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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)

Gene L. Colice, MD, FCCP; Shirin Shafazand, MD, FCCP; John P. Griffin, MD, FCCP; Robert Keenan, MD, FCCP; and Chris T. Bolliger, MD, FCCP

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: **Current guidelines and medical literature applicable to this issue were identified by computerized search and evaluated using standardized methods. Recommendations were framed using the approach described by the Health and Science Policy Committee.**

Results: **The preoperative physiologic assessment should begin with a cardiovascular evaluation and spirometry to measure the FEV_1. If diffuse parenchymal lung disease is evident on radiographic studies or if there is dyspnea on exertion that is clinically out of proportion to the FEV_1, the diffusing capacity of the lung for carbon monoxide (DLCO) should also be measured. In patients with either an FEV_1 or DLCO < 80% predicted, the likely postoperative pulmonary reserve should be estimated by either the perfusion scan method for pneumonectomy or the anatomic method, based on counting the number of segments to be removed, for lobectomy. An estimated postoperative FEV_1 or DLCO < 40% predicted indicates an increased risk for perioperative complications, including death, from a standard lung cancer resection (lobectomy or greater removal of lung tissue). Cardiopulmonary exercise testing (CPET) to measure maximal oxygen consumption ($\dot{V}O_2$max) should be performed to further define the perioperative risk of surgery; a $\dot{V}O_2$max of < 15 mL/kg/min indicates an increased risk of perioperative complications. Alternative types of exercise testing, such as stair climbing, the shuttle walk, and the 6-min walk, should be considered if CPET is not available. Although often not performed in a standardized manner, patients who cannot climb one flight of stairs are expected to have a $\dot{V}O_2$max of < 10 mL/kg/min. Data on the shuttle walk and 6-min walk are limited, but patients who cannot complete 25 shuttles on two occasions will likely have a $\dot{V}O_2$max of < 10 mL/kg/min. Desaturation during an exercise test has not clearly been associated with an increased risk for perioperative complications. Lung volume reduction surgery (LVRS) improves survival in selected patients with severe emphysema. Accumulating experience suggests that patients with extremely poor lung function who are deemed inoperable by conventional criteria might tolerate combined LVRS and curative-intent resection of lung cancer with an acceptable mortality rate and good postoperative outcomes. Combining LVRS and lung cancer resection should be considered in patients with a cancer in an area of upper lobe emphysema, an FEV_1 of > 20% predicted, and a DLCO of > 20% predicted.**

Conclusions: **A careful preoperative physiologic assessment will be useful to identify those patients who are 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 for this disease.** ***(CHEST 2007; 132:161S–177S)***

Key words: cardiopulmonary exercise testing; diffusing capacity of the lung for carbon monoxide; lung cancer; lung resection surgery; predicted postoperative lung function; preoperative assessment; spirometry

Abbreviations: CPET = cardiopulmonary exercise test; DLCO = diffusing capacity of the lung for carbon monoxide; LVRS = lung volume reduction surgery; PPO = predicted postoperative; %PPO = percent predicted postoperative; $\dot{V}O_2$max = maximal oxygen consumption

Surgery is the best option for achieving a cure in patients with lung cancer, but many potentially resectable tumors occur in individuals with abnormal pulmonary function that is usually due to cigarette smoking. These patients may be at increased risk for both immediate perioperative complications and long-term disability following curative-intent surgical resection of their lung cancer. Cigarette smoking will also predispose these patients to other comorbid conditions, specifically atherosclerotic cardiovascular disease, which will further increase perioperative risk. Consequently, in considering whether a patient should undergo curative-intent surgical resection of lung cancer, the immediate perioperative risk from comorbid cardiopulmonary disease and the long-term risk of pulmonary disability must be balanced against the risk of reduced survival due to suboptimally treated (with radiation therapy rather than surgery) lung cancer.

The task of the preoperative physiologic assessment is to identify patients who are at increased risk for both perioperative complications and long-term disability from surgical resection of lung cancer using the least invasive tests possible. The purpose of this preoperative physiologic assessment is to enable adequate counseling of the patient on treatment options and risks so that they can make a truly informed decision. In the future, hopefully, the preoperative physiologic assessment will serve as the basis for interventions to possibly reduce the risk of perioperative complications and long-term pulmonary disability from curative-intent surgical resection of lung cancer.

To update previous recommendations on the preoperative physiologic evaluation of patients with lung cancer who are being considered for curative-intent surgery,[1] guidelines on lung cancer diagnosis and management published between 2002 and May 2005 were identified by a systematic review of the literature (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter). Those guidelines including recommendations specific to the preoperative physiologic evaluation were identified for inclusion in this section. Supplemental material appropriate to this topic was obtained by literature search of a computerized database (MEDLINE) and a review of the reference lists of relevant articles. Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and reviewed by all members of the lung cancer panel and the Thoracic Oncology Network prior to approval by the Health and Science Policy Committee and the Board of Regents of the American College of Chest Physicians.

Current Guidelines

Although numerous reviews[2–7] have been published on the preoperative risk assessment of patients with lung cancer being considered for curative-intent surgical resection, most available guidelines[8–15] on the management of non-small cell lung cancer (NSCLC) do not address the preoperative evaluation process. The British Thoracic Society[16] and the American College of Chest Physicians[1] have provided guidelines with specific recommendations on the steps needed to evaluate the preoperative risk. The recommendations of these two guidelines follow a similar approach, relying on physiologic testing to estimate perioperative risk and the effect of resection on postoperative lung function.

General Issues Regarding Risk

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.[17–19] Evaluation by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, a medical oncologist, a radiation oncologist, and a pulmonologist, is essential in the risk assessment of patients being evaluated for curative-intent surgery. Multidisciplinary input will be 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.

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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 (*ie*, 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 from standard surgical resection. In this guideline, the effect on average mortality risk with standard surgical lung cancer resection for various physiologic abnormalities will be extrapolated from published data. This risk will be compared to the risk for patients with adequate cardiopulmonary reserve as a basis for estimating relative risk. However, patient preference as to what would be 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.[20] In addition to a discussion of the balance between risks and benefits for standard surgical resection of lung cancer, the responsible physician and patient should also discuss nonstandard treatment options, such as minimally invasive lobectomy, sublobar resections, conventional radiotherapy, stereotactic radiotherapy, and radiofrequency ablation.

Age

Age had been considered to be a factor that might increase perioperative risks, but age alone should not be a reason to deny patients with lung cancer access to curative-intent surgical resection.[21] As the population ages, the number of patients ≥ 70 years of age will rise; it is estimated that ≥ 40% of patients with lung cancer in 2005 were ≥ 75 years of age.[18] For patients > 70 years of age, the reported mortality rate is between 4% and 7% for lobectomy and around 14% for pneumonectomy.[16,22,23] These reported rates are higher than those for patients < 70 years of age (lobectomy, 1 to 4%; pneumonectomy, 5 to 9%); the difference may be more a function of comorbidity than age alone. In a 2003 series[24] of 126 consecutive patients > 70 years of age who were undergoing curative-intent surgical resection, the overall 30-day mortality rate was 3.2%, with comorbid disease being the most important influence on mortality.

Limited information suggests that carefully selected patients who are > 80 years of age can tolerate lung cancer resection. A retrospective analysis[25] from Johns Hopkins Hospital reported that 17% of the octogenarians in whom lung cancer was diagnosed between 1980 and 2002 underwent surgical resection. In this series[25] of 68 patients in their 80s who were undergoing curative-intent surgery for NSCLC, the 30-day mortality rate was 8.8%. Port et al[26] described outcomes for 61 octogenarians who underwent various types of curative-intent surgical resections of lung cancer, including 4 patients who underwent pneumonectomy. The 30-day mortality rate in this series was 1.6%. A comprehensive geriatric assessment might be useful preoperatively in elderly patients. Fukuse and colleagues[27] found that dependence for performing activities of daily living and impaired cognition were important predictors of complications following pulmonary surgery.

Cardiovascular Risk

As with any planned major operation, especially in a population that is predisposed to atherosclerotic cardiovascular disease due to cigarette smoking, a preoperative cardiovascular risk assessment should be performed. The generally recommended approach to this risk assessment (Table 1) has been described in the American College of Cardiology and American Heart Association guidelines for perioperative cardiovascular evaluation for noncardiac surgery.[28] Patients with major factors for increased perioperative cardiovascular risk should undergo a preoperative cardiologic evaluation.

Surgical Experience

It has been recommended that the surgical mortality risk for lobectomy should be expected to be < 4%, and for a pneumonectomy < 9%.[16] Accumulating information indicates that when curative-intent surgical resection is performed by a general surgeon rather than a trained thoracic surgeon[29,30] and in a hospital in which these operations are performed infrequently[30–34] the surgical mortality rates may exceed these threshold values. Also to be considered within the realm of the surgical experience is the efficiency with which the preoperative evaluation takes place. A large retrospective study from Spain[35] has reported a median delay of 35 days between the date of pathologic diagnosis and the date of surgery. A smaller study[36] from the United States documented a median preoperative interval of 82 days. Although postoperative survival times did not seem to be influenced in either study by the preoperative delay, in general, the interval between diagnosis and curative-intent surgery should be minimized. These observations indicate that the experience of both the surgeon performing the procedure

Table 1—*Clinical Predictors of Increased Perioperative Cardiovascular Risk, Including Myocardial Infarction, Heart Failure, and Death**

Clinical Predictors	Description
Major	
Unstable coronary syndromes	Acute (within 7 d) or recent (from 7 to 30 d) myocardial infarction with evidence of important ischemic risk by clinical symptoms or non-invasive study; and Unstable or severe angina (Canadian class III or IV)
Decompensated heart failure	
Significant arrhythmias	High-grade atrioventricular block; Symptomatic ventricular arrhythmias in the presence of underlying heart disease; and Supraventricular arrhythmias with uncontrolled ventricular rate
Severe valvular disease	
Intermediate	
Mild angina pectoris (Canadian class I or II)	
Prior myocardial infarction by history or pathologic Q waves	
Compensated or prior heart failure	
Diabetes mellitus (particularly insulin dependent)	
Renal insufficiency	
Minor	
Advanced age	
Abnormal ECG (left ventricular hypertrophy, left bundle branch block, and ST-T abnormalities)	
Rhythm other than sinus rhythm (*eg*, atrial fibrillation)	
Low functional capacity (*eg*, inability to climb one flight of stairs with a bag of groceries)	
History of stroke	
Uncontrolled systemic hypertension	

*Adapted from Eagle et al.[28]

and the hospital at which surgery occurs should be considered in planning curative-intent surgical resection of lung cancer.

Previous Chemotherapy

Induction chemotherapy may be used prior to curative-intent surgery, but chemotherapy may affect preoperative lung function. Leo and colleagues[37] found in 30 patients with NSCLC who underwent chemotherapy that FEV_1 increased but DLCO decreased prior to surgery. Decreases in postchemotherapy DLCO were significantly associated with postoperative respiratory complications. Matsubara et al[38] observed significantly lower DLCO levels and greater postoperative morbidity and mortality in 92 patients receiving induction chemotherapy compared to 666 patients who underwent surgery without induction chemotherapy.

Recommendations

1. It is recommended that patients with lung cancer be assessed for curative surgical resection by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, a medical oncologist, a radiation oncologist, and a pulmonologist. Grade of recommendation, 1C

2. It is recommended that patients with lung cancer not be denied lung resection surgery on the grounds of age alone. Grade of recommendation, 1B

3. It is recommended that patients with lung cancer being evaluated for surgery who have major factors for increased perioperative cardiovascular risk have a preoperative cardiologic evaluation. Grade of recommendation, 1C

Risk of Suboptimal Treatment of Lung Cancer

Little information is available on the long-term survival of patients who were deemed to be inoperable because of physiologic limitations, especially when compared to a group of patients with similar physiologic limitations who underwent surgical resection. In a study[39] reporting on outcomes for a group of 66 high-risk lung cancer patients, 5 patients who were at very high risk for poor outcome underwent curative-intent surgical resection. One patient died in the perioperative period, but the long-term survival curve for the whole group of 5 high-risk patients undergoing surgery, including surgical death, was no different than that for 39 similar patients who were deemed to be inoperable.[39]

Recent studies from Japan[40] and the United States[41] have provided information on prognosis for patients with early-stage lung cancer who did not undergo curative-intent surgery. From 1982 to 1991, 4,947 patients with clinical stage I lung cancer were identified in the National Chest Hospital Study Group for Lung Cancer in Japan.[40] Of these 4,947 patients, 4,127 (83%) were treated surgically. The 799 patients (16%) who were treated nonoperatively had a 5-year survival rate of 16.6%. Many of these patients were treated with some combination of radiation therapy, chemotherapy, and immunotherapy, but no significant effect of these treatment modalities on survival was seen. Interestingly, 49 of the patients (6%) treated nonoperatively survived for > 5 years. The reasons why surgery was not performed were not provided but probably were related to comorbid disease and patient refusal.

Between 1994 and 1999, stage I or IIa lung cancer was diagnosed in 128 patients at a single US hospital.[41] Of these 128 patients, 49 (38%) did not receive any treatment, and their median (± SD) survival time was 14.2 ± 2.4 months. This was significantly worse than the median survival time of 46.2 ± 3.2 months for the 43 patients (34%) who underwent lobectomy. Another 36 patients (28%) underwent radiation therapy, and their median survival time was 19.9 ± 5.6 months. This survival time was significantly greater than that for the no-treatment group, but the radiation therapy was often for palliative purposes, not curative purposes. The survival results for this single-center study are similar to the data collected on outcomes of patients with stage I lung cancer from 1988 to 2001 that was reported in the Surveillance, Epidemiology, and End Results registry.[42] The median survival time for untreated patients was 14 months; it was 21 months for patients treated with radiation therapy.[42]

The survival benefits of conventional radiation therapy for early-stage NSCLC are small, and a cure should not be expected.[42] Qiao and colleagues[43] evaluated the results of radiation therapy, usually provided to medically inoperable patients, in the treatment of stage I NSCLC from 18 studies. They found that the median survival time from these studies ranged from 18 to 33 months, and that the mean 5-year survival rate was 21 ± 8%. Local control of the cancer and survival seemed to be higher in patients receiving > 60 to 65 Gy of radiation. Newer techniques for administering radiation therapy may improve overall survival with a reduced risk for lung toxicity.[44,45] Three-dimensional conformal radiotherapy may allow the tolerable administration of up to 84 Gy of radiation with potentially improved survival.[46]

These data provide useful background information on the prognosis for patients with stage I and II lung cancer who do not undergo curative-intent surgical resection. Overall survival is poor with no therapy; radiation therapy provides a survival benefit compared to no therapy, but a suboptimal outcome compared to surgery (see "Treatment of Non-small Cell Lung Cancer Stage I and II" chapter). Guidelines for the management of NSCLC strongly advise the use of radiation therapy with or without chemotherapy in patients who choose to not undergo operative resection.[10,12,47,48] However, it should be recognized that the risks of reduced long-term survival due to suboptimal (nonoperative) treatment of early-stage lung cancer are substantial.

Risk of Perioperative Morbidity and Mortality

Morbidity and mortality rates following lung resection have decreased over time.[22] Postoperative cardiopulmonary complications that have historically been noted to be of the greatest concern after lung resection (*eg*, acute hypercapnea, mechanical ventilation lasting > 48 h, arrhythmias, pneumonia, pulmonary emboli, myocardial infarction, and lobar atelectasis requiring bronchoscopy[49]) now may be more effectively managed. For instance, atrial fibrillation occurs in up to 19% of patients following lung cancer resection.[50] The risk of postoperative atrial fibrillation is greater in men > 55 years of age and with a resting heart rate > 72 beats/min.[51] Prophylactic use of either calcium channel blockers or β-blockers will significantly reduce the risk of atrial tachyarrhythmias after thoracic surgery.[52] Newer surgical techniques, such as the use of an intercostal muscle flap to protect the intercostal nerve[53] or video-assisted thoracoscopy,[54] may minimize the postoperative risks of reductions in lung function. However, even with modern anesthetic, surgical, and postoperative care techniques, the risk of perioperative morbidity and mortality following either lobectomy or pneumonectomy are still appreciable. The approach to estimating these risks from underlying pulmonary disease is based on a preoperative physiologic assessment (Fig 1).

Spirometry and Diffusing Capacity

The FEV_1 obtained by spirometry is the most commonly used test to assess the suitability of patients with lung cancer for surgery. Spirometry should be performed according to established methods when the patient is clinically stable and receiving

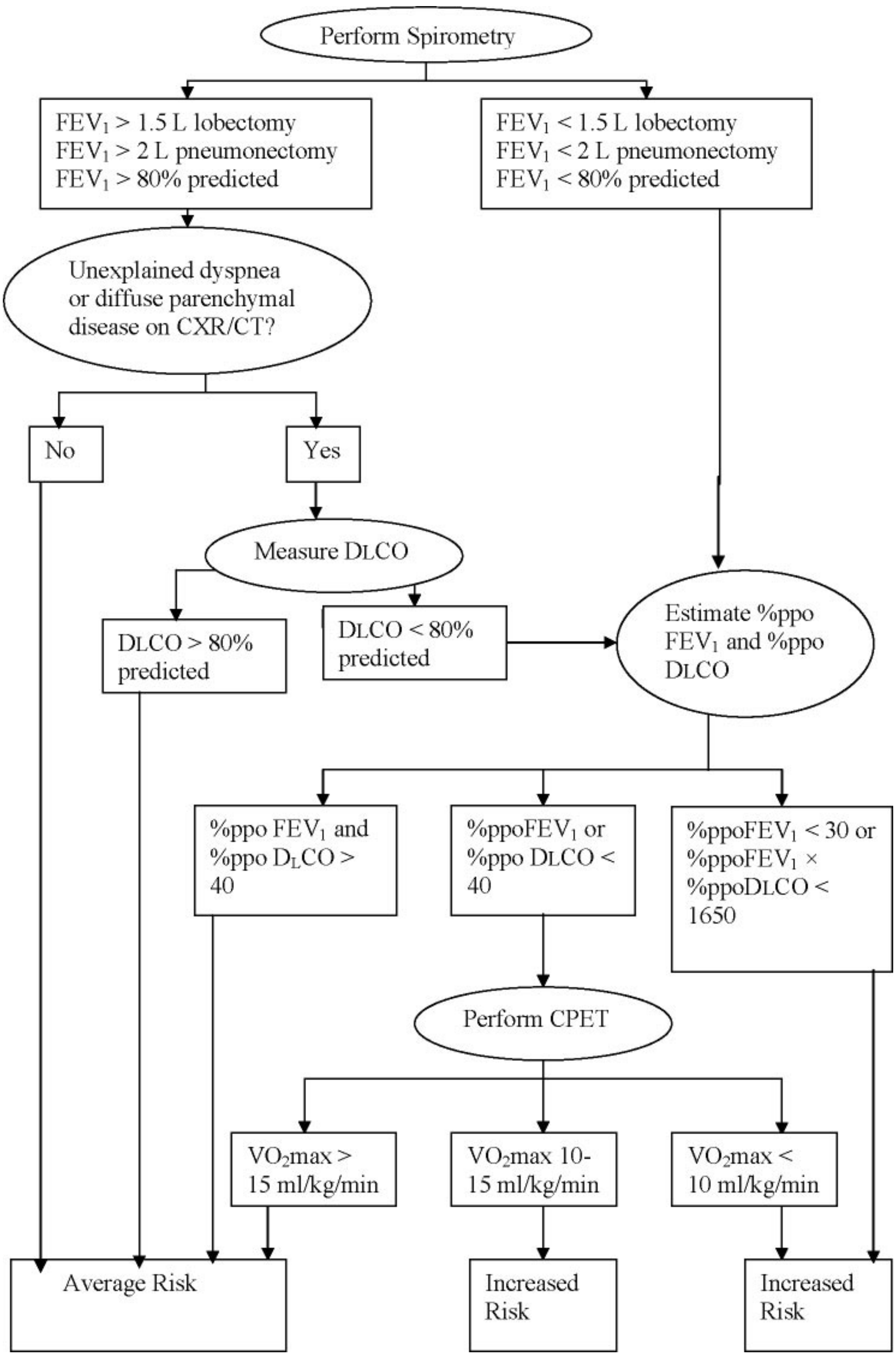

FIGURE 1. Preoperative physiologic assessment of perioperative risk. CXR = chest radiograph.

maximal bronchodilator therapy. The FEV_1 can be expressed in either absolute values or converted into percent predicted values using standard equations. Data from > 2,000 patients in three large series from the 1970s have shown that a mortality rate of < 5% can be achieved if the preoperative FEV_1 is > 1.5 L in patients before undergoing a lobectomy, and > 2 L in patients undergoing a pneumonectomy.[16] Smaller studies[55–57] also agree with these minimal thresholds. Relying on absolute values of FEV_1, though, might create bias against older patients, people of small stature, and women who might tolerate lower levels of lung function. Although it is not possible to recalculate percent predicted values from published data on absolute values, an FEV_1 of > 80% predicted has been accepted as indicating that the patient should be considered suitable to undergo pneumonectomy without further evaluation.[58]

Interest in the diffusing capacity of the lung for carbon monoxide (DLCO) as a useful marker of operative risk was stimulated by Ferguson et al[59] 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 the DLCO, which was also measured. They found the preoperative 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 of < 60% predicted was associated with increased mortality. Also, the risk of pulmonary complications increased twofold to threefold with a DLCO of < 80% predicted.

Spirometry and DLCO measurements should, consequently, be viewed as complementary physiologic tests. If there is evidence of diffuse parenchymal lung disease on radiographic studies or dyspnea on exertion that is thought to be out of proportion clinically to the FEV_1, DLCO should be measured using established methods. In a prospective study of 137 patients with an operable lung cancer, those with an FEV_1 of > 80% predicted, a DLCO of > 80% predicted, and no significant cardiac history were deemed to be suitable to undergo pneumonectomy and survived the operation.[58] In this study, patients with either an FEV_1 or a DLCO of < 80% predicted underwent additional physiologic testing. Further recommended physiologic tests for risk assessment aim to predict remaining lung function following the proposed curative-intent surgical resection.

Recommendations

4. In patients being considered for lung cancer resection, spirometry is recommended. If the FEV_1 is > 80% predicted or > 2 L and there is no evidence of either undue dyspnea on exertion or interstitial lung disease, the patient is suitable for resection including pneumonectomy without further physiologic evaluation. If the FEV_1 is > 1.5 L and there is no evidence of either undue dyspnea on exertion or interstitial lung disease, the patient is suitable for a lobectomy without further physiologic evaluation. Grade of recommendation, 1C

5. In patients being considered for lung cancer resection, if there is evidence of either undue dyspnea on exertion or interstitial lung disease, even though the FEV_1 might be adequate, measuring DLCO is recommended. Grade of recommendation, 1C

6. In patients being considered for lung cancer resection, if either the FEV_1 or DLCO are < 80% predicted, it is recommended that postoperative lung function be predicted through additional testing or calculation. Grade of recommendation, 1C

Predicted Postoperative Lung Function

In patients with a preoperative FEV_1 or DLCO of < 80% predicted, predicted postoperative (PPO) lung function may be calculated by estimating the amount of functioning lung tissue that would be lost with the surgical resection. The methods used for this purpose, including ventilation scans,[56,60–63] perfusion scans,[56,60–66] quantitative CT scans,[67,68] and anatomic estimation, based on counting the number of segments to be removed,[65,69] seem to provide similar quantitative estimates of PPO lung function. The radionuclide perfusion scan method is preferred to estimate the PPO FEV_1 and DLCO after pneumonectomy because the anatomic method tends to underestimate actual postoperative FEV_1 values.[70] The anatomic method is recommended to estimate lung function after a lobectomy.[1,16] However, there are potential advantages to using quantitative CT scan methods. Because this imaging procedure is routinely used for staging purposes, estimating the amount of lung tissue to be lost at surgery from these images may eliminate the need for additional testing (*eg*, perfusion scans) to predict postoperative lung function.[68,71] Quantitative CT scans may also prove to be a more sensitive indicator of diffuse parenchymal lung disease, either emphysema or interstitial lung disease, than the combination of FEV_1 and DLCO.[72] Other techniques in development, such as oxygen-enhanced MRI,[73] may prove to be especially useful in predicting postoperative lung function.

Olsen et al[74] suggested a threshold PPO FEV_1 of 0.8 L as the lower limit for allowing patients to undergo surgical resection. However, Pate and colleagues[75] found that 12 patients with a mean PPO FEV_1 of 0.7 L tolerated thoracotomy for lung cancer resection. This experience might have reflected the resection of less lung tissue than anticipated. However, it demonstrates an important objection to using an absolute value of PPO FEV_1 as a threshold for operability. Using absolute values for PPO lung function suffers from the same objection to their use with preoperative FEV_1. This approach might prevent older patients, people of small stature, and women, all of whom might tolerate a lower absolute FEV_1, from undergoing a potentially curative lung cancer resection. Consequently, the percent PPO (%PPO) values for FEV_1 and DLCO are routinely used instead of absolute values for establishing risk assessment thresholds.

The %PPO FEV_1 after pneumonectomy is calculated using the perfusion method with the following formula:

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

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. The PPO FEV_1 can be converted into the %PPO FEV_1 using standard equations. The PPO and %PPO DLCO postpneumonectomy can be determined using the same formula. Although several studies[56,61,76] have demonstrated good correlation between the actual postoperative FEV_1 and the PPO FEV_1, the %PPO values estimated by the perfusion method may be up to 10% less than the actual measured values 3 months after the patient has undergone resection. This measurement approach, therefore, errs on the side of safety.[65,66,77]

The %PPO FEV_1 after lobectomy is calculated using the anatomic method with the following formula:

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

where the preoperative FEV_1 is taken as the best measured postbronchodilator value, y is the number of functional or unobstructed lung segments to be removed, and z is the total number of functional segments.[71] The PPO FEV_1 can be converted into %PPO FEV_1 using standard equations. The PPO and %PPO DLCO after lobectomy can be calculated using the same formula. The %PPO FEV_1 calculated after lobectomy using the anatomic method is strongly correlated with the actual postoperative FEV_1.[56,69] The anatomic method can also be applied to segmentectomies because lobectomy does not cause a significantly greater loss of function when compared to segmentectomy.[78]

Risk Related to %PPO Lung Function

The perioperative risk increases when the FEV_1 is < 40%PPO.[60,65,66,79,80] Markos et al[60] and Holden et al[79] reported 50% mortality rates (3 of 6 patients and 5 of 10 patients, respectively) when the FEV_1 was < 40%PPO. Wahi et al[80] found a perioperative mortality rate of 16% in patients with an FEV_1 of < 41%PPO vs 3%PPO in those patients with better predicted lung function. Pierce and colleagues[65] found that 5 of 13 patients with an FEV_1 of < 40%PPO died soon after undergoing the operation, and Bolliger et al[66] reported that 2 of 4 patients with similar lung function died of respiratory failure perioperatively. However, others have reported better results in very small numbers of patients with lung function this poor. Olsen et al[81] and Morice and colleagues[82] reported on two and three patients, respectively, who had a preoperative FEV_1 < 40% predicted and survived curative-intent surgery. Beccaria et al[83] described no deaths among seven patients undergoing surgery with an FEV_1 of < 40%PPO, although two patients had prolonged postoperative courses. Nakahara and colleagues[84,85] found, though, an especially high postoperative mortality rate (60% [6 of 10 patients]) when the FEV_1 was < 30%PPO.

Ferguson et al[59] noted that the DLCO, expressed as the %PPO, was a strong predictor of mortality. Others[60,65] have also found that perioperative risk increases substantially with a DLCO of < 40%PPO. Pierce et al[65] suggested that a product of %PPO FEV_1 and %PPO DLCO of < 1,650%PPO might serve as a more discriminating threshold for perioperative risk assessment. Others[86] have made a similar observation.

Although an FEV_1 or DLCO of < 40%PPO indicates an increased risk for perioperative complications, including death, from curative-intent surgery, these patients can successfully undergo lung cancer resection. Ribas et al[86] described a selected group of 65 patients who met these physiologic criteria but still underwent curative-intent lobectomy/wedge resection (n = 44) or pneumonectomy (n = 21). There were only four postoperative deaths (mortality rate, 6.2%) and cardiopulmonary complications in 31 patients (47.7%). Others have also reported[87,88] successful surgical resections of lung cancers in patients with severely reduced FEV_1 and/or DLCO values. Although these studies indicate that lung cancer resection can be performed with an acceptable perioperative risk even in patients with poor lung function reserve, it is prudent to more thoroughly evaluate these patients prior to pulmonary resection.

Recommendations

7. In patients with lung cancer who are being considered for surgery, either an FEV_1 of < 40%PPO or a DLCO of < 40%PPO indicates

an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients undergo exercise testing preoperatively. Grade of recommendation, 1C

8. In patients with lung cancer being considered for surgery, either a product of %PPO FEV_1 and %PPO DLCO of < 1,650%PPO or an FEV_1 of < 30%PPO indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

Cardiopulmonary Exercise Testing

Formal cardiopulmonary exercise testing (CPET) is a sophisticated physiologic testing technique, which includes recording the exercise ECG, the 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. Previous guidelines[1,16] have recommended the use of CPET as the next step in the preoperative risk assessment process in those patients with either FEV_1 or DLCO below 40%PPO.

The risk for perioperative complications has generally, but not always,[86] been reported to be higher in patients with a lower measured $\dot{V}O_2$max. The risk for postoperative mortality can generally be stratified by $\dot{V}O_2$max. Patients with a preoperative $\dot{V}O_2$max of 15 to 20 mL/kg/min can undergo curative-intent lung cancer surgery with an acceptably low mortality rate.[39,49,82,89–92] In several case series,[60,79,81,89] patients with a $\dot{V}O_2$max of < 10 mL/kg/min had a very high risk for postoperative death (Table 2). Bechard and Wetstein[89] reported that 2 of 7 patients with a $\dot{V}O_2$max of < 10 mL/kg/min died in the postoperative period, Olsen et al[81] described deaths in 3 of 11 patients, and Holden and colleagues[79] noted deaths in 2 of 4 patients; however, in another small series[60] there were no deaths among the 5 patients with this very low $\dot{V}O_2$max. A $\dot{V}O_2$max of 10 to 15 mL/kg/min indicates an increased risk of perioperative death[39,60,81,89,90,92–94] (Table 2).

In patients with borderline lung function, $\dot{V}O_2$max may be helpful in further evaluating the risk for perioperative complications. Morice et al[82] reported that eight patients with an FEV_1 of < 33%PPO and a $\dot{V}O_2$max of > 15 mL/kg/min underwent lobectomy with no fatal complications. In patients with both an FEV_1 and a DLCO of < 40%PPO, a $\dot{V}O_2$max of < 15 mL/kg/min indicates a very high surgical risk.[90]

Table 2—*Preoperative Exercise Testing for $\dot{V}O_2$max and Perioperative Mortality*

Study	Deaths/Total (%)
$\dot{V}O_2$max 10–15 mL/kg/min	
Smith et al[93]	1/6 (33)
Bechard and Wetstein[89]	0/15 (0)
Olsen et al[81]	1/14 (7.1)
Walsh et al[39]	1/5 (20)
Bolliger et al[90]	2/17 (11.7)
Markos et al[60]	1/11 (9.1)
Wang et al[94]	0/12 (0)
Win et al[92]	2/16 (12.5)
Total	8/96 (8.3)
$\dot{V}O_2$max < 10 mL/kg/min	
Bechard and Wetstein[89]	2/7 (29)
Olsen et al[81]	3/11 (27)
Holden et al[79]	2/4 (50)
Markos et al[60]	0/5 (0)
Total	7/27 (26)

Pulmonary Artery Pressures and Diffusing Capacity

Measurements of pulmonary arterial pressure during exercise have not proven to be helpful in predicting the patients in whom perioperative complications will develop.[81,86,95] Measuring the DLCO 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.[96]

Stair Climbing and Walking Tests

If CPET were unavailable, then another type of exercise test should be considered. Stair climbing has historically been used as a surrogate CPET. If a patient were able to climb three flights of stairs, they were considered to be a suitable candidate for lobectomy. Pneumonectomy candidates were expected to be able to climb five flights of stairs. This approach was found to correlate with lung function; climbing three flights indicates an FEV_1 of > 1.7 L and climbing five flights of stairs indicates an FEV_1 of > 2 L.[97] Several groups have shown that the ability to climb > 12 to 14 m of stairs, which is approximately three flights of stairs, effectively identifies patients who are at low risk for postoperative complications following usually lobectomy, even though these patients might have had an FEV_1 or DLCO of < 40%PPO.[98,99] However, there are limitations to the usefulness of stair climbing. It has not been performed in a standardized manner. The duration of stair climbing, the speed of ascent, the number of steps per flight, the height of each step, and the criteria for stopping the test have varied from study to study. Patients with, for example, comorbid conditions, such as musculoskeletal disease, neurologic abnormalities, and peripheral vascular insufficiency may be unable to perform the test. In general terms, though, patients who can climb five flights of stairs will have a $\dot{V}O_2$max of > 20 mL/kg/min, and patients who cannot climb one flight of stairs will have a $\dot{V}O_2$max of < 10 mL/kg/min.[100] Brunelli and colleagues[101,102] have found that patients who are unable to perform stair climbing because of comorbid conditions were at an increased risk for perioperative death after lung cancer resection.

Other surrogate tests for CPET are the shuttle walk and the 6-min walk test, but the data on the value of these tests in predicting $\dot{V}O_2$max are limited.[103] The shuttle walk 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,[104] an inability to complete 25 shuttles on two occasions suggested a $\dot{V}O_2$max of < 10 mL/kg/min. For the 6-min walk test, 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.[105]

Desaturation

The shuttle walk and 6-min walk tests may be more effective in identifying patients who desaturate during exercise than is the CPET.[106] The value of this observation, though, is unclear. Greater than 4% desaturation during exercise had been reported[16,60,65,107] to indicate an increased risk for perioperative complications. However, a study[108] from the United Kingdom has reported similar perioperative complication rates for patients who desaturated $> 4\%$ during a shuttle walk and those who did not.

Composite Scores

Investigators have proposed using composite scores to predict perioperative complications. Epstein et al[109] developed the multifactorial cardiopulmonary risk index, an empirically derived score based on points awarded for cardiac and pulmonary risk. There was a strong association between this score and postoperative complications in a group of 42 patients. Birim et al[110] 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 Barrera[111] used regression analysis to develop the predictive respiratory complication quotient, which is based on %PPO FEV_1, %PPO DLCO, and oxygenation. This score also was effective in identifying patients who are at increased risk for perioperative complications. Brunelli et al[112] adapted the physiologic and operative severity score for the enumeration of mortality and morbidity, a score originally used for general surgery issues, to evaluation of post-lung resection problems. They suggested that this score might be a useful method for comparing the complication rates among different institutions. More recently, Ferguson and Durkin[113] developed a simple score based on the FEV_1, DLCO and age of the patient which seems to compare favorably with other scoring systems[109,112] and is easy to administer. Future work is needed to determine whether these scores might replace the current recommended approach based on exercise testing.

Recommendations

9. In patients with lung cancer who are being considered for surgery, a $\dot{V}O_2$max of < 10 mL/kg/min indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. These patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

10. Patients with lung cancer who are being considered for surgery who have a $\dot{V}O_2$max of < 15 mL/kg/min and both an FEV_1 and a DLCO of < 40%PPO are at increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

11. Patients with lung cancer who are being considered for surgery and walk < 25 shuttles on two shuttle walks or less than one flight of stairs are at increased risk for perioperative death and cardiopulmonary complications with standard lung resection. These patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

Arterial Blood Gas Tensions

Historically, hypercapnea ($PaCO_2$, > 45 mm Hg) has been quoted as an exclusion criterion for lung resection.[16,114,115] This recommendation was made on the basis of the association of hypercapnea with poor ventilatory function.[116] The few studies that have addressed this issue, however, have suggest that preoperative hypercapnea is not an independent risk factor for increased perioperative complications. Stein et al[117] showed that hypercapnea was associated with serious postoperative respiratory difficulties in five patients, but there were no deaths. Morice et al[82] reported on three patients with preoperative hypercapnea who survived curative-intent lung cancer surgery. In two series[118,119] of lung cancer patients undergoing surgery, perioperative complications were not higher in patients with preoperative hypercapnea. Preoperative hypoxemia, defined as an arterial oxygen saturation (Sa_{O_2}) of < 90%, has been associated with an increased risk of postoperative complications.[106]

Recommendations

12. In patients with lung cancer who are being considered for surgery, a Pa_{CO_2} of > 45 mm Hg is not an independent risk factor for increased perioperative complications. However, it is recommended that these patients undergo further physiologic testing. Grade of recommendation, 1C

13. In patients with lung cancer who are being considered for surgery, an Sa_{O_2} of < 90% indicates an increased risk for perioperative complications with standard lung resection. It is recommended that these patients undergo further physiologic testing. Grade of recommendation, 1C

Risk of Long-term Pulmonary Disability

Following lung resection, lung function should be expected to decrease. Serial studies have shown that FEV_1 decreases within the first several months following lung cancer resection, but tends to recover to a small extent by 6 months after surgery.[77,120,121] Although the preoperative physiologic evaluation is usually fairly accurate in predicting the PPO FEV_1, some investigators[118,122] have found that the PPO FEV_1 will actually underestimate the eventual postoperative FEV_1. Exercise capacity will also decrease following lung resection. Nezu et al[120] found that, similar to the observations with postoperative changes in FEV_1, the effects on $\dot{V}O_2$max were most evident at 3 months and improved somewhat by 6 months after surgery. Decreases of up to 13% in $\dot{V}O_2$max and work capacity have been described following a lobectomy, and between 20% and 28% after a pneumonectomy.[77,120,123] Surprisingly, the most common limiting symptom in postoperative exercise studies[77,120,123] has been leg discomfort, rather than dyspnea. Bolliger et al[77] found that exercise was limited by leg muscle fatigue in 53% of patients preoperatively. This was not altered after lobectomy, but there was a switch to dyspnea as the limiting factor after pneumonectomy (3 months after resection, 61% of patients; 6 months after resection, 50% of patients).

Early investigators in this field suggested that a postoperative FEV_1 of < 0.8 L would result in an unacceptable incidence of hypercapnea and pulmonary disability.[74] Unfortunately, there are few data available describing changes in quality of life following curative-intent lung resection. A cross-sectional survey[124] examined respiratory symptoms and quality of life in 142 long-term survivors of NSCLC. 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 frequently described. The majority of these patients (63%) described dyspnea when they hurried, 32% had to stop to catch their breath when walking, and 11% were so breathless that they could not leave their house. Dyspnea occurred significantly more often in patients with restrictive and/or obstructive ventilatory abnormalities, but the use of bronchodilators to control dyspnea was not well described. Dyspnea had a significant impact on multiple dimensions of quality of life, such as physical functioning, physical role limits, and social functioning. The findings in this study point out the need for more information on the interplay between changes in lung function (including both FEV_1 and DLCO) and respiratory symptoms, and quality of life following curative-intent surgical resection.

Methods To Reduce Perioperative Risks and Long-term Pulmonary Disability

Lung Volume Reduction Surgery

Lung volume reduction surgery (LVRS) for patients with severe emphysema has been shown in a large prospective, randomized, controlled trial[125] to provide a survival advantage in selected patients with predominantly upper lobe emphysema and low exercise capacity. Patients with an FEV_1 of < 20% predicted and either homogeneous emphysema or a DLCO of < 20% predicted do poorly with LVRS.[126] Anecdotal experience has shown that the lung resected during LVRS occasionally contained unsuspected lung cancers.[127,128] Multiple case series[129–139] have suggested 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.

McKenna et al[129] reported 11 cases of lung cancer (3%) in their group of 325 patients who were referred for LVRS. These 11 patients had an average preoperative FEV_1 of 0.65 L (FEV_1 range, 12 to 29% predicted). None of these patients would have been acceptable candidates to undergo lung cancer resection based on the traditional criteria, but all underwent combined LVRS and resection of stage I lung cancers by either lobectomy or wedge resection. There were no deaths or major complications; lung function and exercise capability were improved postoperatively. Pompeo et al[137] described the outcomes of 16 patients who had undergone both LVRS and curative-intent surgical resection of NSCLC. Postoperatively there were significant improvements in FEV_1 and quality of life. Encouraging long-term survival results were also noted.

Although indications for combined LVRS and lung cancer resection are still evolving, the most promising candidates would be patients who have a cancer in the upper lobe that is also affected by emphysema and who have a DLCO and FEV_1 of $> 20\%$ predicted. However, Mentzer and Swanson[140] have suggested a more aggressive approach. They consider LVRS for patients with severe dyspnea, hypoxia and hypercapnea, and poor lung function (including patients with an FEV_1 of $< 20\%$ predicted), provided there was heterogeneous emphysema and some potential for the recruitment of relatively preserved lung tissue.

Smoking Cessation

A retrospective analysis[141] of 300 patients undergoing lung cancer surgical resection found that postoperative pulmonary complication rates for patients who had quit smoking > 2 months prior to undergoing the operation were similar to those who had quit within 2 months of the surgery (19% vs 23%, respectively; $p > 0.05$). Another retrospective study[142] of 288 consecutive patients undergoing pulmonary surgery suggested that smoking abstinence of at least 4 weeks may be associated with reduced perioperative respiratory complications. Prospective, controlled trials are needed to more clearly define the effect that smoking cessation preoperatively might have on reducing perioperative problems. However, smoking cessation should be strongly encouraged at the time of diagnosis of lung cancer because it might reduce the development of metachronous tumors (see the chapter on "Follow-up and Surveillance").

Pulmonary Rehabilitation

As yet, there are no robust data to recommend the routine use of preoperative pulmonary rehabilitation for patients with lung cancer. However, there is some information suggesting that pulmonary rehabilitation might be helpful in preparing patients for LVRS.[143] In the National Emphysema Treatment Trial,[143] all patients underwent pulmonary rehabilitation prior to randomization to either receive medical treatment or undergo LVRS. Pulmonary rehabilitation provided important benefits in dyspnea, quality of life, and exercise ability. Although there was no comparison group for the pulmonary rehabilitation portion of the study, overall, rehabilitation was thought to play an important role in preparing patients for LVRS. The effects of pulmonary rehabilitation should be evaluated in future studies of patients being prepared for both lung cancer resection and LVRS.

Recommendations

14. In patients with very poor lung function and a lung cancer in an area of upper lobe emphysema, it is recommended that combined LVRS and lung cancer resection be considered if both the FEV_1 and the DLCO are > 20% predicted. Grade of recommendation, 1C

15. It is recommended that all patients with lung cancer be counseled regarding smoking cessation. Grade of recommendation, 1C

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 for perioperative complications, including death, and long-term pulmonary disability after lung cancer resection. A careful preoperative physiologic assessment will be useful to identify those patients who are 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 for this disease.

Summary of Recommendations

1. It is recommended that patients with lung cancer be assessed for curative surgical resection by a multidisciplinary team, which includes a thoracic surgeon specializing in lung cancer, a medical oncologist, a radiation oncologist, and a pulmonologist. Grade of recommendation, 1C

2. It is recommended that patients with lung cancer not be denied lung resection surgery on the grounds of age alone. Grade of recommendation, 1B

3. It is recommended that patients with lung cancer who are being evaluated for surgery and have major factors for increased perioperative cardiovascular risk have a preoperative cardiologic evaluation. Grade of recommendation, 1C

4. In patients being considered for lung cancer resection, spirometry is recommended. If the FEV_1 is > 80% predicted or > 2 L and there is no evidence of either undue dyspnea on exertion or interstitial lung disease, the patient is suitable for resection including pneumonectomy without a further physiologic evaluation. If the FEV_1 is > 1.5 L and there is no evidence of either undue dyspnea on exertion or interstitial lung disease, the patient is suitable for a lobectomy without further physiologic evaluation. Grade of recommendation, 1C

5. In patients being considered for lung cancer resection, if there is evidence of either undue dyspnea on exertion or interstitial lung disease, even though the FEV_1 might be adequate, measuring D_{LCO} is recommended. Grade of recommendation, 1C

6. In patients being considered for lung cancer resection, if either the FEV_1 or D_{LCO} are < 80% predicted, it is recommended that postoperative lung function be predicted through additional testing. Grade of recommendation, 1C

7. In patients with lung cancer who are being considered for surgery, either an FEV_1 of < 40%PPO or a D_{LCO} of < 40%PPO indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients undergo exercise testing preoperatively. Grade of recommendation, 1C

8. In patients with lung cancer who are being considered for surgery, either a product of %PPO FEV_1 and %PPO D_{LCO} of < 1,650%PPO or an FEV_1 of < 30%PPO indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

9. In patients with lung cancer being considered for surgery, a $\dot{V}O_2$max of < 10 mL/kg/min indicates an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. These patients should be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

10. Patients with lung cancer being considered for surgery who have a $\dot{V}O_2$max of < 15 mL/kg/min and both an FEV_1 and a D_{LCO} of < 40%PPO are at an increased risk for perioperative death and cardiopulmonary complications with standard lung resection. It is recommended that these patients be counseled about nonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

11. Patients with lung cancer being considered for surgery who walk < 25 shuttles on two shuttle walks or less than one flight of stairs are at increased risk for perioperative death and cardiopulmonary complications with standard lung resection. Thesepatients should be counseled aboutnonstandard surgery and nonoperative treatment options for their lung cancer. Grade of recommendation, 1C

12. In patients with lung cancer who are being considered for surgery, a Pa_{CO_2} of > 45 mm Hg is not an independent risk factor for increased perioperative complications. However, it is recommended that these patients undergo further physiologic testing. Grade of recommendation, 1C

13. In patients with lung cancer who are being considered for surgery, an Sa_{O_2} of < 90% indicates an increased risk for perioperative complications with standard lung resection. It is recommended that these patients undergo further physiologic testing. Grade of recommendation, 1C

14. In patients with very poor lung function and a lung cancer in an area of upper lobe emphysema, it is recommended that combined LVRS and lung cancer resection be considered if both the FEV_1 and the Dlco are > 20% predicted. Grade of recommendation, 1C

15. It is recommended that all patients with lung cancer be counseled regarding smoking cessation. Grade of recommendation, 1C

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