Functional Evaluation before Lung Resection

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KEYWORDS

- Lung resection • Operability • Preoperative evaluation
- Regional lung function • Cardiopulmonary exercise test

Lung cancer is the leading cause of cancer-related death worldwide, accounting for approximately 160,000 deaths in the United States in 2010.[1] Lung resection remains the only curative approach to lung cancer, despite continuous advances in chemotherapy and radiotherapy.[2,3] In the Western world, lung cancer is one of the main indications for lung resection, despite only 15% to 25% of all lung cancers being operable at the time of presentation. In developing countries, this figure is even lower: recent data from South Africa suggest that only 6% of all patient with lung cancer were operable at the time of presentation.[4] However, post-tuberculous bronchiectasis, complicated by hemoptysis or recurrent lower respiratory tract infections, remains the most common indication for lung resection.[5]

In most cases of operable lung cancer, a substantial part of functional lung tissue has to be resected, which leads to a permanent loss of pulmonary function. An estimated 90% of all patients with lung cancer have underlying chronic obstructive pulmonary disease (COPD) and cardiovascular disorders in varying degrees caused by the shared risk factor from tobacco smoking, making lung resection in those patients a procedure associated with a higher risk of intraoperative and postoperative complications.[2,3] Resection in patients with insufficient pulmonary reserves can result in permanent respiratory disability. The assumption that there is a level of respiratory impairment beyond which resection bears a high risk and is prohibitive drives the ongoing search for the ideal test to predict postoperative lung function and identify the patients at high risk.

This article reviews the current standards of preoperative assessment, including tests for measurement of preoperative pulmonary function and gas exchange, calculation of predicted postoperative (ppo) function, exercise testing, and assessment of regional lung function.

PARAMETERS OF FUNCTIONAL OPERABILITY

The main parameters of functional operability are age, general health and performance status, cardiac function, pulmonary mechanics, diffusion capacity, exercise capacity, and extent of resection. All functional parameters must be measured in optimal therapy to achieve the best possible results. Patients' COPD treatment therefore needs to be optimized, smoking cessation should be encouraged, and even short term physiotherapy and rehabilitation need to be considered. The lack of chest physiotherapy has been shown to be an independent risk factor for postoperative complications.[6] In patients who have lung cancer, the potential period for functional improvement is only 4 to 6 weeks, because further delays necessitate reevaluation of tumor staging given the often rapid progression of disease.

Age, General Health, Performance Status

Although age greater than 70 years has been associated with a higher risk of complications,[7,8] it is the comorbidities associated with advanced age rather than age itself that are responsible for this observation.[9] Patients more than 70 years of age with good performance status and preserved

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cardiopulmonary reserves have a long-term survival comparable with younger patients.[10] Newer surgical techniques, such as video-assisted thoracic surgery (VATS),[11] and limited resections for stage Ia lung cancers may also negate some of the effects of comorbidity in elderly patients. Surgery should therefore not be withheld from any patient based on age alone.[2]

COPD is the most frequently identified risk factor for pulmonary complications among patients undergoing any form of surgery, and overt COPD has a relative risk of 4.7 of developing postoperative complications following thoracic surgery.[9] Moreover, both the presence of abnormalities on physical examination and the degree of obstruction correlate with complications. There is currently no prospective evidence to estimate the risk of postoperative complications in patients with restrictive ventilatory impairment.[12] Well-controlled asthma is not associated with postoperative complications, and neither is a short course of oral corticosteroids.[12]

The American Society of Anesthesiologists' (ASA) classification has been shown to predict postoperative complications. The odds ratio for postoperative complications in patients with ASA class III or higher is 2.6 compared with patients with ASA class I and II.[12] Partial and total dependence are major risk factors for postoperative complications.[13] Patients who are dependent are unlikely to be candidates for major pulmonary resection. Metabolic disturbances contribute to postoperative complications. Malnutrition (albumin <30 g/L) reduces ventilatory drive to hypoxia and hypercapnia, contributes to respiratory muscle dysfunction, alters lung elasticity, and impairs immunity. However, nutritional intervention before surgery has not been shown to attenuate the risk. Renal impairment (blood urea >30 mg/dL [10.7 mmol/L]) carries an odds ratio of 2.3 for postoperative complications.[12,13]

Cigarette smoking increases the risk of postoperative pulmonary complications irrespective of the presence of COPD.[9] A significant reduction of this risk is only noted after 8 weeks of cessation.[10] It had previously been suggested that quitting less than 8 weeks before surgery might even increase the risk for complications.[14,15] Recent meta-analyses confirm that smoking cessation before surgery does not increase the risk for postoperative complications. The data indicate that stopping smoking before surgery might lower the risk of complications, with a growing effect with longer duration of smoking cessation.[16,17] Therefore, smokers should be encouraged to quit smoking and should be supported with appropriate treatment.

Cardiac Risk Assessment

Patients with lung cancer and underlying COPD often suffer from cardiovascular disease as well, because smoking is a risk factor for both lung and heart disease. Those patients are at higher risk for postoperative complications than patients without underlying lung and cardiovascular disease. As far back as 1961, Mittman[18] showed that an abnormal resting electrocardiogram (ECG) was associated with an increased risk of intraoperative or postoperative cardiac complications. In the late 1970s, a multifactorial cardiac risk index was published,[19] was revised in 1999.[20] It contains 6 independent variables that correlate with postoperative cardiac complications (**Box 1**). Two or more variables indicate a high risk and are associated with a postoperative cardiac complication rate of greater than 10%. Lung resection represents high-risk surgery (ie, 1 positive variable), and any patient with another positive variable needs evaluation and potential intervention by a cardiologist.

Box 1
Revised Goldman Cardiac Risk Index: the number of positive variables correlates with the risk for postoperative cardiac complications (no risk factors, 0.4%; 1 risk factor, 0.9%; 2 risk factors, 7%; 3 and more risk factors, 11%)

1. High-risk type of surgery
2. History of ischemic heart disease
   a. History of myocardial infarction (within 6 months)
   b. Positive exercise test
   c. Current complaint of ischemic chest pain
   d. Use of nitrate therapy
   e. Pathologic Q waves on ECG

(Not included: prior coronary revascularization procedure unless one of the other criteria for ischemic heart disease is present)

3. History of cardiac failure
4. History of cerebrovascular disease
5. Diabetes mellitus requiring treatment with insulin
6. Preoperative serum creatinine >2.0 mg/dL (177 μmol/L)

From 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(10):1043–9; with permission.

Coronary stenting can be performed before lung resection, although it has not been shown to influence cardiac risk.[3] Coronary artery bypass surgery before lung surgery, as suggested previously, might delay curative resection, which is problematic because of the time constraints in the management of lung cancer. Combining lung cancer surgery and conventional bypass surgery increases the risk of morbidity and mortality.[21,22] Minimally invasive (off-pump) direct coronary artery bypass surgery simultaneous with lung resection has comparable complications with lung resection alone.[23]

Spirometry

Many parameters of pulmonary mechanics have been recommended for preoperative assessment, but only forced expiratory volume in 1 second (FEV_1), suggested in the early 1970s,[24,25] has stood the test of time. It correlates well with the degree of respiratory impairment and provides an indirect measure of pulmonary reserves. Most studies that have reported on FEV_1 have used absolute values. Early recommendations of FEV_1 values for safe resections were more than 2 L for pneumonectomy[26,27] and more than 1.5 L for lobectomy.[27,28] However, the use of absolute values has never been universally accepted, because they do not take gender, height, weight, and age into consideration, nor do they consider the functional contribution of the tissue to be removed . Three investigators suggested cutoffs for FEV_1 in percentage predicted: Mittman[18] suggested greater than 70%, whereas Nagasaki[8] and, more recently, Pate[29] suggested greater than 40%. None of the 3 studies mentioned the extent of resection possible with these values.

The concept of so-called predicted postoperative (ppo) values has recently been introduced. These values are ideally expressed as percent of ppo (%ppo). Thresholds prohibiting resections of various extents have been validated. Patients with preoperative FEV_1 greater than 80% of predicted (in combination with a carbon monoxide diffusion capacity [DL_{CO}] >80% of predicted) are generally considered at low risk for resection up to pneumonectomy. Markos and colleagues,[30] Wahi and colleagues,[31] and Bolliger and colleagues[32] all found mortality rates of approximately 50% in patients with %FEV_1-ppo less than 40%. Nakahara and colleagues[33] found an even higher mortality (60%) in patients with %FEV_1-ppo less than 30%. Technical aspects regarding ppo calculations are discussed later in this article.

DL_{CO}

The DL_{CO} is a proxy measurement of alveolar oxygen exchange.[34] As early as 1963, Cander[35] suggested that a value of less than 50% of predicted precluded pulmonary resections. Ferguson and colleagues[36] showed that the DL_{CO} was an independent predictor of morbidity and mortality after pulmonary resection. They identified a DL_{CO} of less than 60% of predicted as a cutoff value for major pulmonary resection. Similar findings were reported by Markos and colleagues.[30] The predicted postoperative DL_{CO} (ppo-DL_{CO}) is currently used, rather than the actual value, particularly in patients with impaired pulmonary reserves.[34] A ppo-DL_{CO} value of less than 40% identifies high-risk patients.[37] The ppo-DL_{CO} values derived from various methods tend to overestimate immediate postoperative values, but there is a significant correlation between actual values 1 month after resection and ppo-DL_{CO} values.[34] Despite being included in current guidelines, the European Thoracic Surgery Database recently showed that DL_{CO} values were only measured in approximately 25% of patients before pulmonary resection.[38]

Formal Cardiopulmonary Exercise Testing

Formal cardiopulmonary exercise testing (CPET) is a comprehensive investigation that assesses integrated cardiopulmonary reserves. The testing is performed in a controlled environment and has the advantage of good reproducibility. Measured values are dependent on pulmonary function, cardiovascular function, and oxygen use by peripheral tissues, thus assessing the overall fitness of a patient.[2] CPET is well validated, but requires expertise and is not universally available. The most widely used exercise tests are maximal or symptom-limited incremental exercise tests on treadmill or bicycle. Various parameters, including cardiac ischemia, can be assessed with good reproducibility. The most important measurement in CPET is the level of work achieved, measured as maximum oxygen consumption (VO_2max). VO_2max is measured either directly in a noninvasive fashion or can be calculated. Invasive hemodynamic measurements have been shown to add little useful additional information.[39] An early study reported no mortality versus 75% mortality at greater than and less than a threshold of 1 L/min. Expressing VO_2max as mL/kg/min takes the patient's body mass into account and should therefore be used. Until recently, a VO_2max of greater than 20 mL/kg/min or greater than 75% of predicted was considered sufficient to undergo pneumonectomy, whereas a VO_2max of less than 10 mL/kg/min or less than 40% of predicted would preclude any resection.[25,40] Most recently, the VO_2max value precluding any resection was lowered to

35% of predicted.[41] A cutoff of 15 mL/kg/min is considered to be sufficient for lobectomy.[42–44]

Low-Cost Alternatives

The lack of access to sophisticated exercise equipment and expertise often necessitates the use of other forms of exercise testing. Low-technology alternatives have been proposed to evaluate patients before lung resection, stair climbing tests being the most widely used and validated form. The advantages of stair climbing are availability, low cost, and familiarity of patients with this kind of exercise, and it has been reported that stair climbing yields greater values for Vo_2max than cycle ergometry.[45–47] The largest prospective study reports on 160 patients who underwent stair climbing testing before pulmonary resection.[48] It was shown that patients with no complications climbed to a significantly greater height than patients with complications. A cutoff of 20 m was suggested, although the extent of resection was not taken into consideration. The same group investigated the correlation between the height reached and directly measured Vo_2max in 109 patients. They concluded that patients who reached 22 m or more can proceed directly to surgery because they generated high values of Vo_2max.[49] In another recent study, the speed of ascent, rather than the height alone, showed a linear correlation with Vo_2max measured by cycle ergometry.[5] Compared with the oxygen consumption values, a speed of ascent of 15 m/min correlated with a Vo_2max of 20 mL/kg/min, and a speed of 12 m/min correlated with a Vo_2max of 15 mL/kg/min, suggesting potential cutoffs for pneumonectomy and lobectomy, respectively. The use of shuttle walking tests cannot be recommended, because prospective studies failed to validate the tests.[50,51]

ASSESSMENT OF REGIONAL LUNG FUNCTION AND CALCULATING THE EXTENT OF RESECTION

Anatomic Calculations

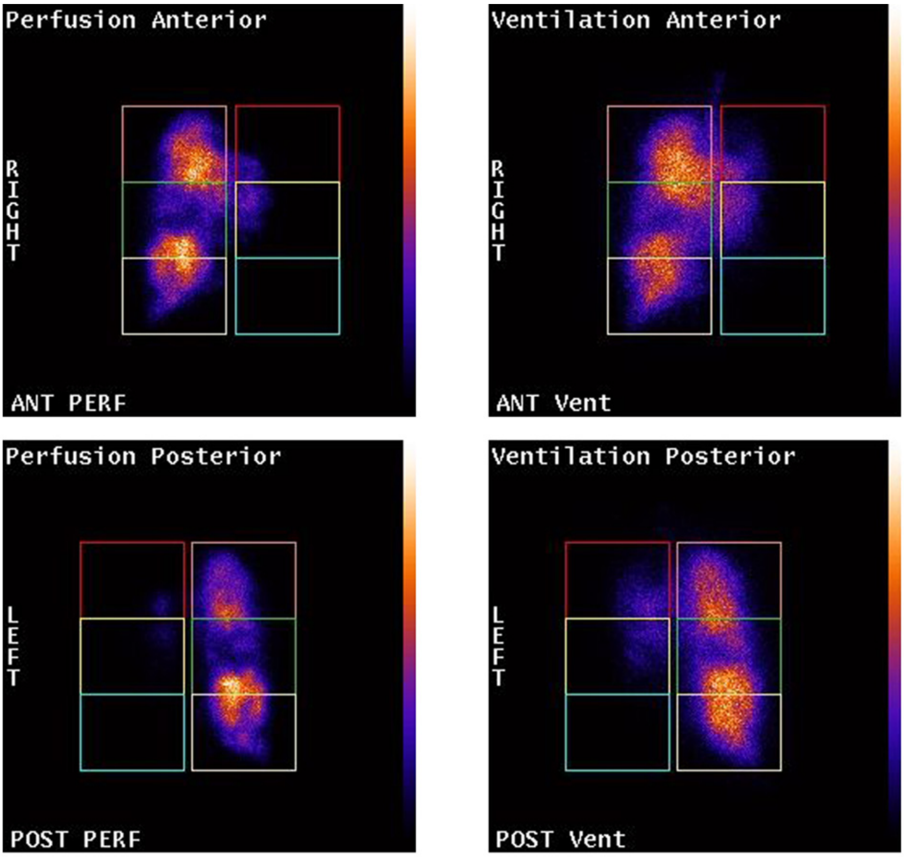
Anatomic calculations are an old, tested, and simple method of assessing regional lung function. With the advent of pulmonary perfusion scintigraphy, they were abandoned to a degree, but were revived in the 1990s and have now been reestablished as reliable predictors of postoperative lung function.[52] Anatomic calculations are based on the number of segments to be resected (ie, the ppo value is a fraction of remaining segments or subsegments). The simplest formula to calculate (eg, ppo-FEV_1) is preoperative $FEV_1 \times [19 - \text{patent segments to be removed}/19]$. Nineteen represents the number of total lung segments. ppo-DL_{CO} and ppo-Vo_2max are calculated in a similar fashion. Anatomic calculations overestimate the extent of functional loss, because destroyed or collapsed lung parenchyma might be resected with little loss of function.[52] Subanalysis of one prospective study showed that anatomic calculations were less accurate than lobectomy at predicting postresectional lung function following pneumonectomy.[53]

Radionucleotide Ventilation/Perfusion Scanning

The usefulness of radionucleotide perfusion scanning was established in the 1970s by a study showing accurate prediction of functional loss 3 months after pneumonectomy by perfusion scanning using intravenous technetium-99 macroaggregates.[54] The feasibility of this method to estimate ventilatory function was subsequently confirmed. Patients are scanned in 4 projections and images obtained by a γ camera (single-photon emission computed tomography [SPECT]). The technetium particles are trapped in the capillary bed of the lungs and emit γ rays proportional to regional pulmonary perfusion. Quantification of regional perfusion is performed by a system-integrated program (**Fig. 1**). A prospective study in 44 patients who had lung resection showed that estimates based on perfusion scanning had the highest correlations with postoperatively measured values for FEV_1, FVC, DL_{CO} and Vo_2max. Perfusion scanning outperformed calculations based on quantitative dynamic computed tomography (CT) scanning anatomic calculations for the range of functional parameters.[53]

Quantitative CT Scanning

Quantitative CT scanning is a simple, universally available method of assessing regional lung function. It has gained in popularity, because almost every lung resection candidate has a staging CT scan. It should be performed at inspiration and viewed with a standard-spatial-frequency reconstruction algorithm. The total functional lung volume (TFLV) is identified by semiautomated analyses. Using a cursor, the lung parenchyma is outlined and 3 quantitative segments are generated according to Hounsfield units (HU) (**Fig. 2**). The part of the lung to be resected is calculated as the regional functional lung volume (RFLV). Values for ppo are calculated as follows (eg, ppo-FEV_1): ppo-FEV_1 = preoperative $FEV_1 \times (1-(RFLV/TFLV))$.



	Perfusion% Geometric Mean		Ventilation% Geometric Mean	
	Right	Left	Right	Left
Upper	28.0	4.5	24.6	8.8
Middle	33.5	7.1	31.0	10.0
Lower	25.6	1.4	23.6	2.0
Total	**87.0**	**13.0**	**79.2**	**20.8**

Fig. 1. Radionucleotide perfusion ventilation scan. An example of a radionucleotide ventilation perfusion scan performed on a patient with almost completely destroyed left lung and only 13% of total perfusion left on that side. Quantification is performed according to zones and evaluation of anterior and posterior views. (*Courtesy of* Prof J. Warwick, Medical Imaging and Clinical Oncology, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa.)

This method has been shown to be accurate in predicting postoperative FEV_1 and FVC.[55–57] One prospective study reported on the correlation of prediction based on quantitative CT scanning for DL_{CO} and VO_2max. Predictions for DL_{CO} correlated well, whereas, for VO_2max, CT-derived estimates were outperformed by radionucleotide scanning.[53]

Dynamic Contrast-Enhanced Perfusion Magnetic Resonance Imaging

The most recently established standard method is perfusion magnetic resonance imaging (MRI), using contrast-enhanced MRI calculating the regional pulmonary blood volume. This technique requires some expertise as well as appropriate software, but has been shown to reliably predict

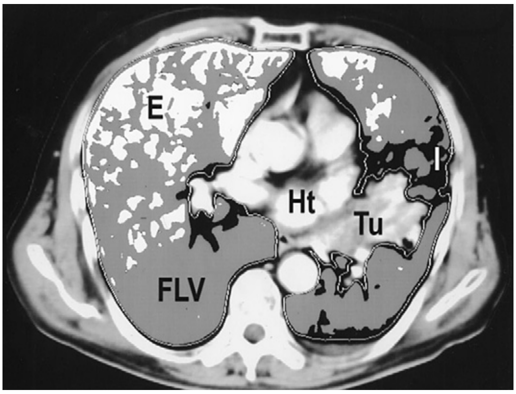


Fig. 2. Pulmonary quantitative CT scan. Functional lung volume of a representative slice is shown on a quantitative CT map. Lung parenchyma is outlined from mediastinum and chest wall with tumor (Tu) being excluded. Then 3 segments in the lung parenchyma are generated. The white area, less than −910 HU, denotes emphysema (E); the black area, more than −500 HU, denotes infiltration and atelectasis; and the gray area, between −500 and −910 HU, denotes functional lung volume (FLV). Ht, heart. (*Reproduced from* Wu MT, Pan HB, Chiang AA, et al. Prediction of postoperative lung function in patients with lung cancer: comparison of quantitative CT with perfusion scintigraphy. AJR Am J Roentgenol 2002;178(3):668; with permission.)

postoperative values.[56,58] Dynamic perfusion MRI studies are performed with a phased array coil and images acquired with a three-dimensional radiofrequency-spoiled gradient-echo sequence (**Fig. 3**). Gadolinium is used as a contrast agent. Regional pulmonary blood volume is calculated from the signal intensity-time course curve. ppo-FEV_1 = preoperative $FEV_1 \times [1-$(% perfusion of resected lobe or lung/100)].[56,58]

A large prospective study compared the performance of perfusion MRI and SPECT in predicting postoperative FEV_1 and showed that MRI is superior to SPECT.[58] Other parameters of lung function (ie, DL_{CO} and V_{O_2}max) were not assessed in that study.

APPROACH TO ASSESSMENT OF REGIONAL LUNG FUNCTION

Values of ppo for FEV_1, DL_{CO}, and V_{O_2}max have to be calculated in every patient who does not qualify for lung resection based on basic lung function (ie, FEV_1 or DL_{CO} <80%) or exercise testing (V_{O_2}max<20 mL/kg/min or <75%). Calculating ppo lung function based on anatomic values is the simplest way of predicting postoperative function, although it is less accurate than other techniques. Anatomic estimations have been shown to overestimate the functional loss, because minimal loss often results after resection of destroyed or collapsed lung or tumor-bearing tissue. Many patients qualify for resection based on these simple calculations, and more sophisticated methods should be reserved for borderline patients.[52] The number of functional segments (segments patent on imagery or bronchoscopy) to be resected is subtracted from the total number of functional segments and then divided by the total number of functional segments. This fraction must be multiplied by preoperative values to determine postresectional function (identical for FEV_1, DL_{CO}, and V_{O_2}max. Thus the general formula for the ppo function (F) is: F-ppo = preoperative F$\times$(19 − the number of functional segments to be resected/19).

Radionucleotide scanning used to be the gold standard in assessing regional lung function, but advances in radiological technology (ie, quantitative CT and dynamic contrast-enhanced perfusion MRI) have been shown to be at least as accurate in predicting certain parameters. Postoperative FEV_1 is predicted well by the different techniques, but direct comparison regarding other functional parameters is difficult because protocols, equipment, and expertise vary throughout the studies. From a practical point of view, most patients undergo staging CT scanning, and only additional software and expertise is needed to predict postoperative lung function using quantitative CT.

In general, anatomic calculations should be performed on all patients who require estimation of postoperative lung function. For patients who require further evaluation, availability, cost, and local expertise usually determine the choice of method.

ALGORITHM FOR THE ASSESSMENT OF THE LUNG RESECTION CANDIDATE

Patients undergoing lung resection surgery should be assessed regarding their fitness for surgery, focusing on cardiovascular and respiratory function. A stepwise approach is useful in assessing patients before pulmonary resection. A widely used algorithm initially proposed by Bolliger and Perruchoud[59] in 1998 has recently been revised by an ERS/ESTS task force and cutoff values have been lowered, because previous thresholds have been shown to be conservative and err on the side of safety (**Fig. 4**).[41,59,60]

Every patient should have a resting ECG and cardiac disease needs to be identified and managed. Ventilatory impairment should be optimized

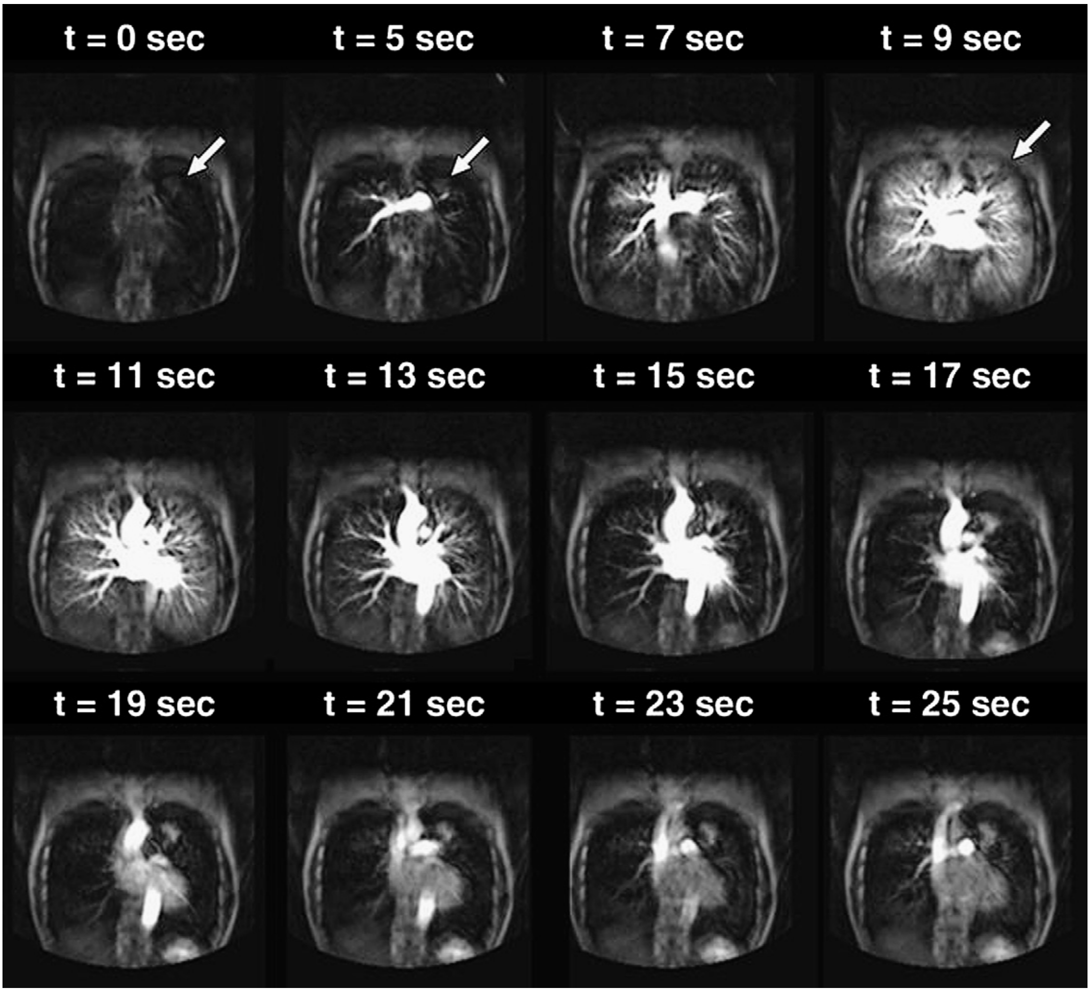


Fig. 3. Dynamic perfusion MRI. A dynamic perfusion MRI of a patient with a left upper lobe adenocarcinoma. The images show heterogeneous, but well-enhanced, pulmonary parenchyma at 5 and 13 seconds in portions of lungs not affected by the cancer (*arrows*). The adenocarcinoma also is enhanced after 13 seconds. (*Reproduced from* Ohno Y, Koyama H, Nogami M, et al. Postoperative lung function in lung cancer patients: comparative analysis of predictive capability of MRI, CT, and SPECT. AJR Am J Roentgenol 2007;189(2):404; with permission.)

before functional evaluation. The first step in assessing pulmonary function should include spirometry (FEV_1) and DL_{CO}. An uncomplicated postoperative course can be assumed in patients with FEV_1 and DL_{CO} values greater than 80% of predicted. Should either of these values be less than 80% of predicted, formal exercise testing with measurement of maximum oxygen consumption is recommended. Thus, for example, a poor FEV_1 can be compensated for by a preserved V_{O_2}max, making the algorithm inclusive rather than exclusive. A V_{O_2}max of greater than 20 mL/kg/min or greater than 75% of predicted allows for surgery up to pneumonectomy. In further steps for patients who do not qualify for a resection up to a pneumonectomy based on the tests mentioned earlier, split functions must be calculated considering the extent of resection. This extent of resection used in the estimation must always be considered when a patient is deemed operable based on split functions.

This and other algorithms not mentioned in this article can only serve as guides but, in general, patients should be considered functionally inoperable if regarded as high risk by any algorithm. Exceptions can be made on an individual basis, provided patients are informed of the significant increased risk of morbidity and mortality. Recent advances in surgical techniques and the advent of minimally invasive surgery

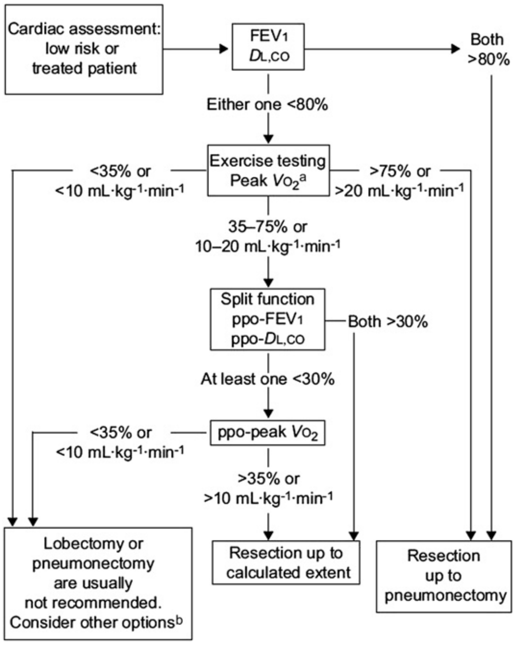


Fig. 4. Revised algorithm for the assessment of cardiorespiratory reserve and operability before pulmonary resection. Patients undergo a stepwise evaluation until they either qualify for varying extent of resection or are deemed inoperable. All percentages refer to percent of predicted value. FEV_1, forced expiratory volume in 1 second; DL_{CO}, carbon monoxide diffusion capacity; Vo_2, maximal oxygen consumption; ppo, predicted postoperative. [a]If peak Vo_2 is not available, cardiopulmonary exercise testing can be replaced by stair climbing. [b]See sections entitled Surgical techniques in lung cancer (p. 27) and Chemo-radiotherapy in lung cancer (p. 28) in original publication. (*Reproduced from* Brunelli A, Charloux A, Bolliger CT, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J 2009;34(1):22; with permission.)

(eg, VATS) have, to an extent, also challenged the current thresholds.

SUMMARY

Lung resection remains a high-risk procedure because many candidates suffer from concomitant obstructive lung disease or cardiovascular disease. For lung cancer, resection represents the only potentially curative treatment. Every pulmonary resection candidate should therefore undergo a careful and structured evaluation while on optimal treatment. This assessment should take cardiac, pulmonary, and general fitness into consideration. Cardiac evaluation should identify patients with cardiovascular disease at the beginning of a stepwise approach. The initial pulmonary function parameters to be obtained are FEV_1 and DL_{CO}. Patients with values greater than 80% of predicted for both parameters have been shown to have an uncomplicated surgical course and can proceed directly to resection up to pneumonectomy. All other patients warrant further evaluation by formal cardiopulmonary exercise testing. Vo_2max greater than 20 mL/kg/min or greater than 75% of predicted allows resection up to pneumonectomy, whereas a Vo_2max less than 10 mL/kg/min or less than 35% of predicted is usually prohibitive for any resection. Patients who are between those thresholds require assessment of their regional lung function by various methods and calculation of ppo lung function. ppo-FEV_1 and ppo-DL_{CO} greater than 30% and a ppo-Vo_2max of 10 mL/kg/min or greater than 35% allow surgery up to the calculated extent. In case sophisticated exercise testing equipment is not available, low-cost alternatives can be used, stair climbing being the most validated test. Lung volume reduction surgery combined with pulmonary resection may improve postoperative lung function in selected patients and thus allow surgery in patients otherwise deemed inoperable. Ongoing developments in surgical and anesthetic techniques, together with the trend for tissue-sparing resections for very small tumors, will lower the minimal required limits of functional reserves in the future.[61]

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