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PREOPERATIVE EVALUATION (BJ SWEITZER, SECTION EDITOR)

Preoperative Evaluation for Lung Resection Surgery

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Abstract

Purpose of Review The purpose of this article is to review the literature surrounding preoperative assessment and management of patients undergoing lung resection surgery.

Recent Findings The traditional preoperative cardiovascular risk assessment can be further refined in patients undergoing lung resection surgery with the Thoracic Revised Cardiac Risk Index and cardiac biomarkers such as B-type natriuretic peptide. Cardiorespiratory exercise testing parameters such as the maximal achieved oxygen consumption (VO_2 peak) and the minute ventilation to carbon dioxide output (VE/VCO_2) slope are strong preoperative prognosticators in patients with borderline lung function. Preoperative pulmonary rehabilitation holds promising benefits in improving surgical candidacy and postoperative outcomes.

Summary The preoperative assessment of lung resection candidates must evaluate perioperative cardiorespiratory risk. The patient's comorbidities should be optimized as time permits. A clear perioperative plan should be established and may include cardiology consultation, prevention strategies for arrhythmias, preoperative pulmonary rehabilitation, smoking cessation, intensive perioperative monitoring, and enhanced recovery protocols.

Keywords Preoperative evaluation · Lung cancer · Lung resection surgery · Preoperative pulmonary rehabilitation

Introduction

Lung cancer is the most common cancer worldwide, with over 2.09 million cases in 2018 [1]. In the United States only, it is estimated that lung cancer will lead to over 142,000 deaths in 2019, being by far the most common cause of cancer death (23.5% of all cancer deaths) [2].

When diagnosed at an early stage, surgical resection of lung cancer is required for optimal oncologic outcomes. Lung cancer pathogenesis is strongly related to tobacco exposure, a risk factor shared with chronic obstructive pulmonary disease (COPD) and multiple cardiovascular comorbidities. When evaluating candidates for lung resection surgery, perioperative physicians are therefore often faced with patients with decreased cardiorespiratory reserve and increased postoperative risk of pulmonary and cardiovascular complications. Specific goals of the preoperative evaluation for lung resection surgery are to assess the patient's cardiorespiratory reserve and capacity to survive the planned lung resection, to optimize cardiovascular and pulmonary comorbidities, to weigh perioperative risks versus potential benefits of surgery, and to plan perioperative care.

The purpose of this article is to review the most recent literature surrounding this clinical challenge, with emphasis on the cardiovascular evaluation in this specific patient population, the predictive value of cardiac biomarkers, the resectability evaluation, and the role of prehabilitation and smoking cessation.

This article is part of the Topical Collection on *Preoperative Evaluation*

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Cardiovascular Evaluation

Cardiovascular complications (supraventricular arrhythmias, myocardial infarction, thromboembolic events, and heart failure) are an important cause of postoperative morbidity and mortality in patients undergoing non-cardiac thoracic surgery, occurring in up to 30% of cases [3].

Supraventricular arrhythmias, the most common cardiac complication, have a complex pathophysiologic mechanism

that involves stress from surgical manipulation and altered postoperative cardiopulmonary physiology. Major lung resection surgery (lobectomy, pneumonectomy, and lung volume reduction surgery) is considered an important risk factor for development of postoperative atrial fibrillation or flutter (incidence above 15%), as is male sex, advanced age, hypertension, coronary artery disease, heart failure, and elevated cardiac biomarkers (see following section). In patients at high risk for postoperative atrial fibrillation or flutter, preventive strategies such as continuation of β-blockers, correction of hypomagnesemia, or initiation of calcium-channel blockers or amiodarone may be considered as per current guidelines [4•].

Due to shared risk factors, the prevalence of coronary artery disease in patients undergoing lung resection surgery is high (11%–17%) [5, 6]. Myocardial infarction is an uncommon complication (< 5% incidence after pulmonary resection) but with potentially devastating consequences (mortality rates as high as 40% in pneumonectomy patients) [7, 8••].

As with any patient undergoing major surgery, cardiac risk evaluation and management is based on current guidelines and clinical judgment [9, 10•]. For that purpose, one of the most validated and used tools to stratify cardiovascular risk in patients who undergo non-cardiac surgery is the Revised Cardiac Risk Index [3, 9]. This score was originally derived from a mixed surgical population including only 12% of thoracic surgery patients. More recently, this risk stratification tool has been modified into the Thoracic Revised Cardiac Risk Index (ThRCRI, see Table 1) specifically for patients undergoing lobectomy and pneumonectomy [5]. Multiple subsequent studies have externally validated this score, including a large retrospective cohort study using the American College of Surgeons National Surgical Quality Improvement Program database which reported a threefold increase in postoperative major cardiac complications in patients with ThRCRI score ≥ 2 compared with those with a score of 0 (4.8% vs 1.4%, $p < 0.05$) [6, 11•]. In this study, patients who sustained a major cardiac complication had a dramatically increased rate of 30-day mortality (53% vs 1.3%, $p < 0.01$). Of note, this score has also been shown to be a useful prognosticator of 5-year cancer-specific survival as well as long-term cardiac mortality [12].

Moreover, the American College of Chest Physicians (ACCP) has incorporated this risk stratification method into their clinical practice guidelines. Accordingly, cardiology consultation and further noninvasive cardiac testing are indicated when the ThRCRI score is greater than 1.5, the patient has a cardiac condition requiring medications, a new cardiac condition is suspected, or the patient is unable to climb 2 flights of stairs (see Fig. 1 in reference [8••]). Despite these expert recommendations, the validity of these evaluation methods and the clinical utility of preoperative noninvasive cardiac testing has been challenged [10•, 13].

Other identified risk factors of cardiovascular complications following lung resection surgery include male sex, American Society of Anesthesiologists' class status 3 or higher, diabetes mellitus, and an open surgical approach compared to video-assisted thoracic surgery (VATS) [11•, 14].

Table 1 Thoracic Revised Cardiac Risk Index [5]

History of ischemic heart disease	1.5pts
History of cerebrovascular disease	1.5pts
Preoperative creatinine > 2 mg/dl	1.0pts
Pneumonectomy	1.5pts

Cardiac Biomarkers

There has been increasing interest in the development and clinical use of laboratory tests to predict postoperative outcomes after non-cardiac surgery. Natriuretic peptide biomarkers such as B-type natriuretic peptide (BNP) or N-terminal fragment of proBNP (NT-proBNP) are polypeptides secreted by the myocardium in response to mechanical stretch or ischemia. Multiple studies have shown their prognostic capabilities of predicting postoperative cardiovascular outcomes when measured preoperatively or early postoperatively [15]. Determination of BNP is now a cornerstone of preoperative cardiac evaluation according to the Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment [10•].

Specifically relating to the thoracic surgical population, there is evidence from multiple cohort studies and meta-analyses that patients with elevated preoperative BNP levels are at significantly increased risk of postoperative atrial fibrillation [16•, 17].

A few reports have associated an elevated preoperative BNP with other postoperative outcomes such as functional capacity decline, cardiopulmonary complications, and mortality [18–20]. For example, a recent retrospective cohort study of 675 patients undergoing lung resection surgery reported an incidence of postoperative complications of 11%, 47%, and 85%, respectively, for patients with normal, mildly, and severely elevated levels of preoperative BNP ($p < 0.0001$) [19]. In that study, preoperative BNP was the strongest predictor of postoperative complications and performed better than predicted postoperative forced expiratory volume in 1 s ($ppoFEV_1$) and surgical technique (open vs VATS).

Despite these promising advances in preoperative prognostication of cardiovascular risk, research is still needed to clarify the best perioperative management to reduce cardiovascular complications in patients undergoing lung resection surgery.

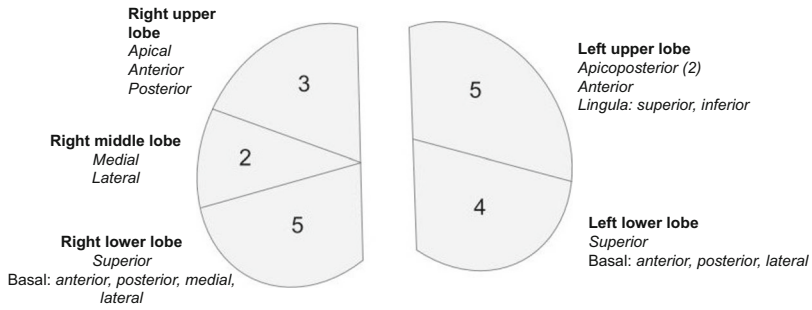

Fig. 1 Number of segments in each lobe used to estimate postoperative pulmonary function [8]

ppoFEV1%= preoperative FEV1% x (1 - functional segments to be removed / total functional segments)

ppoDLCO%= preoperative DLCO% x (1 - functional segments to be removed / total functional segments)

Respiratory Function Testing

The respiratory assessment prior to lung resection surgery is based on the concept that a minimal cardiorespiratory reserve is necessary to tolerate resection of a certain amount of capillary-alveolar units. Indeed, pulmonary complications (pneumonia, atelectasis, respiratory failure, pulmonary embolism, and prolonged air leak) are the major cause of morbidity and mortality following lung resection surgery. However, the specific required post-resectional lung function is difficult to define on an individual patient basis. Nevertheless, preoperative assessment of respiratory function can be conceptualized as a "3-legged stool," evaluating the lungs' ability to move gas in and out of the alveoli (lung mechanics), gas exchange at the alveolar-capillary interface (lung parenchymal function), and the ability to distribute oxygen to tissues (cardiopulmonary reserve) [21].

Lung Mechanics

When considering the effect of surgery on an individual patient's lung mechanics, the physiology of the patient (height, age, and sex) and the planned extent of lung resection are taken into account. The most useful predictor of postoperative lung mechanics is the percent ppoFEV_1. It is estimated by the following formula, taking into account the preoperative post-bronchodilator percent of predicted FEV_1 (see Figure):

$$\text{ppo}FEV_1\% = \text{preoperative } FEV_1\% \text{x } (1 - \%\text{functional lung tissue removed}/100)$$

In the last decades, multiple studies have validated the ability of ppoFEV_1 to predict postoperative complications using various cutoff values [22–25]. Significantly elevated postoperative morbidity and mortality have often been associated with ppoFEV_1% below 30%–40%. For example, one study reported major postoperative pulmonary complications (PPC) only in patients with ppoFEV_1 < 40%, and all patients with ppoFEV_1 < 30% required prolonged mechanical ventilation after lung cancer surgery. Another study reported a 50% mortality rate in patients with ppoFEV_1 < 40% who had thoracotomies, whereas none of the 47 patients with higher ppoFEV_1 died [23].

Other measures of lung mechanics that have been associated with outcomes following lung resection include maximal voluntary ventilation and forced vital capacity. However, they are more dependent on patient's efforts and are rarely used for clinical prognostication.

Lung Parenchymal Function

The most useful preoperative test for assessing gas exchange capacity of the alveolar-capillary interface is the diffusing capacity for carbon monoxide (DLCO). Since it is a specific measure of diffusion impairment, it is to some extent independent of the FEV_1 and provides additional information in the preoperative pulmonary assessment. As with the FEV_1, its post-resection value can be estimated based on the amount of lung tissue to be resected (see Figure) and is a useful predictor of postoperative morbidity and mortality [21]. For example, in a retrospective cohort study of 854 patients who underwent major lung resection, each 10 percentage-point decrease in ppoDLCO was strongly associated with increased mortality with a hazard ratio of 1.06 ($p = 0.02$) [26].

Other measures of gas exchange such as arterial PO_2 or PCO_2 have not been shown to be reliable discriminators of lung resectability and perioperative risk [21].

Cardiopulmonary Reserve

In order to maintain energetic homeostasis, the ultimate physiologic objective of the cardiorespiratory system is to deliver enough oxygen from the atmosphere to the tissues. Testing of exercise capacity allows for physiologic evaluation of this complex interaction of pulmonary, cardiac, circulatory, and metabolic systems to assess the body's reserve. For this purpose, cardiopulmonary exercise testing (CPET) is the recommended technique and usually consists of recording the electrocardiogram, heart rate, blood pressure, ventilation parameters, pulse oximetry, oxygen uptake, and CO_2 production during standardized incremental exercise on a bicycle ergometer or treadmill [27]. Other exercise tests exist, such as

standardized stair climbing test (SCT) or shuttle walk test (SWT), that are readily available and less expensive.

One of the advantages of a formal CPET is that it may be able to differentiate poor exercise tolerance due to respiratory or cardiac etiology or simply functional deconditioning without cardiopulmonary pathology, helping to guide further testing and management [28•].

Of the various measurements provided by CPET, the maximal achieved oxygen consumption (VO_2 peak) is an independent and reliable predictor of cardiopulmonary complications and death after lung resection surgery and provides useful preoperative risk stratification in patients with borderline lung function [8••, 29–31]. As with ppoFEV_1 and ppoDLCO, VO_2 peak can be expressed as a percentage of predicted value or as a postresection estimate and has strong predictive value [8••, 31]. A VO_2 peak above 20 mL/kg/min or 75% of predicted has been associated with low risk of postoperative morbidity and mortality [29]. On the other hand, a VO_2 peak below 10 mL/kg/min or 35% of predicted has been associated with very high mortality and is viewed by some authors as a relative contraindication to significant surgical resection [8••, 32].

Another parameter of CPET, the minute ventilation to carbon dioxide output (VE/VCO_2) slope, also called the ventilatory equivalent to carbon dioxide, is a measure of gas exchange efficiency that is increased with worsening in ventilation/perfusion mismatch and dead space [27, 28•]. It has been associated with increased postoperative complications and mortality after lung resection surgery in multiple reports [32, 33]. A recent prospective cohort study of 55 COPD patients undergoing lung resection surgery found that a VE/VCO_2 slope above 35 predicted postoperative complications and mortality better than VO_2 peak, with a hazard ratio of 5.14 (95%CI 1.4–18.7) [33]. To this date, this parameter has not been included in clinical guidelines.

Although CPET is a reliable, well standardized, and informative test that provides significant physiologic information, it is expensive, time-consuming, and not widely available. To circumvent these drawbacks, the SCT and SWT are simple and require little personnel and expertise to perform. They are recommended by the ACCP guidelines as initial exercise testing in patients deemed at moderate risk based on ppoFEV_1 and ppoDLCO measures [8••].

Integration of the Respiratory Evaluation

The most recent recommendations for an integrative respiratory evaluation of patients for lung resection surgery are provided by the 2013 ACCP clinical practice guidelines, and a simple algorithm to assess lung resectability and categorize preoperative patients into low, moderate, or high-risk groups is described [8••].

Each patient being considered for anatomical lung resection should have a FEV_1 and DLCO measured to estimate predicted postoperative values. Patients with both these predicted postoperative values above 60% are deemed at low postoperative pulmonary risk (mortality risk under 1%). Patients who do not meet these criteria may require simple screening exercise testing or formal cardiopulmonary exercise testing. Those with CPET derived VO_2 peak below 10 mL/kg/min or 35% of predicted are deemed at high risk of cardiopulmonary morbidity and mortality and less invasive surgical or non-surgical options should be considered (see Fig. 2 in reference [8••] for details).

When evaluating lung resection candidates, certain considerations are important.

Many clinical conditions may have significant impact on the patient's pulmonary function or cardiopulmonary exercise tests without affecting postoperative impairment proportionally. Examples include poorly optimized cardiopulmonary comorbidities at the time of testing (e.g., COPD, ongoing pneumonia, and heart failure) and pathologies on the operative side such as obstructing endobronchial lesions, atelectasis, or large pleural effusions. If the lung portion to be resected is significantly less functional than the rest of the lungs, then postoperative impairment may be overestimated by previously described calculations. In this context, particularly useful tests for assessing regional lung function and refining postresection estimations include ventilation/perfusion scan, dynamic perfusion magnetic resonance imaging, or quantitative computerized tomography (CT) scan [34]. Of those, the ventilation/perfusion scan is preferred as its derived estimations highly correlate with actual postoperative values [21].

Preoperative predictions of postoperative FEV_1, DLCO, and VO_2 peak tend to overestimate actual long-term post-resection impairment [8••, 35]. This is particularly true in patients with significant COPD: a "lobar volume reduction effect" may be observed, whereby an improvement in lung mechanics and elastic recoil may even lead to enhanced postoperative lung function, especially if the resected lung portion is significantly emphysematous [8••, 36].

Several recent clinical advances such as video-assisted surgical approaches, modern anesthetic and analgesic techniques, and enhanced recovery pathways may allow for postoperative outcomes better than those predicted from older studies [8••, 37].

Finally, given the poor survival prognosis without surgical resection, complex patients or those with estimated borderline perioperative risk should undergo careful risk and benefit analysis that may involve a multidisciplinary team including a thoracic surgeon, an anesthesiologist, a pulmonologist, and an oncologist.

Preoperative evaluation and management includes optimization of the comorbidities commonly encountered in these patients (e.g., COPD, obstructive sleep apnea) [38].

Preoperative Pulmonary Rehabilitation

Many patients presenting for lung resection surgery have advanced lung disease, cardiorespiratory deconditioning, or even pulmonary cachexia syndrome. The preoperative period is an opportunity to optimize patients' cardiorespiratory capacity and promote a healthy lifestyle in an effort to improve perioperative outcomes and long-term health. Pulmonary rehabilitation consists of lifestyle changes made by the patient with the support of comprehensive multidisciplinary therapeutic interventions including nutritional optimization, smoking cessation, exercise training, education, and stress reduction techniques. A key element of pulmonary rehabilitation is improvement in muscle function and exercise capacity through aerobic and strength training [39].

Applied to the preoperative setting, prehabilitation has been shown to improve postoperative clinical outcomes in major colorectal and cardiac surgery [40, 41]. In patients undergoing lung resection surgery, multiple small studies have described the impact of prehabilitation on postoperative clinical outcomes such as pulmonary complications and hospital length of stay. These studies have been compiled into meta-analyses and systematic reviews that concluded a beneficial effect of prehabilitation [42, 43]. Despite the enthusiastic conclusions of some authors, these studies suffer from significant flaws including heterogeneity in study designs and interventions, selection bias, lack of proper randomization or control arms, and small sample sizes [44••]. However, multiple higher quality studies report clearly improved cardiorespiratory capacity after prehabilitation in this patient population. For example, a randomized controlled trial of 40 COPD patients showed that 3 weeks of high-intensity training before lobectomy significantly improves the preoperative VO_2 peak (from 14.9 to 17.8 mL/kg/min, $p < 0.001$) and minimizes its postoperative decline (postoperative VO_2 peak 15.1 vs 11.4 mL/kg/min in the control group, $p < 0.01$) [45]. Clearly, short-term preoperative rehabilitation programs are feasible and safe to implement within the limited preoperative timeframe before lung cancer resection. Further research is still required to understand how these programs impact postoperative clinical outcomes, precluding strong evidence-based recommendation for clinical practice at this point [8••, 44••].

Another potential benefit of preoperative pulmonary rehabilitation is to improve preoperative cardiopulmonary reserve in patients deemed at high perioperative risk, thereby improving surgical candidacy in patients who may have otherwise been denied tumor resection. Evidence to support this purpose is currently limited. However, a very promising pilot study recruited 8 COPD patients who were initially denied lung cancer resection because of severe pulmonary or exercise capacity impairment (with FEV_1 as low as 18% of predicted or 6-min walking distance as short as 120 m). After 4 weeks of an intensive inpatient rehabilitation program, all patients underwent lobectomy with no postoperative mortality and acceptable morbidity (one hemorrhage and one atrial fibrillation) [46].

Smoking Cessation

In the perioperative setting, tobacco smoking causes a variety of detrimental effects: increased carbon monoxide levels, increased mucous production and airway reactivity, coronary vasoconstriction, increased myocardial oxygen consumption, impaired immune function and tissue healing, and enhanced platelet aggregation. These pathophysiologic effects lead to major postoperative adverse consequences such as PPC, myocardial ischemia, surgical site infections, and thromboembolic complications [47, 48]. More specifically related to thoracic surgery, in a recent retrospective study of 666 patients undergoing lung cancer resection surgery, smoking was associated with significantly increased risk of PPC (22.3% vs 3.5%, $p < 0.001$) and higher postoperative mortality (2% vs 0%, $p = 0.025$) [49].

Being the most important risk factor for lung cancer, tobacco smoking has been reported in more than 20% of patients at the time of lung resection surgery [50]. Preoperative evaluation and management of this major potentially modifiable risk factor is therefore critical. The long-term benefits of smoking cessation on surgical patients are undisputed and intensive preoperative smoking cessation strategies have clearly been shown to reduce the incidence of postoperative complications as well as increase long-term abstinence rates [51, 52••]. Earlier studies have raised concerns of a paradoxically increased complication rate associated with short-term (<4–8 weeks) preoperative smoking cessation [53]. However, more recent studies have refuted such concerns [54]. Nevertheless, most retrospective reports on lung resection surgery suggest that longer durations of preoperative cessation are associated with improved clinical outcomes [49, 50, 53, 55]. Based on this evidence, international guidelines recommend a minimum duration of preoperative smoking cessation of 4 weeks to improve short-term postoperative outcomes after lung surgery [56••].

Various strategies have been employed to aid preoperative smoking cessation. Interventions that have demonstrated benefits include intensive counseling and pharmacotherapy such as nicotine replacement therapy, bupropion, and varenicline [52••, 57].

Nutritional Support

Whether defined as hypoalbuminemia (< 30 g/L), significant recent weight loss or underweight (body mass index < 18.5 kg/m^2), malnutrition is highly prevalent in the thoracic

surgical population and is strongly associated with worse postoperative clinical outcomes including mortality [58–61]. However, it remains unclear whether optimizing nutritional state prior to lung resection surgery results in lower complication rates. In a historical cohort study of patients undergoing lung cancer surgery, addition of intensive nutritional support to conventional pulmonary prehabilitation improved postoperative complication rates only in the subgroup of patients with worse preoperative comorbidities and risk [62]. One small randomized trial ($n = 32$) reported decreased length of stay after lung resection surgery in patients receiving 10 days of micronutrient supplementation preoperatively, without significant differences in complication rates [63]. Another small randomized trial ($n = 58$) showed a decreased complication rate and improved postoperative albumin levels in non-malnourished patients receiving immune-modulating diets preoperatively [64]. Current guidelines acknowledge the current limited level of evidence but recommend nutritional screening in patients assessed for lung surgery and preoperative oral nutritional supplements in patients deemed at nutritional risk [56••].

Conclusion

Patients undergoing lung resection surgery are at particular risk of postoperative cardiovascular and pulmonary complications due to shared risk factors and the physiologic consequences of surgery and anesthesia. In this specific patient population, cardiovascular risk assessment can be refined using the Thoracic Revised Cardiac Risk Index and cardiac biomarkers. A "3-legged stool" approach to respiratory assessment, including evaluation of lung mechanics, parenchymal function, and cardiopulmonary reserve is essential to estimate perioperative risk and determine surgical candidacy in all patients undergoing anatomical lung resection. Preoperative pulmonary rehabilitation, including exercise training, nutritional support, and smoking cessation programs, has shown promising results in improving postoperative clinical outcomes and surgical candidacy and will likely play a more important role in perioperative management in the near future. Despite the above-described encouraging data, further research is still needed to elucidate specific controversies in the preoperative management of patients undergoing lung resection. Individualized precise risk assessment to evaluate surgical candidacy with acceptable perioperative risk, management strategies to minimize cardiac and respiratory complications, and long-term clinical benefits of prehabilitation are yet to be defined.

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Compliance with Ethical Standards

Conflict of Interest Alonso Blanch, Florin Costescu, and Peter Slinger declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any original studies with human or animal subjects performed by any of the authors.

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