménez MF, Novoa N. Utility of standardized exercise oximetry to predict cardiopulmonary morbidity after lung resection. Eur J Cardiothorac Surg. 2001;19:351-4.

76. von Dossow V, Welte M, Zaune U, Martin E, Walter M, Ruckert J, et al. Thoracic epidural anesthesia combined with general anesthesia: the preferred anesthetic technique for thoracic surgery. Anesth Analg. 2001;92:848-54.
77. Bardoczky GI, Szegedi LL, d'Hollander AA, Moures JM, de Francquen P, Yernault JC. Two-lung and one-lung ventilation in patients with chronic obstructive pulmonary disease: the effects of position and FiO_2. Anesth Analg. 2000;90:35-41.
78. Varela G, del Barrio E, Jiménez M, García Cosmes P, Criado M, López Novoa JM. Papel del óxido nítrico en la adaptación del lecho vascular pulmonar a la ventilación unilateral durante intervenciones torácicas. Arch Bronconeumol. 1998;34:194-8.
79. Mascotto G, Bizzarri M, Messina M, Cerchierini E, Torri G, Carozzo A, et al. Prospective, randomized, controlled evaluation of the preventive effects of positive end-expiratory pressure on patient oxygenation during one-lung ventilation. Eur J Anaesthesiol. 2003;20:704-10.
80. Craig SR, Leaver HA, Yap PL, Pugh GC, Walker WS. Acute phase responses following minimal access and conventional thoracic surgery. Eur J Cardiothorac Surg. 2001;20:455-63.
81. Nagahiro I, Andou A, Aoe M, Sano Y, Date H, Shimizu N. Pulmonary function, postoperative pain, and serum cytokine level after lobectomy: a comparison of VATS and conventional procedure. Ann Thorac Surg. 2001;72:362-5.
82. Yim AP, Wan S, Lee TW, Arifi AA. VATS lobectomy reduces cytokine responses compared with conventional surgery. Ann Thorac Surg. 2000;70:243-7.
83. Kaseda S, Aoki T, Hangai N, Shimizu K. Better pulmonary function and prognosis with video-assisted thoracic surgery than with thoracotomy. Ann Thorac Surg. 2000;70:1644-6.
84. Nakata M, Saeki H, Yokoyama N, Kurita A, Takiyama W, Takashima S. Pulmonary function after lobectomy: video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg. 2000;70:938-41.
85. Kirby TJ, Mack MJ, Landreneau RJ, Rice TW. Lobectomy—video-assisted thoracic surgery versus muscle-sparing thoracotomy. A randomized trial. J Thorac Cardiovasc Surg. 1995;109:997-1001.
86. Landreneau RJ, Pigula F, Luketich JD, Keenan RJ, Bartley S, Fetterman LS, et al. Acute and chronic morbidity differences between muscle-sparing and standard lateral thoracotomies. J Thorac Cardiovasc Surg. 1996;112:1346-50.
87. Damhuis RA, Schutte PR. Resection rates and postoperative mortality in 7899 patients with lung cancer. Eur Respir J. 1996;9:7-10.
88. Ginsberg RJ, Rubinstein LV. The Lung Cancer Study Group. Randomized trial of lobectomy versus limited resection for T1N0 non-small cell lung cancer. Ann Thorac Surg. 1995;60:615-2.
89. Sekine Y, Iwata T, Chiyo M, Yasufuku K, Motohashi S, Yoshida S, et al. Minimal alteration of pulmonary function after lobectomy in lung cancer patients with chronic obstructive pulmonary disease. Ann Thorac Surg. 2003;76:356-62.
90. Keenan RJ, Landreneau RJ, Maley RH Jr, Singh D, Macherey R, Bartley S, et al. Segmental resection spares pulmonary function in patients with stage I lung cancer. Ann Thorac Surg. 2004;78:228-33.
91. Licker M, de Perrot M, Hohn L, Tschopp JM, Robert J, Frey JG, et al. Perioperative mortality and major cardio-pulmonary complications after lung surgery for non-small cell carcinoma. Eur J Cardiothorac Surg. 1999;15:314-9.
92. Wada H, Nakamura T, Nakamoto K, Maeda M, Watanabe Y. Thirty-day operative mortality for thoracotomy in lung cancer. J Thorac Cardiovasc Surg. 1998;115:70-3.
93. Yano T, Yokoyama H, Fukuyama Y, Takai E, Mizutani K, Ichinose Y. The current status of postoperative complications and risk factors after a pulmonary resection for primary lung cancer. A multivariate analysis. Eur J Cardiothorac Surg. 1997;11:445-9.
94. Breyer RH, Zippe C, Pharr WF, Jensik RJ, Kittle CF, Faber LP. Thoracotomy in patients over age seventy years: ten-year experience. J Thorac Cardiovasc Surg. 1981;81:187-93.
95. Weiss W. Operative mortality and five-year survival rates in men with bronchogenic carcinoma. Chest. 1974;66:483-7.
96. Wahi R, McMurtrey MJ, deCaro LF, Mountain CF, Ali MK, Smith TL, et al. Determinants of perioperative morbidity and mortality after pneumonectomy. Ann Thorac Surg. 1989;48:33-7.
97. Klemperer J, Ginsberg RJ. Morbidity and mortality after pneumonectomy. Chest Surg Clin N Am. 1999;9:515-25.
98. Wright CD, Wain JC, Mathisen DJ, Grillo HC. Postpneumonectomy bronchopleural fistula after sutured bronchial closure: incidence, risk factors, and management. J Thorac Cardiovasc Surg. 1996;112: 1367-71.
99. de Perrot M, Licker M, Robert J, Spiliopoulos A. Incidence, risk factors and management of bronchopleural fistulae after pneumonectomy. Scand Cardiovasc J. 1999;33:171-4.
100. Jalal A, Jeyasingham K. Bronchoplasty for malignant and benign conditions: a retrospective study of 44 cases. Eur J Cardiothorac Surg. 2000;17:370-6.
101. Kruger M, Uschinsky K, Hassler K, Engelmann C. Postoperative complications after bronchoplastic procedures in the treatment of bronchial malignancies. Eur J Cardiothorac Surg. 1998;14:46-52.
102. Suen HC, Meyers BF, Guthrie T, Pohl MS, Sundaresan S, Roper CL, et al. Favorable results after sleeve lobectomy or bronchoplasty for bronchial malignancies. Ann Thorac Surg. 1999;67:1557-62.
103. Yoshino I, Yokoyama H, Yano T, Ueda T, Takai E, Mizutani K, et al. Comparison of the surgical results of lobectomy with bronchoplasty and pneumonectomy for lung cancer. J Surg Oncol. 1997;64:32-5.
104. Tedder M, Anstadt MP, Tedder SD, Lowe JE. Current morbidity, mortality, and survival after bronchoplastic procedures for malignancy. Ann Thorac Surg. 1992;54:387-91.
105. Kodama K, Higashiyama M, Yokouchi H, Takami K, Yasuda T, Kabuto T. Survival and postoperative complications after extended surgery for non-small-cell lung cancer. A retrospective study. Jpn J Thorac Cardiovasc Surg. 1999;47:546-51.
106. Pairolero PC, Trastek VF, Payne WS. Treatment of bronchogenic carcinoma with chest wall invasion. Surg Clin North Am. 1987;67:959-64.
107. Busch E, Verazin G, Antkowiak JG, Driscoll D, Takita H. Pulmonary complications in patients undergoing thoracotomy for lung carcinoma. Chest. 1994;105:760-6.
108. Hsia CCW, Peshock RM, Estrera AS, McIntire DD, Ramanathan M. Respiratory muscle limitation in patients after pneumonectomy. Am Rev Respir Dis. 1993;147:744-52.
109. Maeda H, Nakahara K, Ohno K, Kido T, Ikeda M, Kawashima Y. Diaphragm function after pulmonary resection: relationship to postoperative respiratory failure. Am Rev Respir Dis. 1988;137:678-81.
110. Jones JG, Sapsford DJ, Wheatley RG. Postoperative hypoxaemia: mechanisms and time course. Anaesthesia. 1990;45:566-73.
111. Nomori H, Horio H, Fuyuno G, Kobayashi R, Yashima H. Respiratory muscle strength after lung resection with special reference to age and procedures of thoracotomy. Eur J Cardiothorac Surg. 1996;10:352-8.
112. Watkins WD, Lumb PD. Efectos perioperatorios de la anestesia en atención del paciente quirúrgico. Vol. 2. México D.F.: Ed. Científica Médica Latinoamericana; 1991. p. 6.
113. Aldren CP, Barr LC, Leach RD. Hypoxaemia and postoperative pulmonary complications. Br J Surg. 1991;78:1307-8.
114. Entwistle MD, Roe PG, Sapsford DJ, Berrisford RG, Jones JG. Patterns of oxygenation after thoracotomy. Br J Anaesthesia. 1991;67:704-11.
115. Overend TJ, Anderson CM, Lucy SD, Bhatia C, Jonsson BI, Timmermans C. The effect of incentive spirometry on postoperative pulmonary complications: a systematic review. Chest. 2001;120:971-8.
116. Weiner P, Man A, Weiner M, Rabner M, Waizman J, Magadle R, et al. The effect of incentive spirometry and inspiratory muscle training on pulmonary function after lung resection. J Thorac Cardiovasc Surg. 1997;113:552-7.
117. Duque Medina JL. Edema pulmonar postneumonectomía. In: Ramos G, editor. Complicaciones en cirugía torácica. Valladolid: Universidad de Valladolid. Secretariado de Publicaciones e Intercambio internacional; 2002. p. 17-22.
118. Duogenis D, Patrinou V, Filos KS, et al. Blood use in lung resection for carcinoma: perioperative elective anaemia does not compromise the early outcome. Eur J Cardiothorac Surg. 2001;20:372-7.
119. Stehling L, Luban NLC, Anderson KC, et al. Guidelines for blood utilization review. Transfusion. 1994;34:438-48.
120. Hebert P, Wells G, Blajchman MA, et al. Canadian critical care trials group. A multicenter randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med. 1999;340:409-17.
121. Karmakar MK. Thoracic paravertebral block. Anesthesiology. 2001;95:771-80.
122. Covino BG. Interpleural regional anesthesia [editorial]. Anesth Analg. 1987;67:427-9.
123. Aldrich TK, Prezant DJ. Adverse effects of drugs on the respiratory muscles. Clinics in Chest Medicine. 1990;11:177-89.
124. Ginsberg RJ. Multimodality therapy for stage III N2 lung cancer. An overview. Chest. 1993;103:356S-9S.
125. Doddoli C, Thomas P, Thirion X, et al. Postoperative complications in relation with induction therapy for lung cancer. Eur J Cardiothorac Surg. 2001;20:385-90.
126. Novoa N, Varela G, Jiménez MF. Morbidity after surgery for non-small cell lung carcinoma is not related to neoadjuvant chemotherapy. Eur J Cardiothorac Surg. 2001;20:700-4.
127. Leo F, Solli P, Spaggiari L, Veronesi G, De Braud F, Leon ME, et al. Respiratory function changes after chemotherapy: an additional risk for postoperative respiratory complications? Ann Thorac Surg. 2004;77:260-5.