Fitness for radical treatment of lung cancer patients

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Educational aims

❭ To discuss the strengths and weaknesses of lung function tests, exercise tests and split-function studies used to assess fitness before lung resection
❭ To outline the importance of the perioperative management of lung cancer patients
❭ To understand the lack of clear recommendations and the need for further studies to assess fitness before chemoradiotherapy

Summary

Surgical pulmonary resection and chemoradiotherapy both induce significant mortality and morbidity in lung cancer patients. Many studies have intended to identify the patients at increased risk of treatment-induced complications. In this review, we will describe the various tests proposed to assess fitness before radical treatment of lung cancer. We will also consider the strategies aimed at using the less invasive and most powerful investigations, summarised as functional algorithms in scientific societies' guidelines. The main recent studies, published after the guidelines were available, will also be reviewed.

Resting pulmonary function tests and measurements of pulmonary haemodynamics have traditionally been used to assess fitness before resection of lung tumours [1]. In the 1970s, split-function studies based on combined scintigraphic perfusion scans and spirometric measurements allowed prediction of the functional loss after lung resection [2]. Today, the calculation of the predicted post-operative (ppo) values is part of the pre-operative work-up of lung cancer patients. In the 1990s, exercise testing was presented as an ideal tool to evaluate the patient's fitness, providing parameters to estimate not only the pulmonary, but the whole cardiopulmonary reserve [3]. Maximal oxygen uptake ($V'O_{2,max}$) measurement was demonstrated to have a strong predictive value for perioperative mortality. Since then, algorithms, including resting lung function tests, split-function studies and exercise testing, have been elaborated, offering a basis for functional guidelines.

Surgery remains the best treatment option for non-small cell lung cancer, but only 20–25% of lung cancer patients are operable. Therefore, offering surgery to patients deemed to be inoperable remains highly relevant. The recent advances in anaesthetic and surgical techniques, as well as improvement in perioperative management, have led to reconsideration of lower limits of operability. However, most lung cancer patients are treated with chemo- and/or radiotherapy, which have well-known lung toxicity. In addition to impairing quality of life, this toxicity may be dose-limiting or may increase the risk of post-operative complications in patients included in neoadjuvant protocols. For these reasons, elaborating strategies to assess the risk of pulmonary complications in nonoperated lung cancer patients is also of importance, and has

been one of the aims of a European Respiratory Society (ERS)/European Society of Thoracic Surgery (ESTS) task force [4].

In this review, the various tests and cut-off values used to evaluate fitness before lung cancer treatment, as well as the algorithms published by the British Thoracic Society (BTS) [5], the American College of Chest Physicians (ACCP) [6] and the ERS/ESTS [4] will be considered, and the most recent studies published in this field will be presented.

Assessment before major lung resection

A cardiological evaluation has been integrated in all guidelines. As a second step, the ACCP [6] and the ERS/ESTS [4] have recommended measuring lung function and exercise capacity. They provide cut-off values beyond which the risk of complications is regarded as high, and summarise these recommendations in algorithms. Such algorithms are easy to put into practice and are widely used. However, operability does not rely exclusively on functional data, and there is usually no real threshold beyond which the risk of complications change radically. Consequently, the BTS [5] has recently elaborated an original algorithm based on a tripartite assessment. It includes the evaluation of post-operative cardiac events, perioperative death (based on the Thoracoscore, which will not be detailed in this review) and post-operative dyspnoea (based on forced expiratory volume in 1 s (FEV1) and diffusing capacity of the lung for carbon dioxide ($D_{L,CO}$)). The objective is to facilitate the assessment of individual outcomes that may be discussed by the multidisciplinary team and the patient [5]. Studies aimed at evaluating the results of this approach will be of interest.

Cardiological assessment

A cardiological evaluation is justified, as 10% of major complications and 50% of minor complications after lung resection have a cardiovascular cause [7]. The guidelines published by the BTS, ACCP and ERS/ESTS recommend using the American College of Cardiology and American Heart Association guidelines. The ERS/ESTS provides an algorithm based on a well validated score system, the revised cardiac risk index (RCRI), to estimate the patient's risk [8]. The calculation of this index is simple, since it is based on the medical history, physical examination,

baseline ECG and plasma creatinine measurement. Items encompass high-risk surgery (lobectomy or pneumonectomy), ischaemic heart disease (prior myocardial infarction or angina pectoris), heart failure, insulin-dependent diabetes, previous stroke or transient ischaemic attack (box 1). If the RCRI is $\geqslant 2$, or if the patient has a known or suspected cardiac condition or is unable to climb two flights of stairs, a specialised cardiac consultation is needed. The BTS and the ERS/ESTS guidelines also provide more detailed recommendations about the cardiological testing and treatments recommended before lung surgery. Updated recommendations can also be found in the recently published guidelines for pre-operative cardiac risk assessment, proposed the European Society of Cardiology and the European Society of Anaesthesiology [9].

Lung function tests

FEV1

Spirometry is widely available, well standardised and cheap. Among the multiple parameters measured, FEV1 has stood the test of time and has been included in all the published functional algorithms. However, its predictive value for post-operative complications is not very high, even if

Box 1 Calculating the revised cardiac risk index (RCRI) based on history, physical examination, baseline ECG and serum creatinine

Each item is assigned 1 point
- High-risk surgery (including lobectomy or pneumenectomy)
- Ischaemic heart disease (prior myocardial infarction or angina pectoris)
- History of heart failure
- Insulin-dependent diabetes
- Previous stroke or transient ischemic attack
- Pre-operative serum creatinine >2.0 mg per dL

If
- RCRI $\geqslant 2$,
- the patient has any cardiac condition requiring medications,
- the patient has a newly suspected cardiac condition, or
- the patient is unable to climb two flights of stairs,

a cardiological consultation is needed

the extent of resection is taken into account through the calculation of a ppoFEV1. In a recently published multivariate analysis, $V'O_{2,max}$, but not ppoFEV1, was an independent predicitve factor for cardiopulmonary complications [10]. In some series, patients with very low FEV1 have been operated upon with a reasonable rate of complications and without reduction of lung function, the latter result being attributed to a "volume reduction effect". Moreover, the ppoFEV1 overestimates the actual FEV1 observed in the first post-operative days. For these reasons, the decision to operate or not should not be based on ppoFEV1 alone. Finally, it is recommended to express FEV1 as % predicted rather than an absolute value. Indeed, a FEV1 of 1.5 L is 32% pred for a 35-year-old, 1.90 m tall male, but 71% pred for a 65-year-old, 1.60 m tall female.

$D_{L,CO}$

$D_{L,CO}$ evaluates the alveolar–capillary integrity, and reflects the surface area and pulmonary capillary blood volume available for gas exchange. It has been shown to be an independent predictor of post-operative mortality and morbidity after lung resection. A recent study demonstrated that the pre-operative $D_{L,CO}$ value predicted death from non-lung cancer-related causes and in a multivariate analysis, that only $D_{L,CO}$, and not FEV1, was prognostic [11]. In addition, patients with normal FEV1 may present with decreased $D_{L,CO}$ [12]. For these reasons, $D_{L,CO}$, combined with FEV1, comprises the first step of pulmonary assessment in the BTS and ERS/ESTS algorithms. The ACCP recommends measuring this parameter in patients with FEV1 <80% pred, or with dyspnoea or diffuse parenchymal disease on chest radiography.

Split-function study: calculation of ppo functional values

The evaluation of the residual lung function after surgery, through the calculation of ppoFEV1 and ppo$D_{L,CO}$, is widely recommended in patients with altered lung function [4–6]. Before lobectomy, the calculation using lung segment counting can predict post-operative FEV1 as accurately as ventilation–perfusion scintigraphy, and performing a scintigraphic study is usually not necessary, as the contribution of individual lobes to the overall ventilation or perfusion are usually not provided. Before pneumonectomy, the contribution of the lung to be resected can be evaluated using either ventilation or perfusion scintigraphy, both offering a good prediction of ppo values. The equations to calculate ppo

values before lobectomy or pneumonectomy are given in box 2 [4]. For the BTS, ventilation or perfusion scintigraphy is recommended if a ventilation or a perfusion mismatch is suspected [5].

When available, quantitative computed tomography (CT) scan, which has been shown to be as accurate as perfusion scintigraphy before pneumonectomy, can be used to evaluate the residual lung function, both before lobectomy and pneumonectomy. The nonfunctional lung areas are identified after applications of dual thresholds of -500 H (areas >-500 H denote areas of tumour, fibrosis or atelectasis) and -910 H (areas >-910 H denote areas of emphysema). The volumes are calculated by multiplying the area by the slice thickness. The regional and total functional lung volumes are determined by subtracting from the entire lung volume the nonfunctional lung volume resulting from pulmonary emphysema, tumour, atelectasis, and fibrosis. Magnetic resonance imaging, single-photon emission CT, which can be combined with CT scan, may also be used in the near future.

In the earliest guidelines [13–15], patients with ppoFEV1 and/or ppo$D_{L,CO}$ <40% were considered at high risk for major lung resection. Recently, some studies suggested that in algorithms including exercise testing, ppoFEV1 and ppo$D_{L,CO}$ cut-off values could be lowered from 40 to 30% [16–18]. These lower limits of operability have been integrated in the ERS/ESTS recommendations. The ERS/SETS guidelines also included in their algorithm, as the last step of the functional assessment, the calculation of the ppo$V'O_{2,max}$ proposed by BOLLIGER and PERRUCHOUD [15].

Exercise tests

Formal cardiopulmonary exercise test

Exercise tests are thought to mimic the post-operative increase in oxygen consumption and have been used to select patients at high risk of cardiopulmonary complications after thoracic, but also abdominal, surgery. The aim of exercise tests is to stress the whole cardiopulmonary system and estimate the physiological reserve that may be available after lung resection [15]. The most used and best validated exercise parameter is $V'O_{2,max}$. In the literature, $V'O_{2,max}$ appears to be a very strong predictor of post-operative complications, as well as a good predictor of long-term post-operative exercise capacity. This was confirmed in a recent and

Box 2 Calculation of predictive post operative (ppo) forced expiratory volume in 1 s (FEV1), diffusing capacity of the lung for carbon dioxide ($D_{L,CO}$) or maximal oxygen uptake ($V'_{O_2,max}$)

Calculation of ppoFEV1 is taken as a model. Similar equations are used for the calculation of ppo$D_{L,CO}$ or ppo$V'_{O_2,max}$, and include pre-operative $D_{L,CO}$ or $V'_{O_2,max}$, respectively.

For ppoFEV1 before lobectomy, the calculation is based on the segment counting method, as follows.

Number of functional segments: 19

Right lung:
- Upper lobe: 3
- Middle lobe: 2
- Lower lobe: 5

Left lung:
- Upper lobe: 3
- Lingula: 2
- Lower lobe: 4

ppoFEV1 = pre-operative FEV1 × (1 - *a*/*b*)

where *a* is the number of unobstructed segments to be resected and *b* is the total number of unobstructed segments. An unobstructive segment is defined as one where the patency of the bronchus and the segment structure are preserved, according to bronchoscopy and computed tomography (CT) scan.

For ppoFEV1 before pneumonectomy, the calculation is based on scintigraphy or quantitative CT scan, as follows.

ppoFEV1 = pre-operative FEV1 × (1 - FP)

where FP is the fraction of total perfusion for the lung to be resected.

large study showing that, on logistic regression analysis, $V'_{O_2,max}$ was an independent risk factor of both cardiovascular and pulmonary complications [10]. However, the lack of data available to show how cardiopulmonary exercise testing (CPET) can help predict unacceptable levels of post-operative dyspnoea has been underlined [5]. The position on exercise testing differs according to the published algorithms. The BTS and the ACCP recommend performing exercise testing only in patients with moderate-to-high risk of post-operative dyspnoea [5] or low ppo values (<40%) [6]. In contrast, the ERS/ESTS propose to perform an exercise test in all patients with decreased lung function (FEV1 or $D_{L,CO}$ <80%), emphasising the good predictive

value of these tests and the validation of this strategy by WYSER *et al.* [19]. This approach has been discussed, putting forward that CPET may not be essential in patients with moderate lung function impairment and/or before lobectomy, and should be performed only in patients with "very" impaired lung function. However, given the published data, the degree of lung function impairment justifying the prescription of CPET remains to be defined and validated before altering the algorithm.

For the BTS and ACCP, patients with $V'_{O_2,max}$ <15 mL per min per kg are at average risk, and patients with $V'_{O_2,max}$ <10mL per min per kg (ACCP) are at high risk of complications after lung resection. These values have been widely validated but, again, absolute values should be used with caution. A nonobese, 50-year-old, 75-kg male has a predicted $V'_{O_2,max}$ of 34 mL per min per kg, whereas a 65-year-old, 55-kg female has a predicted $V'_{O_2,max}$ of 21 mL per min per kg. The cut-off values recommended by the ERS/ESTS are presented in table 1 and the algorithm in figure 1. These cut-off values are not validated, but encouraging results have been published. One study reanalysed a series of 208 patients using this amended algorithm and showed low mortality rates in the patients qualified for major lung resections [16].

Low-technology exercise tests
Formal CPET with $V'_{O_2,max}$ measurements may not be readily available in all centres. Therefore, low-technology tests have been used to evaluate fitness before lung resection, including the 6-min walk test (6MWT), the shuttle test and the stair climbing test. However, two different strategies have been proposed. The ACCP uses lower limits of operability, in order to select patients who will be offered other treatment modalities. For instance, a patient who walks <25 shuttles or climbs fewer than one flight of stairs is considered at high surgical risk. In contrast, the ERS/ESTS define cut-off values corresponding to a $V'_{O_2,max}$ of 15–20 mL per min per kg. Patients with low exercise capacity according to these values will undergo formal CPET before concluding about operability.

6MWT
The 6MWT is the most used low-technology test, but the distance walked does not correlate with the $V'_{O_2,max}$ in all (especially in fit) patients. Moreover, post-operative complications have been found to be associated with the distance

Table 1 Cut-off values for lung function and exercise tests

Cut-off value	Recommendation
Lung function and $V'_{O_2,max}$	
FEV1 and $D_{L,CO}$ >80% pred	Resection up to pneumonectomy
$V'_{O_2,max}$ >75% pred or >20 mL per kg per min	Resection up to pneumonectomy
$V'_{O_2,max}$ <35% pred or <10 mL per min per kg	High risk of complications. A pneumonectomy or a lobectomy are usually not recommended
$V'_{O_2,max}$ 35–75% pred	Calculate ppo values
ppo values	
ppoFEV1 and ppo$D_{L,CO}$ >30% pred and $V'_{O_2,max}$ >35% pred	Resection up to pneumonectomy
ppoFEV1 or ppo $V'_{O_2,max}$ <30% pred	Calculate ppo$V'_{O_2,max}$
ppo$V'_{O_2,max}$ >35% pred or >10 mL per kg per min	Resection up to pneumonectomy
ppo$V'_{O_2,max}$ <35% pred or <10 mL per kg per min	High risk of complications. A pneumonectomy or a lobectomy are usually not recommended

Modified from the European Respiratory Society/European Society of Thoracic Surgeons guidelines [4]. $V'_{O_2,max}$: maximal oxygen uptake; FEV1: forced expiratory volume in 1 s; $D_{L,CO}$: diffusing capacity of the lung for carbon dioxide; % pred: % predicted value; ppo: predicted post-operative value.

walked in some but not all studies. As a result, the 6MWT is not recommended to select patients for lung resection [4–6].

Shuttle test

In contrast, there is a good correlation between the distance walked during a shuttle test and $V'_{O_2,max}$. Chronic obstructive pulmonary disease patients walking 420 m have a mean $V'_{O_2,max}$ of 21 mL per kg per min and those walking 120 m of 11 mL per kg per min [20]. In another study, it has been shown that some patients walking <400 m have $V'_{O_2,max}$ <15 mL per min per kg [21]. As a result, the ERS/ESTS recommend performing CPET in patients walking <400 m [4] and the BTS considers walking >400 m as good function [5].

Stair climbing test

The stair climbing test has also been used as a screening test. The height of ascent correlates with $V'_{O_2,max}$, 98% of patients climbing >22 m demonstrating $V'_{O_2,max}$ >15 mL per min per kg [22]. The speed of ascent also correlates with $V'_{O_2,max}$, a speed >15 m per min corresponding to $V'_{O_2,max}$ >20 mL per kg per min [23]. In addition, in a series of 640 patients, those climbing <12 m had two- and 13-fold higher rates of complications and mortality, respectively, compared with those climbing >22 m,
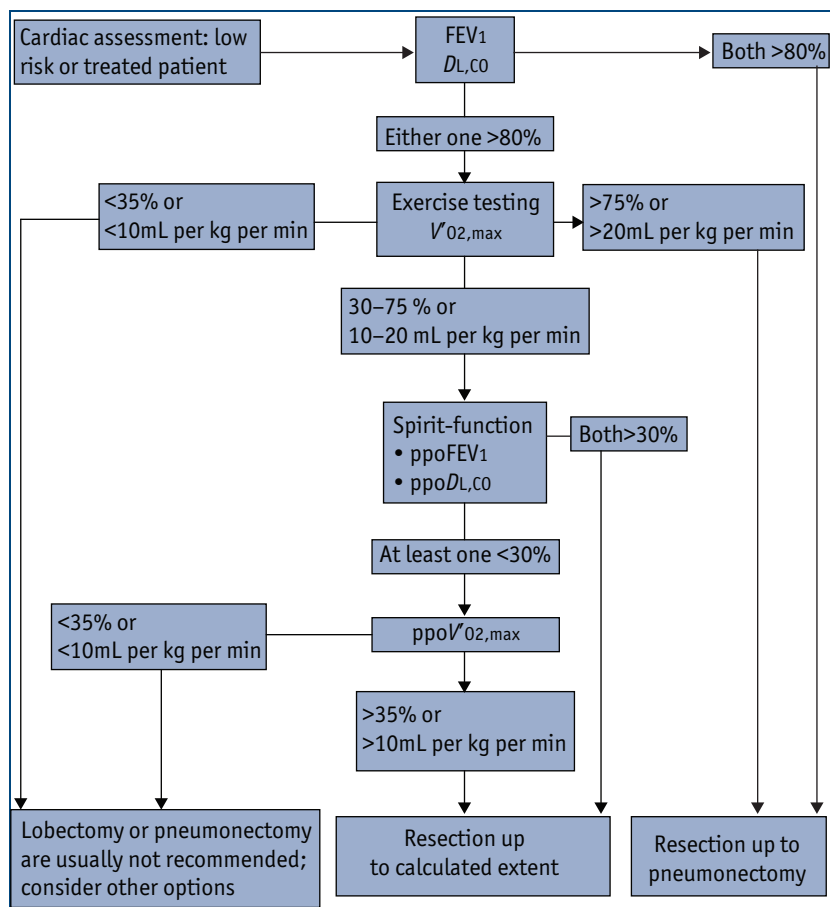
Figure 1
Algorithm for assessment of pulmonary reserve before major lung resection. Modified from [4].

who showed a <1% mortality rate [24]. The ERS/ESTS recommend that patients climbing <22 m (6.6 flights of 3.3 m each) should undergo CPET. The use of stair climbing can be limited by the difficulty in standardising this test according to the characteristics of the stairs and ceilings.

Perioperative management of patients

There are multiple risk factors for surgery of lung cancer patients, including the underlying disease (tumour extent and location), comorbidities, pre-existing medications, alcohol and tobacco addictions, age, weight loss, type and duration of surgery and anaesthesia [13, 25]. To what extent these risk factors influence the prognosis and how they interact is difficult to assess precisely. Nevertheless, in order to reduce the incidence of post-operative complications, identification of the patient's risk factors is recommended. It will allow for adjusting or instituting treatment of comorbidities. It will also allow determining the patient's admission criteria to a high-dependency unit, as recommended by the ERS/ESTS guidelines. Even if age appeared as an independent risk factor of complications in several studies, treatment should not be withheld from elderly patients without a careful evaluation of fitness and comorbidities.

Risk-reduction strategies also include pre-operative smoking cessation, physiotherapy and exercise training. Pre-operative smoking cessation should be recommended, as the risks of hospital death and pulmonary complications after lung cancer resection slightly decrease after smoking cessation. Nevertheless, at present, no optimal interval of smoking cessation can be recommended [26]. The efficiency of chest physiotherapy in decreasing the risk of post-operative atelectasis or facilitating post-operative bronchial toilette is widely recognised and, even if few studies support this role, chest physiotherapy is regarded as part of the perioperative management of lung cancer patients. Also, recent small studies suggest that exercise training, including inspiratory muscle training, may favourably influence lung cancer management by improving performance status, $V'_{O2,max}$, exercise tolerance and quality of life. However, the impact on operability and post-operative outcome needs to be investigated in large trials. In addition, the modalities of exercise training remain to be defined [27].

In summary, the BTS, ACCP and ERS/ESTS support a multidisciplinary management of lung cancer patients in order to shorten the time between diagnosis and treatment, increase the proportion of treated (and appropriately treated) patients and improve mortality rates. The treatment of lung cancer patients must be performed in specialised centres [4, 6].

Surgical alternatives to major lung cancer resection

The published algorithms have been designed to identify patients at risk for a major lung resection (e.g. lobectomy and pneumonectomy) and should not be used for other purposes. However, surgical treatment of lung cancer should not be denied without considering other surgical approaches, such as bronchoplastic and angioplastic resections, combined cancer surgery and lung volume reduction, and sublobar resection.

Resections of hyperinflated and poorly functional areas of the lung can be performed in patients with very low pre-operative FEV_1 and $D_{L,CO}$, marked hyperinflation, and severe disability. This procedure has been shown to improve chest wall mechanics, lung elastic recoil, and diaphragm position and function. This "volume reduction effect" is thought to explain the gain in FEV_1 observed in patients operated with low FEV_1, and the relatively low predictive value of FEV_1 and $ppoFEV_1$ in lung cancer surgery. The well-established operability criteria for lung volume reduction surgery should be applied to candidates for combined surgery [28]. The intraoperative strategies for this combined surgery have been reviewed recently by CHOONG et al. [29].

Decreased pulmonary reserve is one of the potential indications of parenchymal sparing resections. From an oncological viewpoint, anatomical segmentectomy could ideally be recommended in stage IA (tumour size 2–3 cm), with margins of resection >1 cm. It could also be offered to patients after prior lobectomy, with stage I lung cancer. Wedge resection could be recommended in stage IA lung cancer and in small peripheral adenocarcinoma with ground glass opacity on CT scan [4]. However, at the present time, no parameter or threshold can be recommended to evaluate the patient's fitness before segmentectomy.

Eventually, minimally invasive surgical lobectomy or segmentectomy (video-assisted thoracoscopic surgery) could also be offered to lung cancer patients. Several studies have reported that it reduces the length of stay, post-operative pain and respiratory complications [30–33]. Interestingly, in a series of 340 patients with either $FEV1$ or $D_{L,CO}$ ⩽60%, independent predictors of pulmonary complications were $FEV1$, $D_{L,CO}$ and open thoracotomy (*versus* thoracoscopy). But when patients were analysed according to the operative approach, $FEV1$ and $D_{L,CO}$ were no longer predictors of pulmonary morbidity for patients undergoing thoracoscopy [34].

Together, these results question the predictive value of commonly used lung function parameters for surgical alternatives to major lung cancer resection.

Fitness for chemoradiotherapy

Neoadjuvant chemoradiotherapy

The addition of induction radiochemotherapy to surgical resection increases mortality after pneumonectomy. Some recent studies focused on the chemoradiotherapy-induced lung toxicity and its consequences on operability. Interestingly, severe and diffuse interstitial alterations of lung parenchyma have been found in eight out of 10 patients who underwent pneumonectomy after chemotherapy for lung cancer (cisplatin plus gemcitabine), compared with controls. Six of these patients developed post-operative respiratory complications. The only predictor of severe diffuse damage was $D_{L,CO}$ [35]. In another study, 20 out of 73 patients showed a reduction in forced vital capacity or $D_{L,CO}$ >20%, and two out of the 85 eligible patients did not undergo surgery due to lung function reduction after chemotherapy [36]. In a retrospective study of 132 patients, on multivariate analysis, a decrease in $D_{L,CO}$/alveolar volume ratio >8% was associated with major or respiratory morbidity [37]. Eventually, in another retrospective study of neoadjuvant high-dose (⩾60 Gy) chemoradiotherapy, major morbidity occurred in 17% of the 216 patients [38]. Consequently, after induction chemotherapy and/or radiotherapy, a new

functional evaluation (particularly of $D_{L,CO}$) before surgery should be recommended [4].

Radical radiotherapy and/or chemotherapy

To date, the best predictors for radiation pneumonitis remain the dose–volume parameters. Therefore, three-dimensional treatment planning should be performed before radiotherapy [4, 5, 39]. The predictive value of pre-radiotherapy pulmonary function tests is controversial. As a result, the lung function limits beyond which radiotherapy for lung cancer is at risk can not be defined. More studies are needed to identify patients at risk of radiation-induced lung toxicity, including treatment-related but also patient-related characteristics [40]. Similarly, if the adverse effects in the lung of some chemotherapeutic agents, such as taxanes and gemcitabine, are well-known, safe lower limits of respiratory function ($FEV1$ or $D_{L,CO}$) for chemotherapy have not been defined [4].

Conclusion

At present, a meticulous pre-operative assessment combined with a multidisciplinary perioperative care may offer a surgical chance to lung cancer patients deemed at high surgical risk. However, algorithms designed to identify patients at risk for a major lung resection (*e.g.* lobectomy and pneumonectomy), or clear recommendations for the evaluation of fitness before alternative treatments, such as parenchyma-sparing resections, radiochemotherapy or other radical treatment, have not yet been elaborated. The usual lung function parameters may be less valuable predictors of complications for these alternative treatments than for major lung resection. More research is necessary to build prediction models, including functional factors, and patient- and treatment-related factors, to evaluate the risk of complications. Finally, in addition to mortality, morbidity and functional status, future clinical trials should evaluate patients' quality of life before and after treatment, and in all treatment arms. These results should help the physician and the patient to consider the risk and the benefit of each treatment option.

Suggested answers

1. False
2. True
3. False
4. True
5. True

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