Definition and assessment of high risk in patients considered for lobectomy for stage I non–small cell lung cancer: The American Association for Thoracic Surgery expert panel consensus document

Arjun Pennathur, MD, Co-Chair Writing Committee, Alessandro Brunelli, MD, Gerard J. Criner, MD, Homa Keshavarz, PhD, Peter Mazzone, MD, Garrett Walsh, MD, James Luketich, MD, Michael Liptay, MD, Q. Eileen Wafford, MSt, MLIS, Sudish Murthy, MD, PhD, M. Blair Marshall, MD, Betty Tong, MD, Michael Lanuti, MD, Andrea Wolf, MD, MPH, Brian Pettiford, MD, Billy W. Loo, Jr, MD, PhD, Robert E. Merritt, MD, Gaetano Rocco, MD, Matthew Schuchert, MD, Thomas K. Varghese, Jr, MD, MPH, and Scott J. Swanson, MD, Co-Chair Writing Committee, The AATS Clinical Practice Standards Committee: Thoracic Surgery

ABSTRACT

Objective: Lobectomy is a standard treatment for stage I non–small cell lung cancer, but a significant proportion of patients are considered at high risk for complications, including mortality, after lobectomy and might not be candidates. Identifying who is at risk is important and in evolution. The objective of The American Association for Thoracic Surgery Clinical Practice Standards Committee expert panel was to review important considerations and factors in assessing who is at high risk among patients considered for lobectomy.

Methods: The American Association for Thoracic Surgery Clinical Practice Standards Committee assembled an expert panel that developed an expert consensus document after systematic review of the literature. The expert panel generated a priori a list of important risk factors in the determination of high risk for lobectomy. A survey was administered, and the expert panel was asked to grade the relative importance of each risk factor. Recommendations were developed using discussion and a modified Delphi method.

Results: The expert panel survey identified the most important factors in the determination of high risk, which included the need for supplemental oxygen because of severe underlying lung disease, low diffusion capacity, the presence of frailty, and the overall assessment of daily activity and functional status. The panel determined that factors, such as age (as a sole factor), were less important in risk assessment.

Conclusions: Defining who is at high risk for lobectomy for stage I non–small cell lung cancer is challenging, but remains critical. There was impressive strong consensus on identification of important factors and their hierarchical ranking of perceived risk. The panel identified several key factors that can be incorporated in risk assessment. The factors are evolving and as the population ages, factors such as neurocognitive function and frailty become more important. A minimally invasive approach becomes even more critical in this older population to mitigate risk. The determination of risk is a clinical decision and judgment, which should also take into consideration patient perspectives, values, preferences, and quality of life.

From the *Department of Cardiothoracic Surgery, University of Pittsburgh School of Medicine, University of Pittsburgh Medical Center, and UPMC Hillman Cancer Center, Pittsburgh, Pa; †Department of Thoracic Surgery, St. James University Hospital, Leeds, United Kingdom; ‡Department of Thoracic Medicine and Surgery, Lewis Katz School of Medicine at Temple University, Philadelphia, Pa; §The American Association for Thoracic Surgery, Beverly, Mass; Departments of "Pulmonology and "Thoracic and Cardiovascular Surgery, Cleveland Clinic, Cleveland, Ohio; ¶Department of Thoracic Surgery, University of Texas M.D. Anderson Cancer Center, Houston, Tex; ‡Department of Cardiovascular and Thoracic Surgery, Rush University Medical Center, Chicago, Ill; ‡Division of Thoracic Surgery, Brigham and Women’s Hospital, Boston, Mass; ‡Department of Thoracic Surgery, Duke University Hospital, Durham, NC; †Department of Thoracic Surgery, Massachusetts General Hospital, Boston, Mass; The Icahn School of Medicine at Mount Sinai and Mount Sinai Hospital, New York, NY; ¶Section of Cardiothoracic Surgery, Ochsner Health System, New Orleans, La; ¶Department of Radiation Oncology & Stanford Cancer Institute, Stanford University School of Medicine, Stanford, Calif; ¶Division of Thoracic Surgery, The Ohio State University-Wexner Medical Center, Columbus, Ohio; ¶Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; ¶Division of Thoracic Surgery, University of Utah, Huntsman Cancer Institute, Salt Lake City, Utah; and ¶Division of Thoracic Surgery, Harvard Medical School and Brigham and Women’s Hospital, Boston, Mass.

Funded by The American Association for Thoracic Surgery.
The standard treatment for stage I non–small cell lung cancer (NSCLC) is lobectomy with systematic mediastinal lymph node dissection. It has been recommended that preoperative assessment should primarily focus on cardiopulmonary function because respiratory complications are among the most frequent causes of perioperative morbidity.\(^1\) A significant proportion of patients with early-stage NSCLC might not be candidates for curative lobectomy or are considered at high risk while undergoing lobectomy because of frailty, pulmonary comorbid conditions, nonpulmonary comorbid conditions, or other factors.

Although lobectomy is increasingly performed with less invasive techniques, alternative therapies such as sublobar resection, ablation or stereotactic ablative radiotherapy (SABR), also known as stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT), have emerged as options for patients who are considered at high risk for complications after lobectomy. Although cardiopulmonary evaluation has been the primary factor used for risk assessment, the relative importance of other potential risk factors, such as frailty, has increased. Defining which patients are at high risk for complications from lobectomy is important and is a process in evolution. The objective of The American Association for Thoracic Surgery (AATS) Clinical Practice Standards Committee (CPSC) expert panel was to review the important considerations and factors in the definition and assessment of high risk in patients considered for lobectomy for stage I NSCLC.

The main objective of this expert consensus document from The AATS CPSC was to systematically review the literature and update how stage 1 NSCLC patients should be evaluated and what factors should determine who will be considered high risk when planning a standard lobectomy for stage I NSCLC. It is hoped that this assessment might serve as a useful reference for practitioners who are considering therapy for stage I NSCLC and might also help inform patients with regard to treatment choices.

**METHODS**

**The AATS CPSC and Assembly of a Task Force of Experts**

The CPSC co-chairs and members of the committee were appointed by The AATS. The CPSC selected the topic for definition and assessment of patients with stage I NSCLC at high risk when undergoing lobectomy and treatment options for this high-risk group. The co-chairs of the

Dr. Arjun Pennathur, MD, Co-Chair, a
Dr. Scott J. Swanson, MD, Division of Thoracic Surgery, Harvard Medical School and Brigham and Women’s Hospital, 75 Francis St, Boston, MA 02115 (E-mail: sjswanson@bwh.harvard.edu).

Drs Brunelli and Criner contributed equally to this work. Drs Pennathur and Swanson were co-chairs of the writing group and contributed equally to this work.
Consensus for the expert consensus document. Initially, the co-chairs, after discussion with the writing group and expert panel, generated a priori a list of important risk factors in determining if a patient is high risk during lobectomy. The expert consensus panel identified a priori these potential important risk factors on the basis of their experience, expertise, and interpretation of the medical literature. The systematic review of the literature was used to identify which factors were considered important risk factors for decision-making in the target population. There were also several additional potential risk factors identified by the panel. After the identification of these potentially important risk factors, the second step was for the panel to rank the relative importance of the risk factors. A survey to grade the relative importance of risk factors was sent to the expert panel, and recommendations were developed using a modified Delphi method.\(^1\) The expert consensus panel was asked to rank the importance of each risk factor on a scale from 1 to 10 according to their importance in decision-making (1 being least important and 10 being most important or critically important). This initial round of voting was used to rank the importance of the risk factors and develop the consensus statements evaluated in the second round of voting. For the second round of voting, a 5-point Likert scale was used (graded as: 1 = strongly disagree; 2 = disagree; 3 = neutral; 4 = agree; 5 = strongly agree).

A predetermined threshold of a minimum of 75% agreement (“agree” or “strongly agree”) was required for the consensus statements to be accepted.\(^1\) Consensus was developed with discussion and a modified Delphi method. These discussions were performed through online or teleconference meetings.

**SUMMARY OF SYSTEMATIC REVIEW**

**Assessment of Risk in Patients Undergoing Evaluation for Treatment of Stage I Lung Cancer**

**I. Pulmonary function.** Assessment of pulmonary function is clearly important during the preoperative evaluation of patients considered for surgical resection to identify perioperative risks from underlying lung disease. Spirometry with the evaluation of forced expiratory volume in 1 second (FEV1), predicted postoperative (ppo) FEV1, diffusion capacity of the lung for carbon monoxide (DLCO), and ppoDLCO are important tests in the evaluation of pulmonary function. There have been several studies that show the importance of FEV1, with a low FEV1 <30% predictive of an increase in morbidity.\(^3\) DLCO is also strongly associated with postoperative pulmonary morbidity after lung resection.\(^3\) A particular circumstance, although not applicable to stage I NSCLC, is the use of induction therapy before lung resection. Takeda and colleagues\(^5\) observed a significant decline (21%) in DLCO after induction therapy and reported that ppoDLCO alone was a significant independent predictor of pulmonary morbidity. Similarly, other studies have reported that percentage decrease in DLCO after induction therapy might predict pulmonary complications.\(^7\) Preinduction and postinduction evaluation of DLCO can be considered in the risk assessment of these patients. Guidelines on preoperative functional assessment from the European Respiratory Society (ERS)/European Society of Thoracic Surgeons (ESTS) and the American College of Chest Physicians (ACCP) proposed ppoDLCO (<30%) and the maximum volume of oxygen consumed (VO2 max; <10 mL/kg/min) to define a
patient as high risk for lobectomy. An overview of previously published guidelines and thresholds for identification of high-risk individuals on the basis of pulmonary function and cardiopulmonary testing are summarized as we discuss the status of current guidelines in the following sections.

High-resolution chest computed tomography imaging. Estimation of postoperative pulmonary function is typically obtained using quantitative ventilation/perfusion scans. High-resolution chest computed tomography (HRCT) imaging can also be used quantitatively to estimate pulmonary function and has been used to estimate perioperative risk in patients undergoing lung cancer surgery. In a study by Ueda and colleagues, total lung volume, emphysematous lung volume, and regression equations for FEV1 and forced vital capacity (FVC) were developed on the basis of HRCT-derived variables. Regression-based FVC and FEV1 derived from HRCT data correlated with physiologically measured FVC and FEV1 suggesting that HRCT imaging could be used to estimate preoperative pulmonary function in patients unable to perform spirometry. Postoperative pulmonary morbidity has been reported to be greater in patients who undergo lobectomy or segmentectomy with larger volumes of emphysema and patients with lower lung density measured using preoperative HRCT.

Additionally, using the standard calculation of postoperative FEV1 might be misleading in patients with concomitant emphysema. Edwards and colleagues performed anatomic lobectomy for NSCLC in 14 patients with a postoperative predicted FEV1 <40% who had an emphysematous target lobe that received <10% of overall perfusion and had evidence of hyperinflation on imaging assessment. No significant reduction in postoperative FEV1 was observed 3 months after lobectomy. More recently, radiomic approaches have been explored for quantification of lung function and in the prediction of pulmonary function.

II. Cardiopulmonary exercise testing. A variety of exercise tests have been used to assess preoperative risk. These include some low-technology tests, such as 6-minute walk tests, exercise desaturation, and stair-climbing tests, and high-technology tests including formal cardiopulmonary exercise testing (CPET). A cut point value of 500 m on a 6-minute walk test has been reported to identify patients at an increased risk of postoperative complications of atrial fibrillation and increased transfusion requirements after lobectomy. A greater decrease in oxygen saturation and lower level of oxygen saturation measured using pulse oximetry (SpO2) during the 6-minute walk test predicted the need for postoperative oxygen therapy and greater surgical morbidity and 90-day mortality. A >4% decrease in SpO2 and <89% to 91% nadir during the 6-minute walk test was associated with the need for postoperative supplemental oxygen, surgical morbidity, and 90-day mortality.

A stair-climbing test might also produce a significant decrease in SpO2 and an increase in pulse rate. A decrease in SpO2 after 40 steps and a shorter duration of test performance were associated with increased postoperative complications after lobectomy. The altitude reached during the stair-climbing test has been shown to be associated with increased cardiopulmonary complications, mortality, and costs. Patients who climbed less than 12 m had significantly increased cardiopulmonary complications, mortality, and costs compared with those who were able to climb more than 22 m.

High-technology tests include formal CPET with electrocardiographic monitoring as well as measuring heart rate response, minute ventilation, oxygen uptake, and maximal oxygen consumption. A decreased peak oxygen uptake of <61% of the predicted maximum during symptom-limited cardiopulmonary testing might identify patients more likely to experience a postoperative complication within 30 days of pulmonary resection. Caution should be taken in interpreting these values in patients taking β-blocker therapy, however, because chronotropic intolerance might limit maximum cardiopulmonary performance.

Another study compared the effect of VO2 max using ACCP guidelines and the National Emphysema Treatment Trial (NETT) patient population with non–upper lobe-predominant emphysema. When VO2 max values in participants with non–upper lobe-predominant emphysema in the NETT were retrospectively compared with the ACCP guideline VO2 max values, the NETT data suggested a lower postoperative risk than expected in patients with a high-risk designation. The study suggested that potential curative resection is feasible in selected high-risk patients. However, there are differences between the patient population in the NETT trial and patients who typically present with stage I NSCLC, and caution should be exercised in the use of NETT trial data in the selection of stage I NSCLC patients for lung resection.

Another measure to consider in risk assessment is the minute ventilation-to-carbon dioxide output (VE/VCO2) ratio. This is a measure of ventilator efficiency and is obtained during CPET. In a study of 225 patients who underwent lobectomy, the strongest predictor of respiratory complications was VE/VCO2 slope (P = .004) after adjusting for other variables. Further, VE/VCO2 slope was a better predictor of respiratory complications than peak volume of O2, and this measure was relatively independent of VO2 max and chronic obstructive pulmonary disease (COPD) in prediction of outcomes.

Cardiac evaluation is an important component of risk assessment for patients who are being evaluated for lung resection. A Thoracic Revised Cardiac Risk Index (ThRCRI) incorporates a weighted score assigned for patients on the basis of history of ischemic heart disease, cerebrovascular disease, renal function, and extent of lung.
resection.\textsuperscript{24} On the basis of the score, patients were then stratified into 4 groups (A-D), from low risk to high risk. This score was validated in a study of 4625 patients from the American College of Surgeons National Surgical Quality Improvement Program data set, for which increasing complications were noted in classes C and D, compared with classes A and B.\textsuperscript{25} Ferguson and colleagues\textsuperscript{26} evaluated the ThRCRI in 26,085 patients from the Society of Thoracic Surgeons database and reported that this risk score significantly stratified major postoperative cardiovascular events after major lung resection. These investigators concluded that the ThRCRI scoring system might be helpful in identifying patients who would benefit from additional preoperative evaluation and from closer perioperative monitoring.

\section*{III. Overview of previously published guidelines and statements.} During the past decade, there have been at least 2 practice guidelines and an expert statement assembled and published by professional societies focused on the definition and preoperative workup of high-risk candidates prior to anatomic lung resection.\textsuperscript{1,13,19} Although consensus was achieved on some points, there were differences in some of the parameters recommended for determining whether a patient was considered high-risk in both guidelines.

The ERS/ESTS guidelines and the ACCP guidelines highlight the importance of a preliminary cardiac risk stratification and management of any underlying cardiac status that might increase perioperative risk.\textsuperscript{1,5} This is largely in agreement with the American College of Cardiology and American Heart Association guidelines for perioperative cardiologic evaluation for noncardiac surgery.\textsuperscript{27} If the patient is deemed to be at low cardiac risk for surgery, the team can then proceed to a formal preoperative evaluation of pulmonary function, which is based on 3 main parameters: pulmonary function testing with spirometry and systematic measurement of the DLCO, calculation of the predicted postoperative lung function on the basis of the volume of lung to be resected (ppoFEV1 and ppoDLCO), and exercise tests in patients with reduced pulmonary function.

The definition of which patients are considered high risk during lobectomy on the basis of pulmonary function varies in these 2 guidelines. In the European guidelines, patients are deemed to be at prohibitive risk for lobectomy if either FEV1 or DLCO is lower than 80\% of predicted values and VO2 max measured with CPET is <10 mL/kg/min or <35\% of predicted value.\textsuperscript{3} However, patients with split lung function that is 30\% to 60\% of predicted values who perform poorly in low-technology exercise tests (ie, shuttle-walk test distance <400 m or stair climb height <22 m), and proceed to formal CPET with VO2 max <10 mL/kg/min are also regarded as high risk. According to the ACCP task force, high-risk patients might have a risk of mortality >10\% after anatomic resection. These patients should be counseled about alternative surgical options, such as sublobar resection, or nonsurgical options.\textsuperscript{3}

Finally, in the ACCP and Society of Thoracic Surgeons consensus statement on the evaluation and management of high-risk patients with early-stage lung cancer, Donington and colleagues\textsuperscript{7} suggested the same tests and measurements to define a lung resection candidate as high risk for lobectomy. In particular, they suggested that DLCO should be measured in all patients regardless of their FEV1, because these 2 parameters are often not correlated, and a large proportion of patients with normal FEV1 might have a reduced DLCO. In addition, they acknowledged the importance of CPET and VO2 max in identifying patients at prohibitive risk for surgery. Notably, patients with ppoFEV1 or ppoDLCO <40\% and VO2 max <10 mL/kg/min should be regarded as high risk when considering a major lung resection. However, an important consideration stated in the consensus statement was that although there are general thresholds to identify patients at prohibitive risk for surgery, these algorithms and values should be periodically revised and updated in light of the improvements in perioperative care, and surgical and anesthetic techniques.

\section*{IV. Other factors to consider in the assessment of perioperative risk.} 1. Effects of underlying lung disease. The presence of COPD, defined as a FEV1/FVC <0.70, is associated with the increased need for tracheostomy and development of pneumonia and decreased disease-free and overall survival compared with patients without COPD in patients who undergo lobectomy with lymph node dissection for stage IA lung cancer.\textsuperscript{28} Previous studies suggest that a FEV1 <35\% predicted in COPD patients predicts a mortality of 10\% per year (estimated 5-year survival of 50\%).\textsuperscript{1} Others have reported that in addition to older age, male sex, and the extent of surgical procedure, the degree of air trapping measured by the residual volume/total lung capacity ratio might also contribute to increased operative hospital length of stay.\textsuperscript{29} This has importance because air trapping might be a modifiable risk by intervening with more aggressive bronchodilator therapy. An increased pulmonary complication rate in patients with COPD might be because of either a decreased lung reserve before lung resection or decreased reserve after resection or SABR (SRS/SBRT) of the tumor and regional functional lung
tissue. A review of 6 studies focused on short-term changes in lung function after lobectomy for lung cancer in 195 patients with lung function assessed before and 3 to 6 months after surgery showed an average loss of FEV1 of 0.11 L (range, 0.33-0.09 L).30 A decline in DLCO has also been noted after SABR/SRS/SBRT. A decrease in DLCO of 1.11 mg/min/mm Hg per year has been associated with SABR/SRS/SBRT in patients with moderate to severe COPD treated for stage I NSCLC.31 Patients with idiopathic pulmonary fibrosis also have an increased risk for complications after resection.1

Patients who present with lung cancer and underlying interstitial lung disease present a unique challenge when considering surgical resection because acute exacerbations of interstitial lung disease might be precipitated by the surgical resection. A risk score to predict acute exacerbations of interstitial pneumonia has been proposed that includes a history of previous acute exacerbations, male sex, use of preoperative systemic steroids, low vital capacity, and higher levels of serum sialylated carbohydrate antigen.32 Prospective validation of this score is necessary to determine its validity.

2. Pulmonary hypertension. The presence of pulmonary hypertension (PH) has been evaluated as a predictor of outcomes after noncardiac surgery. Kaw and colleagues33 evaluated 173 patients who had right heart catheterization and noncardiac surgery in a retrospective study. In this cohort, 55% of patients had PH. These investigators reported that patients with PH had a significantly increased risk of congestive heart failure, hemodynamic instability, sepsis, and respiratory failure. Ramakrishna and colleagues34 in another study of morbidity of noncardiac surgery in patients with PH reported a higher morbidity in thoracic surgery patients (61.5%) compared with patients who underwent gynecologic/urology or plastic/dermatologic/breast surgical procedures. However, Wei and colleagues,35 in a study of 19 selected patients with PH who underwent lobectomy, did not find the presence of PH to be a factor associated with a significantly increased incidence of adverse outcome. More recently, some investigations have shown a correlation of pulmonary artery size, determined using computed tomography imaging, and the presence of PH. Shen and colleagues,36 in a meta-analysis, reported an estimated sensitivity of 0.79 and specificity of 0.83 for main pulmonary artery diameter measurement in the diagnosis of PH. Asakura and colleagues37 reported that the presence of pulmonary artery enlargement on computed tomography imaging was a predictor of postoperative complications in a series of 237 patients who underwent lung resection. Lobectomy or bilobectomy was performed in 185 patients. Kneuertz and colleagues38 evaluated the effect of pulmonary artery size on complications in 736 patients after lobectomy. The surgical side pulmonary artery diameter was an independent factor associated with major complications after lobectomy.

3. Current tobacco use. Current smoking plus severe air flow obstruction might adversely affect surgical outcomes.39 Postoperative complications (eg, prolonged air leak, pneumonia, tracheostomy, and atelectasis) were significantly higher and relapse-free survival significantly lower in currently smoking Gold stage 2/3 patients.40

4. Age. In a review of the National Cancer Database, age, treatment at a community center, and a higher comorbidity index were predictive of higher mortality rates.41 In patients older than 75 years, the extent of surgical resection was also predictive of a higher 30-day mortality rate. In another study of patients older than 75 years who underwent lobectomy, performance status, coronary heart disease, history of stroke, restrictive lung disease, male sex, and the presence of interstitial pneumonia were found to be associated with increased postoperative complications.42 Curative resections are performed less often in elderly patients, and lobectomies are performed more commonly in younger patients, which confers a significantly greater survival benefit. However, survival benefits might not be greater in patients older than 71 years compared with limited resection.43

Lobectomy via video-assisted thoracoscopic surgery (VATS) in patients at high risk (eg, age older than 75 years, FEV1 <50% predicted, DLCO <50% predicted, history of coronary heart disease) has been reported to have a low rate, but not negligible incidence, of major complications compared with VATS lobectomy in low-risk patients. The 30-day or in-hospital mortality rates were similar in the 2 groups.44 The definition of the high-risk patient group for lung cancer resection therapy has been debated. Although a high-risk designation did not confer a greater overall risk for complications, older age and the presence of heart disease conferred a greater risk for complications; female sex was protective.45 In a meta-analysis that compared VATS and open lobectomy it was suggested that VATS lobectomy is associated with lower risk for pulmonary morbidity in patients with compromised lung function.46

Age by itself is not an exclusion for consideration of surgical treatment. Okami and colleagues37 reported satisfactory long-term outcomes and low mortality rates with surgical resection in 367 patients, 82 years of age or older with stage I lung cancer. The presence of comorbidities and extent of resection were more important than age in influencing outcome.

5. Comorbidities. Lung cancer most commonly affects an older patient population with significant smoking exposures—2 factors that increase the prevalence of comorbid medical conditions.38 In patients with lung cancer who are candidates for surgical resection, the nature and extent of comorbid conditions might heavily influence patient outcomes.49,50 In a retrospective study of 400 patients with...
NSCLC who underwent surgical resection, postoperative complications were identified in 39% of patients, of whom 19% had severe complications as defined by the ESTS.\textsuperscript{51} There was significantly higher risk of complications in patients with cardiac arrhythmias, COPD, and diabetes mellitus. Serious complications were observed more often in patients older than 65 years of age with coexisting comorbid conditions, especially hypertension.

6. Frailty. The importance of frailty in operative risk assessment has been increasingly recognized in recent years. Kaneda and colleagues\textsuperscript{52} assessed the predictive value of frailty for postoperative complications in lung cancer patients with various risk indicators, namely FEV1, ppo-FEV1, Zubrod performance status, the American Society of Anesthesiologists score, and risk scores using the Japan National Clinical Database and the European Thoracic Surgeons database. Frailty was defined by unintentional weight loss, fatigue, poor grip strength, inactivity, and slow walking speed. Although the risk models based on societal databases were reported to have a significant predictive value, frailty was not a significant predictor of postoperative complications.\textsuperscript{52}

In a recent analysis from the American College of Surgeons National Surgical Quality Improvement Program database, Wan and colleagues\textsuperscript{53} reported that the Risk Analysis Index was not an effective predictor of 30-day mortality in high-risk operations. However, Hirpara and colleagues\textsuperscript{54} reported that a modified frailty index might be useful in predicting outcomes. Although there appears to be conflicting data on the association of frailty with postoperative complications, one of the important determinants of outcome is the failure to rescue (FTR) after a major complication has occurred. In a recent study on outcomes after cardiac surgery, the incidence of FTR was significantly higher in frail patients.\textsuperscript{55} The association of frailty on FTR after thoracic surgical operations requires further study.

7. Nutritional status. Nutritional status might also affect postoperative recurrence and death. Shoji and colleagues\textsuperscript{56} used the Controlling Nutritional Status (CONUT) score, which has been used to assess immune-related nutritional conditions in patients with cancers of the digestive tract, to investigate the role of preoperative CONUT score to predict survival after curative surgery in 138 patients with pathologic stage I non–small cell cancer. Patients with a high CONUT score had significantly shorter recurrence-free survival, cancer-specific survival, and overall survival. Poor nutritional status with history of weight loss and decrease of preoperative serum albumin levels have been reported as associated with an increased risk of pulmonary complications.\textsuperscript{57} The evaluation of body mass index (BMI) might be useful in risk assessment. Fiorelli and colleagues\textsuperscript{58} examined the influence of BMI and weight loss in a cohort of 117 patients who underwent lung resection and reported that BMI <18.5 and more than 5% weight loss were significant independent risk factors for mortality. The effect of obesity and the obesity paradox on lung cancer prognosis after resection have also been reviewed.\textsuperscript{59} In a study of 203 patients who underwent lobectomy, the presence of obesity (BMI >30) was not associated with postoperative morbidity.\textsuperscript{60} In another study, Paul and colleagues\textsuperscript{61} analyzed the effect of obesity on perioperative outcomes after lung resection in 5216 patients from the American College of Surgeons National Surgical Quality Improvement Program database and reported that obesity does not negatively affect perioperative morbidity and mortality after pulmonary resection. Additionally, a systematic review of several studies on obesity and lung resection showed that inhospital mortality and overall morbidity were significantly decreased in obese patients.\textsuperscript{62}

8. Sarcopenia. The presence of sarcopenia, a progressive and generalized loss of skeletal muscle and strength, has also been reported to predict postoperative complications and survival in patients who undergo lung cancer surgery. Kawaguchi and colleagues\textsuperscript{63} evaluated the effect of sarcopenia in 173 patients older than 75 years, who were treated with lobectomy for NSCLC; these authors used psoas muscle cross-sectional area of different cutoffs to define sarcopenia. Postoperative complications were significantly higher (62.5% vs 22.7%) and 5-year survival lower (26.5% vs 66.3%) in patients with sarcopenia compared with patients without sarcopenia. Other investigators have evaluated the effect of sarcopenia and did not report a statistically significant association with postoperative complications.\textsuperscript{64-66} Miller and colleagues,\textsuperscript{65} using erector muscle area to define sarcopenia, did not note an association with postoperative complications; however, they did note a significant association of sarcopenia with mortality and length of hospital stay. Shinohara and colleagues\textsuperscript{67} reported no association of immediate postoperative complications in patients with sarcopenia; however, they reported a significant increase in pneumonia after discharge in patients with sarcopenia. After propensity matching, one of the interesting findings in this study was that there was no difference in 5-year overall survival in sarcomenic patients who underwent limited resection versus those who underwent lobectomy (53.2% limited resection vs 60.7% lobectomy). These findings might have implications in the selection of therapy for patients at high risk during lobectomy. Finally, in a recent systematic review on the effect of sarcopenia, an analysis of 4 studies that reported perioperative outcomes showed an increase in the risk of postoperative complications in patients with sarcopenia.\textsuperscript{68}

9. Activities of daily living, functional status, and cognitive function. In an interesting prospective study, Fukuse and colleagues\textsuperscript{69} evaluated 120 patients older than 60 years who underwent thoracic surgery, of whom 85 had lung cancer. Two weeks before surgery, patients underwent a comprehensive geriatric assessment (CGA) that included...
evaluation of functional status, nutrition, and cognitive function. Functional status evaluation included performance status and the activities of daily living (ADL) using the Barthel index. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE). This study showed that patients with dependence for performing the ADL and dementia were more likely to develop postoperative complications ($P = .041$ and $P = .0065$, respectively). Interestingly, all patients who developed delirium had low scores on the preoperative MMSE ($P = .0003$). Using multiple logistic regression, the best model for prediction of complications was obtained with a combination of MMSE ($P = .031$) to assess cognitive function and the Barthel index ($P = .04$), which evaluated ADL. In addition, longer operation time was significantly associated with complications. These authors concluded that dependence on others for the performance of ADLs and impaired cognitive conditions are important predictors of postoperative complications, especially when the operation time is long. They stressed the importance of a CGA in addition to the conventional cardiopulmonary functional assessment in elderly patients. With an aging population in the United States, this study is particularly relevant and highlights the importance of a comprehensive geriatric examination, which might assist the surgeon in determination of high risk. The expert panel survey categorized functional status as one of the most important factors in risk assessment.

10. Baseline quality of life. It has been suggested that low preoperative baseline quality of life (QOL) might predict worse survival in patients who undergo resectional therapy. Fernando and colleagues$^{70}$ reported on serial QOL assessments in 212 patients who underwent sublobar resection with or without brachytherapy. In high-risk patients, poor baseline QOL scores did not predict for worse overall survival, recurrence-free survival, or higher risk for adverse events after sublobar resection with or without brachytherapy.$^{70}$ The VATS approach was associated with improved physical performance 3 months post resection and less dyspnea after 12 months.

11. Composite risk calculators. Few composite risk calculators estimate outcomes accurately in patients undergoing SABR or surgery for stage I NSCLC. Samson and colleagues$^{72}$ reported on the ability of the National Surgical Quality Improvement Program risk calculator to stratify risk for patients undergoing SABR/SRS/SBRT or surgical resection. The authors reported that the risk calculator did not profile risk sufficiently to reliably dichotomize inoperable SABR/SRS/SBRT patients from surgical patients or estimate a surgical patient’s risk of serious complications. Another multi-institutional study from the Japanese Association for Chest Surgery (J1303) evaluated a comprehensive risk scoring system predicting complications in medically operable octogenarians who underwent surgical resection for NSCLC.$^{72}$ The predictive factors that were significantly associated with postoperative complications included sex, memory as determined using the CGA, and a simplified comorbidity score incorporating diabetes mellitus, albumin, and percentage vital capacity. These investigators developed a simplified risk score incorporating these factors and concluded that octogenarians can be successfully treated for lung cancer with surgical resection with an acceptable rate of severe complications and mortality.

12. Other factors. Physician and patient sex might be important in estimating surgical risk. Ferguson reported that male physicians had larger changes in estimated surgical risk compared with female physicians after initially reviewing data from clinical vignettes and then performing a final assessment of surgical risk after reviewing a video interview with a potential patient.$^{73}$ These differences could potentially influence recommendations for surgical treatment.

EXPERT SURVEY RESULTS

A total of 16 additional panel members with expertise in lung cancer were invited by the 2 co-chairs, and all agreed to participate (total $N = 18$). The specialties represented by this multidisciplinary group of panel members were thoracic surgery ($n = 15$), pulmonology ($n = 2$), and radiation oncology ($n = 1$). In addition, an evidence-based methodologist and epidemiologist ($n = 1$), a librarian with expertise in systematic literature review ($n = 1$), and members of the CPSC committee formed part of the writing group. The first survey conducted asked the expert panel to rank the relative importance of the factors to consider for risk assessment prior to lobectomy, and each member of the panel graded each factor from 1 to 10. All 18 members voted with a 100% response rate. The expert panel survey results on the assessment of the relative importance of factors to consider for risk stratification for lobectomy are summarized in Figures 2 to 4. The relative importance of each factor for risk stratification before lobectomy, as determined by the expert panel, was examined using the mean importance score (Figure 2) and the median importance score (Figure 3). Finally, the relative importance was examined using a cutoff value (importance score $\geq 7$ of 10) and the frequency with which the expert panel ranked the risk factor as important (Figure 4). As shown in the figures, the top-ranked factors included the need for supplemental oxygen, severe underlying lung disease, the presence of frailty, low diffusion capacity (ppoDLCO), the overall assessment of daily activity, functional status, and the presence of PH. Significantly decreased spirometry (ppoFEV1), end-stage liver disease/cirrhosis, a careful cardiac assessment, dementia or other neurocognitive problems, and oxygen saturation testing with activity that included 6-minute walk, stair-climbing, and exercise desaturation were ranked next in importance. The panel ranked age (as a sole factor) among the least important factors.
The results of the first-round survey were discussed by the expert panel. These results were then stratified into groups from most important, to less important on the basis of their ranking and a second-round Delphi survey was sent to the panel. Consensus was developed with discussion through online or teleconference meetings and a modified Delphi method. For the second round of voting, a 5-point Likert scale was used ranging from 1 = strongly disagree to 5 = strongly agree, as described previously.\textsuperscript{3} The response rate for this second-round Delphi survey was 100\%, and this met the predetermined threshold of >80\% response rate. Agreement (“agree” or “strongly agree”) among the expert panel members was 100\% for all of the statements on the relative importance of the risk factors (Figures E1-E6). This met the predetermined threshold of >75\% agreement for consensus statements to be accepted.

The results of the first-round survey were discussed by the expert panel. These results were then stratified into groups from most important, to less important on the basis of their ranking and a second-round Delphi survey was sent to the panel. Consensus was developed with discussion through online or teleconference meetings and a modified Delphi method. For the second round of voting, a 5-point Likert scale was used ranging from 1 = strongly disagree to 5 = strongly agree, as described previously.\textsuperscript{3} The response rate for this second-round Delphi survey was 100\%, and this met the predetermined threshold of >80\% response rate. Agreement (“agree” or “strongly agree”) among the expert panel members was 100\% for all of the statements on the relative importance of the risk factors (Figures E1-E6). This met the predetermined threshold of >75\% agreement for consensus statements to be accepted.

FIGURE 2. Survey results; relative importance of risk factors ranked according to mean. Survey results of the expert panel assessment of the relative importance of factors to consider for risk stratification for lobectomy ranked as per the mean ± standard error of the mean. Factors considered the most important are on the left of the graph and factors considered least important are to the right. \textit{SEM}, Standard error of the mean; \textit{DLCO}, diffusion capacity of the lung for carbon monoxide; \textit{PPO}, predicted postoperative; \textit{FEV1}, forced expiratory volume in 1 second; \textit{ESLD}, end-stage liver disease; \textit{BMI}, body mass index.

FIGURE 3. Survey results; relative importance of risk factors ranked according to median. Expert panel assessment of the relative importance of factors to consider for risk stratification before lobectomy, ranked according to the median score. Factors considered the most important are on the left of the graph and factors considered least important are to the right. \textit{DLCO}, Diffusion capacity of the lung for carbon monoxide; \textit{PPO}, predicted postoperative; \textit{FEV1}, forced expiratory volume in 1 second; \textit{ESLD}, end-stage liver disease; \textit{BMI}, body mass index.
The following consensus statements were developed with discussion and a modified Delphi method:

I. The expert panel survey identified the most important factors that can be considered in the determination of high risk including the need for supplemental oxygen, severe underlying lung disease, the presence of frailty, low diffusion capacity (ppoDLCO), the overall assessment of daily activity and functional status, and the presence of PH (strongly disagree, 0; disagree, 0; neutral, 0; agree, 16.7%; strongly agree, 83.3%).

II. The panel identified very important factors that can be considered in determination of risk including significantly decreased spirometry (ppoFEV1), end-stage liver disease (ESLD, cirrhosis), a careful cardiac assessment, dementia or other neurocognitive problems, and oxygen saturation testing with activity that includes 6-minute walk, stair-climbing, and exercise desaturation (strongly disagree, 0; disagree, 0; neutral, 0; agree, 27.8%; strongly agree, 72.2%).

III. The panel identified important factors that can be considered in determination of risk including lack of ability to live independently, sarcopenia, and diminished oxygen consumption (strongly disagree, 0; disagree, 0; neutral, 0; agree, 72.2%; strongly agree, 27.8%).

IV. The panel identified less important factors, based on the survey, that can be considered in determination of risk including age (as sole issue), renal dysfunction, and obesity (strongly disagree, 0; disagree, 0; neutral, 0; agree, 72.2%; strongly agree, 27.8%).

V. The decision on determination of patients who are at a high risk for lobectomy should take into consideration multiple factors and is a clinical decision that also should take into consideration the patient perspectives, patient values, preferences, and QOL (strongly disagree, 0; disagree, 0; neutral, 0; agree, 5.6%; strongly agree, 94.4%).

These results are depicted in Figures E1 to E6.

DISCUSSION

In this expert consensus document, we have summarized the findings of a systematic review on the definition and assessment of high risk before pulmonary lobectomy for patients with early-stage NSCLC. This includes a summary of the current status of consensus documents on cardiopulmonary risk evaluation for lung resection. Although cardiopulmonary evaluation has been the mainstay of preoperative evaluation, there is an emerging literature on other factors that are of importance in the preoperative evaluation of the high-risk patient. These factors, which include frailty, a comprehensive geriatric examination, and an assessment of functional status, are particularly important with an aging population in the United States. With well-described details of cardiopulmonary evaluation in the literature, one of the unique aspects of this expert consensus document is that we have focused on the relative importance of several factors.
factors for risk assessment beyond the traditional cardiopulmonary risk evaluation. The expert panel was asked to rank the relative importance of the various factors in defining risk and assessing which patients are at high risk for pulmonary lobectomy, and consensus was reached with a modified Delphi approach. An important finding was that some of the most important factors selected by the panel for the determination of high risk, besides severe underlying lung disease and need for supplemental oxygen, included the presence of frailty, the overall assessment of daily activity and functional status, and low diffusion capacity. In addition, the panel determined that age as a sole issue was a less important factor in risk assessment, and a comprehensive evaluation of the functional status is more important than age in risk assessment.

Patient preferences and values should also be taken into account when deciding on treatment options. Sullivan and colleagues conducted a prospective multicenter study of patients who were treated for stage I NSCLC to understand participant values and treatment preferences. They reported that most participants valued maintaining independence and QOL as most important compared with survival or recurrence of cancer; participants were also willing to accept high periprocedural mortality, but not severe deficits that would affect QOL when considering treatment. Samson and colleagues described a stepwise approach for shared decision-making and communication of risks and benefits, to identify patient values and preferences to assist patients in decisions regarding treatment.

The importance of a comprehensive geriatric examination was highlighted in a prospective study, which showed that patients with dependence on others for performing the ADL and dementia were more likely to develop postoperative complications. With an aging population in the United States, this study is particularly relevant and highlights the importance of a comprehensive geriatric examination to evaluate functional status and cognitive function in addition to cardiopulmonary evaluation. This comprehensive evaluation might assist the surgeon in determination of high risk particularly in elderly patients. The expert panel survey categorized functional status as one of the most important factors in risk assessment. Another factor that is increasingly being studied is the presence of frailty, and its effect on complications. In an interesting study on the interaction between the presence of frailty and the FTR after cardiac surgery, the presence of frailty was associated with FTR after complications occurred. The effect of frailty on FTR after thoracic surgical operations and outcomes require further study.

In addition, the panel ranked the relative importance of various factors that might be used in risk assessment. Although this list might not be fully comprehensive, it covers many emerging concepts in the evaluation of patients including frailty and sarcopenia. Other factors identified by the panel that might be considered in risk assessment before lobectomy include previous chest surgery (lung resection, pleurodesis), location of the tumor in relation to the most diseased lung, mediastinal radiation, nutritional status, other comorbidities (such as cerebrovascular accident), patient-reported level of dyspnea, patient values, life expectancy, and requirements for anticoagulation. As more literature emerges, other risk factors might need to be added to the list of variables. Other limitations of this study were that the panel was mostly composed of experts from North America, with some participation of experts from the United Kingdom and China, and might not be globally representative. Further, the expert panel was mainly from academic rather than community-based centers.

The definition of the high-risk patient group for lung cancer resection therapy has been debated. Puri and colleagues reviewed 1066 patients who underwent resection for stage I NSCLC and classified them as high risk and normal risk according to the American College of Surgery Oncology Group definitions. High-risk patients were older but similar to control participants in terms of sex and prevalence of heart disease, diabetes, and hypertension. High-risk patients were less likely to undergo lobectomy compared with normal-risk patients, but the high-risk and normal-risk populations had similar morbidity and 30-day mortality. In addition, the list of risk factors is not mutually exclusive. For example, a patient with frailty might also have sarcopenia and underlying lung disease, which adds to the complexities of evaluation. Therefore, ultimately risk assessment is a clinical decision that should take the various factors into account. It is particularly important that the risk assessment is made with all factors being considered. One factor alone, such as poor pulmonary function tests, might not make a patient ineligible. The location of the tumor in relation to the diseased area of the lung should also be taken into consideration. In a study of a highly selected group of early-stage NSCLC patients with poor pulmonary function tests (mean FEV1 0.7; 29% of predicted), the results of surgical resection with or without associated lung volume reduction surgery were reported with an estimated 5-year overall survival of 68%. The study illustrates that the decision on operability or inoperability is complex and should be made after a comprehensive evaluation of the patient.

With higher-risk patients being evaluated for surgical resection, there continues to be an increased interest in measures to mitigate risk before surgical resection. With the degree of air trapping contributing to perioperative outcomes, there might be a role for bronchodilator therapy to decrease the extent of air trapping. Other measures include recommending smoking cessation before surgery and considering...
pulmonary rehabilitation before resection. 77,78 In addition, the use of inspiratory muscle training and incentive spirometry has been reported to decrease the rate of postoperative respiratory complications. 77 In a small randomized controlled trial, 2 weeks of additional postoperative inspiratory muscle training did not preserve respiratory muscle strength compared with standard physiotherapy alone, but improved oxygenation in high-risk patients after lung cancer surgery. 75 It has been reported that a preoperative exercise program also significantly reduced postoperative pulmonary complications. 76 Although the prehabilitation literature has previously focused on cardiopulmonary reserve and function, it is now increasingly evident that frailty and nutrition are important for identification of potentially modifiable risk factors. 78,80 Evaluating the effect of addressing the modifiable risk factors on perioperative outcomes, particularly in patients who are potentially at high risk during pulmonary lobectomy, is a promising area for future work.

A meta-analysis of studies that compared VATS and open lobectomy suggested that VATS lobectomy is associated with lower rates of risk for pulmonary morbidity in patients with compromised lung function. 46 Anatomical lung resection has been reported to be performed safely in carefully selected, high-risk patients on the basis of preoperative lung function without a significant increase in morbidity or mortality and with acceptable QOL postoperatively. 51 However, for these high-risk patients, an assessment of the patient’s fitness for surgery should be thoroughly discussed in a multidisciplinary fashion that includes the patient and his or her caregivers as well. Although guidelines might help in working up a patient before surgical treatment, the identification of patients who are at excessive risk if they undergo lobectomy should remain a clinical decision that should also take into consideration patient perspectives, values, preferences, and QOL.

CONCLUSIONS

In this document, we have summarized current guidelines, and the expert consensus panel has identified several key factors that can be incorporated into the determination of high risk in patients being evaluated for pulmonary lobectomy for stage I NSCLC. Further, areas in which there are knowledge gaps in risk assessment and areas of future research were identified. Defining who is at high risk before lobectomy for stage I NSCLC is challenging and becoming more important in this era of transparency and alternative treatment options for lung cancer. Measures to mitigate risk in selected patients, including consideration of prehabilitation, optimization of modifiable risk factors, and the use of minimally invasive surgical techniques, are very important. The determination of risk is a clinical decision and judgement that should also take into consideration patient perspectives, values, preferences, and QOL.

Conflict of Interest Statement

Dr Rocco disclosed royalties from Scanlan International; Dr Lanuti is a consultant for Bristol Myers Squibb and PrecisCa; Dr Tong is a consultant for Medtronic, Inc; Dr Marshall is a consultant for Ethicon; Dr Merritt is a speaker for Intuitive Surgical; Drs Swanson and Brunelli are consultants for Johnson and Johnson and Medtronic, Inc; Dr Pet-tiford is a speaker for Astra Zeneca; and Dr Loo is a board member of TibaRay. All other authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

The authors wish to thank The AATS for their support. We also wish to thank Ms Lori Burrows, Ms Jill Colsch, and Mr Adam Silva of The AATS for their sincere and enthusiastic efforts.

References


Key Words: risk assessment, lobectomy, stage I non–small cell lung cancer
APPENDIX E1. SEARCH STRATEGY AND RESULTS (QUESTION 1: DEFINING AND ASSESSMENT OF HIGH RISK; PubMed SEARCH STRINGS UPDATED ON NOVEMBER 25, 2020)

Search last performed: December 8, 2020
Limits: English, 2000 to present
Total results: 1018


OR


AND (candidate*[ti] OR patient*[ti] OR population*[ti])

APPENDIX E2. SEARCH STRATEGY AND RESULTS (UPDATED TARGETED SEARCH; PubMed SEARCH STRINGS UPDATED ON MARCH 6, 2021)

Home O2


Frailty


AND (“Frailty”[Mesh] OR frail*[tiab] OR frailty*[tiab])

Independent Living


(Psychiatry/Neurocognitive (eg, Measure of Dementia)


Function Status (eg, Measure of Activities of Daily Living [ADL])


Sarcopenia

(Sarcopenia*[Mesh] OR sarcopenia*[tiab])

BMI (Body Mass Index, Obesity)

Participation - 18/18 100%

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Agreement%</th>
<th>≥ 75%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- The most important factors identified, which can be considered in determination of risk include: Need for supplemental oxygen, severe underlying lung disease, presence of frailty, low diffusion capacity (PPO DLCO), the overall assessment of daily activity and functional status and the presence of pulmonary hypertension.</td>
<td>100</td>
<td>yes</td>
</tr>
<tr>
<td>2- Very important factors identified, which can be considered in determination of risk include: Significantly decreased spirometry (PPO FEV1), end stage liver disease (ESLD; cirrhosis), a careful cardiac assessment, dementia or other neurocognitive problems and oxygen saturation testing with activity that include six-minute walk, stair climbing and exercise desaturation.</td>
<td>100</td>
<td>yes</td>
</tr>
<tr>
<td>3- Important factors identified, which can be considered in determination of risk include: Lack of ability to live independently, sarcopenia and diminished oxygen consumption.</td>
<td>100</td>
<td>yes</td>
</tr>
<tr>
<td>4- Based on the survey, less important factors identified, which can be considered in determination of risk include: Age (as sole issue), renal dysfunction, and obesity</td>
<td>100</td>
<td>yes</td>
</tr>
<tr>
<td>5- The decision on determination of patients who are at a high-risk for lobectomy should take into consideration multiple factors and is a clinical decision which also takes into consideration the patient perspectives, patient values, preferences, and quality of life.</td>
<td>100</td>
<td>yes</td>
</tr>
</tbody>
</table>

FIGURE E1. Results of the Expert Consensus Panel Delphi Survey of Consensus Statements. Summary of consensus statements developed by the expert panel. *75% agreement from the panel members was required for acceptance of the statement.

FIGURE E2. Results of the Expert Consensus Panel Delphi Survey of Consensus Statements. Distribution of responses of the expert panel for consensus statement 1. The survey was written using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree).
FIGURE E3. Results of the Expert Consensus Panel Delphi Survey of Consensus Statements. Distribution of responses of the expert panel for consensus statement 2. The survey was written using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree).

FIGURE E4. Results of the Expert Consensus Panel Delphi Survey of Consensus Statements. Distribution of responses of the expert panel for consensus statement 3. The survey was written using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree).
FIGURE E5. Results of the Expert Consensus Panel Delphi Survey of Consensus Statements. Distribution of responses of the expert panel for consensus statement 4. The survey was written using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree).

FIGURE E6. Results of the Expert Consensus Panel Delphi Survey of Consensus Statements. Distribution of responses of the expert panel for consensus statement 5. The survey was written using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree).