Review Article

Preoperative functional workup for patients with advanced lung cancer

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Abstract: Locally advanced lung cancer remains a surgical indication in selected patients. This condition often demands larger resections. As a consequence preoperative functional workup is of paramount importance to stratify the risk and choose the most appropriate treatment. We reviewed the current evidence on functional evaluation with a special focus on specific aspects related to locally advanced lung cancer stages (i.e., risk after neoadjuvant treatment, pneumonectomy). Evidence is discussed to provide information that could assist clinicians in their preoperative workup of these challenging patients.

Keywords: Preoperative evaluation; exercise test; pulmonary function test; complications; mortality; quality of life; lung cancer

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Introduction

Locally advanced lung cancer remains a surgical indication in selected patients. This condition often demands extended resections involving larger amount of lung tissue (i.e., pneumonectomy) and resection of adjacent organs or structures (chest wall, large vessels, complex airways reconstruction etc.).

The resulting pathophysiologic impact of surgery in these patients is therefore greater than after standard anatomic resections performed for earlier cancer stages.

As a consequence, preoperative functional evaluation appears of paramount importance to reliably assess the risk of operation, an important element in the shared decision making process.

The principle steps of the preoperative functional workup do not differ compared to standard lung resections.

They include a preliminary cardiologic evaluation and a cardiopulmonary assessment.

Current algorithms

For practical reasons, published evidence on operability and functional assessment is often summarized in algorithms. Algorithms are generic guides to standardize the preoperative clinical practice minimizing variations and inappropriate exclusions. However, this schematic representation cannot capture the entire spectrum of patients and exceptions may occur. Patients should always be evaluated on an individual basis.

The most recent functional algorithm is the one proposed by the American College of Chest Physicians (1).

In summary, after a preliminary cardiologic evaluation, patients with low cardiologic risk or with an optimized cardiologic treatment may proceed with the rest of functional workup. Forced Expiratory Volume in 1 second (FEV_1) and carbon monoxide lung diffusion capacity (DLCO) should be measured in all patients, expressed as percentage of predicted values and their predicted postoperative values (ppo) calculated. Patients deemed at low cardiologic risk (see following paragraph) and with both $ppoFEV_1$ and ppoDLCO greater than 60% are regarded at low risk for surgery (risk of mortality lower than 1%). Patients with either $ppoFEV_1$ or ppoDLCO between 30% and 60% should perform a low technology exercise test (shuttle walk test or stair climbing test) as a screening test. If the performance at low technology exercise test is satisfactory (stair climb >22 m or shuttle walk distance >400 m) patients are regarded at moderate risk (morbidity and mortality rates may vary according to the values of split lung functions, exercise tolerance and extent of resection). Cardiopulmonary exercise test is indicated in cases where either ppoFEV_1 or ppoDLCO are lower than 30% or when the performance at stair climbing test or shuttle walk test is deemed not satisfactory (i.e., altitude reached at stair climbing test <22 m or a shuttle walk distance <400 m). Maximum oxygen consumption (VO_2max) values lower than 10 mL/kg/min or 35% predicted indicate high risk for major anatomic resection through thoracotomy (risk of mortality may be higher than 10%. Considerable risk of severe cardiopulmonary morbidity and residual functional loss is expected). Conversely VO_2max values greater than 20 mL/kg/min or 75% predicted indicate low risk. All values in between indicate intermediate risk.

Cardiac risk evaluation

The risk of major cardiac events, defined as the occurrence of ventricular fibrillation, pulmonary edema, complete heart block, cardiac arrest or cardiac death during admission has been reported to be approximately 3% after major anatomic lung resection (2,3). Typical candidates to pulmonary surgery for lung cancer usually have both pulmonary and cardiac disease as a result of cigarette smoking and are potentially at increased risk for perioperative cardiovascular complications. The risk of postoperative major cardiac events, including cardiac death, is about 3% (2,3). The specific available literature on cardiac risk after lung resection is minimal. In general, the incidence of coronary artery disease (CAD) in surgical candidates with lung cancer ranges from 6.5% to 8% according to the most updated figures from the European Society of Thoracic Surgeons (ESTS) database. The presence of CAD increases surgical risk. An analysis based on data from the Surveillance, Epidemiology, and End Results-Medicare and including patients undergoing lung cancer resection within 1 year after coronary stenting showed higher rates of major cardiovascular events and mortality in stented patients compared to no-stented ones (9.3% and 7.7% *vs.* 4.9% and 4.6%, both P<0.0001) (4).

The available guidelines on preoperative cardiac evaluation in our field (1,5) are substantially based on the American Heart Association/American College of Cardiology guidelines on evaluation and care of cardiac risk in non cardiac major surgery (6).

In general, detailed evaluation for coronary heart disease is not recommended in patients who have an acceptable exercise tolerance (6-8), and in those with a Revised Cardiac Risk Index (RCRI) <2 (1).

The RCRI, as originally published by Lee *et al.* (2) is a 4-class 6-factors cardiac risk score including history of coronary artery disease, cerebrovascular accident, insulin-dependent diabetes, congestive heart failure, serum creatinine level greater than 2 mg/dL and high-risk surgery. All factors are equally weighed and one point is assigned for their presence (2).

Although RCRI has been indicated as the preferable cardiac risk score by the recently published American Heart Association/American College of Cardiology (6) and European Society of Cardiology/European Society of Anesthesiology guidelines (9) and the joint ERS-ESTS task force on fitness for radical treatment of lung cancer patients (5) this score was originally developed from a generic surgical population including only a small group of thoracic patients. Most recently, Brunelli *et al.* (3) recalibrated the RCRI in a large population of candidates to major anatomic lung resection, generating a simplified weighed score, in which only 4 of the original 6 factors remained associated with major cardiac morbidity with different weights (history of coronary artery disease, 1.5 points; cerebrovascular disease 1.5 points; serum creatinine level greater than 2 mg/dL, 1 point; and pneumonectomy, 1.5 points). The resulting aggregate score, ranging from 0 to 5.5 points and named Thoracic RCRI, was found to be more accurate than the traditional one in this population (c index 0.72 *vs.* 0.61, P=0.004). Patients in the highest class of risk have a risk of major cardiac events as high as 23% *vs.* 1.5% in those with the lowest score (no risk factors). This recalibrated score was subsequently validated by a number of studies (3,10,11).

Based on these recent evidences, the ACCP guidelines included this parameter in their updated cardiac algorithm.

For patients whose exercise capacity is limited, those with a ThRCRI >1.5 or those with known or newly suspected cardiac condition, non-invasive cardiac evaluation is recommended as per AHA/ACC guidelines (6).

Appropriately aggressive cardiac interventions however should be instituted prior to surgery only in patients who would need them irrespective of the planned surgery. In fact, prophylactic coronary revascularization prior to surgery in patients who otherwise do not need such a procedure does not appear to reduce perioperative risk (12).

Finally, cardiopulmonary exercise testing (CPET) has been shown to be a useful tool to detect both overt or occult exercise-induced myocardial ischemia with a diagnostic accuracy similar to single photon emission computed tomographic myocardial perfusion study (13,14) and superior to standard electrocardiogram stress testing (15). For this reason, CPET can be proposed as a non-invasive test to detect and quantify myocardial perfusion defects in patients at increased risk for coronary artery disease.

Pulmonary function evaluation

The two parameters most frequently used in pulmonary risk assessment are predicted postoperative FEV_1 ($ppoFEV_1$) and predicted postoperative Carbon Monoxide Lung Diffusion capacity (ppoDLCO). They are calculated based on the number of functioning segments to be removed during operation.

Perusion scan, bronchoscopy and CT scan findings can be used to estimate the patency of the bronchus and segmental structure.

Many studies have shown the role of $ppoFEV_1$ in predicting postoperative complications and in selecting patients for surgery.

Markos *et al*. found that half of the patients with a $ppoFEV_1$ <40% died in the perioperative period (16). These authors were the first to use percentage of predicted values instead of absolute values. Subsequently, others have confirmed that perioperative risk increase substantially when the $ppoFEV_1$ is <40% of predicted normal (17-23).

However, these findings have been challenged by other authors who have shown acceptable postoperative mortality rates in patients with prohibitive $ppoFEV_1$ (24,25).

Brunelli *et al*. (24) showed that whereas $ppoFEV_1$ was the only significant predictor of cardiopulmonary complications in patients without airflow limitations (FEV_1 >70%), it failed to predict complications in those with FEV_1 <70%.

The weak association between complications and $ppoFEV_1$ in obstructed patients can be explained by the so-called "lobar volume reduction effect". In candidates for lobectomy with lung cancer and moderate to severe COPD, the removal of the most affected parenchyma may determine an actual improvement in the elastic recoil, a reduction of the airflow resistance, and an improvement in pulmonary mechanics and V/Q matching, similar to what happens in typical emphysema candidates for lung volume reduction surgery.

Many studies have shown the minimal loss or even the improvement in pulmonary function after lobectomy in COPD patients with cancer, questioning the traditional operability criteria mostly based on pulmonary parameters (26-33).

DLCO has firstly been shown to be a predictor of adverse outcomes after pulmonary resection in the 1980s' by Ferguson *et al*. (34). They showed that patients with DLCO <60% had a mortality rate of 20%. These findings have been subsequently confirmed by other authors (16,17).

Similarly, patients with ppoDLCO <40% had a mortality rate of 23% (35). Moreover, a linear inverse correlation exists between pulmonary complications and ppoDLCO (36) with patients with ppoDLCO <30% that may have a risk of pulmonary complications greater than 80%.

Recent papers have shown that the FEV_1 and DLCO are poorly correlated and that more than 40% of patients with normal FEV_1 (>80%) may have DLCO <80%, and 7% of them may have a ppoDLCO <40% (37).

In addition, a reduced ppoDLCO has been shown to be a predictor of cardiopulmonary morbidity and mortality not only in patients with reduced FEV_1 but also in those with normal respiratory function (37-39). Based on these evidences recent functional guidelines (1,5) recommend the measurement of DLCO in all candidates to lung resection regardless their preoperative FEV_1 value.

Exercise testing

Exercise testing has the capability to assess the entire oxygen transport system and to detect possible deficits that may predispose to postoperative complications (40).

In the lung, exercise determines an increase in ventilation, VO_2, carbon dioxide excretion and blood flow, similar to those experienced after lung resection.

Several tests can be used in the clinical practice and they can be classified as low-technology test, with a limited use of resources and personnel, and high-technology tests, such as the cardiopulmonary test with direct measurement of the expired gases during incremental exercise on a bike or treadmill.

Low-technology test

The most frequently used low-tech tests in our specialty are the shuttle walk test and stair climbing test.

Shuttle walk test: it has been estimated by regression analysis that 25 shuttles on the shuttle walk test indicate a VO_2max of 10 mL/kg/min (41).

Benzo *et al*. (42) have recently shown that VO_2 measured during shuttle walk test is highly correlated with the level (or minute) of the test. A cut off of 25 shuttles walked had a PPV of 90% for predicting a VO_2max >15 mL/kg/min.

Stair climbing test: Olsen *et al*. (43) found that the ability to climb three flights of stairs most clearly separated those patients with longer hospital stay, postoperative intubation and greater frequency of complications. Girish *et al*. (44) found that the inability to climb two flights of stair was associated with a positive predictive value for occurrence of complications of 80%, conversely the ability to climb more than five flights of stairs was associated with a negative predictive value of 95%.

In a large series of 640 major anatomic resections (45), Brunelli *et al*. found that compared to patients able to climb more than 22 m those not reaching 12 m had 2.5-fold higher rate of cardiopulmonary complications, 3-fold higher rate of cardiac complications and a mortality rate of 13% versus only 1%. In the 73 patients with prohibitive pulmonary function (ppoFEV_1 <40% or ppoDLCO <40% or both), all of those climbing more than 22 m survived the operation, whereas 2 of 10 climbing lower than 12 m died.

Cardiopulmonary exercise test (CPET)

Cardiopulmonary exercise test is the gold standard in preoperative evaluation of lung resection candidates. It is performed in a controlled environment with continuous monitoring of various cardiologic and pulmonary parameters, it is standardized and easily reproducible in different settings, and in addition to VO_2max provides several other direct and derived measures that permit to identify possible deficits in the oxygen transport system.

The European guidelines emphasized the role of high technology exercise testing. Ideally all patients with FEV_1 or DLCO or both <80% predicted and those with a significant history of cardiac disease should perform this test (5).

The recent ACCP functional guidelines also put emphasis on this methodology (1). In patients with lung cancer and candidates to lung resection with either ppoFEV_1 or ppoDLCO <30% predicted, or with an altitude <22 m reached at stair climbing test or with a positive high risk cardiac evaluation, a cardiopulmonary exercise test is recommended.

This recommendation is based on several evidences showing the importance of VO_2max in predicting cardiopulmonary complications and mortality in our specialty.

Several small studies in the 80's and early 90's found an association between low VO_2max and mortality after lung resection (46-48).

In 1995, Bolliger *et al*. demonstrated that the probability of developing complications in patients with a VO_2max greater than 75% of predicted was only 10% whereas the probability of developing complications was as high as 90% in those with VO_2max below 40% of predicted (49).

In a large series including more than 400 patients from the Cancer and Leukemia Group B national multicenter database, Loewen and colleagues showed that complicated patients had a significantly lower VO_2max compared to non-complicated ones and confirmed the above mentioned investigations (50).

Brunelli *et al*. confirmed the safety threshold of 20 mL/kg/min (no mortality, 7% cardiopulmonary morbidity rate), but found that values of VO_2max below 12 mL/kg/min increased the risk of mortality (51). In these patients, the cardiopulmonary morbidity and mortality rates were 33% and 13%, respectively.

A recent meta-analysis confirmed the importance and the ability of VO_2max in predicting cardiopulmonary complications or mortality after pulmonary resection (52). Most of the studies generally agreed that a value of VO_2max below 10–15 mL/kg/min was to be regarded as a high-risk threshold for lung resection and that values above 20 mL/kg/min are safe for any kind of resection, including pneumonectomy.

In addition to VO_2max, several authors have published about other derived parameters (i.e., efficiency slope, oxygen pulse, VE/VCO_2 slope), which proved to be predictive of cardiac and pulmonary complications (53-56). In particular a VE/VCO_2 slope greater than 34 was associated with increased risk of pulmonary complications and mortality after lung resection independent of VO_2max (53,54,56).

Specific situations

Neoadjuvant therapy

Many patients with locally advanced lung cancer receive preoperative chemotherapy or radio-chemotherapy before surgery as part of their multimodality treatment. Evidence shows that induction chemotherapy or radio-chemotherapy can increase the risk of mortality after pneumonectomy, especially right pneumonectomy, up to 30% (57-61), although recent reports have mitigated these findings (62-64).

Unlike pneumonectomy, the risk of mortality or respiratory complications does not appear increased after lobectomy (5).

Recent reports suggest that chemotherapy can be associated with a 10% to 20% reduction in DLCO despite stable or improved spirometric values (65-68). These changes are associated with drug-induced structural lung damages (69) and have been associated with an increase in postoperative respiratory complications (66,67,70). Therefore, re-assessment of pulmonary status and DLCO after induction therapy and prior to resection is recommended to ensure that the operative risk has not increased as a result of newly impaired DLCO (1,5).

Pneumonectomy

Locally advanced cancers may more often require pneumonectomy to guarantee an oncologically radical resection. In the most updated European database report pneumonectomy represents 10.8% of all lung excisions for cancer and its in-hospital mortality rate is 6% (3 fold higher than after lobectomy). In the Society of Thoracic Surgeons (STS) database the 30 days mortality rate after pneumonectomy is reported as 4.9% (71).

Evidence shows that these rates increase at 90 days after discharge of an additional 6% (72). In a recent study from the national cancer database on approximately 8,000 pneumonectomies operated on in four years the conditional 90 days mortality rate was 6% for a total mortality rate at 90 days after surgery of 14% (73).

In addition to an immediate increased risk of mortality, pneumonetomy is also a strong adverse factor influencing long-term prognosis in patients with early stage lung cancer (74).

This is particularly evident in patients with T1N0 stage in whom the 5-year survival after pneumonectomy is only 41% versus 68% after lesser resections. This finding was confirmed by other authors who found an additional risk of right sided pneumonectomy in early stage lung cancer with a 5-year survival after right pneumonectomy of only 33% (75). Pneumonectomy is also a consistent factor associated with a poorer quality of life after surgery (76-78) and greater functional loss (32). The average FEV_1 and DLCO losses three months after pneumonectomy have been reported to be 34% and 20% respectively compared to the preoperative values.

In addition to the respiratory impairment, pneumonectomy determines late cardiac effects such as a cardiac repositioning, reduced stroke volume and cardiac output, reduced left ventricle ejection fraction, increased right ventricle end diastolic volume, increased pulmonary artery systolic pressure (79-821).

For the above mentioned reasons, although the current guidelines do not recommend additional tests specific for pneumonectomy, I prefer to refer all pneumonectomy candidates to CPET for detecting underlying coronary artery disease, pulmonary hypertension and ventilatory inefficiency.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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