

Review

## Cardiopulmonary Exercise Testing (CPET) as Preoperative Test Before Lung Resection

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**Abstract.** Lung resection is still the only potentially curative therapy for patients with localized non-small lung cancer (NSCLC). However, the presence of cardiovascular comorbidities and underlying lung disease increases the risk of postoperative complications. Various studies have evaluated the use of different preoperative tests in order to identify patients with an increased risk for postoperative complications, associated with prolonged hospital stay and increased morbidity and mortality. In this topic review, we discuss the role of cardiopulmonary exercise testing (CPET) as one of the preoperative tests suggested for lung cancer patients scheduled for lung resection. We describe different types of exercise testing techniques and present algorithms of preoperative evaluation in lung cancer patients. Overall, patients with maximal oxygen consumption ( $VO_{2max}$ )  $<10$  mL/kg/min or those with  $VO_{2max}$   $<15$  mL/kg/min and both postoperative FEV1 and DLCO  $<40\%$  predicted, are at high risk for perioperative death and postoperative cardiopulmonary complications, and thus should be offered an alternative medical treatment option.

Lung cancer is one of the leading causes of death and is associated with poor prognosis, even when diagnosed in early stages (1). Lung resection is considered to be the only potentially curative treatment and remains the treatment of choice in early stage lung cancer (2). However, most lung cancer patients are elderly, smokers or have serious

comorbidities, thus are excluded from surgery and directed toward medical or non-invasive treatments. Given the recent advances in operative techniques and perioperative care, which have considerably reduced surgical morbidity and mortality, an effort is being made to expand the group of candidates for surgical resection.

Postoperative cardiopulmonary complications include respiratory failure (acute respiratory distress syndrome, ARDS), prolonged postoperative mechanical ventilation or reintubation, pneumonia, atelectasis requiring bronchoscopy, myocardial infarction, and arrhythmias requiring intravenous treatment. Various single and combined parameters of functional operability have been proposed to assess the surgical risk. Pulmonary function tests adequately assess the pulmonary risk, and baseline or stress electrocardiography, echocardiography and nuclear cardiac studies assess cardiac risk. The cardiopulmonary risk index (CPRI), a multifactorial tool assessing cardiovascular and pulmonary parameters (e.g., obesity, cigarette smoking within 8 weeks of surgery, productive cough within 5 days of surgery,  $FEV_1/FVC <70\%$ ,  $PaCO_2$ ), has been used in lung cancer patients scheduled for surgery and has also been found to be associated with a higher rate of postoperative complications (3).

The aim of the present review was to discuss the role of cardiopulmonary exercise testing (CPET) in the preoperative evaluation of patients scheduled to undergo lung resection. We searched MEDLINE (1962 to 2010) and EMBASE (March, 1974 to February, 2005) using the terms lung/surgery, lung resection/cancer, bronchogenic carcinoma, thoracotomy, pneumonectomy, exercise test, cardiopulmonary exercise testing and postoperative pulmonary complications. We augmented our search by reviewing the reference lists of retrieved articles, including review articles, as well as the reference lists of related articles in our files. Initially, pulmonary function tests traditionally used in the preoperative evaluation of lung cancer and split functions techniques are

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reported; subsequently, exercise capacity tests are described and discussed, and algorithms of preoperative evaluation of lung cancer patients are presented.

## Pulmonary Function Tests

**Spirometry and maximum voluntary ventilation.** Spirometry is a simple, inexpensive, standardized, and readily-available test. All patients scheduled for lung resection should have spirometry as a first step in the preoperative evaluation. Forced vital capacity (FVC), forced expiratory volume in one second (FEV<sub>1</sub>) and their ratio (FEV<sub>1</sub>/FVC) remain the most decisive indexes (4-6). Patients with a preoperative post-bronchodilator FEV<sub>1</sub> >2.0 L or FEV<sub>1</sub> >80% predicted are considered operable for pneumonectomy, while a preoperative FEV<sub>1</sub> >1.5 liters permits lobectomy (7-10) and FEV<sub>1</sub>>0.6 L permits wedge or segmental resection (10) without further testing. Furthermore, patients with a maximum voluntary ventilation (MVV) <50% predicted (4, 5) are considered high-risk patients for post-pneumonectomy complications, while the cut-off point for lobectomy is 40% predicted (6).

**Diffusion capacity.** Diffusing capacity of the lung for carbon monoxide (DLCO) reflects alveolar membrane integrity and pulmonary capillary blood flow in the patient's lungs. In a retrospective study of 247 patients by Ferguson and colleagues (12), DLCO was found to be the most important predictor of mortality and the sole predictor of postoperative pulmonary complications. In a meta-analysis by Benzo *et al.* (13), preoperative DLCO values were significantly higher in patients without postoperative complications versus those with postoperative complications. Patients with preoperative DLCO <50% predicted (14) or 60% predicted (4, 6, 10, 12) should not be submitted to major pulmonary resections, as they are associated with increased risk of postoperative complications. According to the ERS guidelines, DLCO should be routinely measured in all patients scheduled for pulmonary resection, regardless of normal spirometric values (9) and DLCO >80% predicted permits pneumonectomy without further tests needed (provided that FEV<sub>1</sub> is also greater than 80% predicted).

**Arterial blood gas levels.** Arterial blood gas (ABG) levels have not been extensively studied as a predictor of postoperative complications. It has been suggested that an arterial oxygen tension of <50 mmHg (15) or 60 mmHg (14) is associated with an increased risk of post-resection complications. Also, hypercapnia (*i.e.*, PCO<sub>2</sub>>45 mm Hg) has been considered a relative contraindication to lung resection as it indicates chronic respiratory failure (4,10). However, several studies have shown that a preoperative PCO<sub>2</sub> value of >45 mm Hg is not an independent predictor of postoperative complications (16-18).

## Split-function Studies

According to the ACCP and BTS guidelines (7, 8), patients with normal pulmonary function, as defined by FEV<sub>1</sub> ≥80% predicted and DLCO ≥80% predicted, can undergo major lung resections without further investigation. Patients with FEV<sub>1</sub> and/or DLCO <80% should not be excluded from surgery, but further evaluated. Split function studies predict postoperative pulmonary function (mainly postoperative FEV<sub>1</sub> and DLCO) through either quantitative ventilation-perfusion scanning results or through formulas involving bronchopulmonary segments to be resected.

In quantitative ventilation-perfusion scan, Xe is inhaled or <sup>99</sup>Tc-labeled macroaggregates are injected intravenously. The uptake of radioactive ions by the lung by inhalation of the <sup>133</sup>Xe or perfusion of the <sup>99</sup>Tc macroaggregates is measured by a gamma camera and processed by a computer. The percentage of radioactivity contributed by each lung correlates with the contribution to the function of that lung. Normally, the right lung contributes to 55% of lung function, while the left lung to 45% of lung function. Based on the measured radioactive uptake of the lung that will not be operated on, the predicted FEV<sub>1</sub> of the residual lung following surgery was calculated by Kristersson *et al.* (19) using the following formula:

Postoperative FEV<sub>1</sub> × % of radioactivity contributed by non-operated lung

According to Kristersson and coworkers (19), a predicted postoperative (ppo) FEV<sub>1</sub> of <1 L is indicative of physiologic inoperability, while others lower the cut-off point to 800 mL (5).

Wernly and colleagues (20) developed and tested the following formula for predicting postlobectomy pulmonary function using ventilation-perfusion scanning:

$$\text{Expected loss of function} = \frac{\text{Preoperative FEV}_1 \times \% \text{ of function of affected lung} \times \frac{\text{No of segments in lobe to be resected}}{\text{Total no of segments in the whole lung}}}{1}$$

No prospective study has established a cut-off limit of ppo-FEV<sub>1</sub> that precludes a safe resection. Markos and colleagues (21) found that a higher mortality rate was associated with ppo-FEV<sub>1</sub> <40%. Gass and Olsen (22) suggested a ppo-FEV<sub>1</sub> of <35% of predicted as a low threshold for all patients. Several investigators have reported that the simple calculation using lung segment counting can predict postoperative FEV<sub>1</sub> as accurately as ventilation/perfusion scintigraphy (23-26), while perfusion scintigraphy is the most widely used method to predict postoperative lung function in patients undergoing pneumonectomy (7, 8).

Other tests assessing differential lung function include bronchspirometry, lateral position testing, and total unilateral pulmonary artery occlusion (27). All are invasive methods, and require specialized equipment and a high level of technical expertise for their performance. For these reasons, and given the advantages of ventilation-perfusion scanning, these tests are no longer performed in the preoperative evaluation of patients who are awaiting lung resection.

## Exercise Testing

Cardiopulmonary exercise testing is based on the principle that system failure occurs while the system (muscle-energetic, cardiovascular or pulmonary) is under stress (28). Cardiac output, ventilation, oxygen uptake and carbon dioxide output increase during exercise and in proportion to the severity of exercise. Since CPET stresses the entire cardiopulmonary and oxygen delivery system while monitoring cardiopulmonary variables (such as minute oxygen uptake -  $\dot{V}O_2$ , minute pulmonary  $CO_2$  output -  $\dot{V}CO_2$ , minute ventilation - VE, cardiac frequency), it evaluates cardiopulmonary status and function under stress and provides a good estimate of cardiopulmonary reserve. And since both thoracotomy and the immediate postoperative period represent a severe stress for both the circulatory and respiratory reserve, preoperative exercise should be evaluated as a predictor of post-thoracotomy morbidity and mortality (26).

## Types of Exercise Testing

Two major types of exercise tests have been used in the preoperative evaluation of high-risk patients being considered for lung resection surgery. These are: (1) incremental exercise testing, in which the work rate is sequentially increased to a desired end-point, and (2) fixed exercise challenge, in which a sustained level of work is performed. These two types are further divided into maximal or sub-maximal, based on their end-points. The maximal end point can be defined as an exercise, usually incremental, that is performed until a plateau (*i.e.*,  $\dot{V}O_{2max}$ ) is reached at which further work will not produce any increase in  $\dot{V}O_2$ . The submaximal end point can be defined as exercise performed short of achieving the plateau (maximum  $\dot{V}O_2$  attained, thus designated  $\dot{V}O_2$  peak).

**Maximal exercise testing.** Eugene and colleagues (29) were the first to use incremental exercise to the point of maximal exertion and measure  $\dot{V}O_{2max}$  in patients being evaluated for lung resection surgery. They found that no death occurred in patients with  $\dot{V}O_{2max}$  values of  $>1$  L/min, while the mortality rate was 100% in those with  $\dot{V}O_{2max} < 1$  L/min. They reported that  $\dot{V}O_{2max}$  during symptom-limited exercise was a better

predictor of post-operative mortality than  $FEV_1$  and  $FEV_1/FVC$ . Smith and colleagues (30) reported significantly more postoperative complications in patients with  $\dot{V}O_{2max} < 15$  mL/kg compared to patients with  $\dot{V}O_{2max} > 20$  mL/kg. With this study the researchers demonstrated that  $\dot{V}O_2$  at peak exercise was a valuable non-invasive method of preoperative evaluation and they introduced the value of 20 mL/kg/min as a cut-off point for operability. Berggren and colleagues (31) reported a postoperative mortality rate of 7.7% in 26 patients who completed 83 Watts of work for 6 min versus a postoperative mortality rate of 22% in the remaining 18 patients who were unable to perform that amount of work.

In 1992, Bechard and Wetstein (32) studied 50 patients that underwent exercise testing by cycle ergometry, with 1-min increments of 12.5 Watts until exhaustion or dyspnea occurred, while measuring  $\dot{V}O_{2max}$  and anaerobic threshold. The postoperative mortality rate was 4%, and it occurred in all patients with  $\dot{V}O_{2max}$  levels of  $< 10$  mL/kg/min. Based on these results, the authors propounded that a patient with  $\dot{V}O_{2max}$  values of  $< 10$  mL/kg should not undergo lung resection surgery. In the same year, Morice *et al.* (16) measured exercise capacity in 37 patients during an incremental exercise test on cycle ergometer and reported that even in patients with  $FEV_1 < 40\%$ , ppo- $FEV_1 < 33\%$  or  $PaCO_2 > 45$  mmHg, the prognosis is excellent when  $\dot{V}O_{2max}$  is  $> 15$  mL/kg/min. The same authors in 1996 (33) found that  $\dot{V}O_{2max} \geq 50\%$  was a better predictor of operability than  $\dot{V}O_{2max} \geq 15$  mL/kg/min. On the other hand, Smith and coworkers (30) had earlier analyzed  $\dot{V}O_{2max}$  as a percentage of predicted normal values and found it to be inferior to absolute values in predicting postoperative complications. Bechard and Wetstein (32) and Smith *et al.* (30) set a lower cut-off value of 20 mL/kg/min for pneumonectomy.

In 1993, Epstein *et al.* (3), using an incremental exercise protocol, reported that patients with a  $\dot{V}O_{2max}$  per body surface area (BSA)  $< 500$  mL/min/m<sup>2</sup> were 6 times more likely to experience a cardiopulmonary complication ( $p < 0.05$ ), while  $\dot{V}O_{2max}$  was not found to be an independent predictor of postoperative complications. Pate and colleagues (34) also suggested that patients with  $\dot{V}O_{2max} > 10$  mL/kg/min could safely undergo lung resection surgery. However, Markos and colleagues (21) in their study observed that  $\dot{V}O_{2max}$  was significantly lower in patients with postoperative complications compared to those without complications, but they found that oxygen desaturation during a 12-min walk, ppo-DLCO, and ppo- $FEV_1$  were more reliable predictors of postoperative mortality than  $\dot{V}O_{2max}$ . Bolliger and colleagues (35) studied 25 patients at increased risk for postoperative complications ( $FEV_1 < 2$  L or  $DLCO < 50\%$  or  $FEV_1$  and  $DLCO \leq 80\%$  and NYHA [New York Heart Association] index  $\geq 2$ ) and observed that patients with postoperative complications had a significantly lower

preoperative  $\text{VO}_{2\text{max}}$  ( $p < 0.01$ ) and postoperative  $\text{VO}_{2\text{max}}$  (ppo- $\text{VO}_{2\text{max}}$ ,  $p < 0.05$ ); they reported that  $\text{VO}_{2\text{max}}$ , expressed as a percentage of the predicted value, was the single best predictor of postoperative complications.

More recently, in 2005, Win *et al.* (26), in a prospective study involving 99 patients who were submitted to a symptom-restricted treadmill exercise test prior to lung cancer surgery, reported that  $\text{VO}_{2\text{max}}$  percentage, but not the absolute oxygen uptake values, was significantly related with postoperative complications and a poor surgical outcome. In 2007, in a prospective multi-institutional study by Loewen *et al.* (36), subjects underwent a symptom-limited incremental ramp workload exercise on a cycle ergometer; patients with  $\text{VO}_{2\text{max}} < 65\%$  predicted were more likely to suffer complications ( $p = 0.0001$ ) and had a poorer outcome ( $p = 0.0356$ ).

Using the formula for calculating postoperative FEV1 based on radionuclide ventilation-perfusion scanning, Corris and colleagues (37) were able to predict postoperative  $\text{VO}_{2\text{max}}$ . Bolliger and colleagues (38) used this formula to estimate ppo- $\text{VO}_{2\text{max}}$  in a group of 25 patients, and reported a good correlation between estimated ppo- $\text{VO}_{2\text{max}}$  and measured postoperative  $\text{VO}_{2\text{max}}$  values. The value of ppo- $\text{VO}_{2\text{max}}$  needs to be studied prospectively to establish its utility in the preoperative assessment of patients prior to lung resection surgery.

### Submaximal Exercise Testing

Submaximal exercise testing is particularly useful in patients who are unable to tolerate exercise stress due to dyspnea or fatigue, such as elderly or COPD patients, and might therefore not be motivated to perform exercise to exhaustion (10). During submaximal CPET, the patient is submitted to a designated sub-maximal workload exercise for a specific period of time, while various parameters, such as oxygen uptake, ventilation volume, carbon dioxide output, carbon dioxide and oxygen arterial pressures and lactate levels, are measured. In these studies,  $\text{VO}_2$  peak is used instead of  $\text{VO}_{2\text{max}}$ , *i.e.* the maximum attained oxygen consumption before it reaches a plateau.

In 1989, Olsen and colleagues (39) studied 52 elderly male patients with a lung mass and  $\text{FEV}_1 < 2.0\text{L}$  who were scheduled for lung resection, and submitted them to cycle ergometry at two sub-maximal workloads (25 and 40 Watts). Patients were also catheterized with a flow directed balloon-tipped pulmonary artery catheter for the measurement of pulmonary arterial pressure and pulmonary vascular resistance. The authors found that variables significantly associated with postoperative complications were cardiac index (*i.e.*, cardiac output/body surface area;  $p < 0.01$ ), oxygen delivery ( $p < 0.01$ ) and calculated  $\text{VO}_2$  ( $p < 0.001$ ).

Nakagawa *et al.* (40) evaluated oxygen transport in thirty-one lung cancer patients during incremental sub-maximal

exercise under right heart catheterization. Their assumption followed a previous proposal that oxygen consumption per body surface area at an arterial lactate level of 20 mg/dl ( $\text{VO}_2/\text{BSA}_{\text{La20}}$ ) is a risk predictor following thoracotomy (41, 42).

Miyoshi and colleagues (41) studied 33 patients undergoing thoracotomy using cycle ergometry to submaximal levels (reaching a heart rate of 140 beats/min or a respiratory quotient - carbon dioxide eliminated/oxygen consumed - of  $> 1$ ) with arterial lactate levels measured during the last 3 seconds of each work rate period. They found that  $\text{VO}_2/\text{BSA}_{\text{La20}}$  was significantly different between survivors and nonsurvivors and that the blood lactate threshold expressed by  $\text{VO}_2/\text{BSA}$  at La-20 was an important indicator of the risk of hospital mortality. They also found that pulmonary function parameters such as  $\text{FEV}_1/\text{BSA}$ ,  $\text{FEV}_1/\text{FVC}$ , DLCO/lung volume, and MVV/BSA showed significant differences between patients with post-thoracotomy pulmonary complications and those without such complications. This study suggested that in-house mortality could be predicted by submaximal exercise  $\text{VO}_2$  when the work level achieved was corrected for a fixed level of lactate production.

**Fixed challenge exercise testing.** Fixed challenge exercise testing involves assessing performance status by doing a fixed amount of work, such as climbing a certain number of stairs or walking a fixed distance. Long before the introduction of pulmonary function tests, surgeons evaluated their patients' preoperative functional status by asking them to climb flights of stairs. Following that observation, several studies were performed based on the assumption that the number of flights climbed can serve as an indicator of cardiopulmonary reserve and of the patient's ability to tolerate pre- and postoperative cardiopulmonary stress. Van Nostrand and colleagues first used stair climbing as a test for endurance in the preoperative evaluation of 119 patients scheduled for lung surgery (43). He reported a postoperative mortality rate of 50% in patients who were unable to climb one flight of stairs with minimal dyspnea compared to a mortality rate of 11% in those able to climb two flights of stairs with minimal dyspnea.

Holden and colleagues (44), in a prospective study of sixteen patients at increased risk submitted to stair climbing as part of the evaluation prior to surgery, reported that 5 of the 16 patients who died in the perioperative period had a significantly shorter 6-min walk distance test and a smaller number of stairs climbed than patients with minor or no complications. They found that a 6-min walking test distance of  $> 1,000$  ft or  $> 44$  steps of stair climbing were predictive of successful surgical outcome. Olsen *et al.* (45) suggested that patients able to climb 5 flights of stairs could be submitted to pneumonectomy, while patients climbing at



least 3 flights of stairs could undergo lobectomy. Girish and colleagues (46) prospectively evaluated the role of symptom-limited stair climbing as a predictor of postoperative cardiopulmonary complications in 83 patients undergoing thoracic and upper abdominal surgery. They found that complications occurred in 89% of patients who were unable to climb one flight of stairs. The inability to climb two flights of stairs had a positive predictive value of 80%, while the inability to climb five flights of stairs had a positive predictive value of 32%. No complications were seen in patients that could climb seven flights of stairs. The ability of patients to climb stairs was inversely related to the length of postoperative hospital stay. The number of stairs climbed was a strong predictor of postoperative complications ( $p=0.00002$ ), along with FEV<sub>1</sub> ( $p=0.02$ ) and FVC ( $p=0.04$ ). Although stair climbing as a measure of exercise capacity could predict postoperative complications, more studies are needed to determine whether it can supplant more sophisticated exercise testing.

A disadvantage of stair climbing in the preoperative evaluation of patients is that it is not a standardized method, *e.g.*, the height of stairs climbed varies in different Institutions. Having this in mind, Pollock *et al.* (47) in 1993 standardized stair climbing (height and width of steps, number of steps per floor) and reported that an achievement of 4.6 flights (83 steps) corresponded to a VO<sub>2</sub> of 20 mL/kg/min. Pate *et al.* (34) expressed the number of steps climbed as height climbed in meters to provide standardization. When this standardized value was applied in elderly patients undergoing lobectomy, it proved to be an important predictor of post-operative cardiopulmonary complications (48). Koegelenberg *et al.* (49) have proposed standardizing stair climbing by looking at the speed of ascent and not just height achieved.

The 6-min walk distance test and shuttle walk test are two other methods used for the preoperative evaluation of cardiopulmonary reserve (50, 51). During 6-min walk test, patients are instructed to walk as far as possible in 6 min. According to Holden and colleagues (37), a 6-min walk distance >1000 ft is associated with a good surgical outcome. However, the results of other studies have been inconsistent (52, 53).

In the shuttle walk test, patients walk a distance of 10 m between two shuttles. When the patient is too breathless to proceed or cannot keep up with the pace, the test is ended. Patients who cannot complete 25 shuttles on two occasions are considered to have a VO<sub>2max</sub> of <10 mL/kg/min (54, 55). According to Brunelli (9), stair-climbing could be used for selecting patients, but not the shuttle walk or the 6-min walk tests. On the other hand, both the BTS and ACCP guidelines recommend the use of the incremental shuttle walk test (ISWT) because it is reproducible, correlates well with VO<sub>2max</sub> and can serve as a good alternative if CPET is unavailable (7, 8).

## Conclusion

Patients diagnosed with anatomically-resectable lung cancer should be evaluated for surgical operability. Pneumonectomy has a significantly higher rate of complications and mortality than lobectomy (56), thus the selection of lung resection candidates and treatment modality should be performed prudently. Over the last years, a considerable number of studies have focused on preoperative evaluation methods in order to identify lung cancer patients who would more likely benefit from surgery. The analysis of the results and conclusions of these studies has led to official statements and issued guidelines by the British Thoracic Society (BTS), the American College of Chest Physicians (ACCP) and the European Respiratory Society (ERS) (7, 8, 9).

According to the guidelines of the British Thoracic Society (7), no further respiratory function tests are required if FEV<sub>1</sub>>2 lt (for pneumonectomy) and >1.5 lt (for lobectomy), provided there is no evidence of interstitial lung disease or shortness of breath (20). In every other case, DLCO should be measured and the patient should undergo split-function studies (using the perfusion scanning method), in order to estimate postoperative FEV<sub>1</sub> (ppo-FEV<sub>1</sub>) and DLCO (ppo-DLCO) predicted as a percentage of the absolute normal values. If both ppo-FEV<sub>1</sub> and ppo-DLCO are >40% predicted, no further tests are required, the patient is considered average risk and can safely undergo the suggested operation. If both ppo-FEV<sub>1</sub> and ppo-DLCO are <40% predicted, the patient is considered inoperable (18, 21, 34, 37). If any of ppo-FEV<sub>1</sub> or ppo-DLCO is <40%, BTS guidelines suggest shuttle walk test and, if the patient achieves >25 shuttles with <4% desaturation, a full cardiopulmonary exercise test (57). If VO<sub>2max</sub> is >15 mL/kg/min, the patient is operable to the extent of resection calculated; if VO<sub>2max</sub> is <15 mL/kg/min, the patient is considered inoperable (16, 21, 30, 32, 35).

The guidelines of the American College of Chest Physicians (ACCP) (8) issued in 2007 are similar to those of BTS, with the exception of the shuttle walk test, which they have omitted (Figure 1). According to these guidelines, also based on previous studies, in patients with lung cancer being considered for lung resection, VO<sub>2max</sub><10 mL/kg/min indicates a very high risk for perioperative death and cardiopulmonary complications (21, 32, 37, 39). These patients should be given non-operative treatment options. Patients being considered for lung cancer resection, who have VO<sub>2max</sub><15 mL/kg/min and both a %ppo-FEV<sub>1</sub> and DLCO<40% should be considered at very high risk for perioperative death and cardiopulmonary complications (21, 26, 30, 32, 35, 37, 39). These patients should be counseled about non-operative treatment options for their lung cancer. Patients being considered for lung cancer resection who walk <25 shuttles on two occasions or less than one flight of stairs should be considered as very high risk for perioperative

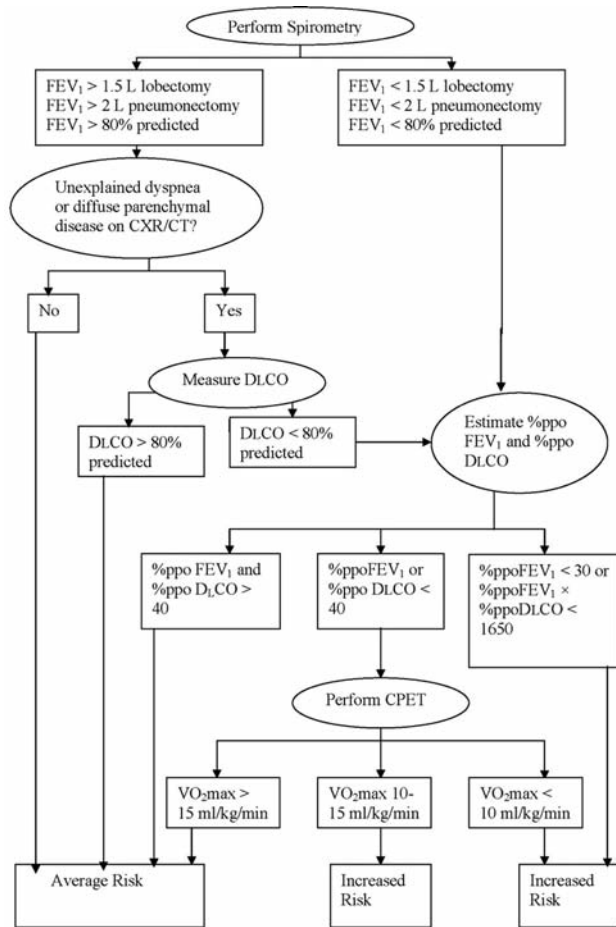


Figure 1. Guidelines of ERS for the preoperative evaluation of lung cancer patients. FEV1, forced expiratory volume in 1 second; CXR, chest X-ray; CT, computerized tomography; DLCO, diffusing capacity of the lung for carbon monoxide; ppoFEV1, predicted postoperative forced volume in 1 second; ppoDLCO, predicted postoperative diffusing capacity of the lung for carbon monoxide; CPET, cardiopulmonary exercise testing;  $VO_{2max}$ , maximum oxygen uptake (9).

death and cardiopulmonary complications (53). These patients should be counseled about non-operative treatment options for their lung cancer.

The European Respiratory Society (ERS) guidelines present a slightly different approach to the preoperative evaluation of lung cancer patients (9). The authors suggest that exercise testing should proceed to split function studies. They set a cut-off point for  $VO_{2max}$  of  $>20$  mL/kg/min or 75% predicted for pneumonectomy and  $<10$  mL/kg/min or 35% predicted for non-operability; patients with  $VO_{2max}$  35-75% or 10-20 mL/kg/min should undergo split function tests (16, 26, 30, 34-36). If both ppo-FEV1 and ppo-DLCO are  $>30\%$  predicted, the patient can be submitted to resection up

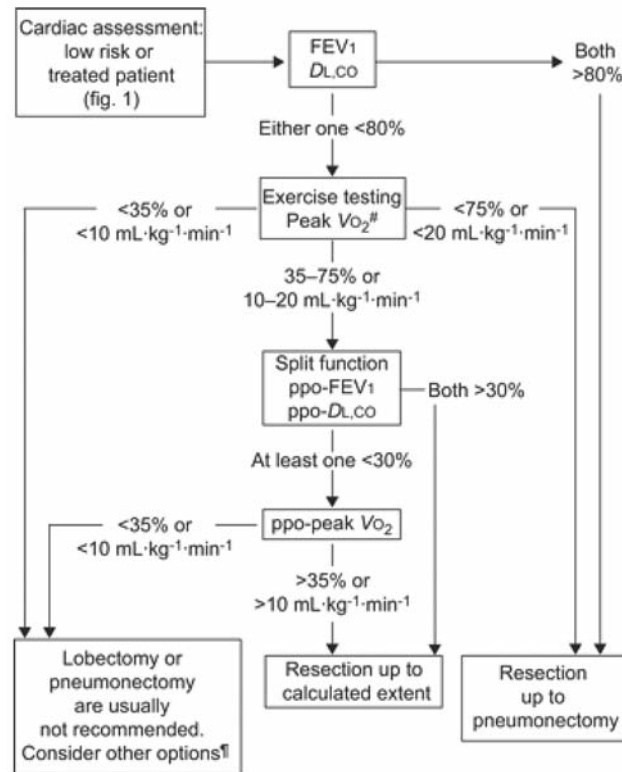


Figure 2. Guidelines of ACCP for the preoperative evaluation of lung cancer patients. FEV1, forced expiratory volume in 1 second; DL, CO, diffusing capacity of the lung for carbon monoxide; peak  $VO_2$ , peak oxygen uptake (alternative for  $VO_{2max}$ ); ppo-FEV1, predicted postoperative forced expiratory volume in 1 second; ppo-DLCO, predicted postoperative diffusing capacity of the lung for carbon monoxide; ppo-peak  $VO_2$ , predicted postoperative peak oxygen uptake (alternative for ppo- $VO_{2max}$ ) (8).

to the calculated extent (18, 21, 35, 44). If at least one is  $<30\%$  predicted, ppo- $VO_{2max}$  should be calculated; a ppo- $VO_{2max} >35\%$  predicted or 10 mL/kg/min permits resection up to the calculated extent, while a ppo- $VO_{2max} <35\%$  predicted or 10 mL/kg/min renders the patient inoperable (35) (Figure 2). ERS guidelines also suggest that if  $VO_{2max}$  is unavailable, cardiopulmonary exercise test could be replaced by stair climbing; but if a minimum height of 22 m cannot be achieved, full cardiopulmonary exercise test is highly recommended (43, 44, 45).

This is not a systematic review as no statistical analysis was conducted. However, in their majority, the results of studies presented are clear in showing that cardiopulmonary exercise testing provides an overall assessment of the patient's ability to tolerate lung resection, as it simulates the post-resection status of the remaining lung. It is now evident that some patients once excluded from surgery based on FEV1 and FVC

or DLCO results, could undergo surgery, a potentially curative treatment, if CPET permits it. That is why the conclusions of these studies are incorporated in the abovementioned guidelines issued by BTS, ACCP and ERS regarding the preoperative evaluation of lung cancer patients. Cardiopulmonary exercise testing is performed in a controlled environment with continuous monitoring of several parameters and ensures early standardization and good reproducibility of results. However, its widespread use is limited by the low availability of appropriate equipment and well-trained personnel.

## Conflicts of Interest

Authors have no conflicts of interest to declare.

## References

- Jemal A, Siegel R, Xu J and Ward E: Cancer statistics, 2010. *CA Cancer J Clin* 60(5): 277-300, 2010.
- Schiller JH: Current standards of care in small-cell and non-small-cell lung cancer. *Oncology* 61(Suppl 1): 3-13, 2001.
- Epstein SK, Faling LJ, Daly BD and Celli BR: Predicting complications after pulmonary resection. Preoperative exercise testing vs. a multifactorial cardiopulmonary risk index. *Chest* 104(3): 694-700, 1993.
- Cottrell JJ and Ferson PF: Preoperative assessment of the thoracic surgical patient. *Clin Chest Med* 13(1): 47-53, 1992.
- Subotic D: Fit for surgery? Assessment of marginal lung cancer patient. *Breathe* 6: 127-139, 2009.
- Datta D and Lahiri B: Preoperative evaluation of patients undergoing lung resection surgery. *Chest* 123(6): 2096-2103, 2003.
- British Thoracic Society; Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party: BTS guidelines: guidelines on the selection of patients with lung cancer for surgery. *Thorax* 56(2): 89-108, 2001.
- Colice GL, Shafazand S, Griffin JP, Keenan R and Bolliger CT: American College of Chest Physicians. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest* 132(3 Suppl): 161S-77S, 2007.
- Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier JP, Varela G, Licker M, Ferguson MK, Faivre-Finn C, Huber RM, Cline EM, Win T, De Ruysscher D and Goldman L; European Respiratory Society and European Society of Thoracic Surgeons joint task force on fitness for radical therapy: ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J* 34(1): 17-41, 2009.
- Bolliger CT and Perruchoud AP: Functional evaluation of the lung resection candidate. *Eur Respir J* 11(1): 198-212, 1998.
- Marshall MC and Olsen GN: The physiologic evaluation of the lung resection candidate. *Clin Chest Med* 14: 305-320, 1993.
- Ferguson MK, Little L, Rizzo L, Popovich KJ, Glonek GF, Leff A, Manjoney D and Little AG: Diffusing capacity predicts morbidity and mortality after pulmonary resection. *Thorac Cardiovasc Surg* 96: 894-900, 1988.
- Benzo R, Kelley GA, Recchi L, Hofman A and Sciurba F: Complications of lung resection and exercise capacity: a meta-analysis. *Respir Med* 101(8): 1790-7, 2007.
- Nagasaki F, Flehinger BJ and Martini N: Complications of surgery in the treatment of carcinoma of the lung. *Chest* 82: 25-29, 1982.
- Cander L: Physiologic assessment and management of the preoperative patient with pulmonary emphysema. *Am J Cardiol* 12: 324-326, 1963.
- Morice RC, Peters EJ, Ryan MB, Putnam JB, Ali MK and Roth JA: Exercise testing in the evaluation of patients at high risk for complications from lung resection. *Chest* 101(2): 356-361, 1992.
- Stephan F, Boucheseiche S, Hollande J, Flahault A, Cheffi A, Bazelly B and Bonnet F: Pulmonary complications following lung resection: a comprehensive analysis of incidence and possible risk factors. *Chest* 118: 1263-1270, 2000.
- Kearney DJ, Lee TH, Reilly JJ, DeCamp MM and Sugarbaker DJ: Assessment of operative risk in patients undergoing lung resection. Importance of predicted pulmonary function. *Chest* 105(3): 753-759, 1994.
- Kristersson S: Preoperative evaluation of differential lung function (133Xe radiospirometry) in bronchial cancer. *Scand J Respir Suppl* 85: 110-7, 1974.
- Wernly JA, DeMeester TR, Kirchner PT, Myerowitz PD, Oxford DE and Golomb HM: Clinical value of quantitative ventilation-perfusion lung scans in the surgical management of bronchogenic carcinoma. *J Thorac Cardiovasc Surg* 80: 535-543, 1980.
- Markos J, Mullan BP, Hillman DR, Musk AW, Antico VF and Lovegrove FT: Preoperative assessment as a predictor of mortality and morbidity after lung resection. *Am Rev Respir Dis* 139: 902-910, 1989.
- Gass GD and Olsen GN: Preoperative pulmonary function testing to predict postoperative morbidity and mortality. *Chest* 89: 127-135, 1986.
- Ali MK, Mountain CF, Ewer MS, Johnston D and Haynie TP: Predicting loss of pulmonary function after pulmonary resection for bronchogenic carcinoma. *Chest* 77: 337-342, 1980.
- Cordiner A, De Carlo F, De Gennaro R, Pau F and Flore F: Prediction of postoperative pulmonary function following thoracic surgery for bronchial carcinoma. *Angiology* 42(12): 985-989, 1991.
- Zeihner BG, Gross TJ, Kern JA, Lanza LA and Peterson MW: Predicting postoperative pulmonary function in patients undergoing lung resection. *Chest* 108(1): 68-72, 1995.
- Win T, Jackson A, Sharples L, Groves AM, Wells FC, Ritchie AJ and Laroche CM: Cardiopulmonary exercise tests and lung cancer surgical outcome. *Chest* 127(4): 1159-1165, 2005.
- Walkup RH, Vossell LF, Griffin JP and Proctor RJ: Prediction of postoperative pulmonary function with the lateral position test. A prospective study. *Chest* 77(1): 24-27, 1980.
- ERS Task Force, Palange P, Ward SA, Carlsen KH, Casaburi R, Gallagher CG, Gosselink R, O'Donnell DE *et al*: Recommendations on the use of exercise testing in clinical practice. *Eur Respir J* 29(1): 185-209, 2007.
- Eugene J, Dajee A, Kayaleh R, Gogia HS, Dos Santos C and Gazzaniga AB: Reduction pneumonoplasty for patients with a forced expiratory volume in 1 second of 500 milliliters or less. *Ann Thorac Surg* 63(1): 186-190, 1997.
- Smith TP, Kinasevitz GT, Tucker WY, Spillers WP and George RB: Exercise capacity as a predictor of postthoracotomy morbidity. *Am Rev Respir Dis* 129: 730-734, 1984.
- Berggren RB: Physician workforce definition: who is responsible? *Plast Reconstr Surg* 96(3): 715-717, 1995.

- 32 Bechard D and Wetstein L: Assessment of exercise oxygen consumption as preoperative criterion for lung resection. *Ann Thorac Surg* 44(4): 344-349, 1987.
- 33 Morice RC, Walsh GL, Ali MK and Roth JA: Redefining the lowest exercise peak oxygen consumption acceptable for lung resection of high risk patients. *Chest* 110: 161S, 1996.
- 34 Pate P, Tenholder MF, Griffin JP, Eastridge CE and Weiman DS: Preoperative assessment of the high-risk patient for lung resection. *Ann Thorac Surg* 61: 1494-1500, 1996.
- 35 Bolliger CT, Wyser C, Roser H, Solèr M and Perruchoud AP: Lung scanning and exercise testing for the prediction of postoperative performance in lung resection candidates at increased risk for complications. *Chest* 108: 341-348, 1995.
- 36 Loewen GM, Watson D, Kohman L, Herndon JE 2nd, Shennib H, Kernstine K, Olak J et al; Cancer and Leukemia Group B: Preoperative exercise Vo2 measurement for lung resection candidates: results of Cancer and Leukemia Group B Protocol 9238. *J Thorac Oncol* 2(7): 619-625, 2007.
- 37 Corris PA, Ellis DA, Hawkins T and Gibson GJ: Use of radionuclide scanning in the preoperative estimation of pulmonary function after pneumonectomy. *Thorax* 42(4): 285-291, 1987.
- 38 Bolliger CT, Jordan P, Solèr M, Stulz P, Tamm M and Wyser C: Pulmonary function and exercise capacity after lung resection. *Eur Respir J* 9: 415-421, 1996.
- 39 Olsen GN, Weiman DS, Bolton JW, Gass GD, McLain WC and Schoonover GA: Submaximal invasive exercise testing and quantitative lung scanning in the evaluation for tolerance of lung resection. *Chest* 95: 267-273, 1989.
- 40 Nakagawa K, Nakahara K, Miyoshi S and Kawashima Y: Oxygen transport during incremental exercise load as a predictor of operative risk in lung cancer patients. *Chest* 101(5): 1369-1375, 1992.
- 41 Miyoshi S, Yoshimasu T, Hirai T, Hirai I, Maebeya S, Bessho T and Naito Y: Exercise capacity of thoracotomy patients in the early postoperative period. *Chest* 118(2): 384-390, 2000.
- 42 Nakahara K, Miyoshi S and Nakagawa K: A method for predicting postoperative lung function and its relation to postoperative complications in patients with lung cancer. *Ann Thorac Surg* 54: 1016-1017, 1992.
- 43 van Nostrand D, Kjelsberg MO and Humphrey EW: Preresectional evaluation of risk from pneumonectomy. *Surg Gynecol Obstet* 127(2): 306-312, 1968.
- 44 Holden, DA, Rice, TW, Stelmach, K and Meeker DP: Exercise testing, 6-min walk, and stair climb in the evaluation of patients at high risk for pulmonary resection. *Chest* 102: 1774-1779, 1992.
- 45 Olsen GN, Bolton JW, Weiman DS and Hornung CA: Stair climbing as an exercise test to predict the postoperative complications of lung resection. Two years' experience. *Chest* 99(3): 587-590, 1991.
- 46 Girish M, Trayner E Jr, Dammann O, Pinto-Plata V and Celli B: Symptom-limited stair climbing as a predictor of postoperative cardiopulmonary complications after high-risk surgery. *Chest* 120(4): 1147-1151, 2001.
- 47 Pollock M, Roa J, Benditt J and Celli B: Estimation of ventilatory reserve by stair climbing. A study in patients with chronic airflow obstruction. *Chest* 104(5): 1378-1383, 1993.
- 48 Brunelli A, Monteverde M, Al Refai M and Fianchini A: Stair climbing test as a predictor of cardiopulmonary complications after pulmonary lobectomy in the elderly. *Ann Thorac Surg* 77: 266-270, 2004.
- 49 Koegelenberg CFN, Diacon AH, Irani S and Bolliger CT: Stair climbing in the functional assessment of lung resection candidates. *Respiration* 75: 374-379, 2008.
- 50 Solway S, Brooks D, Lacasse Y and Thomas S: A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest* 119: 256-270, 2001.
- 51 Beckles MA, Spiro SG, Colice GL and Rudd RM: The physiologic evaluation of patients with lung cancer being considered for resectional surgery. *Chest* 123(suppl): 105S-114S, 2003.
- 52 Carter R, Holiday DB, Nwasuruba C, Stocks J, Grothues C and Tiep B: 6-minute walk work for assessment of functional capacity in patients with COPD. *Chest* 132: 1408-1415, 2003.
- 53 Win T, Jackson A, Groves AM, Sharples LD, Charman SC and Laroche CM: Comparison of shuttle walk with measured peak oxygen consumption in patients with operable lung cancer. *Thorax* 61: 57-60, 2006.
- 54 Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE: Development of a shuttle walking test of disability in patients with chronic airway obstruction. *Thorax* 47: 1019-1024, 1992.
- 55 Revill SM, Morgan MD, Singh SJ, Williams J and Hardman AE: The endurance shuttle walk: a new field test for the assessment of endurance capacity in chronic obstructive pulmonary disease. *Thorax* 54(3): 213-222, 1999.
- 56 Damhuis RAM and Schütte PR: Resection rates and postoperative mortality in 7,899 patients with lung cancer. *Eur Respir J* 9: 7-10, 1996.
- 57 Ninan M, Sommers KE, Landreneau RJ, Weyant RJ, Tobias J, Luketich JD, Ferson PF and Keenan RJ: Standardized exercise oximetry predicts postpneumonectomy outcome. *Ann Thorac Surg* 64(2): 328-332; discussion 332-333, 1997.

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