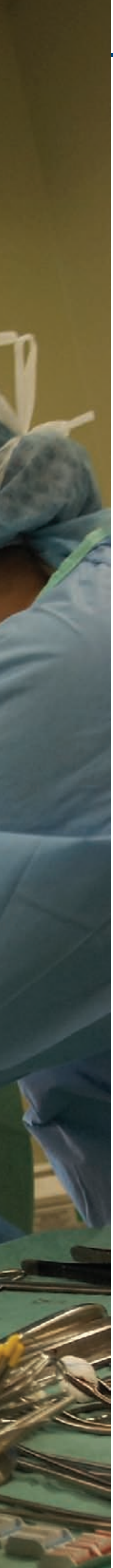
Key points

- Improved selection criteria result in decreases in the overall number of candidates for surgery.
- Improved risk assessment causes an increase in the number of marginal candidates for surgery.
- FEV_1 and $D_{L,CO}$ reflect the status of two different components of pulmonary function (airflow and gas exchange), which may not necessarily correlate.
- Patients with COPD could have an improved pulmonary function after lobectomy compared with non-COPD patients.
- Age by itself should not disqualify elderly patients from surgical treatment for lung cancer.
- In patients with multiple primary tumours, diaphragmatic motility must be checked before the operation.



Fit for surgery? Assessment of marginal lung cancer patients

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Educational aims

- Outline the risks of surgery for lung cancer and chronic obstructive lung disease (COPD) patients.
- Define the risks of lung resection in patients with lung cancer and cardiac comorbidity.
- Describe complications with lung resection in the elderly.
- Examine the ideal operative procedure for lung resection.

Provenance
Commissioned article, peer reviewed.

Competing interests
None declared.

Summary

Surgical treatment is still a treatment of choice for many stage I–IIIA lung cancer patients. Owing to modern methods of risk assessment, the option of surgery has now extended to patient groups that would have been rejected from surgery 10–15 yrs ago. Patients with COPD constitute the majority of such patients, followed by patients with associated cardiac comorbidity and elderly patients undergoing lung resection. In these patients, the risk of post-operative complications and death exists independently of the level of surgical skills and post-operative care. Similarly, patients undergoing lung resection after neoadjuvant treatment and previous pleural empyema, or patients requiring very extended resections, are exposed to an increased risk of operative morbidity and mortality. The possibility of unpredicted complications makes the pre-operative selection even more delicate. Each of these patient groups requires a specific, multidisciplinary approach that necessitates close collaboration between pulmonary physicians, thoracic oncologists and thoracic surgeons.

The role of surgical treatment in lung cancer has resisted the test of time during the past three decades, either alone or in combination with chemo- and/or radiotherapy. Surgery has remained the treatment modality offering the best chance of prolonged survival in a selected group of patients.

By strictly applying the selection criteria based on noninvasive (high-resolution computed tomography (CT) scan, positron emission tomography, nuclear magnetic resonance imaging and bone scintigraphy) and invasive (mediastinoscopy, endobronchial ultrasound and oesophageal ultrasound) staging of the mediastinum, surgery is now only offered to patients who are likely to benefit in terms of survival. Conversely, modern methods of risk assessment have led to the extension of surgical treatment to some patient groups that would have been rejected from surgery 10–15 yrs ago. The proportion of these marginal candidates for surgery has been continuously increasing in recent years. Although cancer stage is the most important predictor of survival in patients with lung cancer, between 19% and 30% of stage I lung cancer patients who undergo surgery die as a result of other diseases [1, 2].

When discussing the terms "acceptable"

HERMES syllabus link: modules B.1, D.1.1, D.1.3, D.3.1, H.1

DOI: 10.1183/18106838.0602.126

Table 1 Real and potential risks for lung cancer patients undergoing surgery

Real risk	Potential risk
COPD	Previous treatment; neoadjuvant
Cardiac comorbidity	Intrathoracic contamination with/without empyema
Elderly patients	Operative procedure; extended resection, reoperations, multiple primaries
	Unpredictable complications; double *versus* single lung ventilation; prevention of ALI/ARDS

ALI: acute lung injury; ARDS: acute respiratory distress syndrome.

and "unacceptable" risk for surgery in a patient with lung cancer, the following question could be asked: what risk should be accepted for surgery if the goal is to cure a malignant disease with near 100% mortality if left unresected? (table 1).

Lung resection in patients with lung cancer and COPD

Pre-operative work up

In contrast to 15–20 years ago, absolute values of ventilatory parameters are no longer regarded as acceptable as cut-off values for safe lung resection for COPD patients. Instead, forced expiratory volume in 1 s (FEV_1) and vital capacity (VC) are now accepted as more reliable, with 60% predicted as a cut-off value, not for direct rejection from surgery, but for referring these patients for additional lung function assessment (table 2). In other words, the patient with values below those presented in table 2, after properly performed combined treatment, will not be automatically rejected from surgery.

Table 2 Standard spirometry and cut-off values for lung resection

Spirometry	Resectable	Additional LF assessment
FVC % pred	>60	<60
FEV_1 % pred	>60	<60
FEV_1/VC %	>50	<50
MVV % pred	>50	<50
$D_{L,CO}$ % pred	>60	<60
P_{a,CO_2} mmHg	<45	>45

LF: lung function; FVC: forced vital capacity; pred: predicted; VC: vital capacity; MVV: maximum voluntary ventilation; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; P_{a,CO_2}: arterial carbon dioxide tension.

Measurement of diffusion capacity

A study showed that only 25% of over 3,400 lung resection candidates from 27 European centres had diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$) or predicted pre-operative (ppo) $D_{L,CO}$ tests performed [3]. Even commonly accepted guidelines recommend limiting $D_{L,CO}$ measurement to patients with FEV_1 <80% pred [4]. However, it should be remembered that FEV_1 and $D_{L,CO}$ reflect the status of two different components of pulmonary function (airflow and gas exchange), which may not necessarily correlate.

Brunelli *et al.* [5] found that 219 (43%) out of 508 patients with FEV_1 >80% pred had $D_{L,CO}$ <80% pred. In patients with FEV_1 >80%, ppo$D_{L,CO}$ <40% was a significant and reliable predictor of post-operative complications (p=0.004). Furthermore, >40% of patients without airflow limitation had an impaired lung diffusion capacity and 7% of them had a critical ppo$D_{L,CO}$ value (<40%). These patients experienced morbidity and mortality rates two-fold and almost three-fold higher, respectively, than in those with ppo$D_{L,CO}$ >40%. As $D_{L,CO}$ <50% and >60% pred were reported to be associated with an operative mortality of 13% and 3%, respectively, this should be kept in mind when planning surgical treatment. Therefore, even in subjects with otherwise apparently normal pulmonary function, diffusion capacity has a role in predicting post-operative morbidity.

Additional lung function assessment

How many subsegments are to be resected?

Calculating the number of lung subsegments to be resected is a simple method for the prediction of post-operative lung function, which is as accurate as scintigraphy [6]. The Juhl–Frost method, based on the estimate that each lung segment contributes 1/19th (0.056) to the overall lung function, is still widely accepted. According to this method, ppoFEV_1 is calculated using the following equation:

$$ppoFEV_1 = \text{pre-operative } FEV_1 \times (1 - 0.056 \times \text{number of segments to be removed})$$

A more detailed calculation distinguishes between occluded and nonoccluded subsegments [7]:

$$ppoFEV_1 = (1 - (n - a)/(42 - a)) \times \text{pre-operative } FEV_1$$

where n is the total number of subsegments in the resected lobe, which is assumed to be six, four and 12 for the right upper, middle and lower lobe, respectively, and 10 each for the left upper and lower lobes, and a is the number of subsegments obstructed by tumours.

Perfusion lung scintigraphy: technetium

The use of technetium in lung perfusion scintigraphy is a widely accepted method enabling reliable prediction of post-operative FEV$_1$ using a per cent perfusion of each lung.

For pneumonectomy, ppoFEV$_1$ is calculated as follows:

$$\text{ppoFEV}_1 = \text{pre-operative FEV}_1 \times \%\ \text{perfusion of the non-tumour-bearing lung}$$

For lobectomy, the ppoFEV$_1$ is calculated using a stepwise method, first calculating the predicted loss in FEV$_1$ after lobectomy, again by using per cent perfusion of each lung [8]. Then, by subtracting the predicted loss from the measured pre-operative FEV$_1$, the ppoFEV$_1$ is obtained:

$$\text{ppo loss in FEV}_1 = \text{pre-operative FEV}_1 \times \%\ \text{perfusion of the tumour bearing lung} \times n/N$$

where: n = number of segments to be removed and N = total number of segments of the diseased lung.

An example of this method is given in Case 1.

In the above example, the post-operative FEV$_1$ value was slightly overestimated by the calculation. Differences between predicted and measured FEV$_1$ can be related to both the method of prediction or to the lung resection itself. If the subsegment counting method is used, in patients with COPD or with interstitial pneumonia, the difference between the predicted and counted value can be caused by the non-uniform distribution of emphysema and interstitial pneumonia.

With regard to the influence of lung resection in patients with COPD, both the relief of airflow obstruction and improvement of the respiratory muscle function can occur post-operatively, while in patients with emphysema, lung resection usually improves residual lung function. Furthermore, elimination of dead space ventilation in unperfused areas and improved cardiovascular haemodynamics frequently occur post-operatively. Therefore, all these factors can contribute to this unexpected improvement that may cause the underestimation of post-operative lung function.

If the prediction of post-operative lung function is calculated using lung perfusion scintigraphy, despite the degree of COPD, it is not only the calculation that is of interest for the decision: if the perfusion of the non-tumour-bearing lung is

Case 1

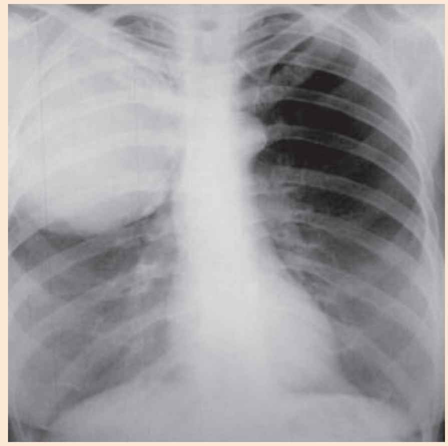

Figure 1
Right upper lobe tumour requiring upper lobectomy in a patient with moderate/severe COPD.

Pre-operative FEV$_1$	1,500 mL
Lung perfusion	Right: 39.6% Left: 60.4%
ppo loss of FEV$_1$	= pre-operative FEV$_1$ × % perfusion of the right lung ×n/N = 1,500 × 39.6/100 × 3/10 = 178.2 mL
ppo FEV$_1$	= 1500 - 178.2 = 1,321.8 mL
Measured post-operative FEV$_1$	1,113 mL

Case 2

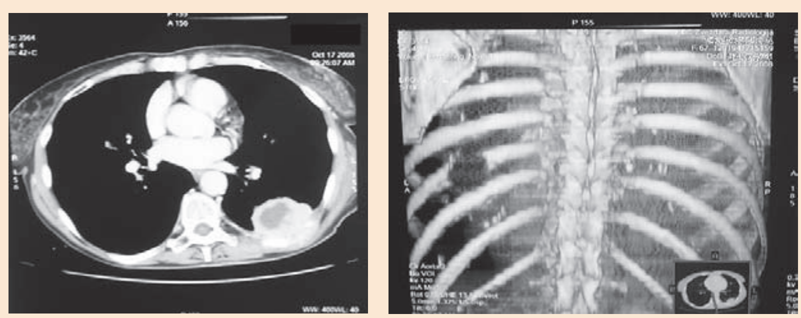

Figure 2
Left lower lobe cancer with chest wall involvement, requiring lower lobectomy and en block resection of the chest wall. Perfusion of the contralateral lung was better than the tumour-bearing lung. The patient had a significant cardiac comorbidity. FEV$_1$: 1.13 L or 58% pred; FEV$_1$/FVC: 44.7%; forced expiratory flow at 50% of VC (FEF$_{50\%}$): 0.46 L or 14%; FEF$_{25}$: 0.17 L or 16%; ppoFEV$_1$: 910 mL or 46%. Perfusion of the left and right lung was 39% and 61%, respectively.

Pre-operative FEV$_1$	1,130 mL 58% pred
FEV$_1$/FVC	44.7%
FEF$_{50}$	460 mL 14% pred
FEF$_{25}$	170 mL 16% pred
Lung perfusion	Right: 61% Left: 39%
ppo FEV$_1$	910 mL 46% pred

Result: resection possible

Case 3

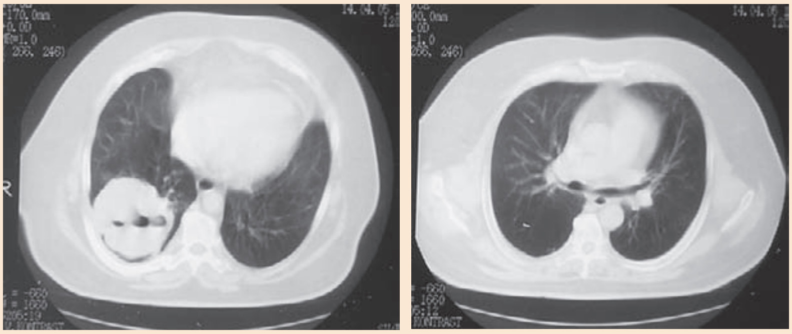

Figure 3
Right lower lobe tumour in a patient with refractory, severe COPD. Drops in oxygenation (from an oxygen tension of 7.6 kPa and 5.1 kPa two and one months before the operation, respectively) required a longer than usual period of combined treatment for obstruction. RRL: right lower lobectomy; Th: treatment.

Pre-operative blood gases

Date	P_{a,O_2} kPa	P_{a,CO_2} kPa	pH
May 13	7.6	5.6	7.44
May 16	7.3	4.8	7.46
June 6	5.1	5.5	7.41

Pre-operative FEV1	1,010 mL 29.7% pred
Pre-operative FEV1 after Th	1,790 mL 52.8% pred

Operation took place July 13; RRL

Post-operative blood gases	P_{a,O_2}	P_{a,CO_2}	pH
	10.3	5.7	7.46

Post-operative FEV1	1,410 mL 43% pred

better than that of the contralateral lung, it is an additional argument for referring the patient for surgery (case 2). This is particularly the case in the presence of a major comorbidity.

Single photon emission computed tomography
The obtained images from single photon emission (SPE) computed tomography (CT) are more precise than planar images; however, identifying the pulmonary lobes remains difficult. This has led to the concept of a fused SPECT and multidetector CT image [9]. In this technique, which uses technetium-99m-macroaggregated human serum albumin, the two scans are performed sequentially with manual fusion of the SPECT and CT images. After the lobe to be resected is traced on a CT image within the region of interest (RI), the SPECT image after lobectomy is shown on the workstation. The prediction of post-operative lung function is performed using the following formula:

$$\text{ppoFEV}_1 = \text{pre-operative FEV}_1 \times (1 - \text{RI count of the target lobe}/\text{RI count in the entire lung before surgery})$$

Quantitative CT
This technique enables the calculation of the volume of the functioning lung from CT images with a CT number in the range of –910 to –500 Hounsfield Units (HU). This range can be used to assess the extent of emphysema [10]. Lung regions with a CT number in the range of –910 to –500 HU are extracted on the workstation, according to the method proposed by Wu *et al*. [11]. After the lobe to be resected has been traced on transaxial CT images within the region of interest, the CT image of the functioning lung after lobectomy is shown on the workstation.

With quantitative CT, it is possible to measure the volume of the lung to be examined by drawing a surgical margin directly on a three-dimensional lung model.

$$\text{ppoFEV}_1 = \text{pre-operative FEV}_1 \times (1 - \text{target lobe volume}/\text{whole lung volume})$$

If this method and lung volume reduction surgery are used in COPD patients with lung cancer, the removal of lung areas with a CT number outside the range –910 to –500 HU is not expected to cause a significant loss of lung function.

Emphysema index
It was recently shown that only the emphysema index contributed to identifying patients whose residual pulmonary function was likely to improve [12]. This means that a lower threshold of FEV1 should be defined in accordance with whether the emphysema index is above or below 10%. It was also demonstrated that the emphysema index was reliable for predicting air leak duration [12], hypoxaemia and prognostic outcome. In combination with FEV1, it is also helpful in identifying patients at an increased risk of post-operative cardiopulmonary complications and prolonged rehabilitation [13].

Effort studies
It has been demonstrated that a maximal oxygen consumption during effort of <1 L was associated with 75% risk of operative mortality. A maximal oxygen uptake ($V'_{O_2,max}$) <15 mL per kg per min indicates not only the high risk of post-operative death, but also a high probability of serious post-operative complications, such as arrhythmia and pneumonia.

In the presence of ppoFEV1/$D_{L,CO}$ <40%, effort studies should be performed either in the form of classic (ECG, changes in heart frequency, minute ventilation or $V'_{O_2,max}$) or alternative tests. Alternative tests include stair climbing and the shuttle walk. If the patient is able to climb five flights of stairs, his/her $V'_{O_2,max}$ is probably >20 mL per kg per min. If a patient is not able to climb one flight of stairs, his/her $V'_{O_2,max}$ is probably <10 mL per kg per min. If, during the shuttle-walk test, a patient's capacity is <25 shuttles in two series, his $V'_{O_2,max}$ is likely to be <10 mL per kg per min [14].

By combining the pre-operatively measured $V'_{O_2,max}$ with relative lung perfusion [15], it is possible to predict a post-operative $V'_{O_2,max}$

$$\text{ppo } V'_{O_2,max} = \text{pre-operative } V'_{O_2,max} \times (1 - \text{fraction of the function of the part of the lung to be removed})$$

If the predicted post-operative $V'_{O_2,max}$ is <10 mL per kg per min, the risk of operative mortality is increased. It is not easy to sort different tests in order of priority and the combination of two tests may be of help for the final decision.

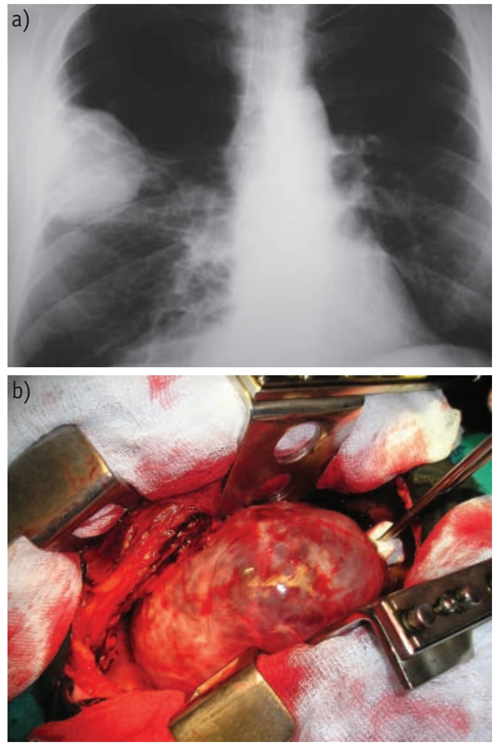

Figure 4
a) Right upper lobe tumour invading the chest wall in a patient with bullous emphysema in the same lobe. b) Operative view before upper lobectomy with chest wall resection.

Influence of lung resection on post-operative lung function

Several studies have demonstrated that post-operative complications, such as prolonged air leak, empyema, bronchopleural fistula, pneumonia and the need for artificial ventilation, were significantly more frequent in COPD than in non-COPD patients [16]. It has also been demonstrated that one lung ventilation, routinely performed in most centres, can cause severe impairment of gas exchange in these patients, especially during right thoracotomy [17].

However, an increasing number of studies are being published that clearly demonstrate that the loss in lung function after lung resection in COPD patients can be smaller compared with non-COPD patients. In a study of 42 COPD and 45 non-COPD patients, there was no significant difference in operative mortality, morbidity and survival between the groups [18]. The loss in FEV_1 6 months after the operation in the COPD group was 3.2% *versus* 14.9% in the control group. This and other similar studies demonstrated that patients with mild-to-severe COPD could have a better preservation of pulmonary function after lobectomy than non-COPD patients [19]. In practice, there are three questions that are important for this subject:

1. Where is the lower limit for safe lung resection?
2. For how long should we prepare these patients in relation to their malignant disease?
3. What about smoking cessation?

In relation to the first question, case 3 demonstrates that even in patients with FEV_1 <30% pred it is possible to improve ventilatory function up to the limit for safe resection. However, administration of combined bronchodilator treatment for several weeks or months can be associated with serious drops in oxygenation that should not discourage the surgeon from preparing the patient adequately. As presented in figure 3, oxygenation improves immediately after the operation. Therefore, if the lower limit for ventilatory function is likely to be individual, there is no doubt that pre-treatment FEV_1 and Tiffeneau index values should not be taken as criteria for rejecting these patients from surgery.

Although the length of pre-operative preparation of COPD patients has not been specifically addressed in the literature, it seems reasonable that 4–6 weeks could suffice for patients with severe and refractory COPD. Such a time frame is supported by our institutional experience [20].

Smoking cessation should be encouraged, because it may decrease post-operative inflammation, and in the long-term, may decrease the risk of recurrence [21].

In patients with emphysema in the tumour-bearing lobe or lung, it is easier to predict post-operative lung function than in COPD patients without emphysema because of the lung volume reduction effect of the operation (figure 4). Main points in the preparation of COPD patients for lung surgery are:

1. smoking cessation
2. combined bronchodilator treatment
3. physiotherapy

Resection in patients with lung cancer and cardiac comorbidity

The incidence of cardiovascular comorbidity in patients with lung cancer is reported to be 13–23% [22]. As these two conditions share common risk factors, such as older age and smoking, such a high incidence is not surprising. The incidence of cardiac comorbidities in patients undergoing surgery for nonsmall cell lung cancer varies between 6% in those aged <60 yrs and 21% in those >60 yrs [23].

Pre-existing cardiac pathology in lung resection candidates can be coronary disease, cardiomyopathy, cardiac rhythm disorders, previous myocardial infarction or previous cardiac surgery. Although one would expect an adverse impact of cardiac comorbidities on the post-operative outcome, literature data are conflicting, ranging from a markedly adverse impact to a minimal impact [24, 25].

In studies by Moro-Sibilot *et al*. [26] with the use of the Charlston comorbidity index (a weighted score of one is allocated to cardiac comorbidities), the post-operative outcome of a patient with score 1–2 was not significantly different from that of patients with score 0, implying that cardiac comorbidities did not have a negative post-operative impact on outcome. The results of the most recent study performed on 199 patients with cardiac comorbidity and 398 patients without, are in concordance with this report [27]. There was no difference in in-hospital mortality (2.5% *versus* 3%; p=0.73), myocardial infarction (0.5% *versus* 0.3%; p>0.99), arrhythmia (15.6% *versus* 14.1%; p=0.62), renal failure (2% *versus* 1.5%; p=0.65), stroke (0.5% *versus* 0.3%; p>0.99), respiratory insufficiency (4% *versus* 3.3%; p=0.64), reintubation (1% *versus* 2.5%; p=0.35), tracheostomy (4% *versus* 7.8%; p=0.08), intensive care readmission (8.5% *versus* 6.5%; p=0.37) and length of stay (8 days *versus* 8 days; p=0.98). Three-year survival was similar (61.4% *versus* 56.2%; p=0.39) and no differences in outcome existed with different cardiac conditions [27].

Independently of the type of cardiac comorbidity, it is mandatory to rule out:

1. pulmonary hypertension
2. prohibitively low ejectional fraction (<25–30%).

That is why a usual work-up in patients with a history of cardiac disease, especially when valvular disease, left ventrical dysfunction or pulmonary hypertension is suspected, includes echocardiography (not older than 2 weeks), an ECG and blood gases on the day of the operation, together with a chest radiograph. Independent of the severity of the cardiac comorbidity, exercise testing is necessary in order to measure oxygen consumption.

Myocardial infarction

The reported frequency of myocardial infarction after thoracic surgery is between 2.8% and 17% [28]. In patients with a history of myocardial infarction, the pre-operative work-up is the same as mentioned above, with the exception that the operation should not be performed inside the first 3 months after the myocardial infarction.

Arrhythmia

The reported incidence of arrhythmias is 12–87% depending on the type of arrhythmia. A correlation has been demonstrated between the incidence of post-operative arrhythmia and history of congestive cardiac failure and previous arrhythmia. Similarly, peripheral vascular disease, hypertension, older age and pneumonectomy also contribute to the occurrence of post-operative arrhythmias.

Post-operative atrial fibrillation is a common complication after cardiac and thoracic surgery that affects 20–40% of patients. Atrial fibrillation increases the risk of mortality and morbidity from:

- stroke
- heart failure
- myocardial infarction
- thromboembolism
- bleeding from anticoagulation and hospital readmission

In a recent meta-analysis by Shrivastava *et al*. [29], 14 randomised clinical trials studied the prophylactic effects against atrial fibrillation of diltiazem, β-blockers, digoxin, verapamil, flecainide, amiodarone, magnesium and epidural anaesthesia. The conclusions of these trials were as follows:

- digoxin and verapamil do not reduce the incidence of atrial fibrillation

- amiodarone may cause acute respiratory distress syndrome (ARDS) and cannot be recommended
- flecainide and β-blockers have not been studied adequately enough for safe recommendations to be made
- from one single trial there was evidence for bupivacaine epidural, magnesium and diltiazem for the prophylaxis of atrial fibrillation

Chronic stable angina

There is no evidence to support preventive pre-operative coronary revascularisation before non-cardiac surgery in patients with chronic stable angina [30]. Coronary revascularisation is usually limited to patients who need the procedure independently of the need for noncardiac surgery. Therefore, the indications for operative or percutaneous revascularisation in lung cancer patients are similar to those in the American Heart Association guidelines for revascularisation for coronary artery disease. Only in patients with a clear need for revascularisation is lung cancer surgery postponed until after the revascularisation is performed, and a highly individualised approach related to both cardiac and malignant disease is adopted.

Cardiac comorbidity associated with COPD

When assessing the overall operative risk in patients with cardiac comorbidity, care should be taken with respect to one technical detail: during the operation it is sometimes impossible to maintain adequate oxygenation in the arterial blood while selectively ventilating only one lung, due to poor respiratory reserve and/or cardiac rhythm disorders. In this situation, the anaesthesiologist switches to double-lung ventilation, which may impose different technical problems, mostly related to incorrect aerostasis, even with the use of staplers, as a consequence of surgical work on a fully inflated lung. In patients with a fissureless lung or poorly developed fissures, the probability of a prolonged air leak is even greater.

As a prolonged air leak has been identified to be a leading cause of respiratory and cardiac post-operative complications, lung resections in such patients should be performed only by experienced surgeons. This specific aspect of the aforementioned association has not been widely addressed in the literature. Based on our experience with this type of marginal surgical candidate [18], despite high-level performance during pre-operative selection, it is not always possible to predict all obstacles in this high-risk patient population. Therefore, it may be appropriate to share our experience with pulmonologists dealing with this problem.

Revised Cardiac Risk Index [31]

Each risk factor is assigned one point.

1. High-risk surgical procedures
   - Intraperitoneal
   - Intrathoracic
   - Suprainguinal vascular

2. History of ischaemic heart disease
   - History of myocardial infarction
   - History of positive exercise test
   - Current complaint of chest pain considered secondary to myocardial ischaemia
   - Use of nitrate therapy
   - ECG with pathological Q waves

3. History of congestive heart failure
   - Pulmonary oedema
   - Paroxysmal nocturnal dyspnoea
   - Bilateral rales or S3 gallop
   - Chest radiograph showing pulmonary vascular redistribution

4. History of cerebrovascular disease
   - History of transient ischaemic attack or stroke

5. Pre-operative treatment with insulin

6. Pre-operative serum creatinine >2.0 mg per dL

Risk of major cardiac event

Points	Class	Risk %
0	I	0.4
1	II	0.9
2	III	6.6
3 or more	IV	11

"Major cardiac events" include myocardial infarction, pulmonary oedema, ventricular fibrillation, primary cardiac arrest and complete heart block.

The use of scores and indexes for cardiac risk assessment

In order to assess cardiac risk, an additional tool, in the form of well-validated indexes, for example the Revised Cardiac Risk Index (see box), may be of help for pre-operative selection [29].

Lung resection for lung cancer in the elderly

In 2003, in developed countries life expectancy was 7.95 and 8.26 yrs in 85-year-old females and males with lung cancer, respectively [32]. Importantly, those were years of a good quality and active life. Therefore, an octogenarian's survival and quality of life are more influenced by cancer-related mortality than by age itself. In younger patients, a post-operative decrease in both VC and FEV_1 was smaller than in the elderly [33]. For this reason, difussion capacity assessment should be obligatory in these patients.

Operative mortality in the elderly decreased from ~20% in initial studies to 13% in later published results, to 3–7% in recent reports [34]. The proportion of pneumonectomies varied in these reports from 51% in the series of Thomas *et al*. [35] through 19% in the series of Ginsberg *et al.* [36] to 10% in the series studied by Breyer *et al.* [37] and 6% in that of Ishida *et al*. [38]. The proportion of pneumonectomies is particularly addressed, because there is a broad consensus that this operation should be avoided in octogenarians.

However, it is not only patients with pneumonectomy and octogenarians who are at high risk of early post-operative death. The adjusted odds ratio for death was 3.6 times greater in septuagenarians when compared with patients <60 yrs old. Although a 38–55% complication rate is most frequently cited in the literature, studies with operation-adjusted data showed that after resections without pneumonectomy, there were 22.8% cardiovascular and 14.4% nonfatal pulmonary complications [39].

Efforts have been made to reduce post-operative complications in the elderly population. Ambroxol has been shown to increase the number and activity of type 2 pneumocytes and, thus, increases surfactant levels and the lecithin/sphyngomyelin ratio and mucociliary clearance. Several studies demonstrated that short-term perioperative administration of ambroxol may reduce the incidence of pulmonary complications after lobectomy and cut average post-operative stay and costs by 2.5 days [40].

Neoadjuvant treatment

In a series of 350 patients who underwent operations after chemoradiation therapy, operative mortality was 7.2% for pneumonectomy and 3.8% for lobectomy/bilobectomy [41]. Operative morbidity was 44%, similar to many other reports. The absense of bronchial stump coverage was found to be a major risk factor for operative morbidity.

Ischaemia in the bronchial mucosa has a central role in the aetiology of the bronchopleural fistula following pneumonectomy after radiation therapy. Therefore, bronchial stump coverage is mandatory in this situation.

Although any radiation therapy bears a potential risk for bronchopleural fistula, limiting radiation to 45 Gy with concurrent chemotherapy has proven to be safe and feasible. Recently, it has been reported that pulmonary resections, even after curative-intent radiotherapy (>59 Gy) and concurrent chemotherapy (bronchial stump reinforcement was performed routinely), were safe and feasible [42].

Chemotherapy and chemoradiotherapy have an impact on diffusing capacity and its relationship to respiratory complications following lung resections. In this sense, the predicted post-operative $D_{L,CO}$ value seems to be more important than lung volume measurements such as VC and FEV_1 % pred [43].

It is clear that, in patients undergoing neoadjuvant treatment with associated major comorbidities, a cumulative risk can be prohibitively high for subsequent surgery. It seems reasonable that the final decision in this situation should be taken by a multidisciplinary team.

Intrathoracic contamination

Lung resection is sometimes performed: 1) in the presence of intrapulmonary infection; or 2) after previously treated pleural empyema. Infection within the lung that can directly influence surgical treatment largely originates from excavated tumours containing different bacterial stains. In studies specifically addressing this problem, infection during the operation occurred in four (5.3%) out of 76 patients [44].

It is practically impossible to predict which necrotic tumours represent a risk for intra-operative contamination. One study demonstrated that in patients with no pre-operative signs of infection, but in whom post-operative infectious complications occurred, potential pathogens were identified from pre-operative sputum samples in 18% of patients, and from intra-operative bronchial swabs in 13% of patients, but in 63%

of post-operative sputum samples (p<0.01) [45]. These data, although useful, are of little help for pre-operative selection. Moreover, in some studies that used intra-operative bilateral protected specimen brush and lung tissue biopsies, despite a relatively high bronchial colonisation (41%) with one or more potential pathogenic micro-organisms, the frequency of post-operative infectious pulmonary complications was low (12%) and no relationship with bronchial colonisation was found [46].

Although it is not always possible to predict intrathoracic contamination, its occurrence can be prevented. Based on scarce data and our experience, prevention steps include:

Before lung resection
- recognise patients with lung infection
- antibiotic prophylaxis

During the operation
- avoid spillage of secretions
- bronchial stump protection
- lavage of the pleural cavity with antiseptic solutions

After the operation
- standard procedures for post-operative empyema regardless of the cause

The combination of lung cancer and pleural empyema has a mortality rate of 60–100%. During 1970–1980, one dominant strain, Gram-positive *Staphylococcus aureus,* existed. The trend remained unchanged between 1984–1988, while more recently, mixed infections with 2–3 strains have become dominant with the increase of Gram-negative bacteria.

In a study by Riquet *et al.* [47] nine (eight pneumonectomies and one lobectomy) patients underwent operations on for lung cancer after pleural empyema; there were no post-operative deaths and two empyemas occurred post-operatively. Since three patients survived 5 yrs, the authors concluded that curative operations are possible.

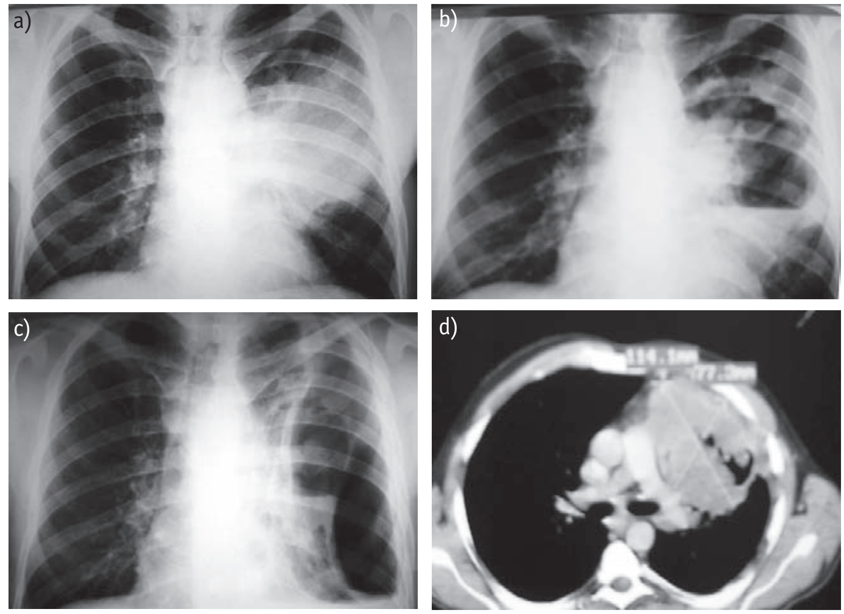

Figure 5
Central tumour of the left lung, subsequent pneumonectomy after healed pleural empyema. a) Initial radiographic aspect; b) tumour necrosis several days after admission; c) pyopneumothorax after 3 weeks of chest tube aspiration; and d) aspect upon full lung expansion was achieved.

In practice, pleural empyema can either be in the form of pyopneumothorax, infected pleural effusion or a localised liquid collection. Neither the form of empyema, nor the treatment modality (thoracentesis or chest tube aspiration) precludes the subsequent surgery (figure 5).

The decision to perform lung resection after pleural empyema is among the most delicate in thoracic surgery. The main points are:
- If the empyema is healed, the surgical procedure for lung cancer can be planned as normal
- Decortication is not always necessary
- Interval between the empyema treatment and the operation:
  - no strict recommendations
  - no sufficient data for comparison
- Post-operative adjuvant therapy should be used if required

Table 3 Sleeve pneumonectomy: complications and survival

Author [ref.]	Year	Patients n	Operative mortality %	Operative morbidity %	5-yr survival rate %
Tsutchiya [48]	1990	20	15	40	59 (at 2 yrs)
Mathisen [49]	1991	37	8	64.8	19
Dartevelle [50]	1995	55	7.2	10.9	40
Roviaro [51]	2001	49	8.2	10.2	24.5
Porhanov [52]	2002	191	17.8	24	24.7
Subotic [53]	2006	42	16.6	35.7	35

Figure 6
Middle lobe tumour 2.5 yrs after left lower lobectomy. Left hemi-diaphragm elevated, the right one is slightly flattened, in this case motility should be checked.

Operative procedure: extended resections/ multiple primaries

It is well known that extended resections (intra-pericardial operations, sleeve pneumonectomies and bronchovascular reconstructions) are associated with a high operative risk. There is no specific preparation of patients for this type of surgery outside that already mentioned. The best preparation is a strict adherence to principles of accurate invasive and noninvasive staging of the mediastinum that has led to a decrease in the number of these operations over recent years. Operative morbidity, mortality and survival after sleeve pneumonectomy are presented in table 3.

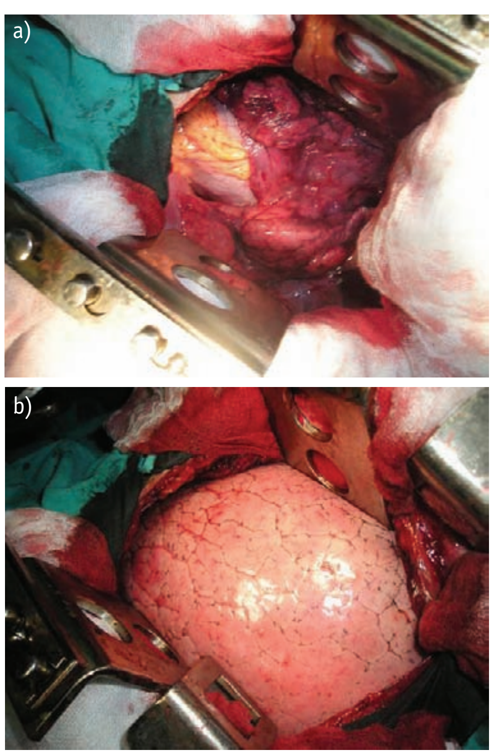

Figure 7
Single lung ventilation. a) Lung collapsed before performing a left lower lobectomy and b) lung fully expanded upon completion of the operation.

Why are patients with multiple primaries at an increased risk?

In patients with synchronous multiple primaries, one should be aware of the possibility of the sudden occurrence of pulmonary hypertension. In these patients, it is of the utmost importance to check the motility of the diaphragm under fluoroscopy or by other methods available (figure 6). Although the role of diaphragm motility has not been specifically addressed in the literature (outside experimental studies), our experience is strongly in favour of pre-operative diaphragm function assessment.

Surgical treatment is possible in ~65% of patients with metachronous tumours. Approximately one-third of resections in these patients are less than complete lobectomy, mostly after previous pneumonectomy. Again the motility of both diaphragms (for lobectomy or less) or at the tumour-bearing side (for pneumonectomy) should be carefully checked. Even after pneumonectomy, surgical treatment should be seriously considered. Operative mortality in these patients is low at 7–13%.

Unpredictable complications

Unpredictable complications refer mostly to the occurrence of acute lung injury (ALI). ALI/ARDS include a variety of life-threatening diseases, such as noncardiogenic pulmonary oedema (including postpneumonectomy oedema) or acute intestinal pneumonia (AIP). The frequency of ALI and ARDS after pulmonary resection is ~3.9% and is responsible for 72.5% of total mortality after pulmonary resection [54]. These complications should always be kept in mind as a potential threat, especially after extended resections.

It was recently demonstrated in a univariate and multivariate analysis that increasing peri-operative fluid administration and low predicted post-operative lung function were significant for lung injury. Mortality for patients with ALI was 25% *versus* 2.6% for the control group [55]. It was also demonstrated that a higher incidence of acute respiratory failure, cardiac arrhythmia and pulmonary hypertension existed in patients with one lung ventilated for >120 min compared with shorter duration of the same type of ventilation [56]. This finding is of great practical importance and should be kept in mind when operating on patients with COPD associated with cardiac comorbidity. The fully collapsed and expanded lung is presented in figure 7.

There is no way to prevent the occurrence of unpredictable complications. If it is impossible to avoid extended surgery that was not anticipated pre-operatively, or if an intra-operative complication occurs requiring blood transfusion, the administration of steroids and specific neutrophil elastase inhibitors immediately after surgery can be considered a preventative for AIP. Sivelestat sodium hydrate, a specific neutrophil elastase inhibitor, may protect endothelial cells against neutrophil-mediated injury. Sivelestat inactivates the extracellular elastase secreted by neutrophils, and also acts directly on neutrophils to suppress the production and secretion of activated elastase [57].

Scoring systems

Several scoring systems for lung resection have been proposed: cardiopulmonary risk index, predictive respiratory quotient, post-operative pulmonary product and the EVAD system (age, FEV_1 and $D_{L,CO}$) [58]. However, their accuracy in predicting individual risks has not been confirmed in practice. Similarly, the European Society of Thoracic Surgeons Subjective and Objective Scores did not appear accurate at the extremes of risk [59]. Currently, although they may be useful for risk stratification between groups of surgical candidates, the use of scoring systems can not be recommended for routine risk assessment in individual patients.

Educational questions

1. In a patient with an FEV_1 <60% pred and FEV_1/VC <50%, in whom a local extent of the tumour requires pneumonectomy:
   a) this operation is *a priori* contraindicated.
   b) the definitive decision is made based on additional lung function assessment before properly performed combined treatment for obstruction.
   c) the definitive decision is made based on additional lung function assessment after properly performed combined treatment for obstruction.
   d) pneumonectomy can be safely done without any additional assessment.
2. The maximal oxygen consumption <15 mL per kg per min:
   a) indicates only the risk of post-operative death.
   b) indicates only the high risk of serious post-operative complications.
   c) indicates the high risk of post-operative death and a high probability of serious post-operative complications.
3. In patients with chronic stable angina and resectable lung cancer:
   a) there is no evidence for performing pre-operative coronary revascularisation before the operation for lung cancer.
   b) coronary revascularisation should always be done before the operation for lung cancer.
4. In lung cancer patients at age >75 yrs:
   a) surgical treatment is contraindicated.
   b) surgical treatment is indicated in the same way as in the younger patients.
   c) surgical treatment can be offered to selected patients, but pneumonectomy should be avoided at age >80 yrs.
5. Lung resection for lung cancer after previous pleural empyema:
   a) is never indicated.
   b) can be done as if there was no empyema.
   c) can be done in a selected group of patients only if the empyema is healed.
6. A higher incidence of acute respiratory failure, cardiac arrhythmia and pulmonary hypertension occurs during one lung ventilation if:
   a) operative time exceeds 90 min compared with a shorter duration of the same type of ventilation
   b) operative time exceeds 120 min compared with shorter duration of the same type of ventilation
   c) the operative time never correlates with the aforementioned complications

Answers
1. c
2. c
3. a
4. c
5. c
6. b

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