ERS/ESTS clinical guidelines on the fitness of patients for radical treatment of lung cancer (surgery and chemo-radiotherapy)

Maria Kokosi[1], Polixeni Batiani[1], Vlasis Polychronopoulos[2]

[1]Pneumonologist Fellow,
[2]Pneumonologist, Director
3rd Pneumonology Department,
"Sismanogleio" General Hospital of Athens

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Correspondence to:
Vlasis Polychronopoulos
3rd Pneumonology Department
Sismanoglio General Hospital
E-mail: vlasispo@hotmail.com

SUMMARY. Collaboration of a multidisciplinary team of experts on the functional evaluation of patients with lung cancer was 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 their fitness for surgery and chemo-radiotherapy. The subject was divided into various different topics, each of which was then assigned to at least two experts. The authors searched the literature according to their own strategies, with no central literature Review and compiled draft reports on each topic, which were then reviewed, discussed and voted on by the entire expert panel. The evidence supporting each recommendation was summarized, and graded as described by the Scottish Intercollegiate Guidelines Network Grading Review Group. Clinical practice guidelines were generated and finalized in a functional algorithm for risk stratification of the lung resection candidates, with emphasis on the cardiological evaluation, forced expiratory volume in 1 s (FEV_1), systematic carbon monoxide lung diffusion capacity (DLCO) and exercise testing. In contrast to lung resection, for which the scientific evidence is more robust, it was not possible to recommend any specific test, cut-off value, or algorithm for chemo-radiotherapy, due to the lack of data. It is highly recommended that patients with lung cancer should be managed in specialized units by experienced multidisciplinary teams. ***Pneumon 2010, 23(1):91-102.***

INTRODUCTION

Despite refinement of medical treatment, lung resection remains the only curative treatment for lung cancer. However, since only 20-25% of patients with lung cancer have operable lesions, and because of the widespread use of neoadjuvant chemotherapy, most patients are treated with chemo- and/or radiotherapy.

The remit of the task force was reassessment of the functional evaluation of patients before surgery for lung cancer, assessment of the acute and long-term risks related to chemoradiotherapy which should be taken into account when elaborating treatment strategy, and formulation of recommendations for patients who are not eligible for surgery.

The guidelines should provide the physician with a basis for evaluation of the benefit/risk ratio related to each therapeutic option offered to the patient.

METHODS

The task force was composed of 14 participants, identified on the basis of their expertise in the area of lung cancer. The subject was divided into several different topics, which were each assigned to at least two experts who searched the relevant literature, made draft reports and solicited comments in advance of the meetings [2008 European Respiratory Society (ERS) and the European Society of Thoracic Surgery (ESTS) congresses] at which the recommendations were reviewed, discussed and voted upon. The recommendations were graded as described by the Scottish Intercollegiate Guidelines Network Grading Review Group (SIGN) (table 1).

CARDIOLOGICAL EVALUATION BEFORE LUNG RESECTION FOR LUNG CANCER

The cardiological evaluation should be based on a well-validated index providing estimates of patient risks, but more detailed evaluation should be based on the characteristics of the individual patient. Detailed evaluation for coronary heart disease is generally not

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 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
Grade 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: randomized control trial.

recommended for patients with an acceptable exercise tolerance, such as the ability to walk up two flights of stairs without stopping. 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[1]. Furthermore, recovery after coronary bypass surgery may take several months, and the need for aggressive anti-platelet therapy presents a major challenge in the perioperative context[2].

Beta-blockers reduce perioperative myocardial infarction significantly, but the commonly used beta-blocker regimens increase the risk of stroke, presumably due to bradycardia and hypotension, and can increase overall mortality[3,4]. 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[5]. Alternative adrenergic modulation, such as administration of clonidine and related drugs[6], may be useful, but larger randomized trials will be required to evaluate the effectiveness of a_2-adrenergic agonists and statins.

Recommendations for cardiological evaluation before lung resection are given in table 2 and are summarized in an algorithm (figure 1). Patients who are at low cardiological risk or who have optimized cardiological treatment may proceed with the pulmonary evaluation.

PULMONARY EVALUATION BEFORE LUNG RESECTION FOR LUNG CANCER

The predicted post-operative forced expiratory volume in 1 s (ppo)-FEV_1 is pivotal in choosing further tests or excluding patients from operation without further tests[7]. Many case series have shown that the peri-operative risk increases substantially when ppo-FEV_1 is <40% predicted, with reported mortality rates in the range of 16-50%[8]. Nakahara and coworkers found a mortality rate as high as 60% when ppo-FEV_1 was <30% predicted[9]. More recently, Brunelli et al[10], showed that ppo-FEV_1 was not a reliable predictor of complications in patients with pre-operative FEV_1 >70% predicted, and also that in patients with a ppo-FEV_1 <40% predicted, 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 moderate or severe chronic obstructive pulmonary disease (COPD)[11,12].

Immediate post-operative estimation of pulmonary function

Although ppo-FEV_1 is fairly accurate in predicting the definitive residual value of FEV_1 3-6 months after surgery, it substantially overestimates the actual FEV_1 observed in the initial post-operative days, when most complications occur[13].

Varela et al[13] showed also that on post-operative day 1 after lobectomy the actual FEV_1 was 30% lower than predicted, and as a result was a better predictor of complications than ppo-FEV_1[14,15]. According to these findings, an attempt should be made to predict FEV_1 early after lobectomy and pneumonectomy.

Recommendation: The ppo-FEV_1 should not 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 initial 1-3 postoperative days and does not appear to be a reliable predictor of complications in patients with COPD. A ppo-FEV_1 value of 30% predicted is suggested to be a high risk threshold for this parameter when included in algorithm 2.

Use of DLCO before surgical resection for lung cancer

Early reports demonstrated that the carbon monoxide lung diffusion capacity (DLCO) decreases after lung resection, and that DLCO <40% predicted is associated with a high risk of postoperative mortality. Based on data collected by the panel experts, the limit should be lowered to 30% predicted[16,12]. DLCO is very important test even in patients with a normal FEV_1 (>80%) or normal FEV_1/FVC ratio (>70%)[16].

Recommendation: DLCO should be measured and evaluated in combination with FEV_1 in algorithm 2 (Level of evidence 2++, grade of recommendation B).

It is suggested that the limit of 40% predicted for the DLCO is high and should be decreased to 30% predicted because of the advancements in preoperative and perioperative technology and surgical technique.

Split function studies

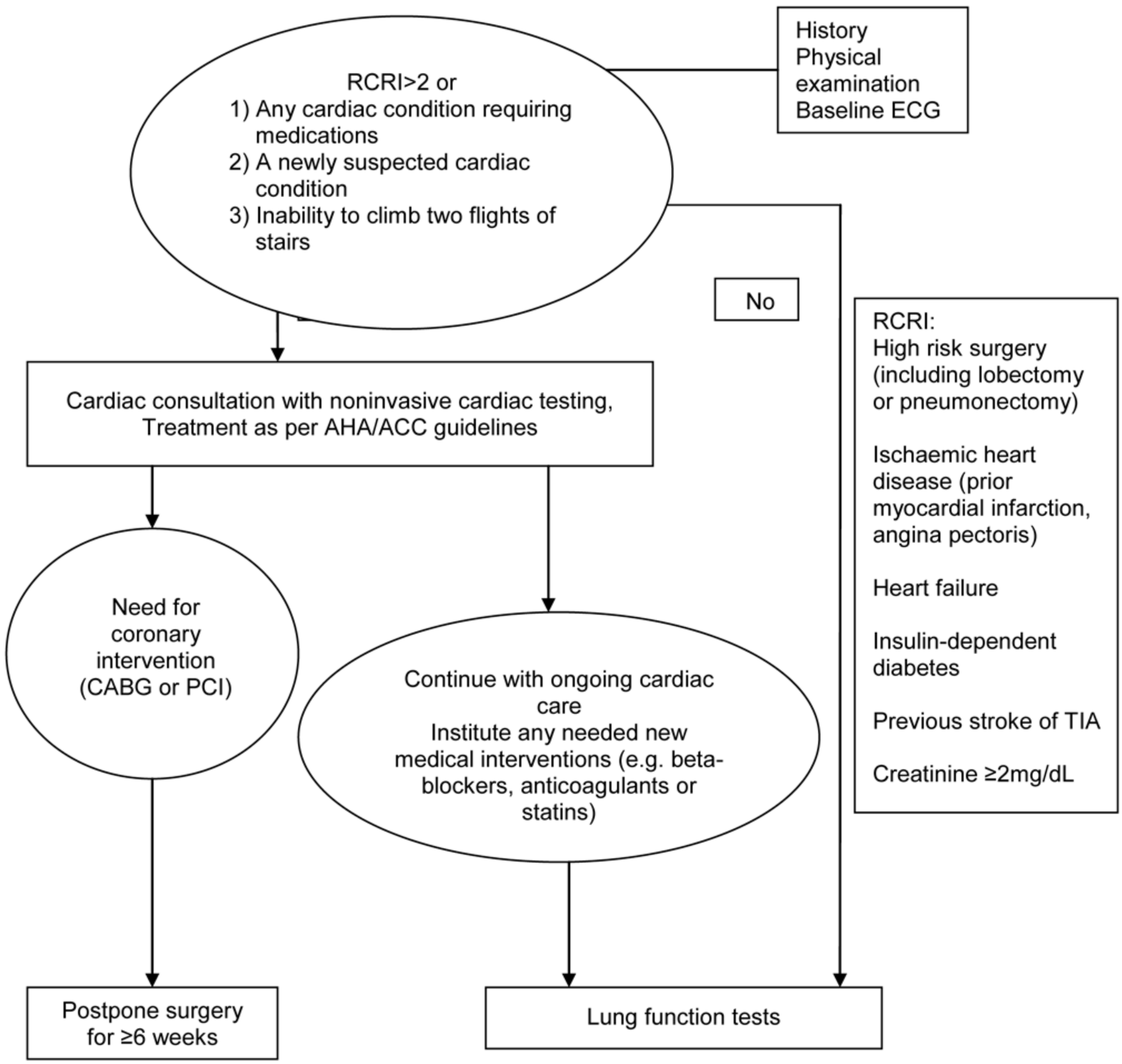
Ventilation scintigraphy and perfusion scintigraphy both provide good prediction of post-operative lung function, but only one of the two is needed as there is no additional benefit in performing both. (Level of evidence 2+).

Teams concerned with research in preoperative evaluation before lung cancer surgery should be encouraged

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

Issue	Recommendations and evidence
Estimating pre-operative cardiac risk	
Summary recommendation	Patients should be risk stratified using validated risk indices, which should direct any additional testing (Recommendation grade B, evidence level 2++)
Noninvasive stress test	Patients with: 1) poor functional status (<4 METs) and 1-2 RCRI criteria, and 2) a history of angina or claudication should generally be 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 risk, 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 noninvasive testing are not of proven value
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++)
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++)
Cardiological approaches for reducing risks	
Patients with hypertension	Anti-hypertensive medications should be administered up until the morning of surgery and be continued orally or intravenously as soon as possible post-operatively (Recommendation grade D, evidence Level 4)
Patients with pulmonary hypertension or congenital heart disease	Beneficial long-term treatment could be generally recommended during the peri-operative period (Recommendation grade D, evidence Level 4)
Patients with hypertrophic cardiomyopathy	Management could be similar to the chronic setting (Recommendation grade D, evidence Level 4)
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)
Pulmonary artery catheterization	Few, if any, non-cardiac surgery patients must receive routine pulmonary artery catheterization (Recommendation grade A, evidence Level 1++)
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)
Peri-operative a-adrenergic modulation	Modulation of the a-adrenergic systems with drugs such as clonidine may be beneficial for vascular surgery but are of less certain benefit for other operations (Recommendation grade A, evidence Level 1+)
Other anti-ischaemic medication	Prophylactic nitrates can reduce ischaemia but not major events; prophylactic calcium channel blockers are of uncertain benefit (Recommendation grade B, evidence Level 2++)
Peri-operative use of HMG-CoA reductase inhibitors (statins)	Statin lipid-lowering agents could be started before non-cardiac surgery whenever long-term lipid-lowering therapy is indicated (Recommendation grade D, evidence Level 4)
Peri-operative coronary revascularisation	Patients at high risk clinically or based on noninvasive testing must be considered for diagnostic catheterization. Coronary revascularization must be recommended only for patients who would benefit in the absence of the planned surgery of lung (Recommendation grade A, evidence Level 1++)

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



AHA/ACC: American Heart Association/American College of Cardiology Foundation, CABG: coronary artery bypass graft - PCI: primary coronary intervention, RCRI: Revised Cardiac Risk Index -TIA: transient ischaemic attack.

FIGURE 1: Algorithm for cardiac assessment before lung resection in lung cancer patients.

to use quantitative CT, MRI or SPECT. (Level of evidence 2+).

Exercise tests: systematic or selective?

The aim of exercise testing is to stress the overall 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.

A recently published meta-analysis showed that the exercise capacity, expressed as VO_2, peak is lower in patients who develop post-operative cardiorespiratory complications after lung resection[17].

Several authors have found a good correlation between

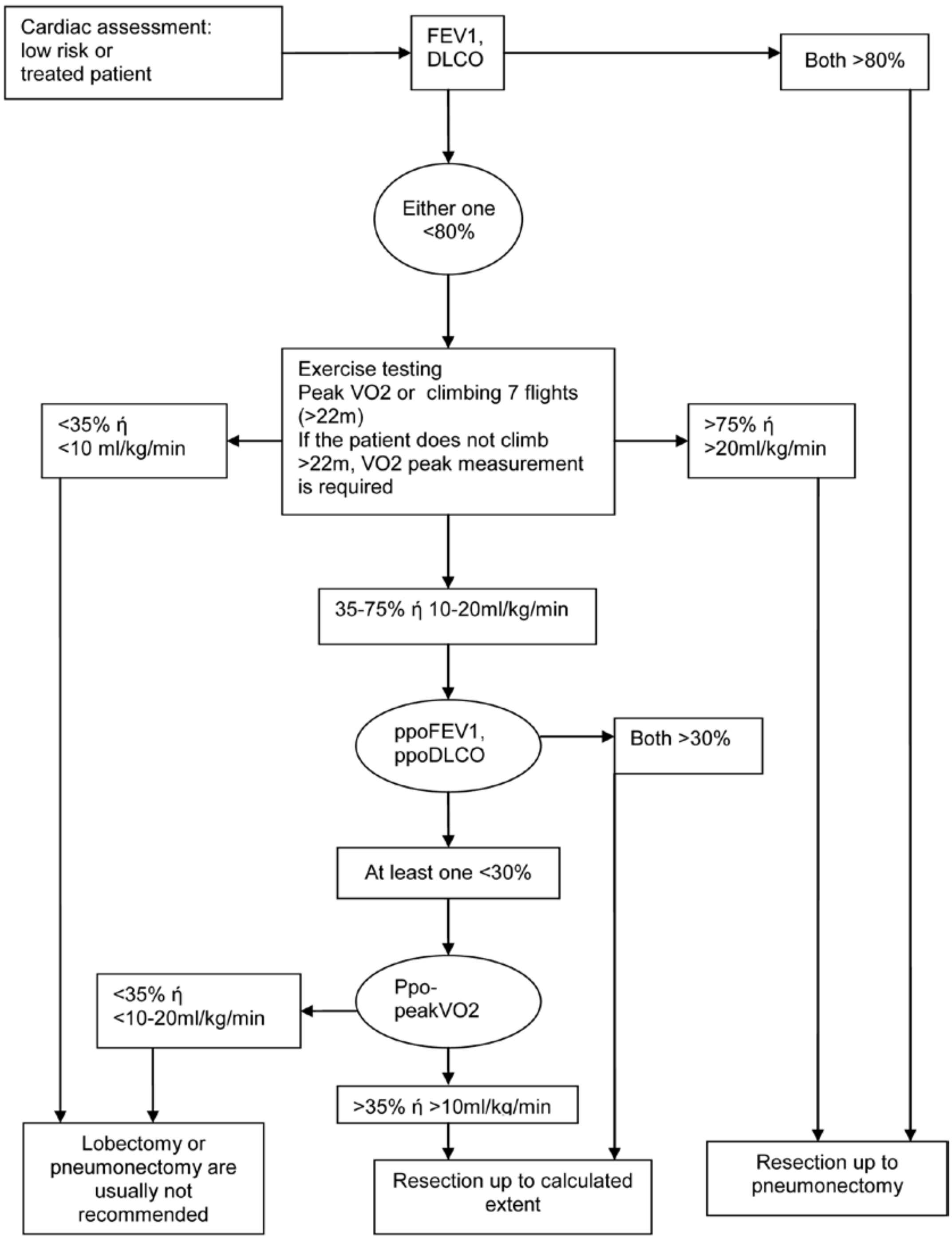


Figure 2. Algorithm for assessment of cardiopulmonary reserve before lung resection in patients with lung cancer.

a low VO_2 peak (% of predicted) and poor post-operative outcome[18,19]. It is generally reported that a value <50-60% predicted increases the surgical mortality risk. Surgical treatment was contraindicated for patients with a VO_2 peak <40% or <10 ml kg/min. Patients who had a VO_2 peak <16 mL/kg/ min or <20 mL/kg/min-1 were more likely to suffer complications[19,20].

Recommendation: Exercise tests are indicated for all patients undergoing surgery for lung cancer with FEV1 or DLCO <80% of normal values. (Level of evidence 2++, grade of recommendation B).

Low-technology exercise

Distance walked in 6-12 min has been shown to be highly reliable in estimating VO2 peak in healthy subjects, patients with COPD and transplant candidates, but non-unequivocal findings have been published regarding its association with post-operative outcome after lung resection[21-23].

Several papers have reported the effectiveness of the stair climbing test in predicting major cardiopulmonary complications after 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); even in patients with pro-FEV_1 and/or pro DLCO <40% predicted, the mortality rate in those climbing >22 m was zero[24].

It has been reported that oxygen desaturation <90% during standardized incremental cycle ergometry was not a significant predictor of post-operative cardiopulmonary morbidity[25]. It was recently found, however, that a desaturation of >4% was significantly associated with post-operative complications, even after adjusting for other factors with regression analysis[26].

Recommendation: The stair climbing test (height of ascent >22 m) should be used as a first-line functional screening test to select patients who can safely undergo operation or to identify those who need more sophisticated exercise testing. (Level of evidence 2++, grade of recommendation C).

The role of cardiopulmonary exercise testing (CPET)

In 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; 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 the case of limitation of exercise capacity, it also enables elucidation of the reason for this, such as pulmonary, cardiovascular or musculoskeletal limitations.

There is currently wide consensus that values of VO_2 peak of >20 mL/kg/min qualify the patient for lung resection procedures up to pneumonectomy, whereas values <10 mL/kg/min indicate a high risk for any level of resection. Expressed as per cent of predicted the respective values are >75% and <40% predicted. CPET should be performed according to the published ATS guidelines[27].

Recommendation: 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 it is highly predictive of post-operative complications. (Level of evidence 2++, grade of recommendation B).

The following basic cut-off values for VO_2 peak should be considered: >75% predicted or >20 mL/kg/min qualifies for pneumonectomy; <35% or <10ml/kg/min indicates high risk for any resection. The evidence is not sufficient to recommend separate cut-off values for lobectomy.

Wang et al found, in 57 patients, that the increase in DLCO from rest to 70% of maximal workload was the best pre-operative predictor of post-operative complications, followed by VO_2 peak measurement[28].

PATIENT CARE MANAGEMENT

The role of rehabilitation before and after lung resection surgery

Pulmonary rehabilitation is effective in respiratory patients with disability.

Chest physiotherapy was found to be more effective than incentive spirometry in reducing the rate of pulmonary atelectasis after lobectomy. Pre-operative inspiratory muscle training may decrease the prevalence of late complications after cardiac surgery[29,30].

Comprehensive pulmonary rehabilitation was shown to improve VO_2 rate before surgery in patients wit COPD who had low VO_2 (15mL/kg/min), reducing late complications and not influencing operability and prognosis[31]. Pre-operative training programmes have led to a reduction of the length of hospital stay and complications in patients with COPD operated on for lung cancer[32].

Recommendation: For smokers, smoking cessation of sufficient duration (2-4 weeks) before surgery should be recommended, since it may decrease post-operative complications. (Level of evidence 2+, grade of recommendation B).

Early pre- and post-operative rehabilitation should be recommended, since it may produce functional benefits in patients with resectable lung cancer. (Level of evidence 2+, grade of recommendation C).

Although lacking accuracy for assigning specific risk for individual patients, models incorporating functional characteristics, comorbidity factors, and surgical variables are valid and useful tools for predicting relative operative death or major cardiopulmonary complications in groups of patients.

Do we need to send all patients with thoracotomy to the intensive care unit (ICU)?

Systematic admission to the ICU after thoracotomy should not be recommended. (Level of evidence 2++, grade of recommendation C).

Patients undergoing complex pulmonary resection, those with marginal cardiopulmonary reserve and those with moderate to high risk (i.e., patients with coronary disease, EF <40%, arrhythmia, symptomatic cerebrovascular disease, FEV_1 <50% predicted, central or obstructive sleep apnoea, VO_2 max <15ml/kg/min, liver dysfunction, pneumonectomy or bilobectomy) should be admitted to a high dependency unit (HDU). (Level of evidence 2++, grade of recommendation B).

Residual function and quality of life (QoL) after radical treatment

Many studies have shown that after lobectomy there is a disproportionate functional early loss. FEV_1, DLCO and VO_2 peak may reach values as high as 90-95% of preoperative values, 3-6 months after operation[33-36]. In general, exercise tolerance displays 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.

Several studies have shown that lung resection is associated with a transient worsening of QoL one month following the operation, but with most of the scales returning to pre-operative values after 3-6 months. An exception to this trend is represented by patients undergoing pneumonectomy, who display a persistent deterioration of physiological and mental QoL[37,38]. With the exception of DLCO, the objective measures of cardiorespiratory function do not appear to correlate well with QoL which mainly depends on the patients' symptoms such as dyspnea and post-thoracotomy pain[33,39,40].

Surprisingly, elderly patients and those considered at increased surgical risk showed no difference in the post-operative physiological and mental QoL status from those of lower risk counterparts[38].

Recommendation: Specific QoL instruments should always be used for QoL evaluation. Perception of symptoms has been reported to be more important for QoL, implying the need for monitoring respiratory symptoms and pain after thoracotomy or chemotherapy. (Level of evidence 2+).

SURGICAL TECHNIQUES IN LUNG CANCER

Combined cancer surgery and lung volume reduction surgery (LVRS)

A subgroup of patients with upper lobe emphysema appeared to be the ideal candidates for lung volume reduction surgery (LVRS) with significant improvement in exercise capacity and survival despite their severe pre-operative pulmonary function defect (PFTs). After anatomical lobectomy, patients with normal or mildly diseased lungs have the greatest post-operative decrease in FEV_1, whereas those with poor baseline function present minimal change or even improvement in post-operative FEV_1.

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 (ventilation and perfusion scintigraphy) may provide useful information about these effects[45].

Recommendation: 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 or the risks of major adverse events. (Level of evidence 2++, grade of recommendation B).

Surgical techniques charcterized by minor degrees of intervention (segmentectomy and wedge resection)

Comparison of effectiveness (regarding the likelihood of recurrence) between wedge resection and lobectomy showed 38/122 recurrence for wedge resection and 23/125 for lobectomy[46], but other studies show equivalent survival[47]. In patients with lung cancer who have low reserves, it appears that segmentectomy offers similar survival to lobectomy with less stress on respiratory function[48]. Comparison of the outcome of wedge resection and segmentectomy shows that in tumours of 2-3 cm in diameter segmentectomy is associated with less recurrences[49], while for tumours smaller than 2 cm it appears that wedge resection offers similar survival to segmentectomy[50].

Recommendation

A) Segmentectomy can be carried out:

- In patients with stage 1A cancer (2-3 cm tumour) with margins of resection of >1cm (Level of evidence 2, grade of recommendation D)
- In patients with stage 1 cancer with poor functional capacity (Level of evidence 2, grade of recommendation D)
- In patients who have undergone a prior lobectomy (Level of evidence 2, grade of recommendation D)

B) Wedge resection can be carried out:

- In patients with stage 1A cancer (1-2 cm tumour) (Level of evidence 2, grade of recommendation D)
- For a small (<2cm) peripheral adenocarcinoma with an air-containing image (ground glass opacity) on HRCT. (Level of evidence 2, grade of recommendation D)

CHEMO-RADIOTHERAPY IN LUNG CANCER

Neoadjuvant chemotherapy for lung cancer may have several advantages, including: 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.

The evidence from randomized phase III trials indicates improved resectability after chemotherapy and suggests a marginal survival advantage for lobectomy[51].

Significantly overall morbidity and mortality rates have been reported for pneumonectomy after chemotherapy, and in particular, for right pneumonectomy[52,53].

Induction of chemo-radiotherapy may, however, be a prelude to significant morbidity and mortality, although recent evidence from institutional studies shows increased safety in adding radiotherapy to chemotherapy induction regimens[54,55]. A prospective randomised trial powered on post-operative morbidity and mortality is needed to compare chemotherapy versus chemo-radiotherapy followed by surgery.

Radiotherapy of the lung may cause radiation pneumonitis in 5-15% of patients with lung cancer[56]. Several chemotherapeutic agents are known sensitizers to radiotherapy, including, among others, doxorubicin, taxanes, mitomycine, vinorelbine, gemcitabine and platinum derivatives[57].

Recommendation: After induction chemotherapy and/or radiotherapy, a new functional evaluation (particularly of DLCO) before surgery is recommended. (Level of evidence 2+, grade of recommendation C).

Statements

The addition of induction chemotherapy to surgical resection of a degree less than pneumonectomy does not significantly increase morbidity and mortality. (Level of evidence 1).

The addition of radiotherapy to neoadjuvant chemotherapy followed by pneumonectomy increases mortality. (Level of evidence 1).

The effects of radiotherapy on pulmonary function

It is generally assumed that patients with preexisting pulmonary disease, particularly COPD, are at increased risk of radiation morbidity[58].

In reports based not exclusively on patients with lung cancer, low arterial oxygen tension value (<80mmHg) and low DLCO have been associated with increased lung toxicity and morbidity[59,60]. A model including preradiation lung volumes and DLCO could not segregate patients at high risk from those at low risk for radiation pneumonitis.

The effects of chemotherapy on pulmonary function

Safe lower limits of respiratory function (FEV_1 or DLCO) for radical chemotherapy have not been defined as they have for surgery. (Level of evidence 2++).

The patient at prohibitive surgical risk: alternatives to surgery

1) Among 2000 patients with medically inoperable lung cancer stage I and IIA treated with radiation alone, survival was 13-19% at 5 years. 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 (continuous, hyperfractionated, accelerated radiotherapy) must be preffered to conventional radiotherapy as it improves 2 year survival. (Level of evidence 1, grade of recommendation B)[61].

Recommendations

1) For medically inoperable NSCLC, radiation alone must be regarded as the best established alternative treatment to surgery. (Level of evidence 1, grade of recommendation B).
2) The use of continuous, hyperfractionated, acceler-

ated radiotherapy (CHART) must be preferred to conventional radiotherapy, as it achieves better local control rates and survival. (Level of evidence 1, grade of recommendation B).

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

According to the ACCP guidelines (accepted by ESTS and the EORTC Radiotherapy Group), qualified thoracic surgeons achieved better results than nonspecialized surgeons in terms of perioperative mortality and resection rates.

The management of patients with lung cancer must be undertaken by a multidisciplinary team (ideally a thoracic surgeon specializing in lung cancer, a medical oncologist and a pulmonologist). (Level of evidence 2++, grade of recommendation B).

The surgical treatment of lung cancer patients must be performed in specialized centres by qualified thoracic surgeons, since specialization has been shown to have a positive impact on resectability, postoperative mortality and long-term survival. (Level of evidence 2++, grade of recommendation B).

Lung cancer surgery should be performed in centres with an adequate volume of cases (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).

Radiotherapy should be applied by radiotherapists in centres that routinely treat patients by this combined modality.

ALGORITHM FOR THE ASSESSMENT OF RISK BEFORE LUNG RESECTION

The panel of experts agreed to emphasise the role and importance role of exercise tests in the preoperative assessment of candidates for lung resection. 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 as a possible surrogate and as 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.

Owing to the advances in surgical techniques and the ongoing improvement in post-operative care, the limits of functional operability are constantly being lowered. The algorithm emphasizes the importance of a preliminary cardiological assessment. Those patients at low cardiological risk or with optimized cardiological treatment may proceed with pulmonary evaluation. Complete spirometry and DLCO assessment is recommended for all patients. All those patients with either FEV_1 or DLCO or both <80% predicted should undergo an ergometric assessment. Ideally, a format CPET with VO_2 peak measurement should be performed. A low-technology exercise test, preferentially stair climbing, may be used as a screening test. Those patients showing suboptimal performance (<22m) on tests for stair climbing should have a formal CPET.

A limitation of such an algorithm, which is centred on 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 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.

Most of the evidence in these guidelines is of level 2, and most of the recommendations are graded at B or C levels. This is mainly due to the nature of the subject, which makes the design of randomized trials difficult and impractical.

Age alone [elderly (>70 yrs) or very elderly (>80 yrs) should not be used as selection criteria for surgery. The increased risk for radical treatment observed in elderly patients is probably a function of their underlying comorbidities. In contrast to suitability for lung resection, for which the scientific evidence is more robust, the panel was unable to recommend any specific test, cut-off value, or algorithm for chemo-radiotherapy, owing to lack of relevant data.

REFERENCES

1. McFalls EO, Ward HB, Morits TE, et al. Coronary-artery revascularization before elective major vascular surgery. NEJM 2004; 351:2795-2804.
2. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(Suppl. 6):299S-339S.
3. Poldermans D, Boersma E, Bax JJ, et al. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk

patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. NEJM 1999; 341:1789-1794.

4. Juul AB, Wetterslev J, Gluud C, et al. Effect of perioperative betablockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. BMJ 2006; 332:1482.
5. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008; 371:1839-1847.
6. Wallace AW, Galindez D, Salahieh A, et al. Effect of clonidine on cardiovascular morbidity and mortality after non-cardiac surgery. Anesthesiology 2004; 101:284-293.
7. Codice GL, Shafazand S, Griffin JP, et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2th Edition). Chest 2007; 132(Suppl 3):161-177S.
8. Bollinger CT, Jordan P, Soler M, et al. Exercise capacity as a preditor of postoperative complications in lung resection candidates. AJRCCM 1995; 151:1472-1480.
9. Nakahara K, Ohno K, Hashimoto J, et al. Prediction of postoperative respiratory failure in patients undergoing lung resection for lung cancer. Ann Thor Surg1988; 46:549-552.
10. Brunelli A, Al Refai M, Monteverde M, et al. Predictors of early morbidity after major lung resection in patients with and without airflow limitation. Ann Thor Surg 2002; 74:999-1003.
11. Varela G, Brunelli G, Rocco G et al. Evidence of lower alteration of expiratory volume in patients with airflow limitation in the immediate period after lobectomy. Ann Thor Surg 2007; 84:417-422.
12. Brunelli A, Refai MA, Salati M, et al. Carbon monoxide lung diffusion capacity improves risk stratification in patients without airflow limitation: evidence for systematic measurement before lung resection. EJ Cardiothor Surg 2006; 29:567-570.
13. Varela G, Brunelli A, Rocco G, et al. Predicted versus observed FEV1 in the immediate postoperative period after pulmonary lobectomy. EJ Cardiothor Surg 2006; 30:644-648.
14. Varela G, Brunelli A, Rocco G, et al. Measured FEV1, in the first postoperative day, and not ppo FEV1, is the best predictor of cardio-respiratory morbidity after lung resection. EJ Cardiothor Surg 2007; 31:518-521.
15. Brunelli A, Varela G, Rocco G, et al. A model to predict the immediate postoperative FEV1 following major lung resections. EJ Cardiothor Surg 2007; 32:783-786.
16. Ferguson MK, Reeder LB, Mick R. Optimizing selection of patients for major lung resection. J Thorac Cardio Surg 1995; 109:275-281.
17. Benzo R, Kelly GA, Recchi L, et al. Complications of lung resection and exercise capacity: a meta-analysis. Resp Med 2007; 101:1790-1797.
18. Win T, Jackson A, Sharples L, et al. Cardiopulmonary exercise tests and lung cancer surgical outcome. Chest 2005; 127:1159-1165.
19. Loewen GM, Watson D, Kohman L, et al. Preoperative exercise VO2 measurement for lung resection candidates: results of Cancer and Leucemia Group B Protocol 9238. J Thor Onc 2007; 2:619-625.
20. Brunelli A, Belardinelli R, Refai M, et al. Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. Chest 2008; [Epub ahead of print PMID: 19029436].
21. Holden DA, Rice TW, Stelmach K, et al. Exercise testing, 6-min walk, and stair climb in the evaluation of patients at high risk for pulmonary resection. Chest 1992; 102:1774-1779.
22. Pierce RJ, Copland JM, Sharpe K, et al. Preoperative risk evaluation for lung cancer resection: predicted postoperative product as a predictor of surgical mortality. AJRCCM 1994; 150:947-955.
23. Bagg LR. The 12-min walking distance; its use in the preoperative assessment of patients with bronchial carcinoma before lung resection. Respiration 1984; 46:342-345.
24. Brunelli A, Refai M, Xiume F, et al. Performance at symptom-limited stair-climbing test is associated with increased cardiopulmonary complications, mortality, and costs after major lung resection. Ann Thor Surg 2008; 86:240-247.
25. Ninan M, Sommers KE, Landreneau RJ, et al. Standardized exercise oximetry predicts postpneumonectomy outcome. Ann Thor Surg 1997; 64:328-332.
26. Brunelli A, Refai M, Xiume F, et al. Oxygen desaturation during maximal srair-climbing test and complications after major lung resections. EJ Cardiothor Surg 2008; 33:77-82.
27. ATS/ACCP Statement on cardiopulmonary exercise testing. AJRCCM 2003; 167:211-277.
28. Wang JS, Abboud RT, Evans KG, et al. Role of CO diffusing capacity during exercise in the preoperative evaluation for lung resection. AJRCCM 2000; 162: 1435-1444.
29. Varela G, Ballesteros E, Jimenez MF, et al. Cost-effectiveness analysis of prophylastic respiratory physiotherapy in pulmonary lobectomy. EJ Cardiothor Surg 2006; 29:216-220.
30. Hulzebos EH, Helders PJ, Favie NJ, et al. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. JAMA 2006; 296:1851-1857.
31. Bobbio A, Chetta A, Ampollini L, et al. Preoperative pulmonary rehabilitation in patients undergoing lung resection for non-small cell lung cancer. EJ Cardiothor Surg 2008; 33:95-98.
32. Sekine Y, Chino M, Iwata T, et al. Preoperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. Jpn J Thorac Cardiovasc Surg 2005; 53:237-243.
33. Larsen KR, Svendsen UG, Milman N, et al. Cardiopulmonary function at rest and during exercise after resection for bronchial carcinoma. Ann Thor Surg 1997; 64:960-964.
34. Win T, Groves AM, Ritchie AJ, et al. The effect of lung resection on pulmonary function and exercise capacity in the lung cancer patients. Resp Care 2007; 52:720-726.
35. Brunelli A, Xiume F, Refai M, et al. Evaluation of expiratory volume, diffusion capacity, and exercise tolerance following major lung resection: a prospective follow-up analysis. Chest 2007; 131:141-147.
36. Bollinger CT, Jordan P, Soler M, et al. Pulmonary function and exercise capacity after lung resection. ERJ 1996; 9:415-421.
37. Sugimura H, Yang P. Long-term-survivorship in lung cancer :

a review. Chest 2006; 129:1088-1097.
38. Brunelli A, Socci L, Refai M, et al. Quality of life before and after major lung resection for lung cancer: a prospective follow-up analysis. Ann Thor Surg 2007; 84:410-416.
39. Handy JR, Asaph JW, Skokan L, et al. What happens to patients undergoing lung cancer surgery? Outcomes and quality of life before and after surgery. Chest 2002; 122:21-30.
40. Sarna L, Padilla G, Holmes C, et al. Quality of life of long-term survivors of non-small-cell lung cancer. J Clin Oncol 2002; 20:2920-2929.
41. Meyers BF, Yusen RD, Guthrie TJ, et al. Results of lung volume reduction surgery in patients meeting a national emphysema treatment trial high-risk criterion. J Thor Cardiovasc Surg 2004; 127:829-835.
42. DeRose JJ Jr, Argenziano M, El-Amir N, et al. Lung reduction operation and resection of pulmonary nodules in patients with severe emphysema. Ann Thor Surg 1998; 65:314-318.
43. Baldi S, Ruffini E, Harari S, et al. Does lobectomy for lung cancer in patients with chronic obstructive pulmonary disease affect lung function? A multicenter national study. J Thor Cardiovasc Surg 2005; 130:1616-1622.
44. Subotic DR, Mandaric DV, Eminovic TM, et al. Influence of chronic obstructive pulmonary disease on postoperative lung function and complications in patients undergoing operations for primary non-small cell lung cancer. J Thor Card Surg 2007; 134:1292-1299.
45. Ohno Y, Koyama H, Nogami M, et al. Postoperative lung function in lung cancer patients: comparative analysis of predictive capability of MRI, CT, and SPECT. AJR Am J Roentgenol 2007; 189:400-408.
46. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995; 60:615-622.
47. Griffin JP, Eastridge CE, Tolley EA, et al. Wedge resection for non-small cell lung cancer in patients with pulmonary insufficiency: prospective ten-year survival. J Thor Onc 2006; 1:960-964.
48. Martin-Ucar AE, Nakas A, Pilling JE, et al. A case-matched study of anatomical segmentectomy versus lobectomy for stage I lung cancer in high-risk patients. EJ Cardiothor Surg 2005; 27:675-679.
49. Okada M, Nishio W, Sakamoto T, et al. Effect of tumor size on prognosis in patients with non-small cell lung cancer: the role of segmentectomy as a type of lesser resection. J Thor Cardiov Surg 2005; 129: 87-93.
50. Nakayama H, Yamada K, Saito H, et al. Sublobar resection for patients with peripheral small adenocarcinomas of the lung: surgical outcome is associated with features on computed tomographic imaging. Ann Thor Surg 2007; 84:1675-1679.
51. Burdett S, Stewart LA, Rydzewska L. A systemic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. J Thor Onc 2006; 1:611-621.
52. Martin J, Ginberg RJ, Abolhoda A, et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: the risk of right pneumonectomy. Ann Thor Surg 2001; 72:1149-1154.
53. Stamatis G. Risks of neoadjuvant chemotherapy and radiation therapy. Thor Surg Clin 2008; 18:71-80.
54. Gilligan D, Nicolson M, Smith I, et al. Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/ NVALT 2/ EORTC 08012 multicentre randomised trial and update of systematic review. Lancet 2007; 369:1929-1937.
55. Garrido P, Gonzalez-Larriba JL, Insa A, et al. Long-term survival associated with complete resection after induction chemotherapy in stage IIIA (N2) and IIIB (T4N0-1) non-small-cell lung cancer patients: the Spanish Lung Cancer Group Trial 9901. J Clin Onc 2007; 25: 4736-4742.
56. McDonald S, Rubin P, Phillips TL, et al. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. Int J Rad Onc Biol Phys 1995; 31:1187-1203.
57. Leo F, Solli P, Spaggiari L, et al. Respiratory function changes after chemotherapy: an additional risk for postoperative respiratory complications? Ann Thor Surg 2004; 77:260-265.
58. Borst GR, De Jaeger K, Belderbos JS, et al. Pulmonary function changes after radiotherapy in non-small-cell lung cancer patients with long-term disease-free survival. Int J Rad Onc Biol Phys 2005; 62:639-644.
59. Abratt RP, Willcox PA, Smith JA. Lung cancer in patients with borderline lung functions - zonal lung perfusion scans at presentation and lung function after high dose irradiation. Radioth Onc 1990; 19:317-322.
60. Videtic GM, Stitt LW, Ash RB, et al. Impaired diffusion capacity predicts for decreased treatment tolerance and survival in limited stage small cell lung cancer patients treated with concurrent chemoradiation. Lung Cancer: Amsterdam 2004; 43:159-166.
61. Rowell NP, Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable): a systematic review. Thorax 2001; 56:628-638.
62. Saunders M, Dische S, Barrett A, et al. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. Radioth Onc 1999; 52:137-148.
63. Brunelli A, Sabbatini A, Xiume F, et al. Inability to perform maximal stair climbing test before lung resection: a propensity score analysis on early outcome. EJ Cardiothor Surg 2005; 27:367-372.