CHEST Supplement
DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Physiologic Evaluation of the Patient With Lung Cancer Being Considered for Resectional Surgery

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **This section of the guidelines is intended to provide an evidence-based approach to the preoperative physiologic assessment of a patient being considered for surgical resection of lung cancer.**
Methods: **The current guidelines and medical literature applicable to this issue were identified by computerized search and were evaluated using standardized methods. Recommendations were framed using the approach described by the Guidelines Oversight Committee.**
Results: **The preoperative physiologic assessment should begin with a cardiovascular evaluation and spirometry to measure the FEV_1 and the diffusing capacity for carbon monoxide (DLCO). Predicted postoperative (PPO) lung functions should be calculated. If the % PPO FEV_1 and % PPO DLCO values are both > 60%, the patient is considered at low risk of anatomic lung resection, and no further tests are indicated. If either the % PPO FEV_1 or % PPO DLCO are within 60% and 30% predicted, a low technology exercise test should be performed as a screening test. If performance on the low technology exercise test is satisfactory (stair climbing altitude > 22 m or shuttle walk distance > 400 m), patients are regarded as at low risk of anatomic resection. A cardiopulmonary exercise test is indicated when the PPO FEV_1 or PPO DLCO (or both) are < 30% or when the performance of the stair-climbing test or the shuttle walk test is not satisfactory. A peak oxygen consumption ($\dot{V}O_2$peak) < 10 mL/kg/min or 35% predicted indicates a high risk of mortality and long-term disability for major anatomic resection. Conversely, a $\dot{V}O_2$peak > 20 mL/kg/min or 75% predicted indicates a low risk.**
Conclusions: **A careful preoperative physiologic assessment is useful for identifying those patients at increased risk with standard lung cancer resection and for enabling an informed decision by the patient about the appropriate therapeutic approach to treating his or her lung cancer. This preoperative risk assessment must be placed in the context that surgery for early-stage lung cancer is the most effective currently available treatment of this disease.**

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Abbreviations: ACCP = American College of Chest Physicians; CPET = cardiopulmonary exercise test; DLCO = diffusing capacity for carbon monoxide; ERS = European Respiratory Society; ESTS = European Society of Thoracic Surgeons; LVRS = lung volume reduction surgery; PICO = population, intervention, comparator or control group, outcome; % PPO = percent predicted postoperative; PPO = predicted postoperative; RCRI = revised cardiac risk index; STS = Society of Thoracic Surgeons; SWT = shuttle walk test; ThRCRI = thoracic revised cardiac risk index; VATS = video-assisted thoracic surgery; $\dot{V}O_2$max = maximal oxygen consumption; $\dot{V}O_2$peak = peak oxygen consumption

Summary of Recommendations

2.6.1. In patients with lung cancer who are potential candidates for curative surgical resection, it is recommended that they be assessed by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, medical oncologist, radiation oncologist and pulmonologist (Grade 1C).

2.6.2. In elderly patients with lung cancer who are potential candidates for curative surgical resection it is recommended that they be fully evaluated regardless of age (Grade 1C).

2.6.3. In patients with lung cancer being considered for surgery who have increased perioperative cardiovascular risk, a preoperative cardiologic evaluation is recommended, with further management according to existing cardiologic guidelines for non cardiac surgery (Grade 1C).

3.1.1.1. In patients with lung cancer being considered for surgery, it is recommended that both FEV_1 and diffusing capacity for carbon monoxide (DLCO) be measured in all patients and that both predicted postoperative (PPO) FEV_1 and PPO DLCO are calculated (Grade 1B).

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3.2.1.1. In patients with lung cancer being considered for surgery, if both PPO FEV_1 and PPO DLCO are > 60% predicted, no further tests are recommended (Grade 1C).

Remark: Values of both PPO FEV_1 and PPO DLCO > 60% indicate low risk for perioperative death and cardiopulmonary complications following resection including pneumonectomy.

3.2.1.2. In patients with lung cancer being considered for surgery, if either the PPO FEV_1 or PPO DLCO are < 60% predicted and both are above 30% predicted, it is recommended that a low technology exercise test (stair climb or shuttle walk test [SWT]) is performed (Grade 1C).

3.2.1.3. In patients with lung cancer being considered for surgery, with either a PPO FEV_1 < 30% predicted or a PPO DLCO < 30% predicted performance of a formal cardiopulmonary exercise test (CPET) with measurement of maximal oxygen consumption ($\dot{V}O_2$max) is recommended (Grade 1B).

Remark: Either a PPO FEV_1 < 30% predicted or a PPO DLCO < 30% predicted indicate an increased risk for perioperative death and cardiopulmonary complications with anatomic lung resection.

3.9.1. In patients with lung cancer being considered for surgery who walk < 25 shuttles (or < 400 m) on the SWT or climb < 22 m at symptom limited stair climbing test, performance of a formal CPET with measurement of $\dot{V}O_2$max is recommended (Grade 1C).

Remark: Walking < 25 shuttles (or < 400 m) on the SWT or climbing < 22 m at symptom limited stair climbing test suggests an increased risk for perioperative death and cardiopulmonary complications with anatomic lung resection.

3.9.2. In patients with lung cancer being considered for surgery and a $\dot{V}O_2$max < 10mL/kg/min or < 35% predicted it is recommended that they are counseled about minimally invasive surgery, sublobar resections or nonoperative treatment options for their lung cancer (Grade 1C).

Remark: a $\dot{V}O_2$max < 10mL/kg/min or < 35% predicted indicates a high risk for perioperative death and cardiopulmonary complications with major anatomic lung resection through thoracotomy.

Remark: For values of $\dot{V}O_2$max in the range of 10 to 15 mL/kg/min an increased risk of mortality is expected. However, data are less definitive for making decisions based solely on those values without taking into account other factors like PPO FEV_1 and DLCO as well as patient comorbidities.

6.1.1. In patients with lung cancer being considered for surgery who undergo neoadjuvant therapy, it is suggested that repeat pulmonary function testing with diffusion capacity be performed after completion of neoadjuvant therapy (Grade 2C)**.**

7.4.1. In patients with lung cancer in an area of upper lobe emphysema who are candidates for lung volume reduction surgery (LVRS), combined LVRS and lung cancer resection is suggested (Grade 2C)**.**

7.4.2. In all patients with lung cancer being considered for surgery who are actively smoking, tobacco dependence treatment is recommended (Grade 1C)**.**

Remark: Smoking cessation is associated with short-term perioperative and long-term survival benefits(see also specific recommendations in chapter 6, 3.1.1, 3.1.2, 3.1.3).

7.4.3. In patients with lung cancer being considered for surgery and deemed at high risk (as defined by the proposed functional algorithm, ie, PPO FEV_1 or PPO DLCO < 60% and $\dot{V}O_2$max < 10 mL/kg/min or < 35%), preoperative or postoperative pulmonary rehabilitation is recommended (Grade 1C)**.**

Surgery is the best option for cure in patients with early-stage non-small cell lung cancer, but many potentially resectable tumors occur, usually due to cigarette smoking, in individuals with abnormal pulmonary function. These patients may be at increased risk of both immediate perioperative complications and long-term disability following curative-intent surgical resection of their lung cancer. Cigarette smoking also predisposes these patients to other comorbid conditions, specifically atherosclerotic cardiovascular disease, which further increases perioperative risk. Consequently, in considering whether a patient should undergo curative-intent surgical resection of lung cancer, the possible short-term perioperative risk from comorbid cardiopulmonary disease and the long-term risk of pulmonary disability must be balanced against the possible risk of reduced survival if an oncologically suboptimal treatment strategy is chosen.

The task of the preoperative physiologic assessment is to identify patients at increased risk of both perioperative complications and long-term disability from lung cancer resection surgery using the least invasive tests possible, and to assess the magnitude of that risk. This assessment allows the patient to be counseled regarding treatment options and risks, so that an informed decision can be made. Identification of patients at an elevated risk by the preoperative physiologic assessment also provides a basis for developing interventions to reduce the risk of perioperative complications and long-term pulmonary disability from curative-intent surgical resection of lung cancer.

1.0 Methods

The goal of this article is to update previous recommendations on the preoperative physiologic evaluation of patients with lung cancer being considered for curative-intent surgery.[2,3] A formal process was followed. The topic editor and writing committee drafted evidence questions using a population, intervention, comparator or control group, outcome (PICO) format whenever possible. These PICO questions can be accessed in the online supplementary materials for each article where they were developed. Outcomes were restricted to those that are patient important, not simply research focused. Searches occurred for relevant clinical evidence, mostly in the form of original research or systematic reviews. Original research included all levels of evidence (randomized controlled trials as well as observational studies), as long as they appeared in peer-reviewed publications, which was the minimal threshold.

The PICO questions then informed the search strategies, which are available upon request. The writing committee conducted their literature searches in PubMed, Google Scholar, and Scopus. Searches were not limited by publication date; however, most covered the period 2005 to the present. The references in the second edition of the American College of Chest Physicians (ACCP) Lung Cancer Guidelines were used for the majority of articles written before 2005.

Recommendations were developed by the writing committee, graded by a standardized method (see the article by Lewis et al,[1] "Methodology for Guidelines for Lung Cancer," in the ACCP Lung Cancer Guidelines), and were reviewed by all members of the Lung Cancer Panel and the Thoracic Oncology Network prior to approval by the Guidelines Oversight Committee and the Board of Regents of the ACCP.

Although numerous reviews have been published on the preoperative risk assessment of patients with lung cancer being considered for curative-intent surgical resection,[4-9] most available guidelines on the management of non-small cell lung cancer do not address the preoperative evaluation process.[10-16] The British Thoracic Society,[17] the ACCP,[3] and the European Respiratory Society (ERS) jointly with the European Society of Thoracic Surgeons (ESTS)[18] have provided two guidelines with specific recommendations on the steps needed to evaluate preoperative risk. The recommendations of these guidelines follow a similar approach, relying on physiologic testing to estimate perioperative risk and the effect of resection on postoperative lung function.

2.0 General Issues Regarding Risk

2.1 Multidisciplinary Team

Patients with lung cancer who are seen by a physician with expertise in the management of this disease are more likely to have histologic confirmation of lung cancer and referral for potentially curative treatment.[19,20] Evaluation by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, a medical oncologist, a radiation oncologist, and a pulmonologist, as is the practice now in many countries, is important in the assessment of risk and benefit of curative-intent surgery. Multidisciplinary input is especially useful in patients who are marginal surgical candidates as a basis for discussing the proposed surgical procedure and treatment options with the patient and appropriate family or surrogates.

Two of the eight comparative studies included in a systematic review[21] reported an improvement in survival in patients evaluated by a multidisciplinary team (in inoperable patients and in elderly patients, respectively).[22,23] Although the other studies did not find a difference in survival, three reported increased resection rates[24,25] and two reported increased rates of receiving chemotherapy or radiotherapy.[22,23] Similar findings were noted in the two most recent observational reports, which showed that multidisciplinary team evaluation was associated with improved practice patterns (ie, pathologic diagnosis, receipt of chemotherapy or radiotherapy, complete staging, adherence to guidelines, and shorter interval from diagnosis to treatment).[26,27]

2.2 Risk Thresholds

In presenting the option of curative-intent surgical therapy to a patient with lung cancer, it is important to recognize that risk assessment is a complex process. Risks related to standard surgical resection for lung cancer (lobectomy or greater removal of lung tissue) include perioperative morbidity and mortality and long-term functional disability. Individual patient circumstances increase or decrease the risks of standard surgical resection. In this guideline, the effect on perioperative mortality, morbidity, residual functional status, and quality of life with curative lung cancer resection for various physiologic abnormalities is extrapolated from published data. However, patient preference as to the maximal acceptable surgical risk (eg, the threshold mortality rate above which the patient would not accept the procedure) should also be explored. Mathematical approaches, based on decision analysis techniques, have been useful for conceptually describing the interplay between risk and patient preference, but are not routinely used for individual patient care.[28] The use of minimally invasive thoracic surgery and sublobar anatomic resections (segmentectomy), whenever technically and oncologically feasible, needs to be taken into account when discussing the risk of surgery with the patient. In fact, both these techniques have been shown to substantially reduce the perioperative risk and the physiologic impact and to provide comparable or even superior oncologic results. The responsible physician should also keep in mind and discuss nonsurgical treatment alternatives, such as conventional radiotherapy, stereotactic radiotherapy, and radiofrequency ablation, if the risk of surgery is deemed unacceptably high by both surgeon and patient.

2.3 Age

The prevalence of lung cancer increases with age. In North America it has been estimated that the prevalence of lung cancer increases from 14 per 100,000 population at age 40 years to 477 per 100,000 population at age 70 years for men. For women, it increases from 16 per 100,000 population at age 40 to 342 per 100,000 population at age 70 years. Approximately 30% to 35% of candidates for lung resection for lung cancer are > 70 years of age, as reported in the most recent Society of Thoracic Surgeons (STS) and ESTS general thoracic surgery databases. Although age has been traditionally considered a risk factor, the most recent guidelines have emphasized that age alone is not a contraindication to surgery.[3,18] The increased surgical risk, which may be observed in elderly patients, is probably a function of the underlying comorbidities. In this regard, the ERS-ESTS guidelines have recommended that the cardiopulmonary fitness of elderly patients with lung cancer be fully evaluated without any prejudice regarding age.[18] A similar recommendation has been proposed by the European Organization for Research and Treatment of Cancer elderly task force and the Lung Cancer Group, and by the International Society for Geriatric Oncology in a joint expert opinion paper.[29] They advised that surgery in the early stages of disease not be dismissed based solely on chronologic age.

Factors such as tumor stage, patient life expectancy, performance status, and presence of underlying comorbidities should be taken into account in the surgical decision-making process. Careful patient selection with preoperative evaluation is mandatory, however, and could significantly improve the results. Evidence[30-40] has shown that for patients > 80 years old, reported average mortality is between 0% and 9%; however, it should be kept in mind that in most series the most frequent operation was lobectomy or sublobar resections. Very elderly patients have reduced resection rates[40-42] and are more frequently submitted to sublobar resections rather than lobectomy. Relative long-term survival of very elderly patients appears to be comparable to younger ones in some studies,[34,40,42] but not in others in which survival in patients > 80 was shorter than in younger patients.[41,43,44] In general, reported 5-year survival in stage I after pulmonary resection varies between 50% and 60%.[35,36,38,41,42,45-47]

2.4 Cardiovascular Risk

Patients with lung cancer are predisposed to atherosclerotic cardiovascular disease because of cigarette smoking, and the prevalence of underlying coronary artery disease is about 11% to 17%.[48,49] The risk of major postoperative cardiac complications, including myocardial ischemia, pulmonary edema, ventricular fibrillation or primary cardiac arrest, complete heart block, and cardiac-related death,[50] is about 2% to 3% after lung resection.[48,49] As a consequence, a preoperative cardiovascular risk assessment should be performed. Guidelines have recommended the use of cardiac risk scores as a screening tool to select patients needing specialized preoperative cardiologic testing before proceeding to their surgical procedure. The American Heart Association/American College of Cardiology[51] and the European Society of Cardiology/European Society of Anesthesiology guidelines[52] recommend the revised cardiac risk index (RCRI)[50] as the preferred risk scoring tool to assess cardiac risk in patients undergoing noncardiac surgical procedures. Similarly, the joint ERS/ESTS task force on fitness for radical treatment of patients with lung cancer[18] endorsed these recommendations and proposed a cardiologic algorithm incorporating this scoring system as a preliminary screening instrument.

However, the RCRI was originally derived from a mixed surgical population including only a minority of patients undergoing thoracic surgery. For this reason, this scoring system was recalibrated in a lung resection population,[48] and the recalibrated score (defined as thoracic RCRI [ThRCRI]) was then validated in external populations showing a good discrimination ability.[48,53] When using the cardiologic algorithm as a preliminary step in the functional workup of the lung resection candidate, it seems advisable to replace the traditional RCRI with the more specific and recently revised ThRCRI (Fig 1).

In summary, patients with ThRCRI > 1.5 or any cardiac condition requiring medication or a newly suspected cardiac condition or limited exercise tolerance (inability to climb two flights of stairs) should be referred for a cardiac consultation. Noninvasive testing and treatments as per American Heart Association/American College of Cardiology guidelines[51,54] should be indicated in these patients (Fig 1).

On the other hand, aggressive cardiac interventions should be reserved only for patients who need them irrespective of surgery, but interventions specifically for surgery are of limited benefit. For example, prophylactic coronary revascularization has not been demonstrated to reduce risk.[55,56] Furthermore, the need for aggressive antiplatelet therapy, which is recommended for approximately 6 weeks after coronary angioplasty and/or a bare metal stent and for > 1 year after a drug-eluting stent, may represent a major surgical challenge,[57] although evidence has shown that patients who are receiving clopidogrel and who have a coronary artery stent placed can safely undergo general thoracic surgery without increased risk of bleeding and with a reduced risk of perioperative myocardial infarction compared with control subjects undergoing surgery without antiplatelet therapy.[58]

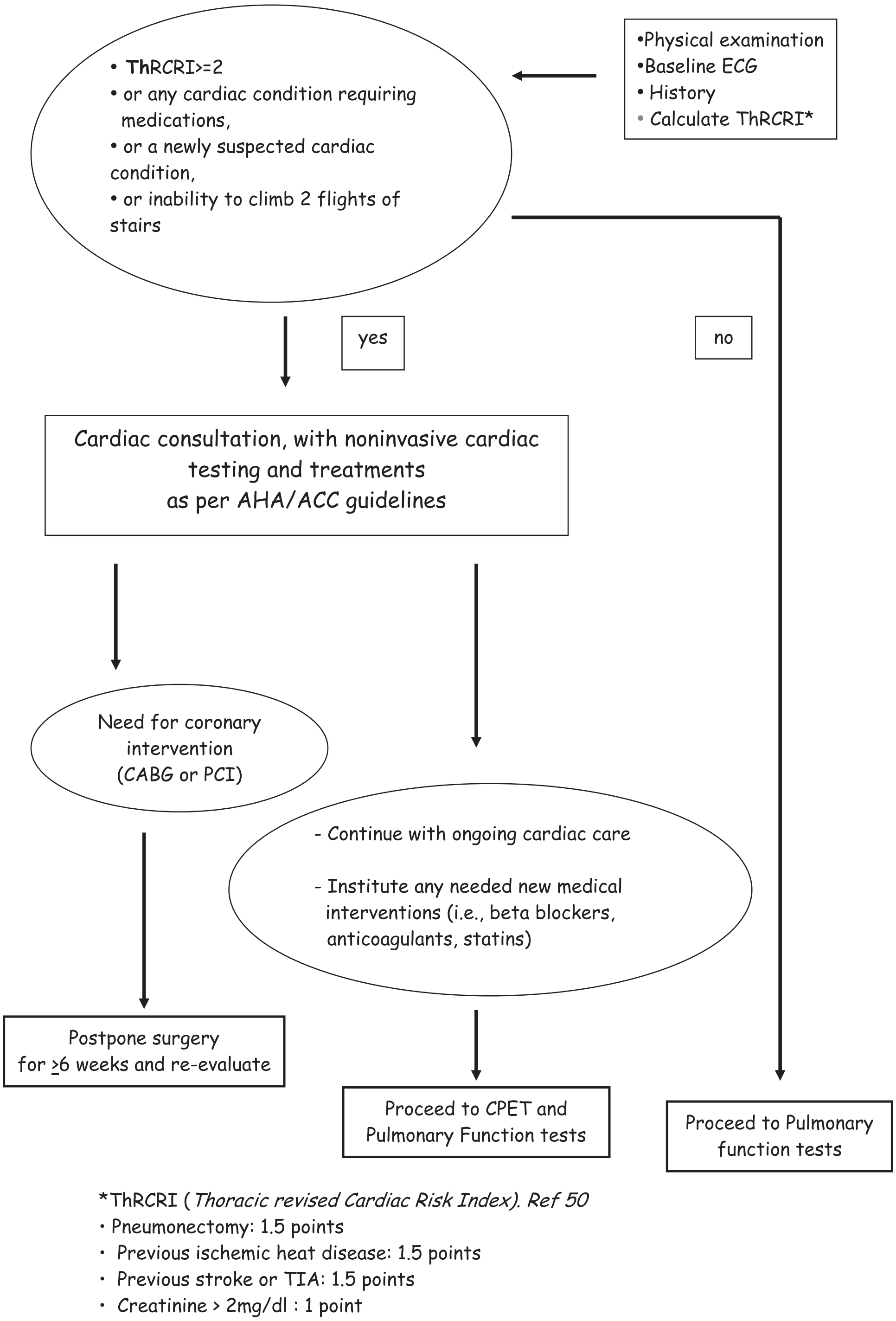
β-Blockers are commonly used to reduce perioperative myocardial infarction.[59,60] However, a randomized trial has shown that commonly used β-blocker regimens increase the risk of stroke, presumably because of bradycardia and hypotension, and can increase overall mortality.[61] Therefore, we do not recommend starting a new perioperative β-blockade in patients with ischemic heart disease, but favor continuation of β-blockers in patients already taking them. β-blockers may be beneficial as new therapy only in very high-risk patients, in whom their cardioprotective benefits may outweigh their bradycardic and hypotensive effects.[62]

Cardiopulmonary exercise testing (CPET) has been proposed as a useful tool for detecting both overt and occult exercise-induced myocardial ischemia, with a diagnostic accuracy similar to that of a single-photon emission computed tomographic myocardial perfusion study[63-65] and superior to standard ECG stress testing.[66] Several variables obtained during CPET, including oxygen consumption relative to heart rate and work rate, provide consistent, quantitative patterns of abnormal physiologic responses to graded exercise when left ventricular dysfunction is caused by myocardial ischemia. For this reason, CPET can be proposed as a noninvasive test to detect and quantify myocardial perfusion defects in patients at increased risk of coronary artery disease. In fact, in addition to providing information on the presence and severity of myocardial ischemia, it will provide data on peak oxygen consumption ($\dot{V}O_2$peak), a parameter that has been associated with postoperative outcome (see paragraph on CPET). We therefore recommend referral of patients with a positive cardiac history and increased cardiac risk for a CPET to better define the coronary reserve and cardiac function (Fig 1).

2.5 Surgical Experience

European guidelines on fitness for radical treatment[18] have recommended that the surgical treatment of patients with lung cancer be performed in specialized centers by qualified thoracic surgeons, because specialization has been shown to have a positive impact on resectability, postoperative mortality,

FIGURE 1. [Sections 2.4, 3.0, 4.0] Physiologic evaluation cardiac algorithm. *ThRCRI.[48] Pneumonectomy: 1.5 points; previous ischemic heart disease: 1.5 points; previous stroke or transient ischemic attack: 1.5 points; creatinine > 2 mg/dL: 1 point. ACC = American College of Cardiology; AHA = American Heart Association; CABG = coronary artery bypass graft surgery; CPET = cardiopulmonary exercise test; PCI = percutaneous coronary intervention. Modified and reproduced with permission of the European Respiratory Society. *Eur Respir J*. July 2009 34:17-41. doi:10.1183/09031936.00184308



and long-term survival. In fact, with the exception of one report,[67] most authors found reduced mortality rates (crude or adjusted for concomitant risk factors) when patients with lung cancer were operated on by board-certified, specialized thoracic surgeons, compared with general surgeons.[68-71] Some authors reported, in addition to reduced operative mortality, a longer survival[71] and increased resection rates[67] in patients with lung cancer managed in hospitals with specialized thoracic surgeons.

Many studies on the association between hospital procedural volume and outcome have been published. Most of the studies reported a favorable influence of high surgical volume on operative mortality[72-80]; however, this association was not confirmed by others.[81-85] Other studies found a better long-term survival associated with high-volume hospitals or surgeons.[74,78,80,86-88] Some studies have shown that surgeon's volume was more strongly associated with mortality than was hospital volume,[89] but others did not confirm this result[76,77] and found that hospital volume, rather than individual surgeon volume, was more linked to outcome. For lung resection, surgeon volume was found to be strongly correlated with hospital volume (ie, high-volume surgeons tend to operate in high-volume hospitals).[76,77] Given the variable volume thresholds that have been used in the literature (ie, the definition of high volume ranges from 20 to > 90 cases/y), it is difficult to identify a minimal surgical volume for individual surgeons or centers. Based on the data from the literature and a consensus opinion of experts, the ERS-ESTS guidelines advised that lung resections be performed in centers with a minimal surgical volume of 20 to 25 major anatomic resections per year.[18]

2.6 Recommendations

2.6.1. In patients with lung cancer who are potential candidates for curative surgical resection, it is recommended that they be assessed by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, medical oncologist, radiation oncologist and pulmonologist (Grade 1C)**.**

2.6.2. In elderly patients with lung cancer who are potential candidates for curative surgical resection it is recommended that they be fully evaluated regardless of age (Grade 1C)**.**

2.6.3. In patients with lung cancer being considered for surgery who have increased perioperative cardiovascular risk, a preoperative cardiologic evaluation is recommended, with further management according to existing cardiologic guidelines for non cardiac surgery (Grade 1C)**.**

3.0 Risk of Perioperative Morbidity and Mortality

Morbidity and mortality rates following lung resection have decreased over time.[79,90] Current rates of mortality reported in the STS or ESTS general thoracic surgery databases are around 1.6% to 2.3% after lobectomy and 3.7% to 6.7% after pneumonectomy. These numbers are somewhat lower than reported previously.[79] Newer or refined surgical techniques, such as the use of muscle-sparing and intercostal nerve-sparing thoracotomy,[91] video-assisted thoracoscopy,[92,93] and robotically assisted lung resection,[94] have certainly contributed to minimizing the postoperative risks of morbidity and reductions in lung function. For instance, a propensity-score case-matched analysis based on the data present in the STS general thoracic surgery database has shown a significantly lower incidence of complications and a shorter length of stay (4 days vs 6 days, $P < .0001$) compared with open lobectomy.[92] However, even with modern anesthetic, surgical, and postoperative care techniques, the risk of perioperative morbidity and mortality following either lobectomy or pneumonectomy is still appreciable. The approach to estimating these risks from underlying cardiopulmonary disease is based on a preoperative physiologic assessment (see Fig 1).

3.1 Spirometry and Diffusing Capacity

Spirometry, and in particular that of FEV_1 and predicted postoperative (PPO) FEV_1, has traditionally represented the key test in the functional workup of surgical candidates with lung cancer. A reduced FEV_1 or PPO FEV_1 has been associated with increased respiratory morbidity and mortality rates.[95-101] Berry et al[95] showed that FEV_1 was an independent predictor of respiratory complications. Patients with a preoperative FEV_1 < 30% had an incidence of respiratory morbidity as high as 43%, whereas those with an FEV_1 > 60% had a morbidity rate of 12%. Ferguson et al[97] used classification and regression tree analysis and found that FEV_1 was an independent predictor of pulmonary morbidity (OR, 1.1 for every 10% decrease in FEV_1) and cardiovascular complications (OR, 1.13 for every 10% decrease in FEV_1). By using receiver-operating characteristic analysis, Licker et al[99] confirmed that the best cutoff value of FEV_1 for predicting respiratory complications was 60%.

Despite these findings, guidelines[18] have questioned their pivotal roles in selecting patients for operation. This conclusion was based on a series of studies showing a limited role of these parameters in predicting complications in patients with COPD,[102,103] likely due to the so-called "lobar volume reduction effect." In patients with lung cancer and moderate to severe COPD, the resection of the most affected parenchyma may determine an improvement in respiratory mechanics and elastic recoil. Several studies have shown a minimal loss or even an improvement in respiratory function 3 to 6 months after lobectomy in these patients.[104-111] A most important finding is that the lobar volume reduction effect takes place immediately after surgery,[112] demonstrating that the impact of operation in patients with COPD is lower than expected in patients without COPD.

Interest in the diffusing capacity for carbon monoxide (DLCO) as a useful marker of operative risk was stimulated by Ferguson et al,[113] who related preoperative DLCO to postresection morbidity and mortality in 237 patients. Patients were selected for surgery on the basis of clinical evaluation and spirometry, but not on the DLCO, which was also measured. They found the preoperative uncorrected DLCO expressed as percent predicted to have a higher correlation with postoperative deaths than the FEV_1 expressed as percent predicted, or any other factor tested. In this study, a DLCO $<60\%$ predicted was associated with a 25% mortality and a 40% pulmonary morbidity. This finding was subsequently confirmed by other authors.[95,97,114-116] Similar to PPO FEV_1, a reduced PPO DLCO has been shown to be strongly associated with the risk of pulmonary complications and mortality following lung resection.[117,118]

Previous guidelines have recommended measuring DLCO in patients with evidence of diffuse parenchymal lung disease on radiographic studies, dyspnea on exertion, or a reduced FEV_1. However, some contributions have shown that the correlation between FEV_1 and DLCO is consistently poor[119,120] and that a reduced PPO DLCO is a predictor of cardiopulmonary complications and mortality even in patients with an otherwise normal FEV_1.[119,120] More than 40% of patients with an FEV_1 $>80\%$ may have a DLCO $<80\%$, and 7% of them may have a PPO DLCO $<40\%$.[119] As a consequence, guidelines have recommended the systematic measurement of DLCO in lung resection candidates regardless of the FEV_1 value.[18]

In addition to postoperative morbidity and mortality, the value of DLCO has been associated with long-term survival[121,122] and residual quality of life.[123] Liptay et al[121] showed that a DLCO $<40\%$ was associated with an increased risk of late death due to causes other than cancer. Ferguson et al[122] showed that a DLCO value $<60\%$ had a hazard ratio of 1.35 for death.

Therefore, we recommend systematically measuring DLCO in all lung resection candidates regardless of their preoperative level of FEV_1 because at least 40% of them can have an abnormal DLCO despite a normal FEV_1 and PPO DLCO has been shown to be a valid predictor of major morbidity even in patients without airflow limitation. Most of the studies analyzing the role of DLCO in risk stratification took into consideration the uncorrected measurement of DLCO. Any form of correction/adjustment (ie, hemoglobin concentration or alveolar ventilation) should be reported in future analysis. DLCO measurement should be performed according to the joint ERS/American Thoracic Society clinical practice guidelines.[124]

3.1.1 Recommendation

3.1.1.1. In patients with lung cancer being considered for surgery, it is recommended that both FEV_1 and DLCO be measured in all patients and that both PPO FEV_1 and PPO DLCO are calculated (Grade 1B)**.**

3.2 PPO Lung Function

Several criteria should be met before using assessment of lung function to predict postoperative clinical outcomes. First, the quality of the patient performance and test reproducibility must be optimal and should conform to standards.[124,125] Once performance is adequate, specific attention must be directed to understanding the cause of abnormal results. For example, reduction in FEV_1 due to weakness may be associated with a different surgical outcome as compared with a patient with COPD, despite identical airflow. In addition, the presence of an obstructing endobronchial lesion may produce abnormalities on baseline testing that can be expected to improve postoperatively. Unfortunately, there are limited data that address these and other similar issues and, therefore, the remainder of this section is specifically targeted to the assessment of subjects with underlying COPD.

The risk of operative complications has been linked to PPO lung function. Separate formulas are used to estimate the PPO lung function for patients undergoing pneumonectomy vs lobectomy. The PPO values can be converted into percent predicted using standard equations. For illustrative purposes, the formulas below are used for estimation of PPO FEV_1; the same equations can be used to estimate the PPO DLCO.

Pneumonectomy: the perfusion method is used with the following formula:

$$\text{PPO FEV}_1 = \text{preoperative FEV}_1 \times (1 - \text{fraction of total perfusion for the resected lung})$$

The preoperative FEV_1 is taken as the best measured postbronchodilator value. A quantitative radionuclide perfusion scan is performed to measure the fraction of total perfusion for the resected lung. Standards for perfusion scan have been published by the American College of Radiology (available at http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/Pulmonary_Scintigraphy.pdf)

Lobectomy: the anatomic method is used with the following formula:

$$\text{PPO FEV}_1 = \text{preoperative FEV}_1 \times (1 - y/z)$$

The preoperative FEV_1 is taken as the best measured postbronchodilator value. The number of functional or unobstructed lung segments to be removed is y and the total number of functional segments is z.[126] The total number of segments for both lungs is 19 (10 in the right lung [three in the upper, two in the middle, five in the lower] and nine in the left lung [five in the upper and four in the lower]).

In a study of > 1,400 subjects undergoing lung resection, Alam et al[127] demonstrated that the OR for development of postoperative respiratory complications increases as the PPO FEV_1 and PPO Dlco fall (a 10% increase in the risk of complications for every 5% decrement in PPO lung function). Accordingly, previous guidelines have recommended estimation of PPO pulmonary function for all patients with an abnormal FEV_1 (< 80% predicted) who are being considered for surgical resection.[3] Historically, the operative risk has been considered acceptable for subjects with a PPO FEV_1 and PPO Dlco > 40% predicted. For patients who do not meet these criteria, recommendations included either assessment of exercise capacity as an additional preoperative risk-stratification method or consideration for alternate and/or limited therapies.

However, although many data established a PPO FEV_1 of > 40% as a criterion for patients who are likely to do well, exactly how patients below this threshold will fare is less well established. Multiple observations suggest that patients who do not meet these criteria may still undergo surgery with an acceptable clinical outcome in series that include sublobar resections. Several studies have demonstrated that low values for morbidity (about 15%-25%) and mortality (about 1%-15%) can be obtained, even in subjects with severe reduction in airflow; mean preoperative FEV_1 in these studies ranges from 26% to 45% predicted.[103,128,129] Note that these values for preoperative FEV_1 were frequently below the threshold recommended for postoperative lung function, highlighting that surgery can be performed safely in selected patients with markedly abnormal lung function at baseline. The surgical techniques used in these studies varied and included limited wedge or segment resections, a combination of resection with lung volume reduction, and both open and video-assisted thoracoscopic approaches.

Long-term survival has been analyzed in subjects with severe airflow limitation undergoing surgical resection of lung tumors. Martin-Ucar et al[128] evaluated 5-year survival in patients with upper-lobe stage I disease. In subjects with severe underlying COPD and a PPO FEV_1 < 40% (mean, 34%) predicted, the survival rate was 35% after lobectomy. Although this was lower than the 65% survival observed in a comparison group with superior lung function (PPO FEV_1 > 40; mean, 61%), the survival was still better than expected if resection had not been performed.[128] In addition, Lau et al[129] reported favorable results in patients with severe COPD when resection was performed using video-assisted thoracic surgery (VATS). In this study, improvements were also noted in both hospital mortality (8% vs 14%) and long-term survival (5-year survival, 48% vs 18%) with VATS compared with thoracotomy.

The favorable clinical outcomes obtained in some patients with markedly abnormal lung function have multiple potential explanations. Improvements in surgical technique and introduction of VATS may be associated with beneficial postoperative results. Endoh et al[130] have demonstrated that postoperative fall in lung function is lower in subjects undergoing VATS compared with subjects treated with an open surgical approach. Similarly, improvement in perioperative management and tailoring of therapy to individual patients may produce benefits in clinical outcome. An additional benefit may be obtained by performing limited resections. In a study by Linden et al,[103] analysis of frozen sections at time of surgery allowed for wedge resections in 65% of subjects. Although limited resection resulted in a favorable short-term outcome, these benefits should be considered after consideration of the risk of local recurrence. Lastly, lung resection is associated with a "lung volume reduction" effect.[105,131-134] Patients with underlying COPD may demonstrate a smaller reduction in FEV_1 postoperatively than do subjects with normal spirometry.[130,131,135] In addition, an inverse relationship between postoperative decline in FEV_1 and baseline severity of airflow obstruction has been demonstrated.[132-134] Lastly, patients with COPD may demonstrate improvement in postoperative FEV_1, despite lung resection.[105,110,134]

Some advances may improve the ability of PPO lung function to predict postoperative complications. Several studies have evaluated the use of PPO Dlco specifically in patients with a normal FEV_1 at baseline.[115,119,120] The rationale for these studies is based on the different components of respiratory function assessed by these tests (lung mechanics assessed by spirometry vs gas exchange assessed by diffusion) and the poor correlation observed between FEV_1 and Dlco.[119,120] These studies identified that assessment of diffusion capacity and calculation of PPO Dlco were predictive of postoperative morbidity and respiratory complications, even in the presence of normal airflow. No relationship was demonstrable between mortality and PPO Dlco.

Because current equations to predict postoperative lung function are only valid 1 to 3 months after surgery,[111] attention has focused on the change in lung function observed in the immediate postoperative period. Varela et al[136] demonstrated that the best predictor of surgical morbidity and mortality was the measured FEV_1 on postoperative day 1 rather than the PPO FEV_1. These results were extended by studies that focused on the evolution of lung function during the immediate postoperative period, when respiratory complications occur. Data demonstrate that lung function during this period is markedly lower than the corresponding PPO values.[111,133,135,136] On postoperative day 1, the FEV_1 was only 71% of the PPO value.[135] The FEV_1 progressively increased through the first week and on day 7 the FEV_1 reached 93% of the PPO value.[135] Based on these results, Brunelli et al[112,137] published methods to estimate the FEV_1 on the first postoperative day and at hospital discharge. Although the estimated values closely matched the observed data, several limitations of these studies affect their applicability at present. These studies evaluated only patients who passed a rigorous screening assessment to determine operative risk, and the relationship to clinical outcomes was not analyzed. Despite these considerations, these studies do highlight the limitations associated with current predictive models.

The considerations mentioned suggest that the existing algorithms for preoperative pulmonary assessment can be extended to offer potentially curative surgery to patients with more severe abnormalities in lung function at baseline. Several studies have demonstrated acceptable postoperative outcome in patients with a PPO lung function as low as 30% predicted. Puente-Maestú et al[138] compared acute morbidity and mortality, as well as 2-year survival, in subjects with a PPO FEV_1 and PPO DLCO > 30% predicted. In this study, preoperative evaluation included estimates of PPO oxygen consumption ($\dot{V}O_2$) during exercise, in addition to estimates of PPO FEV_1 and DLCO. Surgery was performed in subjects with PPO lung function < 40% predicted provided that the estimated PPO oxygen consumption during exercise exceeded 10 mL/kg/min. The operative mortality was 6% despite the inclusion of subjects with severe lung function abnormalities.

In addition, the data demonstrated improved 2-year survival in subjects treated with surgical resection (66%) compared with subjects who either refused surgery or were deemed unfit for surgery (19%). Of importance, although survival was lower in subjects with the most abnormal PPO lung function (between 30% and 40% predicted) compared with healthier subjects (survival = 57% vs 71%), the difference was not statistically significant and far exceeded the expected and observed survival in subjects who did not undergo surgery. Although the results of this study are encouraging, applicability to all clinical centers would be limited based on availability of CPET.

As an alternate approach, several groups have used lower technology tests, such as the stair-climbing test.[112,133,136,137,139] Patients who were able to climb > 12 m during the stair-climbing test were offered surgery. Operative morbidity and mortality using this cutoff value during the stair-climbing test were comparable to data obtained with full CPET. Taken together, these studies suggest that curative lung resection surgery can be performed in patients with PPO lung function as low as 30% predicted, provided the patient demonstrates an acceptable exercise capacity.

3.2.1 Recommendations

3.2.1.1. In patients with lung cancer being considered for surgery, if both PPO FEV_1 and PPO DLCO are > 60% predicted, no further tests are recommended (Grade 1C)**.**

Remark: Values of both PPO FEV_1 and PPO DLCO are > 60% indicate low risk for perioperative death and cardiopulmonary complications following resection including pneumonectomy.

3.2.1.2. In patients with lung cancer being considered for surgery, if either the PPO FEV_1 or PPO DLCO are < 60% predicted and both are above 30% predicted, it is recommended that a low technology exercise test (stair climb or SWT) is performed (Grade 1C)**.**

3.2.1.3. In patients with lung cancer being considered for surgery, with either a PPO FEV_1 < 30% predicted or a PPO DLCO < 30% predicted performance of a formal CPET with measurement of $\dot{V}O_2$max is recommended (Grade 1B)**.**

Remark: Either a PPO FEV_1 < 30% predicted or a PPO DLCO < 30% predicted indicate an increased risk for perioperative death and cardiopulmonary complications with anatomic lung resection.

3.3 Cardiopulmonary Exercise Testing

Formal CPET is a sophisticated physiologic testing technique that includes recording the exercise electrocardiogram, heart rate response to exercise, minute ventilation, and oxygen uptake per minute. Maximal oxygen consumption ($\dot{V}O_2$max) is measured from this type of exercise test and has been recommended by previous guidelines[3,17] as the next step in the preoperative risk-assessment process in those patients with compromised pulmonary function.

European guidelines have emphasized the role of CPET in the preoperative functional workup.[18] CPET was recommended in every patient with either an FEV_1 or a DLCO < 80% predicted value. Patients with a $\dot{V}O_2$max > 20 mL/kg/min or 75% predicted can safely undergo the planned resection (up to pneumonectomy) without further testing. Only in those patients with a $\dot{V}O_2$max < 20 mL/kg/min should split lung functions (% PPO FEV_1 and % PPO DLCO) be taken into consideration for risk stratification. A $\dot{V}O_2$max value < 10 mL/kg/min or 35% predicted is generally regarded as a contraindication to major anatomic resections. Risk of postoperative mortality can generally be stratified by $\dot{V}O_2$max. In several case series, patients with a $\dot{V}O_2$max < 10 mL/kg/min had a very high risk of postoperative death.[114,140-142] However, this assumption is based on a total of only 27 patients in four studies with an overall mortality rate of 26%. A meta-analysis confirmed the role of $\dot{V}O_2$max in discriminating patients at risk of postoperative cardiopulmonary complications. Benzo and colleagues[143] included 955 patients from 14 studies reporting $\dot{V}O_2$max as mL/kg/min and found that those patients developing postoperative complications had a preoperative $\dot{V}O_2$max 3 mL/kg/min lower than those who did not. The authors concluded that this finding supported the use of CPET in risk stratification before lung resection.

A study by Loewen and colleagues[144] represents the largest published series of lung resection candidates evaluated with CPET. Complicated patients had a significantly lower $\dot{V}O_2$max compared with noncomplicated patients, and this finding confirmed previous investigations.[37,144-148] Most of the studies published so far generally agree that a value of $\dot{V}O_2$max between 10 and 15 mL/kg/min or between 35% and 75% predicted values indicates an increased risk of perioperative death compared with higher values of $\dot{V}O_2$max.[114,141,142,149-153] On the other hand, values > 20 mL/kg/min have been reported to be safe for any kind of resection, including pneumonectomy.[141,149,154-159] $\dot{V}O_2$max has been shown to be helpful in further evaluating the risk of complications in patients with borderline lung function. Morice et al,[160] for instance, reported that eight patients with a percent predicted postoperative (% PPO) FEV_1 < 33 and a $\dot{V}O_2$max > 15 mL/kg/min underwent lobectomy with no fatal complications.

Most recently, Brunelli and colleagues[148] published a series including 200 major anatomic lung resections with complete CPET evaluation before surgery. Patients with a $\dot{V}O_2$max > 20 mL/kg/min had no mortality and only a 7% morbidity rate. Importantly, a value of $\dot{V}O_2$max < 12 mL/kg/min was associated with a mortality rate of 13%. Bolliger and colleagues[151] were the first to demonstrate that $\dot{V}O_2$max expressed as a percentage of predicted value had a better discriminatory ability than when expressed in absolute values. The probability of developing complications in patients with a $\dot{V}O_2$max > 75% predicted was only 10% vs a probability of 90% in those with $\dot{V}O_2$max < 40% predicted. As with PPO FEV_1 and PPO DLCO, a segmental estimation of $\dot{V}O_2$max has been proposed by Bolliger and colleagues.[161] They found that a value of $\dot{V}O_2$max PPO < 10 mL/kg/min (or 35% predicted) was the only parameter able to identify all three patients who died in a subgroup of 25 patients at increased risk of complications.

In addition to $\dot{V}O_2$max, CPET can provide several other direct and indirect measures that can add to the preoperative risk stratification. Several authors have published articles about such derived parameters (ie, efficiency slope, oxygen pulse, minute ventilation to CO_2 production ratio slope), which have turned out to be predictive of cardiac and pulmonary complications.[146,162-164] A more liberal use of CPET is warranted by its role in early detecting coronary artery disease,[63-66] the association between $\dot{V}O_2$max and postoperative complications, and the possibility to use additional ergometric parameters to refine the analysis of the oxygen transport system.

3.4 Pulmonary Artery Pressures and Diffusing Capacity

Measurements of pulmonary arterial pressure during exercise have not proven to be helpful in predicting which patients will develop perioperative complications.[142,165,166] Measuring the diffusion capacity during exercise might be a better predictor of perioperative risk than $\dot{V}O_2$max, but is a technically demanding technique and not readily available.[167,168]

3.5 Stair-Climbing and Walking Tests

Stair climbing has been used historically as a surrogate for CPET. Stair climbing is an economic and widely applicable form of exercise. It is simple and rapid and requires few personnel and little equipment. The stair-climbing test appears to be a more stressful form of exercise and involves a larger muscle mass than cycling, yielding greater values of $\dot{V}O_2$max.[140,169,170] The test is extremely motivating for the patients who are pushed to reach a visible objective represented by the next landing. This approach was found to correlate with lung function; climbing three flights indicates an FEV_1 > 1.7 L and five flights an FEV_1 > 2 L.[171]

Several groups have shown that the ability to climb more than 12-14 m of stairs, which is approximately three flights of stairs, effectively identifies patients at low risk of postoperative complications usually following lobectomy, even though these patients might have had a % PPO FEV_1 or % PPO DLCO < 40.[172,173] Brunelli and colleagues[172] reported their preliminary experience in 160 lung resection candidates. The altitude reached during a preoperative stair-climbing test remained the only independent predictor of cardiopulmonary complications after logistic regression analysis. In particular, only 6.5% of subjects climbing > 14 m vs 50% of those climbing < 12 m had major cardiopulmonary complications. We expanded their series and reported on a series including 640 major anatomic lung resections (lobectomy and pneumonectomy)[139] Compared with patients climbing > 22 m, those unable to climb 12 m had an incidence of cardiopulmonary complications and mortality of 2.5- and 13-fold higher, respectively. The mortality rate in this low-performing group (climbing < 12 m) was 13%. In a group of patients with a PPO FEV_1 < 40% or PPO DLCO < 40% or both, no death was observed among those climbing > 22 m, whereas the mortality was 20% among such patients unable to climb 12 m.

A high correlation was found between altitude climbed and $\dot{V}O_2$peak measured during the test ($r = 0.7$).[174] The cutoff of 22 m had a positive predictive value of 86% to predict a $\dot{V}O_2$peak of 15 mL/kg/min. However, there are limitations to the usefulness of stair climbing. It has not been performed in a standardized manner. The duration of stair climbing, speed of ascent, number of steps per flight, height of each step, and criteria for stopping the test have varied from study to study. In an attempt to provide a method of standardization, Koegelenberg and colleagues[175] proposed using the speed of ascent, in addition to altitude; however, others have not found this parameter predictive of complications[176] Patients with comorbid conditions (eg, musculoskeletal disease, neurologic abnormalities, peripheral vascular insufficiency, and others) may be unable to perform the test. Brunelli and colleagues[177,178] found that patients unable to perform stair climbing because of comorbid conditions had a fourfold higher risk of postoperative mortality compared with those able to perform the test (16% vs 4%). Other surrogate tests for CPET are the shuttle walk test (SWT) and the 6-min walk, but data on the value of these tests in predicting $\dot{V}O_2$max are limited.[179] The SWT requires that patients walk back and forth between two markers set 10 m apart. The walking speed is paced by an audio signal and the walking speed is increased each minute in a graded fashion. The end of the test occurs when the patient is too breathless to maintain the required speed. In one study, inability to complete 25 shuttles on two occasions suggested a $\dot{V}O_2$max < 10 mL/kg/min[180]; however, other investigations were not able to find an association between shuttle walk distance and postoperative complications.[181] Nevertheless, SWT distance significantly correlated with $\dot{V}O_2$peak ($r = 0.67$).[157] All patients who walked > 400 m at the SWT had a $\dot{V}O_2$peak measured at CPET > 15 mL/kg/min. On the other hand, nine of 17 patients who walked < 250 m had a $\dot{V}O_2$peak > 15 mL/kg/min, indicating that SWT tends to underestimate exercise capacity at the lower range compared with $\dot{V}O_2$peak measured with CPET.

In a more recent article, Benzo and Sciurba[182] found a high correlation between each level of the SWT and the oxygen consumption measured during the test. The cutoff of 25 shuttles had 90% positive predictive value for predicting a $\dot{V}O_2$peak > 15 mL/kg/min. For the 6-min walk, patients are instructed to walk as far as possible in the time allotted. Rest during the test is permissible. Interpretation of the distance walked in 6 min is currently not well standardized[183] and the few studies evaluating this test in lung resection candidates reported conflicting results.[184] The European guidelines do not recommend using this test for the functional evaluation of patients considered for lung surgery.[18]

3.6 Exercise Oxygen Desaturation

The SWT and the 6-min walk test may be more effective than CPET in identifying patients who desaturate during exercise.[185] The value of this observation, though, is unclear. Greater than 4% desaturation during exercise has been reported to indicate an increased risk of perioperative complications.[114,116,186] However, a study from the United Kingdom reported similar perioperative complication rates for patients who desaturated > 4% on a SWT and those who did not.[181] Similar nonunivocal findings were reported by using other forms of exercise. Three studies[176,187,188] used stair climbing as exercise tests and found that exercise oxygen desaturation was associated with increased risk of complications, such as postoperative respiratory failure, need for ICU admission, prolonged hospital stay, home oxygen requirement, and mortality. On the other hand, Varela and colleagues[189] did not find an association between oxygen desaturation below 90% during standardized incremental cycle-ergometry and postoperative cardiopulmonary morbidity.

3.7 Composite Scores

Investigators have proposed using composite scores to predict perioperative complications. Epstein's group[158] developed the multifactorial cardiopulmonary risk index, an empirically derived score based on points awarded for cardiac and pulmonary risk. A strong association between this score and postoperative complications in a group of 42 patients was shown. Birim et al[154] found that patients with more comorbid conditions, identified by the Charlson comorbidity index, were also more likely to have major complications following lung cancer resection. Melendez and colleagues[190] used regression analysis to develop the predictive respiratory complication quotient, which is based on the % PPO FEV_1, % PPO DLCO, and oxygenation. This score was also effective in identifying patients at increased risk of perioperative complications. Brunelli et al[191] adapted the physiologic and operative severity score for the enumeration of mortality and morbidity, a score originally used for general surgery issues, to evaluate post-lung resection problems. They suggested that this score might be a useful method for comparing the complication rates among different institutions. Ferguson and Durkin[192] developed a simple score based on the FEV_1, DLCO, and age of the patient, which seems to compare favorably with other scoring systems[158,191] and is easy to administer. Data from national or international organizations were used to develop more reliable risk models. The ESTS proposed a model for in-hospital mortality (ESOS) incorporating two factors, age and PPO FEV_1.[193] Similarly, the STS generated a risk model for predicting mortality and major morbidity.[156] Finally, the French Society of Thoracic and Cardiovascular Surgery published the Thoracoscore, a multifactorial index to predict mortality following thoracic surgery.[194] Although useful for risk stratification and benchmarking in specific groups of patients, scoring systems generally lack adequate accuracy for assigning specific risk to individual patients. As suggested by previous guidelines,[23] caution should therefore be used in individual patient selection.

3.8 Arterial Blood Gas Tensions

Historically, hypercapnia ($Pa_{CO_2} > 45$ mm Hg) has been quoted as an exclusion criterion for lung resection.[195,196] This recommendation was made on the basis of the association of hypercapnia with poor ventilatory function.[197] The few studies that address this issue, however, suggest that preoperative hypercapnia is not an independent risk factor for increased perioperative complications. Stein et al[198] showed that hypercapnia was associated with serious postoperative respiratory difficulties in five patients, but there were no deaths, despite a $Pa_{CO_2} > 45$ mm Hg. Morice et al[160] reported on three patients with preoperative hypercapnia who survived curative-intent lung cancer surgery. In two series of patients with lung cancer undergoing surgery,[199,200] perioperative complications were not higher in patients with preoperative hypercapnia. Preoperative hypoxemia, defined as an arterial oxygen saturation < 90%, has been associated with an increased risk of postoperative complications.[185]

3.9 Recommendations

3.9.1. In patients with lung cancer being considered for surgery who walk < 25 shuttles (or < 400m) on the SWT or climb < 22m at symptom limited stair climbing test, performance of a formal CPET with measurement of $\dot{V}O_2$max is recommended (Grade 1C)**.**

Remark: Walking < 25 shuttles (or < 400 m) on the SWT or climbing < 22 m at symptom limited stair climbing test suggests an increased risk for perioperative death and cardiopulmonary complications with anatomic lung resection.

3.9.2. In patients with lung cancer being considered for surgery and a $\dot{V}O_2$max < 10mL/kg/min or < 35% predicted it is recommended that they are counseled about minimally invasive surgery, sublobar resections or nonoperative treatment options for their lung cancer (Grade 1C)**.**

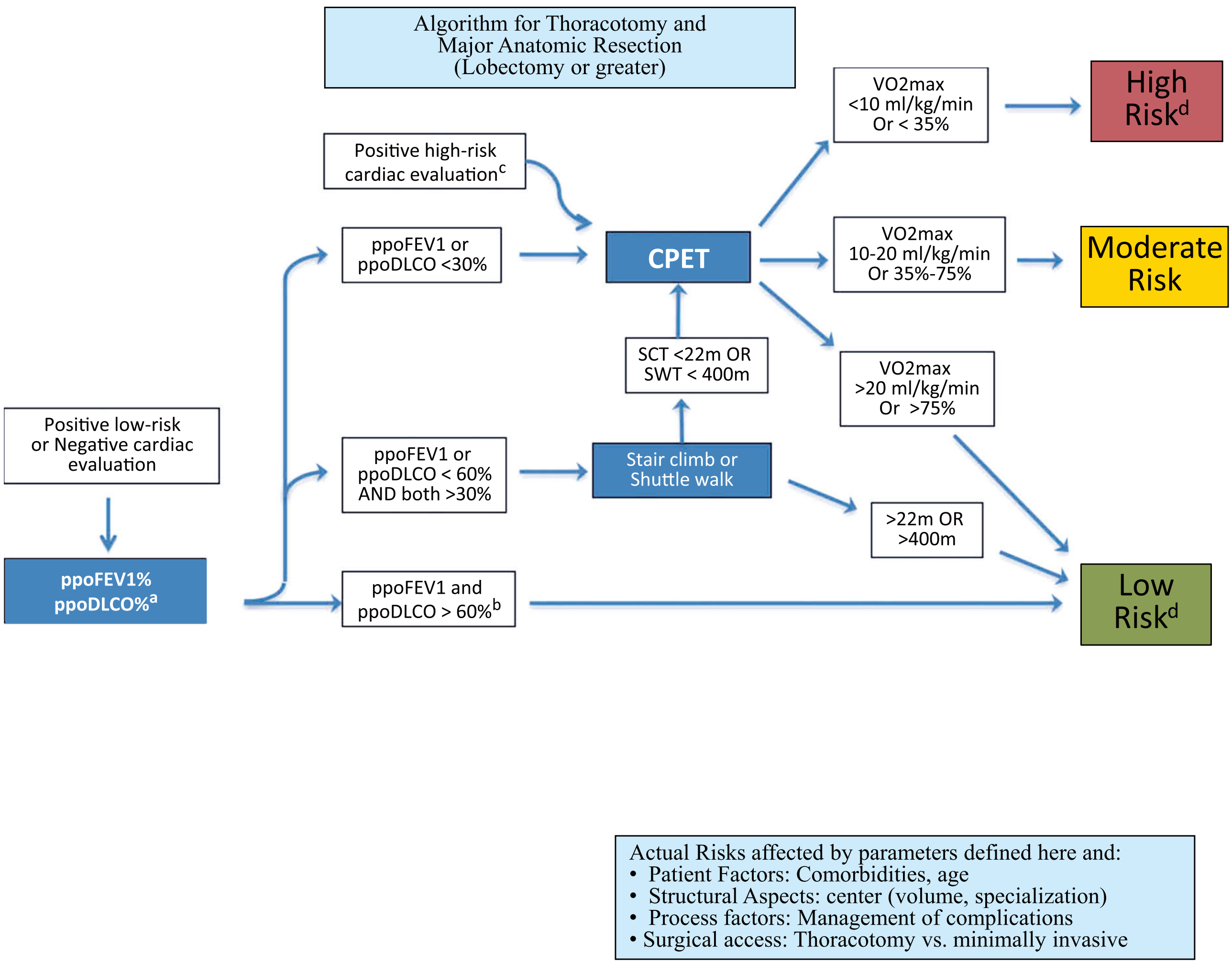
Remark: a $\dot{V}O_2$max < 10mL/kg/min or < 35% predicted indicates a high risk for perioperative death and cardiopulmonary complications with major anatomic lung resection through thoracotomy.

Remark: For values of $\dot{V}O_2$max in the range of 10 to 15 mL/kg/min an increased risk of mortality is expected. However, data are less definitive for making decisions based solely on those values without taking into account other factors like PPO FEV_1 and DLCO as well as patient comorbidities.

4.0 Function Algorithm

We developed a functional algorithm based on the best available scientific evidence and consensus opinion of experts (Fig 2). Patients should be submitted to a preliminary cardiac evaluation (Fig 1). If the patient is deemed to be at increased cardiac risk, he or she should be managed according to American Heart Association/American College of Cardiology guidelines and further reevaluated. If the patient's cardiac evaluation turns out negative, or positive with low risk, he or she can proceed to pulmonary function evaluation and calculation of PPO pulmonary functions. The FEV_1 and DLCO should be measured in all patients and PPO values calculated. Patients with both a PPO FEV_1 and a PPO DLCO > 60% are regarded as at low risk for surgery. Patients with either a PPO FEV_1 or a PPO DLCO between 30% and 60% should perform a low technology exercise test as a screening test. If the performance at the low technology exercise test is satisfactory, patients are regarded as at moderate risk. A CPET is indicated if

FIGURE 2. [Section 4.0] Physiologic evaluation resection algorithm. (a) For pneumonectomy candidates, we suggest to use Q scan to calculate predicted postoperative values of FEV1 or DLCO (PPO values = preoperative values × (1 – fraction of total perfusion for the resected lung), where the preoperative values are taken as the best measured postbronchodilator values. For lobectomy patients, segmental counting is indicated to calculate predicted postoperative values of FEV1 or DLCO (PPO values = preoperative values × (1 – y/z), where the preoperative values are taken as the best measured postbronchodilator value and the number of functional or unobstructed lung segments to be removed is y and the total number of functional segments is z. (b) PpoFEV1 or ppoDLCO cut off values of 60% predicted values has been chosen based on indirect evidences and expert consensus opinion. (c) For patients with a positive high-risk cardiac evaluation deemed to be stable to proceed to surgery we suggest to perform both pulmonary function tests and cardiopulmonary exercise test for a more precise definition of risk. (d) Definition of risk: Low risk: The expected risk of mortality is below 1%. Major anatomic resections can be safely performed in this group. Moderate risk: Morbidity and mortality rates may vary according to the values of split lung functions, exercise tolerance and extent of resection. Risks and benefits of the operation should be thoroughly discussed with the patient. High risk: The risk of mortality after standard major anatomic resections may be higher than 10%. Considerable risk of severe cardiopulmonary morbidity and residual functional loss is expected. Patients should be counseled about alternative surgical (minor resections or minimally invasive surgery) or nonsurgical options. ppoDLCO = predicted postoperative diffusing capacity for carbon monoxide; ppoDLCO% = percent predicted postoperative diffusing capacity for carbon monoxide; ppoFEV1 = predicted postoperative FEV1; ppoFEV1% = percent predicted postoperative FEV1; SCT = stair climb test; SWT = shuttle walk test; VO2max = maximal oxygen consumption. See Figure 1 legend for expansion of other abbreviations.



PPO FEV_1 or PPO DLCO are < 30% or when performance in the stair-climbing test or the SWT is not satisfactory (ie, height reached in stair-climbing test < 22 m or a shuttle walk distance < 400 m). A $\dot{V}O_2$peak < 10 mL/kg/min or 35% predicted indicates a high risk for major anatomic resection through thoracotomy. Conversely, a $\dot{V}O_2$peak > 20 mL/kg/min or 75% predicted indicate a low risk. To ensure reliability of results, a CPET must be performed according to the recommendations published by the American Thoracic Society/ACCP statement on CPET.[201]

Some patients are unable to perform some or all types of exercise tests for incapacitating comorbidities. These patients may have an increased risk of mortality following major anatomic resections.[177] They should be evaluated carefully based on the available cardiac and pulmonary parameters and should be regarded as high-risk patients.

5.0 Risk of Long-term Pulmonary Effects Following Resection

A significant limitation to addressing the potential disabling long-term effects of lung resections is that studies providing objective measures such as pulmonary function tests or exercise capacity typically do not go beyond 6 months. Therefore, any disabling sequelae beyond this period truly remain understudied. With this limitation in mind, some general observations may be made. Following lung resection, lung function will decrease initially. Following thoracotomy, FEV_1 appears to nadir immediately after surgery.[133,135,136] Early investigators in this field suggested that a postoperative $FEV_1 < 0.8$ L was prohibitive to resection, given the unacceptable incidence of hypercapnia and pulmonary disability.[202] Ultimately though, the factors that contribute to long-term pulmonary disability, either individually or in concert, remain largely unknown. This makes predicting who exactly will suffer long-term pulmonary disability following lobectomy or pneumonectomy largely speculative. Some data exist regarding compromised pulmonary function following either a lobectomy or a pneumonectomy, but extrapolating these data to true long-term pulmonary disability is not possible with the existing data.

For a lobectomy, by 6 months postoperatively, the FEV_1 recovers partially so that there is a deficit from the preoperative FEV_1 of between 9% and 11%. In a prospective study, Brunelli and associates[105] demonstrated that recovery of preoperative FEV_1 and Dlco to the levels described in the previous reports at 6 months is achievable by 3 months following lobectomy. Exercise capacity as measured by $\dot{V}O_2$max will also decrease following lung resection, and for lobectomy this decrease has been observed to be between 0% and 13%.[203,204] The most common limiting symptom in postoperative exercise studies has been leg discomfort, rather than dyspnea.[204,205] Bolliger et al[204] found that exercise was limited by leg muscle fatigue in 53% of patients preoperatively, and this observation remained following lobectomy.

For pneumonectomy, the FEV_1 recovery at 6 months is markedly less and ranges between 34% and 41%.[203,204,206] In a prospective study by Brunelli et al,[105] the recovery of the deficit in FEV_1 was 66% of the preoperative value, whereas the Dlco recovery was 80% of baseline. This discrepant observation from their patients undergoing lobectomy may have been secondary to a relatively small percentage of patients undergoing pneumonectomy being included in their prospective study. Following pneumonectomy, and similar to that observed for other pulmonary function tests, the deficit in $\dot{V}O_2$max does not become restored to preoperative values and remains between 20% and 28%.[204,205] Unlike the case for lobectomy, following pneumonectomy there is a switch to dyspnea as the limiting factor (61% of patients at 3 months and 50% at 6 months after resection), rather than leg muscle fatigue.

Unfortunately, few data describing changes in quality of life following curative-intent lung resection are available. Among patients with COPD, the preoperative pulmonary status appears to impact quality of life in the more acute perioperative period in that mechanical ventilation and need for tracheostomy occur with greater frequency than in those without COPD.[96] A cross-sectional survey examined respiratory symptoms and quality of life in 142 long-term survivors of non-small cell lung cancer.[207] Most of these patients (74%) had undergone a lobectomy, with 12% having had a pneumonectomy and 11% a wedge resection. The most commonly reported postoperative respiratory symptom was dyspnea, but cough and wheeze were also described frequently.

6.0 Risk of Long-term Pulmonary Disability With Neoadjuvant Therapy

The risks associated with neoadjuvant therapy that result in long-term pulmonary disability remain a topic that is not well understood. Furthermore, the existing evidence associated with the negative long-term pulmonary effects of neoadjuvant chemotherapy with and without radiation therapy is limited.

Diffusion capacity appears to be the pulmonary function test that is most affected by the use of neoadjuvant chemotherapy. One prospective randomized controlled trial has evaluated the effect of neoadjuvant therapy in this regard, but the long-term effect on pulmonary disability was not presented.[208] Differing regimens of neoadjuvant gemcitabine-chemotherapy were associated with a mean decrease in the hemoglobin-adjusted Dlco of 8%. In fact, 27% of the original 87 patients met the criteria for pulmonary toxicity, and 11% of the patients had a postneoadjuvant Dlco of $\leq 40\%$. Ultimately, however, of the 15% of patients who were deemed to have a significant reduction in their Dlco, none were precluded from undergoing surgical resection.[208] Other retrospective studies have demonstrated similar findings in which neoadjuvant therapy has negatively impacted diffusion capacity among other pulmonary function tests.[115,209,210] Collectively, although all these studies have demonstrated that there is a detrimental effect on pulmonary function tests following neoadjuvant therapy, only limited data exist regarding the impact of these pulmonary function alterations in the long-term setting.[211] Margaritora et al[211] described a significant increase in DLCO at the 1-year mark following neoadjuvant chemoradiation therapy. Because other studies have demonstrated a decrease in diffusion capacity shortly after the completion of neoadjuvant therapy and surgery,[115,209,210] an increase in DLCO suggests that recovery of damaged parenchyma may be occurring in the longer-term period. Although DLCO has been associated with the development of postoperative morbidity and mortality following neoadjuvant therapy and surgery,[210,212] no definitive factors that predict long-term pulmonary disability have been firmly identified. Fujita et al[213] demonstrated that radiation therapy doses of > 45 Gy were predictive of postoperative morbidity, but no factors that were associated with any longer-term sequelae were described. Ultimately, predicting long-term pulmonary disability remains an unresolved issue and an area for potential study.

6.1 Recommendation

6.1.1. In patients with lung cancer being considered for surgery who undergo neoadjuvant therapy, it is suggested that repeat pulmonary function testing with diffusion capacity be performed after completion of neoadjuvant therapy (Grade 2C)**.**

7.0 Methods to Reduce Perioperative Risks and Long-term Pulmonary Disability

7.1 Lung Volume Reduction Surgery

Lung volume reduction surgery (LVRS) for patients with severe emphysema has been shown in a large prospective, randomized controlled trial to provide a survival advantage in selected patients with predominantly upper-lobe emphysema and low exercise capacity.[214] Anecdotal experience has shown that lung resected during LVRS has occasionally contained unsuspected lung cancers.[215,216] Patients eligible for LVRS who also have lung cancer represent a unique subset of individuals. If traditional criteria are used to determine suitability for resection, most LVRS candidates with lung cancer would not be considered acceptable to proceed with resection. However, multiple case series suggest that patients with extremely poor lung function can tolerate combined LVRS and resection of the lung cancer with an acceptable mortality rate and surprisingly good postoperative outcomes.[106,217-225] Others have also described curative-intent surgical resections among patients with LVRS and have found significant and lasting improvements in FEV_1.[224,225]

In terms of mid-term and long-term survival, encouraging results have been observed among patients undergoing LVRS and lung cancer resections.[215,218,224] One prospective case-control study found that patients with heterogeneous upper-lobe emphysema who underwent upper lobectomy for known stage I and II lung cancer had a respectable, but lower overall, survival compared with those patients undergoing conventional LVRS resections (57 months vs 88 months, $P = .06$).[218] In contrast, Nakajima et al[226] reported that patients with severe COPD undergoing curative-intent resections for their lung cancers had a worse 5-year survival (24% vs 59%, $P < .0001$) relative to their patients undergoing more straightforward LVRS. However, this study was skewed in that preoperative baseline difference in smoking status, pulmonary function tests, and COPD grade existed favoring the LVRS population. Although indications for combined LVRS and lung cancer resection are still evolving, the most promising candidates appear to be patients who have a cancer in the upper lobe that is also affected by emphysema and who would otherwise meet the criteria for LVRS (ie, DLCO and $FEV_1 > 20\%$ predicted).Although some have suggested a more aggressive approach,[227] enthusiasm for recruiting patients with relatively preserved lung should be tempered by the fact that conclusions regarding the differences in long-term outcomes between LVRS alone and LVRS with patients with lung cancer may have compared different populations at baseline.

7.2 Smoking Cessation

Retrospective studies have demonstrated that the timing of tobacco cessation prior to surgery, in general, has a minimal impact on postoperative pulmonary complications.[228,229] The combination of smoking cessation and lung cancer surgery is not associated with differences in pulmonary function tests postoperatively.[229] Another retrospective study of 288 consecutive patients undergoing pulmonary surgery suggested that smoking abstinence of at least 4 weeks may be associated with reduced perioperative respiratory complications.[230] An analysis of nearly 8,000 patients from the STS database demonstrated that the perioperative mortality among current and past smokers vs nonsmokers is significantly higher (1.5% vs 0.3%, $P = .001$). In fact, a general trend for decreasing perioperative mortality was associated with length of cessation prior to surgery.[231] Similar findings have been reported elsewhere among former and current smokers.[232] Cumulatively, tobacco dependence cessation appears to be advantageous in reducing short-term outcomes associated with lung cancer resections.

With respect to long-term survival, 5- and 10-year survivals have been found to be worse for stage I lung cancers among current smokers compared with former smokers and nonsmokers.[232] Prospective controlled trials are needed to more clearly define the effect smoking cessation preoperatively may have on reducing perioperative problems. There already are data that demonstrate it is associated with an improved quality of life and cost effectiveness.[233] Despite the limited amount of data that currently exists, smoking cessation should be encouraged at the time of diagnosis of lung cancer because early data suggest that perioperative outcomes and long-term survival are better when compared with those who have not ceased tobacco use. Additionally, there may be a reduction in the development of metachronous tumors (see articles on by Leone et al[234] tobacco treatment and by Colt et al[235] follow-up and surveillance in the ACCP Lung Cancer Guidelines).

7.3 Pulmonary Rehabilitation

As yet, there are no robust data to recommend the routine use of preoperative pulmonary rehabilitation for patients with lung cancer. There is, however, a growing body of evidence that suggests that preoperative conditioning may be advantageous.[236-238] In the National Emphysema Treatment Trial, all patients underwent pulmonary rehabilitation prior to randomization to either medical treatment or LVRS. Pulmonary rehabilitation provided important benefits in dyspnea, quality of life, and exercise ability.[236] Weinstein et al[237] demonstrated that a preoperative regimen was inversely proportional to patients' length of stay. Bobbio et al[238] demonstrated that their preoperative pulmonary rehabilitation program resulted in an increase in $\dot{V}O_2$max at the anaerobic threshold and that there was an increase in workload. Other data, however, are not as supportive, showing that cardiopulmonary performance is not significantly altered.[239] Ultimately, the absence of randomized controlled trial data regarding preoperative pulmonary rehabilitation allows for only the suggestion that it will be beneficial to the patients undergoing it. In the postoperative setting, information is emerging that initiating an inpatient regimen following a lung resection is immediately beneficial for patients. These inpatient programs have been associated with improvements in exercise performance, symptoms, and pulmonary function tests (FEV_1).[240,241] Secondary gains, in the form of improved quadriceps strength, without improvements in objective exercise performance measures, have been found to occur with pulmonary rehabilitation programs.[242] Improvements in exercise performance without any objective improvements in pulmonary function tests have also been observed with postoperative pulmonary rehabilitation.[243] Even in the absence of a formalized rehabilitation program per se, planned ambulation within 4 h following a resection has been associated with improved oxygenation and lower external oxygen requirements.[244] Although the data on pulmonary rehabilitation are difficult to quantify or standardize, what is available seems to confirm intuition that pulmonary rehabilitation following lung cancer surgery is of benefit to patients, albeit in differing forms.

7.4 Recommendations

7.4.1. In patients with lung cancer in an area of upper lobe emphysema who are candidates for LVRS, combined LVRS and lung cancer resection is suggested(Grade 2C)**.**

7.4.2. In all patients with lung cancer being considered for surgery who are actively smoking, tobacco dependence treatment is recommended (Grade 1C)**.**

Remark: Smoking cessation is associated with short-term perioperative and long-term survival benefits(see also specific recommendations in chapter 6, 3.1.1, 3.1.2, 3.1.3).

7.4.3. In patients with lung cancer being considered for surgery and deemed at high risk (as defined by the proposed functional algorithm, ie, PPO FEV_1 or PPO DLCO < 60% and $\dot{V}O_2$max < 10 mL/kg/min or < 35%), preoperative or postoperative pulmonary rehabilitation is recommended (Grade 1C)**.**

8.0 Summary

Patients with lung cancer often have concomitant diffuse parenchymal and/or obstructive airway disease and atherosclerotic cardiovascular disease as a consequence of their smoking habit. These diseases may place these patients at increased risk of perioperative complications, including death and long-term pulmonary disability after lung cancer resection. A careful preoperative physiologic assessment is useful to identify those patients at increased risk with standard lung cancer resection and to enable an informed decision by the patient about the appropriate therapeutic approach to treating their lung cancer. This preoperative risk assessment must be placed in the context that surgery for early-stage lung cancer is the most effective currently available treatment of this disease.

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Dr Brunelli: contributed to the review of the final draft and formatting of the original algorithms and as a panelist.
Dr Kim: contributed to the article as a panelist.
Dr Berger: contributed to the article as a panelist.
Dr Addrizzo-Harris: contributed to the article as the topic editor.

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