



ERS/ESTS TASK FORCE

ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy)

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ABSTRACT: A collaboration of multidisciplinary experts on the functional evaluation of lung cancer patients has been facilitated by the European Respiratory Society (ERS) and the European Society of Thoracic Surgery (ESTS), in order to draw up recommendations and provide clinicians with clear, up-to-date guidelines on fitness for surgery and chemo-radiotherapy.

The subject was divided into different topics, which were then assigned to at least two experts. The authors searched the literature according to their own strategies, with no central literature review being performed. The draft reports written by the experts on each topic were reviewed, discussed and voted on by the entire expert panel. The evidence supporting each recommendation was summarised, and graded as described by the Scottish Intercollegiate Guidelines Network Grading Review Group. Clinical practice guidelines were generated and finalised in a functional algorithm for risk stratification of the lung resection candidates, emphasising cardiological evaluation, forced expiratory volume in 1 s, systematic carbon monoxide lung diffusion capacity and exercise testing.

Contrary to lung resection, for which the scientific evidences are more robust, we were unable to recommend any specific test, cut-off value, or algorithm before chemo-radiotherapy due to the lack of data. We recommend that lung cancer patients should be managed in specialised settings by multidisciplinary teams.

KEYWORDS: Chemotherapy, lung cancer, pre-operative evaluation, pulmonary resection, radical therapy, radiotherapy

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INTRODUCTION

A joint task force of multidisciplinary experts on the functional evaluation of lung cancer patients was endorsed by the European Respiratory Society (ERS) and the European Society of Thoracic Surgery (ESTS) in order to draw up recommendations and provide clinicians with clear, up-to-date guidelines on fitness for surgery and chemo-radiotherapy.

During the past years, an abundance of literature related to pre-operative evaluation before surgical treatment of lung cancer has been published. Indeed, despite refinement of medical treatments, lung resection remains the only curative treatment of lung cancer. Therefore, offering a surgical chance to patients deemed to be at high surgical risk remains highly relevant. The recent advances in operative, and also peri-operative management, as well as in the reassessment of traditional lung function tests and exercise test modalities, justify reviewing the functional evaluation before surgery for lung cancer. However, since only 20–25% of lung cancer patients are operable, and because of the widespread use of neoadjuvant chemotherapy, most patients are treated with chemo and/or radiotherapy. These treatments have specific toxicities, including for the lung, which should be taken into account when elaborating treatment strategy. In this view, this task force also aimed to review the literature on the assessment of acute and long-term risks related to chemo-radiotherapy, to determine if the surgical criteria could be “re-calibrated” for radiotherapy and chemotherapy. The remit of the task force was also to make recommendations, for patients who are not eligible for surgery, on alternative nonsurgical treatments. Ideally, guidelines should give the physician a basis to evaluate the benefit/risk ratio related to each therapeutic option offered to his patient. Whether the available literature allows this goal to be achieved will be discussed.

METHODS

The task force was composed of 14 invited participants, identified on the basis of their expertise in the area of lung cancer. The subject was divided in different topics, which were in turn assigned to at least two experts. The authors searched the literature according to their own strategies, with no central literature review being performed. The draft reports written by the experts on each topic were distributed to the entire expert panel, and comments solicited in advance of the meetings. During the meetings (held at the 2008 ESTS and at the 2008 ERS congresses), the recommendations were reviewed, discussed and voted on by the entire panel. Additional papers from

personal files were added if required. Approval required consensus, which was defined as an overwhelming majority approval. Differences of opinion were accommodated by revising the recommendations, the rationale or the grade, until consensus was reached. The evidence supporting each recommendation was summarised, and recommendations graded as described by the Scottish Intercollegiate Guidelines Network Grading Review Group: grades of recommendation are based on the strength of supporting evidence, taking into account its overall level and the considered judgment of the guideline developers (table 1) [1].

CARDIOLOGICAL EVALUATION BEFORE LUNG RESECTION

Substantial data (table 2) can aid the pre-operative evaluation of cardiac risk for lung resection surgery [2–6], and guide interventions to reduce that risk [2–30]. After a well-validated index provides estimates of patient’s risk [2–5], more detailed evaluation should be based on the individual patient characteristics [5–8]. Detailed evaluation for coronary heart disease generally is not recommended in patients with an acceptable exercise tolerance, such as the ability to walk up two flights of stairs without stopping [6–8]. If exercise capacity is limited, noninvasive testing can identify a relatively small proportion of patients for new or intensified control of heart failure, arrhythmias, or myocardial ischaemia. Appropriately aggressive cardiac interventions should be instituted prior to surgery in patients who would need them irrespective of the surgery, but interventions specifically for surgery are of limited benefit. For example, prophylactic coronary revascularisation does not reduce risk [30]. Furthermore, recovery after coronary bypass surgery may take several months, and the need for aggressive anti-platelet therapy, which is recommended for ~6 weeks after coronary angioplasty and/or a bare metal stent and for ≥ 1 yr after a drug-eluting stent, presents a major challenge in the peri-operative context [31, 32].

Beta-blockers reduce peri-operative myocardial infarction significantly [19, 23], but commonly used beta-blocker regimens increase the risk of stroke, presumably due to bradycardia and hypotension, and can increase overall mortality, perhaps by interfering with stress responses in critically ill patients [22]. In patients with very advanced coronary disease, in whom the risks of myocardial infarction are especially high, the cardioprotective benefits of short-acting beta-blockers, whose potential deleterious effects are easier to reverse, may outweigh their bradycardic and hypotensive effects [23]. Alternative adrenergic modulation, such as with clonidine

TABLE 1 Scottish Intercollegiate Guidelines Network (SIGN) grading system for recommendations in evidence based guidelines

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1	Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	1) High-quality systematic reviews of case-control or cohort studies, or 2) high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Nonanalytical studies, e.g. case reports and case series
4	Expert opinion
Grades of recommendations	
A	1) At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population, or 2) a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	1) A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results, or 2) extrapolated evidence from studies rated as 1++ or 1+
C	1) A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results, or 2) extrapolated evidence from studies rated as 2++
D	1) Evidence level 3 or 4, or 2) extrapolated evidence from studies rated as 2+

RCT: randomised controlled trial. Reproduced from [1] with permission from the publisher.

and related drugs [24–26], may be useful, but larger randomised trials will be required to evaluate α_2 -adrenergic agonists, statins [29] and other potential peri-operative interventions.

Recommendations are given in table 2, and summarised in an algorithm (fig. 1). Patients at low cardiological risk or with an optimised cardiological treatment may proceed with the following pulmonary evaluation.

LUNG FUNCTION TESTS AND EXERCISE TESTS

Spirometry and diffusing capacity of the lung for carbon monoxide

Limitations of predicted post-operative forced expiratory volume in 1 s

In the two most commonly used functional algorithms for the pre-operative evaluation of lung resection candidates [33, 34], the predicted post-operative (ppo)-forced expiratory volume in 1 s (FEV₁) is pivotal in choosing further tests or even excluding patients from operation without further tests.

Many case series have shown that peri-operative risks increase substantially when ppo-FEV₁ is <40% of predicted, reporting mortality rates ranging 16–50% [35–39]. NAKAHARA and co-workers [40, 41] found a mortality rate as high as 60% when ppo-FEV₁ was <30%.

In a larger series, KEARNEY *et al.* [42] found that ppo-FEV₁ was the best predictor of complications after controlling for the effect of other risk factors in a multivariate analysis.

However, others have reported better results in very small numbers of patients with lung function this poor [43–46].

More recently, BRUNELLI *et al.* [47] showed that ppo-FEV₁ was not a reliable predictor of complications in patients with pre-operative FEV₁ >70%. Furthermore, in those patients with a

ppo-FEV₁ <40%, the mortality rate was only 4.8%. These findings have been partly explained by the so-called “lung volume reduction effect” that can reduce the functional loss in patients with airflow limitations. In this regard, many studies have already shown the minimal loss, or even improvement, in pulmonary function after lobectomy in lung cancer patients with moderate to severe chronic obstructive pulmonary disease (COPD), questioning the traditional operability criteria mostly based on pulmonary parameters [48–55]. Recently, BRUNELLI *et al.* [56] and VARELA *et al.* [57] have shown that this lung volume reduction effect takes place in the immediate post-operative period.

A value for ppo-FEV₁ of 40% is currently used to distinguish between normal risk and higher risk lung resection patients [58]. However, given the recent strong improvement in peri-operative management and surgical techniques, and based on data collected by the present experts, we suggest that this limit should be lowered to 30% (fig. 2).

Immediate post-operative estimation of pulmonary function Although ppo-FEV₁ is fairly accurate in predicting the definitive residual value of FEV₁ 3–6 months after surgery [37, 40, 53, 60–66] it substantially overestimates the actual FEV₁ observed in the initial post-operative days, when most complications occur [67].

VARELA *et al.* [67] showed also that on post-operative day 1 after lobectomy the actual FEV₁ was 30% lower than predicted and as a result was a better predictor of complications than was ppo-FEV₁ [68]. According to this finding, an attempt should be made to predict early FEV₁ after lobectomy [69] and pneumonectomy.

TABLE 2 Assessing and addressing cardiac fitness for radical lung cancer surgery

Issue	Recommendations and evidence	[Ref.]
Estimating pre-operative cardiac risk		
Summary recommendation	Patients should be risk stratified using validated risk indexes, which should direct any additional testing (recommendation grade B, evidence level 2++).	[2–4]
Noninvasive stress tests	Patients with 1) poor functional status (<4 METs) and 1–2 RCRI criteria, and 2) a history of angina or claudication should be generally appropriate for noninvasive testing to assess risks for surgery (recommendation grade B, evidence level 2++). Patients at >20% risk according to initial estimates (RCRI >3) may still have high peri-operative risks, despite a negative noninvasive study (>5% post-test probability with negative test) (recommendation grade B, evidence level 2++). However, treatment strategies based on the results of non-invasive testing are not of proven value.	[5–8] [9]
Identifying patients with aortic stenosis	Patients with physical findings consistent with aortic outflow tract obstruction should have pre-operative echocardiography (recommendation grade B, evidence level 2++).	[10–12]
Echocardiography	Pre-operative echocardiography should also be obtained when other valvular disease, left ventricular dysfunction, or pulmonary hypertension is suspected, according to published guidelines (recommendation grade B, evidence level 2++).	[13]
Cardiological approaches for reducing risks		
Patients with hypertension	Anti-hypertensive medications should be given up to the morning of surgery and be continued orally or intravenously as soon as possible post-operatively (recommendation grade D, evidence level 4).	[14]
Patients with pulmonary hypertension or congenital heart disease	Beneficial chronic therapies could be generally recommended during the peri-operative period (recommendation grade D, evidence level 4).	[15, 16]
Patients with hypertrophic cardiomyopathy	Management could be similar to the chronic setting (recommendation grade D, evidence level 4).	[17]
Patients with heart failure or arrhythmias	Elective surgery could be delayed if heart failure or arrhythmias are unstable, meet accepted criteria for new interventions, or are likely to represent inadequately treated ischaemic heart disease. Optimal management of patients with stable heart failure or adequately treated arrhythmias could adhere to published guidelines (recommendation grade D, evidence level 4).	[5, 6]
Pulmonary artery catheterisation	Few, if any, noncardiac surgery patients must receive routine pulmonary artery catheterisation (recommendation grade A, evidence level 1++).	[18]
Peri-operative beta blockade	Patients with ischaemic heart disease generally do not benefit from newly prescribed peri-operative beta blockade (recommendation grade A, evidence level 1++), but beta blockers should be continued in patients who are already taking them (recommendation grade B, evidence level 2++) and may be beneficial as new therapy in very high-risk patients (recommendation grade B, evidence level 1).	[19–23]
Peri-operative α -adrenergic modulation	Modulation of the α -adrenergic systems with drugs such as clonidine may be beneficial for vascular surgery but are of even less certain benefit for other operations (recommendation grade A, evidence level 1+).	[24–26]
Other anti-ischaemic medications	Prophylactic nitrates can reduce ischaemia but not major events; prophylactic calcium channel blockers could be of uncertain benefit (recommendation grade B, evidence level 2++).	[25–27]
Peri-operative use of HMG-CoA reductase inhibitors (statins)	Statin lipid-lowering agents could be started before noncardiac surgery whenever long-term lipid-lowering therapy is indicated (recommendation grade D, evidence level 4).	[28, 29]
Peri-operative coronary revascularisation	Patients at high risk clinically or based on noninvasive testing must be considered for diagnostic catheterisation. Coronary revascularisation must be recommended only for patients who would benefit in the absence of the planned surgery (recommendation grade A, evidence level 1++).	[30]

METs: metabolic equivalents; RCRI: revised cardiac risk index; HMG-CoA: 3-hydroxy-3-methyl-glutaryl coenzyme A.

Spirometry should be performed according to the joint ERS/American Thoracic Society (ATS) clinical practice guidelines [70].

Recommendation

The ppo-FEV₁ should not to be used alone to select patients with lung cancer for lung resection, particularly patients with moderate to severe COPD. It tends to underestimate the functional loss in the early post-operative phase and does not appear to be a reliable predictor of complications in COPD

patients. A ppo-FEV₁ value of 30% pred is suggested to be a high risk threshold for this parameter when included in an algorithm for assessment of pulmonary reserve before surgery (fig. 2). Level of evidence 2+; grade of recommendations C.

Statement

An attempt to predict immediate post-operative pulmonary function seems to be recommendable at least on an investigational basis. Level of evidence 2.

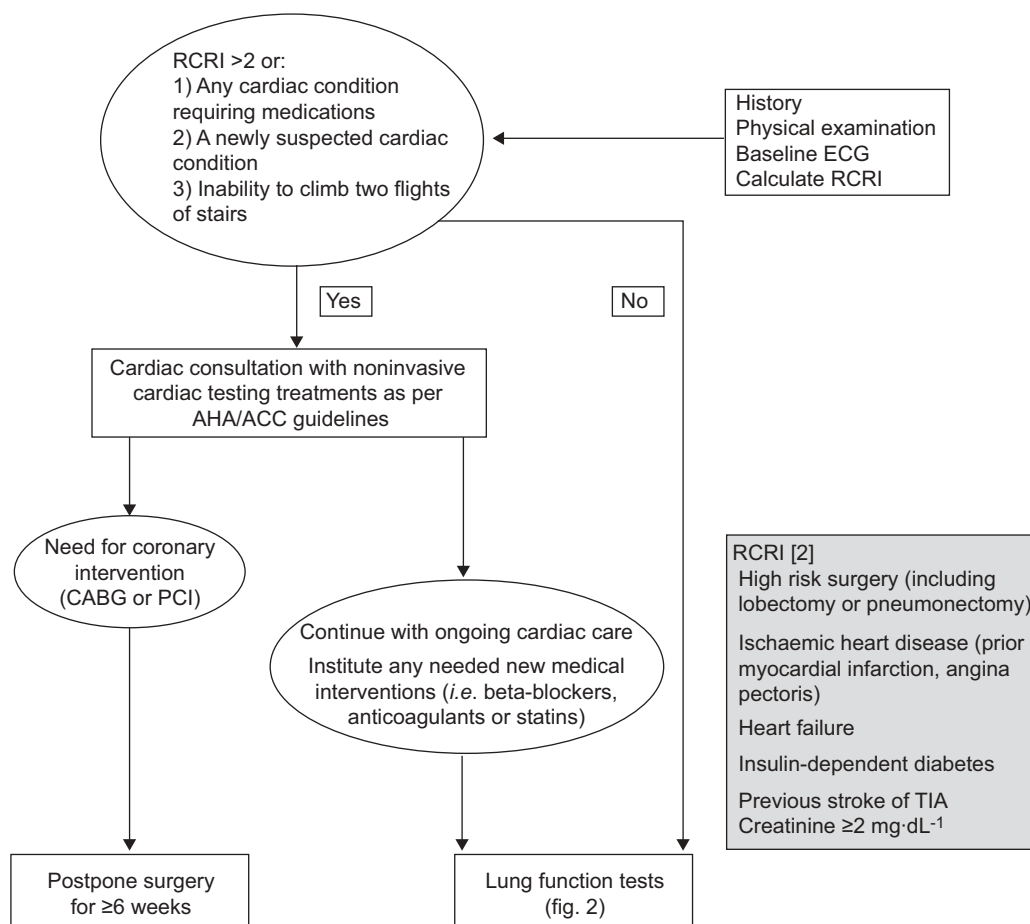


FIGURE 1. Algorithm for cardiac assessment before lung resection in lung cancer patients. For American College of Cardiology Foundation/American Heart Association (AHA/ACC) guidelines see [2–6]. CABG: coronary artery bypass graft; PCI: primary coronary intervention; TIA: transient ischaemic attack.

Diffusing capacity: systematic or selective use in the assessment of candidates for radical therapy for lung cancer

The diffusing capacity of the lung for carbon monoxide (DL_{CO}) is a valuable proxy measurement for alveolar oxygen exchange in the assessment of the lung resection candidate. Early reports demonstrated that DL_{CO} decreased after lung resection [71–74], and that a low DL_{CO} was associated with an increase in operative mortality after major lung resection [75]. In the late 1980s, DL_{CO} was first shown to be an independent predictor of post-operative mortality and morbidity after lung resection. Subsequently, similar findings have also been reported by others [37, 38, 76–80]. A low pre-operative DL_{CO} was related to an increased frequency of readmission to the hospital and a poorer long-term quality of life (QoL) [81]. The utility of the per cent ppo- DL_{CO} as the single strongest predictor of outcomes in unselected patients was subsequently identified [82]. A value for ppo- DL_{CO} of 40% currently is used to distinguish between normal risk and higher risk lung resection patients [58]. However, given the recent strong improvement in peri-operative management and surgical techniques, and based on data collected by the present experts, we suggest that this limit should be lowered to 30% (fig. 2).

One controversial issue is whether diffusing capacity should be measured only in patients who have compromised

spirometric function. In the Society of Thoracic Surgeons' general thoracic database, only 57% of patients undergoing major lung resection had DL_{CO} values reported (unpublished data). In the European Thoracic Surgery database, <25% of such patients had DL_{CO} measured [83]. Published guidelines suggest that DL_{CO} be measured only in patients with compromised per cent FEV₁ [34, 84]. However, recent studies demonstrate that diffusing capacity is very important in predicting post-operative complications, even in patients with a normal FEV₁ (>80% pred) or without COPD (FEV₁/forced vital capacity ratio >0.7) [58, 85]. These studies demonstrate that diffusing capacity is a strong predictor of post-operative complications in patients regardless of COPD status.

DL_{CO} measurement should be performed according to the joint ERS/ATS clinical practice guidelines [86].

Recommendation

DL_{CO} should be routinely measured during pre-operative evaluation of lung resection candidates, regardless of whether the spirometric evaluation is abnormal. A ppo- DL_{CO} value of 30% pred is suggested to be a high risk threshold for this parameter when included in an algorithm for assessment of pulmonary reserve before surgery (fig. 2). Level of evidence 2++; grade of recommendation B.

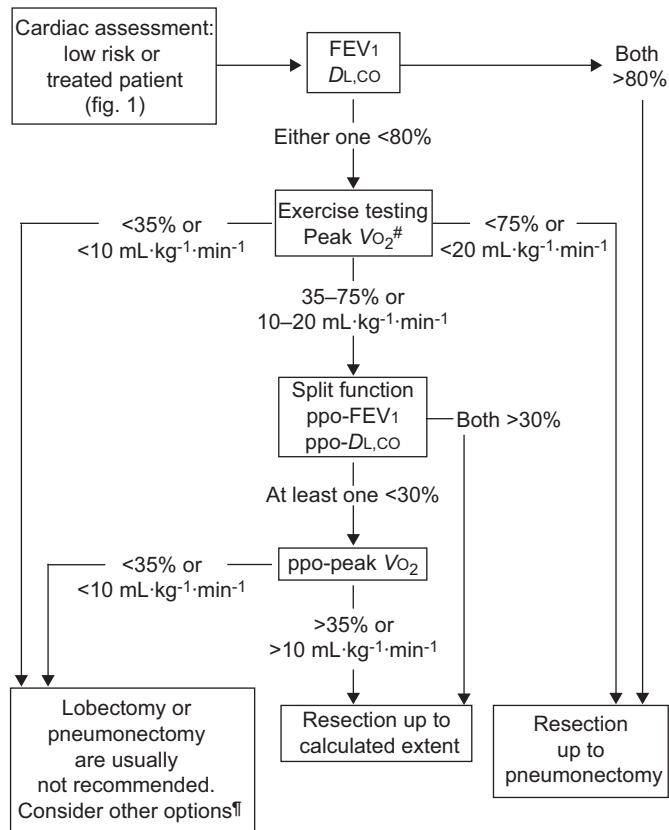


FIGURE 2. Algorithm for assessment of cardiopulmonary reserve before lung resection in lung cancer patients. FEV₁: forced expiratory volume in 1 s; DL_{CO}: diffusing capacity of the lung for carbon monoxide; VO₂: oxygen consumption; ppo: predicted post-operative. #: If peak VO₂ is not available, cardiopulmonary exercise testing can be replaced by stair climbing (see subsection entitled Exercise tests); however, if altitude reaching during stair climbing is <22 m, cardiopulmonary exercise testing with peak VO₂ measurement is highly recommended; †: see sections entitled Surgical techniques in lung cancer and Chemo-radiotherapy in lung cancer. Modified from [59], with permission from the publisher.

Split function studies

Different techniques have been used to predict post-operative lung function. These have included various pulmonary function tests and quantitative ventilation/perfusion scintigraphy [64, 87–89]. In practice, scintigraphy is not widely employed in assessing patients for lobectomy, because of the difficulty in interpreting the contribution of individual lobes to the overall ventilation or perfusion. This may explain why several investigators have reported that the simple calculation using lung segment counting can predict post-operative FEV₁ as accurately as ventilation/perfusion scintigraphy [90–94].

Perfusion scintigraphy is the most widely used method to predict post-operative lung function in lung cancer patients undergoing pneumonectomy [33–34].

The reported correlation between the actual and predicted post-operative FEV₁ using quantitative ventilation/perfusion scintigraphy has been variable, with correlative figures quoted between $r=0.67$ to $r=0.9$ [62, 63, 91, 93, 95–99]. Either ventilation scintigraphy [99] or perfusion scintigraphy [62, 63, 91] offer good prediction of post-operative lung function,

but there seems to be no additional benefit in performing both [99]. The interpretation of the results, however, needs to take into account the fact that these techniques may underestimate the actual post-operative value [63, 93, 98].

The following equations should be used to calculate predicted post-operative values for FEV₁, DL_{CO} and maximal oxygen consumption (VO_{2,peak}) [82, 100], in which T is the total number of functioning segments before the operation; R is the residual number of functioning segments after the operation; a is the number of unobstructed segments to be resected; and b is the total number of unobstructed segments.

19 - number of obstructed segments (estimated by image techniques and/or bronchoscopy) = T

T - number of functioning segments to be resected = R

ppo values = (pre-operative value/T) × R

Or, expressed in another form, ppo-FEV₁ before lobectomy:

$$\text{ppo-FEV}_1 = \text{pre-operative FEV}_1 \times (1 - a/b)$$

ppo-FEV₁ before pneumonectomy:

$$\text{ppo-FEV}_1 = \text{pre-operative FEV}_1 \times (1 - \text{fraction of total perfusion for the lung to be resected})$$

ppo-DL_{CO} before lobectomy:

$$\text{ppo-DL}_{CO} = \text{pre-operative DL}_{CO} \times (1 - a/b)$$

ppo-DL_{CO} before pneumonectomy:

$$\text{ppo-DL}_{CO} = \text{pre-operative DL}_{CO} \times (1 - \text{fraction of total perfusion for the lung to be resected})$$

ppo-VO_{2,peak} before lobectomy:

$$\text{ppo-VO}_{2,\text{peak}} = \text{pre-operative VO}_{2,\text{peak}} \times (1 - a/b)$$

ppo-VO_{2,peak} before pneumonectomy:

$$\text{ppo-VO}_{2,\text{peak}} = \text{pre-operative VO}_{2,\text{peak}} \times (1 - \text{fraction of total perfusion for the lung to be resected})$$

In the past years, imaging techniques have been proposed to predict post-operative pulmonary function: computed tomography (CT) scan, magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), or a combination of these [100–108]. Quantitative CT appeared to be at least as accurate as perfusion scintigraphy.

Recommendations

1) The first estimate of residual lung function should be calculated based on segment counting. Only segments not totally obstructed should be taken into account: the patency of bronchus (bronchoscopy) and segment structure (CT scan) should be preserved. Level of evidence 2+; grade of recommendations C.

2) Patients with borderline function (fig. 2) should need imaging-based calculation of residual lung function: ventilation or perfusion scintigraphy before pneumonectomy, or quantitative CT scan (see statement 3) before lobectomy or pneumonectomy. Level of evidence 2+; grade of recommendations C.

Statements

- 1) Either ventilation scintigraphy or perfusion scintigraphy offer good prediction of post-operative lung function; however, there is no additional benefit in performing both. Level of evidence 2+.
- 2) Apart from FEV₁, DL_{CO} and VO_{2,peak} have been used in split function analysis and successfully included in an algorithm. Level of evidence 2+.
- 3) Teams concerned with research in pre-operative evaluation before lung cancer surgery should be encouraged to use quantitative CT, MRI or SPECT. Level of evidence 2+.

Exercise tests

Exercise tests: systematic or selective?

Exercise testing has been used for a variety of purposes, including pre-operative evaluation for patients undergoing lung resection. The aim of exercise testing is to stress the whole cardiopulmonary/systemic oxygen delivery systems and estimate the physiological reserve that may be available after surgery. During exercise, the lung experiences increases in ventilation, oxygen uptake, carbon dioxide output and blood flow similar to those observed during the post-operative period after lung resection. Therefore, a single test can be used to assess the physiological response after surgery. It is hypothesised that those patients unable to perform adequately on exercise testing may similarly do so in response to surgical stress or adverse post-operative events and, therefore, performance on exercise testing should be correlated to surgical outcome. In fact, a recently published meta-analysis has shown that exercise capacity, expressed as VO_{2,peak} is lower in patients that develop post-operative cardiorespiratory complications after lung resection [109]. Besides early post-operative outcome, performance on exercise tests is also a better predictor of long-term exercise capacity than conventional pre-operative pulmonary function tests [64]. Nevertheless, exercise tests are usually recommended only in selected cases (unfit or reduced FEV₁ and/or DL_{CO}) [33, 34].

Several authors [84, 110–112] have found a good correlation between low VO_{2,peak} (per cent of predicted) and poor post-operative outcome. It is generally reported that a value <50–60% pred increases the surgical mortality risk. In a prospective evaluation of an algorithm for functional assessment of lung resection candidates, measurement of VO_{2,peak} was performed in all patients with an FEV₁ and/or DL_{CO} value <80% [112]. Patients having a VO_{2,peak} >20 mL·kg⁻¹·min⁻¹ or >75% pred were deemed operable, while in cases with a VO_{2,peak} <40% or <10 mL·kg⁻¹·min⁻¹ surgical therapy was contraindicated. Between both values, post-operative FEV₁ and DL_{CO} were estimated and, in those cases having either one >40% and ppo-VO_{2,peak} <35% and >10 mL·kg⁻¹·min⁻¹, surgical resection was performed. The authors communicated a decrease in overall hospital mortality compared to historical controls.

Recently, LOEWEN *et al.* [84] have reported that patients who had a VO_{2,peak} <65% (or <16 mL·kg⁻¹·min⁻¹) were more likely to suffer complications, and BRUNELLI *et al.* [113] found that all deaths after lung resection occurred in patients with a VO_{2,peak} <20 mL·kg⁻¹·min⁻¹.

Recommendation

Exercise tests should be indicated in all patients undergoing surgery for lung cancer with FEV₁ or DL_{CO} <80% of normal values. Level of evidence 2++; grade of recommendation B.

Low-technology exercise: stair, 6-min walk distance or shuttle?

Aside from pulmonary function tests, other measures of cardiopulmonary fitness have been shown to be useful for pre-operative risk stratification. The most widely used low-technology tests include 6-min walking, shuttle walk test and stair climbing.

Although distance walked in 6–12 min has been shown to be highly reliable in estimating VO_{2,peak} in healthy subjects [114], COPD patients [115] and transplant candidates [116], non-univocal findings have been published regarding its association with post-operative outcome after lung resection [36–38, 117].

The shuttle walk test has been reported to be more reproducible and more highly correlated with VO_{2,peak} [118–120]. It has been estimated by regression analysis that 25 shuttles on the shuttle walk test indicate a VO_{2,peak} of 10 mL·kg⁻¹·min⁻¹ [119] and, therefore, this cut-off value has been suggested in the functional algorithm proposed by the British Thoracic Society [33].

However, WIN and co-workers [121, 122] found no statistically significant difference in shuttle walk distance between patients with and without complications after lung resection. They also found that this test tends to underestimate exercise capacity at the lower range compared with VO_{2,peak}, concluding that it should not be used alone to exclude patients from operation, contrary to current recommendations [33]. The same authors found that all patients who walked >400 m at shuttle walk test had a VO_{2,peak} >15 mL·kg⁻¹·min⁻¹ [33].

Several papers have shown the effectiveness of the stair climbing test to predict major cardiopulmonary complications after lung resection [36, 123, 124]. In a more recent study, BRUNELLI *et al.* [125] confirmed his previous findings in a series of 640 patients submitted to major lung resection. Patients climbing <12 m had two-fold and 13-fold higher rates of complications and mortality compared to those climbing >22 m (<1% mortality rate). In this latter paper, they found that, even in patients with ppo-FEV₁ and/or ppo-DL_{CO} <40%, the mortality rate in those climbing >22 m was zero.

Although exercise oximetry has been proposed to be a useful tool in the pre-operative functional evaluation of lung resection candidates [33, 34], the role of exercise oxygen desaturation (EOD) in risk stratification has not been defined regarding its definition and its association with early outcome after lung resection [126–128].

Two studies [126, 127] found that EOD was a better discriminant of post-operative respiratory failure, need for intensive care unit (ICU) admission, prolonged hospital stay and home oxygen requirement with respect to spirometry. However, VARELA *et al.* [128] found that oxygen desaturation <90% during standardised incremental cycle ergometry was not a significant predictor of post-operative cardiopulmonary morbidity. Recently, BRUNELLI *et al.* [129] found that a

desaturation $>4\%$ was significantly associated with post-operative complications, even after adjusting its effect for other factors with regression analysis.

Recommendations

1) Shuttle walk test distance underestimates exercise capacity at the lower range and was not found to discriminate between patients with and without complications. Thus, it should not be used alone to select patients for operation. It could be used as a screening test: patients walking <400 m may have $VO_{2,peak} <15$ mL·kg⁻¹·min⁻¹. Level of evidence 2+; grade of recommendation C.

2) Standardised symptom-limited stair climbing test is a cost-effective test capable of predicting morbidity and mortality after lung resection better than traditional spirometry values. It should be used as a first-line functional screening test to select those patients that can undergo safely to operation (height of ascent >22 m) or those who need more sophisticated exercise tests (compare with the following subsection entitled The role of cardiopulmonary exercise tests) in order to optimise their peri-operative management. Level of evidence 2++; grade of recommendation B.

3) The 6-min walk test should not be used to select patients for operation. Level of evidence 2+; grade of recommendation C.

Statement

Patients with EOD $>4\%$ (arterial oxygen saturation measured by pulse oximetry, measured using correct methodology) during stair climbing may have an increased rate of complications and mortality after lung resection. They need, therefore, to be further assessed with formal cardiopulmonary exercise testing (CPET) for a more precise evaluation of their cardiopulmonary system in order to optimise their peri-operative management. Level of evidence 2+.

The role of cardiopulmonary exercise testing

In high-technology exercise testing, or CPET, maximal or symptom-limited exercise is performed, usually on a bicycle or treadmill. CPET is performed in a controlled environment with continuous monitoring of various parameters; it ensures easy standardisation and good reproducibility of results. $VO_{2,peak}$ is the single most important parameter as a direct measure of exercise capacity. CPET not only allows assessment of overall cardiopulmonary reserves but, in case of a limitation of exercise capacity, also to find the reason for this, such as pulmonary, cardiovascular or musculoskeletal limitations. If a particular organ system can be incriminated as the limiting factor, specific treatment options can be of benefit, such as optimisation of COPD treatment or management of ischaemic heart disease.

Various cut-off values of $VO_{2,peak}$ expressed either in mL·kg⁻¹·min⁻¹ and/or in per cent of predicted values have been suggested, which indicate whether patients can safely undergo pulmonary resections, and most importantly estimate the extent of resection possible [35, 44, 84, 110–112, 130–134]. There is currently wide consensus that values of $VO_{2,peak} >20$ mL·kg⁻¹·min⁻¹ qualify for resection up to pneumonectomy, whereas values <10 mL·kg⁻¹·min⁻¹ indicate high risk for any resection. Expressed as per cent of predicted the respective values

are $>75\%$ and $<40\%$ pred. A further suggestion is the use of predicted post-operative values for $VO_{2,peak}$ based on a very high mortality, with ppo- $VO_{2,peak}$ values of <10 mL·kg⁻¹·min⁻¹ (35% pred) [131]. See also the corresponding paragraph in the subsection entitled Split function.

CPET should be performed according to the published ATS guidelines [135].

Recommendations

1) CPET is performed in controlled environment, and is reproducible and safe. $VO_{2,peak}$ measured during an incremental exercise on treadmill or cycle should be regarded as the most important parameter to consider, as a measure of exercise capacity and as highly predictive of post-operative complications. Level of evidence 2++; grade of recommendation B.

2) The following basic cut-off values for $VO_{2,peak}$ should be considered: $>75\%$ pred or >20 mL·kg⁻¹·min⁻¹ qualifies for pneumonectomy; $<35\%$ pred or <10 mL·kg⁻¹·min⁻¹ indicates high risk for any resection. Evidence is not sufficient to recommend cut-off values for lobectomy. Level of evidence 2++; grade of recommendation C.

Future trends in pre-operative work-up

Evaluation of pre-operative daily physical activity

The inclusion of some simple inexpensive parameters in the pre-operative work-up could result in better knowledge of the patient performance status. According to MANINI *et al.* [136], daily living energy expenditure was strongly associated with lower risk of operative mortality. Motion detectors (pedometers) are considered useful for measuring daily activity, which is related to physiological impairment due to COPD and other diseases [137, 138], and its usefulness to predict post-operative outcome should be tested.

DLCO during exercise

The lung has a large reserve of diffusing capacity that can be recruited as oxygen demand increases. WANG *et al.* [139] found, in 57 patients, that the increase in DL_{CO} from rest to 70% of maximal workload was the best pre-operative predictor of post-operative complications, followed by $VO_{2,peak}$ measurement.

Statements

1) Evaluation of daily physical activity could replace, or be complementary to, sophisticated pre-operative exercise tests. Level of evidence 2.

2) Although it is not easily available and needs confirmation in larger series, exercise DL_{CO} may be an interesting parameter to investigate since its impairment reflects poor recruitment of pulmonary capillary and, to a lesser extent, alveolar volume. Level of evidence 2.

PATIENT CARE MANAGEMENT

The role of rehabilitation before and after lung resection surgery

Adverse events after lung resection are limited [140], but a considerable proportion of patients suffer from significant late complications [141]. Pulmonary rehabilitation, including exercise and education, is effective in respiratory patients with disability [142–144], in candidates for lung volume reduction

[145, 146] and in the pre-post lung transplantation [147, 148], while it is not clearly indicated in surgical patients with lung cancer.

Notwithstanding, pre-operative VO_2 is inversely related to the probability of complications after lung resection [109], which, in turn, is associated with post-operative loss of function [54, 149]. Therefore, it seems rational to hypothesise that pulmonary rehabilitation could decrease the rate of adverse events.

Chest physiotherapy was found to be more effective than incentive spirometry in reducing the rate of pulmonary atelectasis after lobectomy [150]. Pre-operative inspiratory muscle training may decrease the prevalence of late complications after cardiac surgery [151].

Comprehensive pulmonary rehabilitation was able to improve VO_2 rate before surgery in COPD patients with low VO_2 ($<15 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), thus reducing late complications and not influencing operability and prognosis [152].

Pre-operative training programmes have led to a reduction of hospital stay and complications in COPD patients with lung cancer [153]; however, improved accessibility to intervention was found only in treated patients with “quasi normal” respiratory function [154]. Specific programmes that include smoking cessation periods before surgery may change smoking behaviour and positively impact on the risk of complications [155].

The effectiveness of comprehensive inpatient pulmonary rehabilitation has shown benefits indicating that both functional exercise capacity [156] and lung volumes [157] may improve in treated individuals but not in controls.

In light of the limited data underlining the evidence-based benefits of a pre- or post-operative rehabilitation in lung resection candidates [158–160], future research on programme content and duration of pulmonary rehabilitation should be considered priorities.

Pulmonary rehabilitation should be performed according to published guidelines [161].

Recommendations

1) Smoking cessation of sufficient duration (2–4 weeks) before surgery should be recommended, since it may change the smoking behaviour peri-operatively and decrease post-operative complications. Level of evidence 2+; grade of recommendation B.

2) Early pre- and post-operative rehabilitation should be recommended, since it may produce functional benefits in resectable lung cancer patients. Candidate selection, late outcomes (*i.e.* post-operative complications and death), and programme content and duration need to be further investigated. Level of evidence 2+; grade of recommendation C.

Statement

Pre-operative exercise capacity is inversely related to morbidity after lung resection. Level of evidence 1+.

Scoring systems: do they have a place in patient selection?

Effective scoring systems predict the likelihood of selected outcomes in groups of patients, enabling risk stratification. The

Charlson comorbidity index, Kaplan–Feinstein index, American Society of Anesthesiologists score, and the physiological and operative severity score (POSSUM), perform better than individual risk factors and have intermediate power to predict peri-operative mortality and morbidity after lung resection (area under the curve (AUC) <0.7) [162–167]. Scoring systems specific for lung resection have been developed, including the cardiopulmonary risk index (CPRI), the predictive respiratory quotient (equal to $(\text{ppo-FEV}_1 \times (\text{ppo-DLCO})^2) / (\text{alveolar-arterial oxygen tension difference})$) the post-operative pulmonary product (equal to $\text{ppo-FEV}_1 \times \text{ppo-DLCO}$), and the EVAD system (age, FEV_1 , DLCO) [38, 168–170]. The first three fall short either because they most simply dichotomise outcomes, making detailed predictions impossible, or are insufficiently accurate in predicting risk for individuals. EVAD, although its performance equaled or exceeded that of CPRI and POSSUM, was insufficient to assign individual risks accurately (AUC 0.64).

The National Veterans Affairs Surgical Quality Improvement Program (NVASQIP), consisting of $>3,500$ patients, identified nine independent risk factors for bad peri-operative outcomes [171] with acceptable prediction for mortality and morbidity (AUCs of 0.72 and 0.62, respectively). The ESTS Subjective and Objective Scores did not appear accurate at the extremes of risk [83]. In the Thorascore system, nine variables emerged as being significant in the predictive model, with an AUC of 0.86 and a correlation between observed and expected mortality of 0.99 [172]. Some models have been used to assess long-term survival, including the Charlson comorbidity index, the Kaplan–Feinstein index, and the Thorascore system [163, 167, 173–177]. These do not include tumour stage, and so are less relevant for selecting patients for major lung resection for cancer therapy.

Although lacking accuracy for assigning specific risk for individual patients, models incorporating functional characteristics, comorbidity factors, and surgical variables (NVASQIP and Thorascore) are valid and useful tools for predicting relative operative death or major cardiopulmonary complications in groups of patients. 5-yr survival following lung cancer resection is better predicted by scoring systems including comorbidity indices and tumour stage.

Recommendation

The current standard of care should not require the use of scoring systems for adequate evaluation of individual patients for lung resection. However, these tools should be considered as useful instruments for benchmarking and risk stratification among groups of surgical candidates. Level of evidence 2+; grade of recommendation B.

Do we need to send all thoracotomies to the ICU?

Within the first five post-operative days, cardiopulmonary complications occur in as many as 15–40% of patients and markedly prolong the hospital stay [140, 178–182]. Accordingly, implementation of evidence-based medical strategies as well as monitoring and treatment of high-risk patients in dedicated care units are aimed at improving the post-operative outcome while limiting healthcare expenses [183, 184].

TABLE 3 Admission criteria in the high dependency unit: moderate- to high-risk patients**Pre-operative comorbidities and functional status**

Coronary artery disease (angina pectoris, prior myocardial infarction, myocardial revascularisation)
 Cardiac insufficiency (left ventricular ejection fraction <40%, history of heart failure)
 Cardiac arrhythmias or heart conduction block
 Renal dysfunction (plasma creatinine >220 mg·dL⁻¹)
 Symptomatic peripheral arterial or cerebrovascular disease
 Severe COPD (FEV₁ <50% pred)
 Anticipated need for noninvasive ventilation (e.g. central or obstructive sleep apnoea)
 Liver dysfunction (Child–Turcotte–Pugh score class A and/or MELD score >8)[#]
 Maximal VO₂ max <15 mL·kg⁻¹·min⁻¹
 Pneumonectomy, bilobectomy; bilateral lung resection
 Extended lung resection involving the diaphragm, pericardium or parietal wall
 Intra-operative major bleeding

Early post-operative time course in the post-anaesthesia care unit

Unstable haemodynamics
 ECG signs of myocardial ischaemia
 Need for vasopressor support (other than related to epidural anaesthesia)
 Fluid/blood replacement
 Need for noninvasive ventilation support

[#]: according to [185]. COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in 1 s; MELD: model for end-stage liver disease; VO₂: oxygen consumption.

Two distinct patterns of clinical pathways have been reported: 1) routine ICU admission of operated patients (30–100%) providing precautionary cardiopulmonary monitoring and assistance by highly qualified healthcare personnel; 2) selective ICU admission only for ventilatory support and/or on an

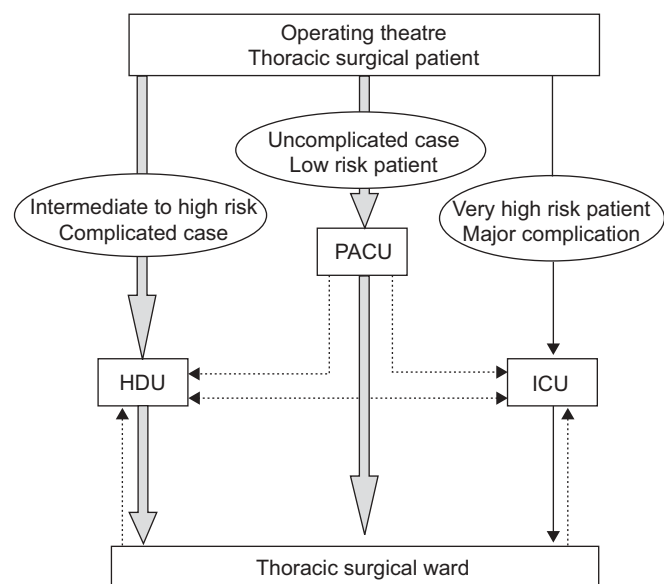


FIGURE 3. Clinical pathways for admission (and discharge) to (and from) the high dependency unit (HDU), intensive care unit (ICU) and thoracic surgical ward. PACU: post-anaesthesia care unit.

emergency basis, due to major peri-operative complications, while the majority of patients are transferred to the surgical ward either after a short 2–4 h stay in the post-anaesthesia care unit (for uncomplicated cases and low-risk patients) or after a 12–36 h stay in a high-dependency unit (HDU; for higher risk cases, see table 3).

The tendency to “over-admit” patients to the ICU may result in inappropriate bed occupation, raising hospital costs, delaying patient’s mobilisation and increasing risk of nosocomial infections [186]. The HDU offers a higher level of care than in the ward (*i.e.* nurse:patient ratio 1:2) with provision of cardiopulmonary monitoring and noninvasive ventilation modalities, as well as drug haemodynamic support [187, 188].

No randomised controlled trials have compared the outcome and treatment costs in similar thoracic surgical patients admitted either to the ICU, HDU or surgical wards. However, observational studies have demonstrated the appropriateness and advantages of the HDU as reflected by low mortality and morbidity rates (2–3% and 10–20%, respectively) while the admission rate to ICU remained <2% [169, 188–191].

In an effort to improve patient outcome and optimise hospital resource utilisation, clinical pathways should be proposed for admission (and discharge) to (and from) HDU, ICU and surgical wards (fig. 3).

Recommendations

- 1) A systematic admission to ICU after thoracotomy should not be recommended. Level of evidence 2++; grade of recommendation C.
- 2) In the presence of an appropriate HDU, nobody should be admitted to ICU on an elective basis. On an emergency basis, those patients requiring support for organ failure (*i.e.* ventilatory mechanical assistance) should be admitted to ICU. Level of evidence 2+; grade of recommendation C.
- 3) Patients undergoing complex pulmonary resection, those with marginal cardiopulmonary reserve and those with moderate to high risk according to table 3 should be admitted to HDU. Level of evidence 2++; grade of recommendation C.
- 4) After surgery, low-risk patients should be sent to a dedicated thoracic surgical unit, and not to a general surgical ward. Level of evidence 2++; grade of recommendation B.

Residual function and QoL after radical treatment

Many studies have shown that after lobectomy there is a disproportionate functional early loss with a gradual recovery in the following months. The residual function (FEV₁, DL_{CO} and VO₂ peak) may reach values as high as 90–95% of pre-operative values 3–6 months after operation. Conversely, after pneumonectomy, the loss in pulmonary function and exercise capacity is larger (20–30% at 6 months) and substantially stable over time [54, 64, 65, 192–195]. In general, exercise tolerance displays a more complete recovery compared to airflow and gas exchange capacities, presumably due to other compensatory mechanisms related to the cardiovascular system and the peripheral oxygen extraction capacity [54, 64, 194].

Most lung cancer patients are psychologically depressed and exhibit an increased tension-anxiety status compared with the

general population before being submitted to operation [196–199].

BRUNELLI *et al.* [197] found that, compared with the general population, candidates for lung resection with lung cancer had physical and psychosocial dysfunction: reduced pre-operative values of role limitation caused by physical problems, general health perception, social functioning, role limitation caused by emotional problems and mental health perception scales. Many of the altered scales remained below 50 (general population mean) even 3 months after operation.

Several studies have shown that lung resection determines a transient worsening of QoL 1 month following the operation with most of the scales returning to pre-operative values after 3–6 months [196–199]. An exception to this trend is represented by pneumonectomy patients that display a persistent deterioration of physiological and mental QoL scales even 3–6 months after operation [197, 198].

Perhaps with the exception of DL_{CO} [199], objective measures of cardiorespiratory function have not been found to correlate well with patients' perceived QoL [64, 192]. In this regard, patients' perception of symptoms, like dyspnoea and post-thoracotomy pain, appear more important to QoL [200]. Thus, an *ad hoc* QoL instrument should always be used for QoL evaluation.

Interestingly, in elderly patients and in those traditionally deemed at increased surgical risk, the post-operative physiological or mental status did not differ from those of lower risk counterparts [197, 201, 202]. These findings may have great importance during patient counselling before the operation. Particularly in patients deemed to be at higher risk for major post-operative cardiopulmonary complications, the information that residual QoL will be similar to the one experienced by younger and fitter patients may help in their decision to proceed with surgery.

QoL has been uncommonly regarded as a primary goal of chemotherapy trials [203, 204]. Moreover, between-trials comparison remains difficult because of heterogeneous QoL reporting and analysis techniques. Nevertheless, improvement in various scales of QoL has been reported in a number of clinical trials. Compared with best supportive care, chemotherapy offers symptom control, not only in patients with objective response to chemotherapy, but also in a proportion of those with disease stabilisation. Symptom palliation correlates well with QoL.

Recommendation

Specific QoL instruments should always be used for QoL evaluation. Level of evidence 2++; grade of recommendation B.

Statement

Pulmonary function assessment alone has been a poor predictor of the perceived residual QoL. Perception of symptoms has been reported to be more important to QoL, implying the need for monitoring respiratory symptoms after thoracotomy or chemotherapy. Level of evidence 2+.

SURGICAL TECHNIQUES IN LUNG CANCER

Combined cancer surgery and lung volume reduction surgery

Lung volume reduction surgery (LVRS) has emerged as a palliative treatment for severe emphysema [205–207]. Randomised trials and observational studies have demonstrated better health status and lung function outcomes in favour of LVRS compared with usual medical care including a rehabilitation programme [208, 209]. A subgroup of patients with upper lobe emphysema appeared to be the ideal candidates, LVRS producing significant improvement in exercise capacity with better survival [210, 211]. Several case series and *post hoc* analysis of hospital registries have indicated acceptable operative death rate and cardiopulmonary morbidity following LVRS in patients with solitary nodules and extremely poor lung function [212–218].

After anatomical lobectomy, patients with normal or mildly diseased lungs have the greatest post-operative decrease in FEV₁, whereas those with poor baseline function present minimal change or even improvement in post-operative FEV₁ [48–52, 54, 55, 57, 219–223]. Among 188 patients, KUSHIBE *et al.* [224] reported that upper lobectomy but not lower lobectomy produced a “volume reduction” effect. In contrast, SEKINE *et al.* [55] identified COPD and pulmonary resection of the lower portion of the lung (lower or middle-lower lobectomies) as independent factors for the minimal deterioration of FEV₁.

Acceptable peri-operative mortality rate (0–6%) with prolonged cancer-free interval and sustained functional improvement (up to 1 yr) have been reported in selected patients with pre-operative FEV₁ <60% [49, 212, 219, 223, 225]. Although long-term survival after lobar LVRS for stage I lung cancer is limited by physiological rather than oncological factors, outcomes are still better than those reported for any other modality of treatment.

Accurate estimation of post-operative pulmonary function should take into account the effect of deflating the over-expanded thorax and reinflating perfused lung areas. Quantitative imaging techniques may give useful information in this regard [105].

Consideration of fitness for surgery should acknowledge the effects of lobar LVRS in patients with severe COPD and early lung cancer stages: resecting a hyperinflated and poorly perfused tumour-containing lobe can outweigh any loss of function as well as the risks of major adverse events. In these selected high-risk patients, anatomical lobectomy, occasionally combined with LVRS has been shown to produce beneficial effects in terms of chest wall mechanics and lung elastic recoil, as well as survival.

Recommendation

Anatomical lobectomy with or without complementary LVRS should be performed in well-selected COPD patients with lung cancer. Level of evidence 2++; grade of recommendation B.

Compromised parenchymal sparing resections and minimally invasive techniques: the balance between oncological radicality and functional reserve

Parenchymal sparing resections, also called sublobar resections, include segmentectomy and wedge resections.

The Lung Cancer Study Group randomised trial

The Lung Cancer Study Group (LCSG) randomised trial, performed in patients with adequate lung function and limited resection, including wedge resections (one-third of patients) and segmental resections (two thirds), showed a 75% increase in recurrence compared with lobectomy (38 out of 122 *versus* 23 out of 125), attributable to an observed tripling of local recurrence rate (21 out of 122 *versus* eight out of 125). Segmentectomy had a lower locoregional recurrence risk than wedge: 0.022 for lobectomy, 0.044 for segmentectomy and 0.086 for wedge resections (rate per person per year) [226].

Lobectomy versus segmentectomy

Retrospective [227–230] and case–control [231] studies provide similar results for small tumours (stage IA <2 or 3 cm). Local recurrence after segmentectomy appears influenced by segment localisation and width of resection [232]. In good risk patients, segmentectomy is associated with slightly better pulmonary function [233, 234].

In patients with poor lung function, anatomical segmentectomy allows resections of stage I without compromising survival and with acceptable lung function preservation [235].

Wedge resection versus lobectomy

A few retrospective studies have reported contradictory results: increased risk of local recurrence in case of wedge resection [226], better survival with lobectomy [236] or similar results [237].

Segmentectomy versus wedge resection

There were fewer locoregional recurrences with segmentectomy in the LCSG trial [226], increased cancer-related survival in a retrospective study in stage IA [238] but significantly decreased survival with wedge resection for tumour of size 2–3 cm in a Japanese trial [228].

Sublobar resection

Some authors do not report data by separating interventions according to wedge or segmental resections, using the term “sublobar” or limited resection [239, 240]. If the trend in those series is shorter survival in comparison to classical lobectomy, a meta-analysis failed to show significant survival difference in stage I NSCLC [241].

Small peripheral adenocarcinoma

For a tumour <2 cm, wedge resection appeared to be associated with similar results in terms of survival or of cancer-specific survival, whatever the type of surgery performed [228] and with excellent results for small adenocarcinoma with an air-containing image on high-resolution CT scan [241].

Lung resection after prior lobectomy

Limited resection after prior lobectomy is associated with decreased and acceptable post-operative morbidity and mortality [242].

Recommendations

Anatomical segmentectomy could be recommended in the following situations.

- 1) Stage IA (tumour size 2–3 cm) with margins of resection >1 cm. Level of evidence 2; grade of recommendation D.
- 2) Stage I in patients with poor lung function. Level of evidence 2; grade of recommendation D.
- 3) Lung resection after prior lobectomy. Level of evidence 2; grade of recommendation D.

Wedge resection could be recommended in the following situations.

- 1) Stage IA (tumour size <2 cm). Level of evidence 2; grade of recommendation D.
- 2) Small peripheral adenocarcinoma with an air-containing image (ground glass opacity) on high-resolution CT scan. Level of evidence 2; grade of recommendation D.

CHEMO-RADIOTHERAPY IN LUNG CANCER**Neoadjuvant chemotherapy and complications**

Neoadjuvant chemotherapy in lung cancer patients may have several advantages: 1) more efficacious distribution of the chemotherapeutic agent prior to surgical manipulation; 2) *in vivo* testing of the chemotherapeutic agent; 3) follow-up not hindered by the residual effects of chemo- or radiotherapy administered after surgery.

According to the above, all resectable and operable lung cancer stages have been, and currently are, the subject of trials of neoadjuvant treatments, despite two major potential drawbacks: the delay of treatment of the primary lung tumour, especially for traditionally “surgical” subsets, like stage I and II nonsmall cell lung cancer (NSCLC); and the suggested increase in mortality and morbidity rates.

The evidence from randomised phase III trials indicates improved resectability after chemotherapy and suggests a marginal survival advantage for the induction arms [243, 244].

Several studies have addressed the issue of post-operative mortality and morbidity following induction treatment. Significant overall morbidity (>40%) and mortality rates have been reported after pneumonectomy. In particular, right pneumonectomy after induction treatment may entail mortality rates of up to 26% [182, 245–248].

Risk of induction chemotherapy in surgery with an extent of less than pneumonectomy

Despite the absence of randomised trials having as end-point the impact of chemotherapy on the post-operative outcome of resections less than pneumonectomy, recent evidence resulting from retrospective and prospective studies [249–254] has shown acceptable morbidity and mortality rates in selected patients.

Risk of induction chemotherapy in pneumonectomy

In the most recently published randomised controlled trials of neoadjuvant chemotherapy [255–257], the concern that has arisen from the previously reported worrying mortality and morbidity rates, especially after right pneumonectomy, is mitigated by the available results, with the only exception of

the Spanish trial confirming a 30% mortality rate for right pneumonectomy following induction chemotherapy [258].

Risk of combined induction chemo- and radiotherapy

Induction chemo-radiotherapy may indeed be a prelude to significant morbidity and mortality [258–260], although recent evidence from institutional studies shows increased safety in adding radiotherapy to chemotherapy induction regimens [261–264]. A prospective randomised trial powered on post-operative morbidity and mortality is needed to compare chemotherapy *versus* chemo-radiotherapy followed by surgery to clarify this issue.

In all of the above mentioned trials, patients who were not considered to be fit for the multimodal treatment were ineligible. The reported complications occurred, thus, in “fit” patients.

Effects of radiotherapy and chemotherapy on pulmonary function

Radiotherapy of the lung may cause radiation pneumonitis, usually several weeks after the end of radiotherapy. In patients with lung cancer, clinical pneumonitis can occur in 5–15% of patients, while radiographic abnormalities may be present in ~60% [265]. Certain chemotherapeutic drugs, which are frequently used for treating lung cancer, like taxanes and gemcitabine, can cause adverse reactions in the lungs with loss of function [266–269].

Furthermore, several chemotherapeutic agents are known sensitisers to radiotherapy, including, among others, doxorubicin, taxanes, mitomycin, vinorelbine, gemcitabine and platinum derivatives. Patients receiving these drugs are at a higher risk of developing radiation-induced lung injury, if administered at full dosages.

Recommendation

After induction chemotherapy and/or radiotherapy a new functional evaluation (particularly of DL_{CO}) before surgery should be recommended. Level of evidence 2+; grade of recommendation C.

Statements

- 1) The addition of induction chemotherapy to surgical resection less than pneumonectomy does not significantly increase morbidity and mortality. Level of evidence 1.
- 2) The addition of induction chemotherapy to surgical resection increases mortality after pneumonectomy. Level of evidence 1.
- 3) The addition of radiotherapy to neoadjuvant chemotherapy followed by pneumonectomy increases mortality. Level of evidence 1.
- 4) The addition of induction chemotherapy to right pneumonectomy increases morbidity and mortality. Level of evidence 1.
- 5) The addition of induction chemotherapy to resection, especially pneumonectomy, increases the risk for post-operative acute respiratory distress syndrome and respiratory failure. Level of evidence 1.

Definitive radiotherapy and chemotherapy: functional selection criteria and definition of risk. Should surgical criteria be re-calibrated for radiotherapy and chemotherapy?

Radiotherapy

The greatest limitation to definitive radiotherapy, apart from acute oesophagitis, is radiotherapy-induced lung toxicity [270]. It has to be emphasised that the comparison of studies on this topic is complex due to considerable heterogeneity in the scoring systems used in the literature to grade radiotherapy-induced lung toxicity.

It is generally assumed that patients with pre-existing pulmonary disease, particularly COPD, are at increased risk of radiation morbidity [271, 272] but the data relating pre-morbid physiology to radiation toxicity are limited. Knowledge of the risks of radiotherapy is usually used to guide the design of the radiotherapy treatment plans, rather than to decide whether or not to treat [273]. However, in many chemo-radiotherapy trials pulmonary function limits, similar to the limits used in surgical series, are set for exclusion of patients.

In the published studies not exclusively based on lung cancer patients, low arterial oxygen tension value (<80 mmHg) [274] and low DL_{CO} [275–278] have been associated with increased lung toxicity and morbidity. Low FEV₁ was associated with radiation pneumonitis in some [279, 280] but not all [281] studies. Moreover, in patients with FEV₁ <50% pred, half of the patients demonstrated a small improvement in lung function [282]. In another study, patients in whom lung perfusion was <35% in the zones at risk tended not to have significantly decreased transfer factor during follow up [275]. A model including mean lung dose, sum of predicted perfusion reduction based on regional dose–response curve and pre-radiation pneumonitis DL_{CO} could not segregate patients at high risk *versus* those at low risk for radiation pneumonitis [283]. The risk of developing radiation pneumonitis-induced lung toxicity can be estimated by calculating the dose–volume histogram of the lungs, including V_{20} and mean lung dose (MLD) [284, 285].

Recommendation

Dose–volume histograms of the lung should be calculated (including V_{20} and MLD) to evaluate the risk of radiation-induced pulmonary toxicity. Level of evidence 2+; grade of recommendation C.

Statements

- 1) Pulmonary physiology cannot accurately determine the acute and long-term risks related to thoracic radiotherapy. Level of evidence 2+.
- 2) Safe lower limits of respiratory function (FEV₁ or DL_{CO}) for radical radiotherapy have not been defined as they have been for surgery. The current evidence base does not permit any statements about what is safe or unsafe. Level of evidence 2++.
- 3) To date, radiotherapy dosimetric parameters are the most effective tools for predicting radiation-related lung damage [285–287]. Models based on combination of radiotherapy planning parameters, lung function tests, and lung perfusion imaging may have a higher predictive value and should be

addressed in further research. Biological markers predicting the risk of radiation-related lung damage should be explored further [288]. In addition, comprehensive lung function testing before and after radiotherapy, as well as the long-term effects of chemo-radiotherapy, including QoL, should be evaluated in each prospective chemo-radiotherapy trial.

Chemotherapy

The results of a meta-analysis published in 1995 based on 9,387 patients with NSCLC from randomised clinical trials supported the addition of cisplatin-containing chemotherapy regimens to thoracic radiotherapy [289]. Subsequently, the NSCLC Collaborative Group meta-analysis showed a significant survival advantage with concurrent chemo- and radiotherapy compared with sequential chemo- and radiotherapy [290].

Very few data have been reported on pre- and post-chemotherapy lung and cardiac function in NSCLC treated by definitive chemo-radiotherapy. Safe lower limits of respiratory function for chemotherapy or concurrent chemo- and radiotherapy have not been defined. The only available data are the observed toxicity in patients without significant comorbidity, as usually selected in chemotherapy-based trials [291–295]. The current evidence does not permit any recommendation for treatment security.

Statement

Safe lower limits of respiratory function (FEV1 or DL_{CO}) for radical chemotherapy have not been defined as they have for surgery. The current evidence base does not permit any formal recommendation about what is safe or unsafe. Level of evidence 2++.

The patient at prohibitive surgical risk: alternatives to surgery

Radiotherapy

A Cochrane review included 2,003 patients with medically inoperable stage I/IIa treated with radical radiotherapy [296]. Cancer-specific survival was 13–39% at 5 yrs. Local failure rates were 6–70%. Radical radiotherapy appeared to result in a better survival than might be expected had treatment not been given. An optimal dose and treatment technique could not be defined.

The CHART (continuous, hyperfractionated, accelerated radiotherapy) trial randomised 563 patients with stage I–IIIB NSCLC (including 203 patients with stage I–II) to receive either CHART or conventionally fractionated radiotherapy. CHART improved 2-yr survival from 20% to 29% [297].

Conformal three-dimensional radiotherapy improves on conventional two-dimensional radiotherapy by optimising target coverage and by reducing the exposure of normal tissues to high-dose radiation [298]. The European Organization for Research and Treatment of Cancer (EORTC) guidelines for treatment planning of high-dose radiotherapy in lung cancer advocates the use of three-dimensional radiotherapy planning [299].

Hypofractionated radiotherapy has been investigated but the evidence to support the use of large fraction size is limited [300, 301].

Dose escalation studies investigating doses >60 Gy have not established an optimal radiotherapy dose, achieving a balance between local control and side effects [302–304].

Increased LC rates of 80–98% at 2–5 yrs with overall survival of 52–83% at 2–5 yrs [305–310] have been reported with hypofractionated stereotactic radiotherapy in stage I and II NSCLC. A variety of doses and fractionations have been used [305–315]. Treatment of tumours adjacent to a primary or secondary bronchus should be avoided as excessive acute toxicity and symptomatic bronchial stenosis have been reported [309, 313, 316].

Radiofrequency ablation

Small series of medially inoperable patients report local relapse rates of 8–53% [317–319]. The ideal patient for radiofrequency ablation would have an isolated, peripheral lesion of <3 cm and be able to tolerate a pneumothorax [320]. These series reported that the technique is safe.

Photodynamic therapy

Photodynamic therapy is a treatment option for stage 0 (TisN0M0) and stage I (T1N0M0) centrally located early stage lung cancer. Photodynamic therapy can preserve lung function, can be repeated, and can be combined with other therapeutic modalities such as chemotherapy. Complete response rates after photodynamic therapy are in the range of 70–92% [321–324].

Recommendations

- 1) Radiation alone for medically inoperable NSCLC must be regarded as the best established alternative treatment to surgery. Level of evidence 1; grade of recommendation B.
- 2) The use of CHART must be preferred to conventional radiotherapy as it achieves better local control rates and survival. Level of evidence 1; grade of recommendation B.
- 3) Stereotactic radiotherapy should be considered a good alternative to surgery and conventional radiotherapy in stage I NSCLC patients at high surgical risk. Level of evidence 2++; grade of recommendation B.

Statement

Other treatment options for selected medically inoperable patients include radiofrequency ablation and photodynamic therapy. Level of evidence 2+.

WHO SHOULD TREAT THORACIC PATIENTS AND WHERE SHOULD THEY BE TREATED?

Multidisciplinary management

The American College of Chest Physicians guidelines [34] and other studies [325] support multidisciplinary management showing significant survival improvement.

Quality of lung cancer surgery

In Europe, there is a lack of homogeneity in the way the thoracic surgical specialty is practised [326]. In this regard, a joint ESTS/European Association for Cardio-thoracic Surgery task force has defined the requirements necessary to exploit a modern thoracic surgical practice [327].

The thoracic surgeon's specialisation

As demonstrated by many studies, qualified thoracic surgeons achieved better results compared to nonspecialised surgeons [328–330] in terms of peri-operative mortality and resection rates.

The surgical volume

Several authors [331–334], although not all [335–338], have found an inverse relationship between surgical volume and post-operative morbidity and mortality rates, and even long-term survival of lung cancer patients.

Quality indicators

Post-operative mortality, however, may not be the most appropriate end-point to evaluate the quality of care [179, 339, 340].

Quality of radiotherapy

There is only one study demonstrating an impact of institutional experience measured by the volume of cases treated by chemo-radiotherapy [341].

Standard dosage with a daily treatment and ≥ 60 Gy over a 6-week period is recommended for routine practice by the European Lung Cancer Working Party. The EORTC Radiotherapy Group recommendations should be followed for treatment planning and administration of radiotherapy for lung cancer [299, 342, 343]. Those recommendations concern patient's positioning, planning CT scan (with the use of spiral CT scan), accounting for tumour mobility, generating target volumes, treatment planning (has to be three-dimensional), treatment delivery and evaluation of response and toxicity.

Volume of chemo-radiotherapy

The RTOG study showed that institutions that treated less than five patients had significantly much poorer results than those which treated more patients by chemo-radiotherapy, with respective median survival times of 13.4 and 20.5 months [341]. Multivariate analysis confirmed that the number of patients enrolled from each institution was an important prognostic factor.

Recommendations

- 1) The management of lung cancer patients must be performed by multidisciplinary teams (a thoracic surgeon specialising in lung cancer, a medical oncologist, a radiation oncologist and a pulmonologist). Level of evidence 2++; grade of recommendation B.
- 2) The surgical treatment of lung cancer patients must be performed in specialised centres by qualified thoracic surgeons, since specialisation has been shown to have a positive impact on resectability, post-operative mortality and long-term survival. Level of evidence 2++; grade of recommendation B.
- 3) Surgical volume has been shown to have a positive impact on resectability, post-operative mortality and long-term survival. Lung cancer surgery should be performed in centres with adequate volume of cases (although volume thresholds reported in the literature varied in size and definition, a minimum surgical volume of 20–25 major lung resections per year, lobectomy or pneumonectomy, should be advised). Level of evidence 2+; grade of recommendation C.

4) There is a positive impact of volume on the results of chemo-radiotherapy. Radiotherapy should be performed by radiotherapists in centres that routinely treat patients by this combined modality. Radiotherapy should be performed according to the EORTC Radiotherapy Group recommendations. Radiotherapy quality: level of evidence 4; grade of recommendation D. Hospital volume: level of evidence 2++; grade of recommendation C.

ALGORITHM FOR THE ASSESSMENT OF RISK BEFORE LUNG RESECTION

Based on the best available scientific evidence and consensus opinion of experts, the task force produced a functional algorithm for the evaluation of candidates for lung resection.

A decision was made to use, as a template, the algorithm originally proposed by BOLLIGER and PERRUCHOU [59], representing the only one prospectively validated [84, 110–112].

The panel of experts agreed to emphasise the importance and role of exercise tests in the work-up of lung resection candidates. As cycle-ergometry may be not readily available in some centres, a low-technology exercise test, such as the stair climbing test, has been proposed to be a possible surrogate and a first-line screening ergometric step in the algorithm, with the strong recommendation, however, that if the performance on the stair climbing test is poor, patients need to be referred for formal CPET.

The task force team agreed to update and modify the algorithm based on the latest evidence [344, 345] showing that, owing to the advances in surgical techniques (minimally invasive procedures, combination of lung cancer surgery with LVRS [178]) and the ongoing improvement in post-operative care, the limits of functional operability are constantly being lowered, thus allowing resections in patients who would have been deemed inoperable a few years ago. The algorithm emphasises the importance of a preliminary cardiological assessment (fig. 1). Those patients at low cardiological risk or with an optimised cardiological treatment may proceed with pulmonary evaluation (fig. 2). Complete spirometry and DL_{CO} assessment is recommended in all patients. All those patients with either FEV_1 or DL_{CO} or both $< 80\%$ pred should undergo an ergometric assessment. Ideally, a formal CPET with $VO_{2,peak}$ measurement should be performed, but the group recognised that many centres may have logistical problems in systematically performing this test. In this latter circumstance, a low-technology exercise test, preferentially stair climbing test (or, as second choice, shuttle walk test) may be used as screening test. Those patients showing suboptimal performance on these tests (< 22 m for stair climbing) should necessarily perform a formal CPET.

A limitation of such an algorithm, which is centred on the ergometric evaluation, may be that a certain proportion of lung resection candidates may be unable to perform any type of reliable exercise test due to concomitant incapacitating comorbidities. Such patients have been shown to have an increased risk of death after major lung resection [346] and, after a careful selection based on the available cardiac and pulmonary parameters, they should be regarded as high-risk

patients and monitored in an advanced care management setting.

LIMITATIONS AND PERSPECTIVES

Most of the evidence in these guidelines is of level 2, and most of the recommendations are at B or C levels. This is mainly due to the nature of the subject, which makes the design of randomised trials difficult and impractical. Recommendations for risk stratification for radical treatment were thus generated based on the best available scientific evidences and, in case these were weak or totally absent, consensus of expert opinions.

Although age has been traditionally regarded as a risk factor, we concur with recent recommendations [34] that age alone should not be used as selection criteria for surgery. The increased risk for radical treatment observed in elderly patients is probably a function of the underlying comorbidities. In this regard, we recommend that cardiopulmonary fitness of elderly (>70 yrs) or very elderly (>80 yrs) lung cancer patients should be fully evaluated following the recommendations expressed by this task force, without any prejudice for age.

Contrary to lung resection, for which the scientific evidences are more robust, we were unable to recommend any specific test, cut-off value, or algorithm for chemo-radiotherapy, owing to the lack of data. Studies aimed at establishing strategies for the assessment of fitness before chemo-radiotherapy should be strongly encouraged.

The algorithm elaborated by this current task force needs to be prospectively validated. In addition, measurements of mortality, post-operative morbidity and long-term disability should be performed for each treatment arm, in order to evaluate the balance between benefits and risks related to each treatment option. This step is crucial, in order to provide valuable information on treatment options and risks to patients. To date, data available in the literature do not allow this goal to be reached.

Although we designed these guidelines to be broadly accepted, implemented and validated in all European centres, the scientific evidence upon which they were based were mainly generated in settings specialised in the management of lung cancer patients. Treatment of these patients outside these settings is strongly discouraged and application of our guidelines and recommendations outside specialist centres is unwarranted.

STATEMENT OF INTEREST

None declared.

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