



Innovative functional staging and assessment of operative risk in candidates for pneumonectomy

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Abstract: Pneumonectomy, removal of the entire lung, first performed in 1933 continues to be an important operation for the thoracic surgeon in 2019. However, given the recognised high mortality and morbidity associated with this procedure, there is concerted effort to try and avoid performing a pneumonectomy wherever possible. The UK thoracic registry shows that this operation now accounts for around 5% of lung cancer operations as opposed to 40% in 1980. When pneumonectomy is necessary, meticulous pre-operative assessment and planning is critical. We evaluate the current literature and review the most relevant evidence in order to define a practical approach for the preoperative functional assessment in patients likely to need pneumonectomy. We also discuss ways in which developments are happening in managing this high-risk group of patients.

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Introduction

The greatest challenges around pneumonectomy are often not in the operating theatre, where the technical aspects of the operation are mostly straightforward. Rather it is around the appropriate selection, investigation and work up of these patients. The process of referral frequently begins with the family doctor or respiratory physician who will see the patient for initial investigations and diagnosis. The surgeon may only become involved at a late stage in the patient's treatment pathway and so this process needs to be streamlined and efficient.

The first point we emphasise is the active involvement of dedicated thoracic surgeons at all lung cancer patient meetings—something that is clearly supported by recommendations (1). In the setting of early stage lung cancer, surgery is recognised as the best treatment option. It is our experience that the patient pathway to surgery can

become unnecessarily extended as further investigations are carried out. The wider multidisciplinary team do not always recognise when surgical resection is only possible in the form of pneumonectomy and therefore the investigations we will discuss are not readily requested necessitating multiple hospital visits. This will not only be distressing for the patient but can ultimately lead to disease progression and in the worst case, inoperability.

Over the past few decades there has been significant work focusing on perioperative risk assessment. The traditional assessment of a patient's pulmonary function risk and cardiovascular status is well described. There had been numerous spirometric values suggested below which patients should be excluded from certain levels of surgical lung resection. These values in isolation did not provide accurate information on surgical risk and outcomes leading to other factors, such as lung diffusion capacity (DLCO)

being used. These measurements were then used as the standard practice for preoperative functional assessment at the end of the last millennium. Since then, the most major development has been the increased role of the ergometric capacity assessment—through the use of the cardiopulmonary exercise test (CPET).

The current evidence now clearly supports pre-operative functional evaluation using pulmonary function tests with DLCO measurements, accurate cardiac assessment and the use of the CPET (1). However, it should be stated that while we continue to develop a greater understanding of surgical risk assessment it is becoming increasingly important that care pathways should be tailored to each patient. We may all have seen patients with cardiac co-morbidity and poor lung function who are then able to climb four flights of stairs in the clinic without becoming breathless. The decision to offer this patient a pneumonectomy can be difficult and the surgeon may need to rely on clinical acumen.

Cardiac risk

Recent algorithms recommend that the first step in risk stratification should focus on cardiac assessment (2). Patients with lung cancer who have been cigarette smokers are at increased risk of atherosclerotic cardiovascular disease with rates of co-existing coronary artery disease up to 20% (3). The risk of major cardiac complications following any lung resection is around 2–3%. Those patients who undergo resection in the form of pneumonectomy are likely to be at the highest risk (3,4).

It is now 20 years since Lee *et al.* developed the Revised Cardiac Risk Index (RCRI) for patients undergoing major non-urgent cardiac surgery (5). Brunelli *et al.* refined this and produced the (thoracic) ThRCRI risk score (4). In calculating the risk of a cardiac complication for a patient undergoing lung resection, four different factors are taken into account—history of coronary artery disease, cerebrovascular disease, serum creatinine greater than 2 mg/dL and pneumonectomy. Pertinently the patient undergoing pneumonectomy has a score of at least 1.5 and a risk of at least 5.8%.

The most recent ACCP guidelines have stated that a ThRCRI with 1.5 or above is one the reasons to refer for a cardiology opinion (1). At this point patients should be investigated as per American Heart Association/American College of Cardiology guidance (6). Noninvasive investigation is indicated including echocardiogram. This test can be used to measure pulmonary artery pressures

and right heart function—important information prior to a planned pneumonectomy. However, measuring pulmonary artery pressures, during exercise, has not been helpful in predicting which patients might develop post-operative complications (7). CPET, as well as providing data on postoperative outcome, has been shown to have a role in the investigation of myocardial ischaemia and is becoming a crucial part of pre-pneumonectomy planning (8).

Spirometry and diffusing capacity

The Forced Expiratory Volume at First Second (FEV1) and Predicted Postoperative (PPO) FEV1 are no longer used in isolation to predict postoperative outcome but remain important measurements for the thoracic surgeon. There are a host of studies showing that a reduced FEV1 or PPO FEV1 is associated with increased morbidity and mortality rates in patients undergoing lung resection. It was Licker *et al.* that showed an FEV1 <60% was an independent risk factor for mortality and respiratory morbidity (9).

Several studies have shown that the FEV1 is not, in isolation, a good indicator of post-operative outcome. It was also demonstrated that the FEV1 had a limited role in predicting complications in patients with chronic obstructive pulmonary disease (COPD) (10). In fact, there is plenty of evidence showing pulmonary function can be improved following lobectomy in patients with severe COPD (11). These differences in study outcomes demonstrate why the FEV1 is not a reliable independent assessment of functional status. The 2013 guidelines by Brunelli *et al.* recommend that it should be used as part of the pre-operative physiological evaluation (1).

The role of the Carbon Monoxide Lung Diffusion Capacity (DLCO) as an independent assessment of surgical risk was first demonstrated by Ferguson *et al.* (12). The study showed that an impaired DLCO correlated with the development of postoperative respiratory complications and death. When the DLCO was <60%, the complication rate was 40% and mortality was 20%. Berry *et al.* confirmed similar findings in 2010—pulmonary complication rate was at approximately 40% when the DLCO <45% (13).

Ferguson also pioneered work looking at the PPO DLCO—his study from 1995 showed that the PPO DLCO and age were the only predictors of outcome in respect of complications and mortality (14). Similarly, Brunelli demonstrated that age and PPO DLCO <40% were the only predictors of morbidity following lung resections in his 2006 study (15). In 2008 Ferguson showed that PPO DLCO

was a significant predictor of pulmonary complications and mortality both in patients with and without COPD (16).

In respect of the planned pneumonectomy, values of PPO FEV1 and PPO DLCO >60% indicate low risk for mortality and cardiopulmonary morbidity. If the values are <60% then the patient should certainly go ahead with further functional assessment as discussed below. It is important to state that a low PPO DLCO should not, on its own, exclude a patient from pneumonectomy (1).

CPET

Cardiopulmonary exercise testing is now the gold standard in functional assessment and risk stratification of patients proceeding with pulmonary resection. It provides a detailed and broad physiological evaluation of the patient that allows for measurement of the maximal oxygen consumption (VO_2max). The VO_2max was the first ergometric measurement found to be associated with postoperative morbidity and mortality. Bollinger *et al* showed that patients with a VO_2max <60% had high rate of post-operative morbidity approaching 90% (17).

In 2009, Brunelli *et al.* demonstrated that the VO_2max was the best predictor of respiratory complications (18). The same study showed that patients with a VO_2max <12 mL/kg/min had a mortality rate of 13 % while patients with a VO_2max >20 mL/kg/min had no post-operative mortality. Licker *et al.* showed that patients submitted to lung resection with a VO_2max <10 mL had a total morbidity of 65% (19).

A patient with a VO_2max >20 mL/kg/min can safely proceed with surgical resection in the form of pneumonectomy (1). There is plenty of evidence to support this—Brunelli *et al.* demonstrated that patients undergoing anatomical lung resection with a VO_2max >20 mL/kg/min had no post-operative mortality (18). A VO_2max <10 mL/kg/min is now generally regarded as a contraindication to lung resection and arguably an absolute contraindication for pneumonectomy (1). Case series have consistently shown that patients with a VO_2max <10 mL/kg/min have a very high risk of postoperative mortality (20). A VO_2max between 10 and 15 mL/kg/min is associated with an increased risk of postoperative mortality (17).

For the patient who presents for pneumonectomy with a VO_2max between 10 and 15 mL/kg/min then the Minute Ventilation to Carbon Dioxide Output (VE/VCO_2) Slope can be helpful. In 2010 it was shown to be an independent predictor of mortality. A $\text{VE}/\text{VCO}_2 \geq 34$ was related to a

mortality rate of 5.5% after lung resection (21). Brunelli *et al.* demonstrated that patients with a $\text{VE}/\text{VCO}_2 \geq 35$ were three times as likely to suffer postoperative respiratory morbidity (22). Shafiek *et al.* confirmed this value and verified a $\text{VE}/\text{VCO}_2 > 35$ as a predictor of increased morbidity and mortality (23). It is hoped that further study will define the role of the VE/VCO_2 in coming years.

Stair climbing

Often seen as a substitute for the CPET, this is something that the surgeon can directly engage with and use themselves during the clinic review. Such is the simplicity of this assessment it can be used alongside the above tests for further validation when the surgeon is presented with borderline results. This assessment involves use of greater muscle mass than cycling and has been shown to yield greater values of VO_2max (20). Undertaking it in the clinic when the patient is not expecting it may help in assessing the patient's level of motivation and attitude. These two factors that are of critical importance when undergoing pneumonectomy and/or assessed to be at high risk.

Formalised care pathways

With decreasing rates of pneumonectomy, it is increasingly important that the patient is cared for in a specialist environment. This is 2-fold—intraoperatively it may actually be possible to avoid resection by pneumonectomy in the hands of an experienced and specialist thoracic surgeon. Secondly, the patient should have their post-operative care in an environment familiar with caring for this particular group of patients. There are numerous studies that have found reduced mortality rates when the patient with lung cancer is operated on by a specialist thoracic surgeon as opposed to a general surgeon (24). Additionally, increased resection rates have been demonstrated when the patient is operated on by the specialist thoracic surgeon (25). European guidance on fitness for radical treatment recommends that lung cancer surgery is performed in specialist centres by thoracic surgeons.

The unit is another factor that has been consistently shown to impact on patients' outcomes. There are numerous studies showing improved operative mortality in high volume centres (26,27). Additionally, long-term survival has been shown to be better in centres with high volume (27). The ERS–ESTS advise that lung resections be performed in specialist centres that have a minimum

caseload of 20–25 anatomic resections per year (2).

Even in the specialist centre, the care of the pneumonectomy patient should be seen as unique. In our own unit, a specialist, high volume centre in the UK, we have had discussions about peri- and post-operative care of these patients. The idea of a standardised care pathway has been discussed. The surgeon must remain mindful that these patients are not solely managed by the surgical team. Just as critical to outcomes are the appropriate management of these patients by the anaesthetic and nursing teams.

High risk surgical meetings

The aim of the physiological assessment is to identify those patients at high risk of surgical morbidity and mortality. As we have discussed, pneumonectomy can immediately place patients into a high-risk group. However, despite high perioperative risk, it must be kept in the context that surgery for early-stage lung cancer is the most effective treatment currently available. The surgeon therefore needs to constantly balance the recommendations of the multi-disciplinary team, patient expectation and patient risk. This can be difficult but be facilitated by working with surgical colleagues and with the wider peri-operative team including the anaesthetist and intensivist.

It is important to state that these challenges continue in an era that is seeing increased emphasis being placed on surgical outcomes. In the coming years, it is likely that the thoracic surgeon will need to become more comfortable at working alongside colleagues. In a high risk meeting setting patients can be discussed with consultant colleagues allowing for open and honest discussion and hence increased rigor in decision making. In the same manner, two consultant operating is likely to gain further momentum. This is not necessarily a reflection of the technical difficulty of the operation but can help with decision making and risk management. In our own unit, all planned and potential pneumonectomy resections are discussed in a high-risk surgical meeting.

Optimisation

One of the outcomes from our own high-risk surgical meetings is suggestion of pre-operative patient optimisation. While a short time to surgical resection remains essential, consideration may be paid to smoking cessation and completion of some form of pulmonary rehabilitation. The problem of patients who continue to smoke up until

surgery are well described in clinical practice—thick, tenacious endobronchial secretions can delay and impair post-operative recovery. The patient who continues to smoke up until operation can present a difficult dilemma for the surgeon with little evidence to support cancellation. Studies have shown that the timing of smoking cessation prior to surgery has minimal impact on postoperative complications (28). However, a longer length of pre-operative smoking cessation has been shown to decrease operative mortality (29). This is important information to share with the patient who continues to smoke despite advice.

Pulmonary rehabilitation is already well known to the thoracic surgeon. In the setting of lung volume reduction surgery (LVRS) it has been shown to improve breathlessness, quality of life and exercise ability (30). However, at present there is no strong evidence to support the use of pulmonary rehabilitation prior to lung cancer resection surgery. One study has shown that a pre-operative regimen reduced patient's length of stay (31). Conversely, a study has shown that cardiopulmonary performance is not improvement following a rehab programme (32). There is certainly a need for a randomised controlled trial to investigate this properly.

Enhanced recovery after surgery (ERAS) is now a widely adopted practice in many specialised thoracic centres. Early mobilisation and rehabilitation following surgery has shown significant benefit in terms of pulmonary function tests, symptoms and exercise performance (33). Mobilisation after pneumonectomy remains critically important to prevent atelectasis and chest infection in the remaining lung.

ACCP guidelines recommend that high risk patients, which arguably includes everyone for which resection with pneumonectomy is likely, should be referred for pulmonary rehabilitation (1). With this in mind, medical colleagues seeing the patient at diagnosis should look to make an early referral. Looking toward the future, the format in which pulmonary rehabilitation can be offered is diverse and developing. There are now app based programmes that can be used to support the patient remotely and immediately (34). Given continuous improvements in technology this is something that may emerge as a further tool to support the patient being submitted to pneumonectomy in the coming years.

Conclusions

Pneumonectomy will continue to remain an important

operation for the thoracic surgeon in the coming years. A careful and thorough pre-operative physiological assessment allows the surgeon and wider team to identify those at the highest risk. This functional assessment can then help the surgeon identify areas for optimisation and ensure that those patients for whom pneumonectomy offers the best chance of cure are not unnecessarily denied the offer of surgery.

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Footnote

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