



European Respiratory Society and European Society of Thoracic Surgeons clinical practice guideline on fitness for curative intent treatment of lung cancer

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Shareable abstract (@ERSpublications)

This multidisciplinary panel of lung cancer experts from different specialties has generated practical and up-to-date recommendations to assess patients' fitness for curative intent treatment for lung cancer <https://bit.ly/4m57e3s>

Cite this article as: Brunelli A, Hardavella G, Huber RM, *et al.* European Respiratory Society and European Society of Thoracic Surgeons clinical practice guideline on fitness for curative intent treatment of lung cancer. *Eur Respir J* 2025; 66: 2500156 [DOI: 10.1183/13993003.00156-2025].

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The articles are identical except for minor stylistic and spelling differences in keeping with each journal's style. Either citation can be used when citing this article.

Received: 23 Jan 2025
Accepted: 1 Aug 2025

Abstract

A multidisciplinary panel of lung cancer experts with a special interest in functional evaluation of lung cancer patients, and lung cancer patient representatives, has been facilitated by the European Society of Thoracic Surgeons and the European Respiratory Society to provide healthcare professionals with practical and up-to-date recommendations for the assessment of patients' fitness for curative intent treatments for lung cancer. The panel formulated four PICO (population, intervention, comparison and outcomes) questions and seven complementary narrative questions. Both types of questions were assigned to groups of at least two experts. A medical librarian conducted the literature searches, and the authors selected relevant studies based on predefined inclusion criteria. Risk of bias was assessed using the QUIPS (Quality in Prognosis Studies) tool. Data were summarised and the certainty of evidence was assessed with GRADE (Grading of Recommendations, Assessment, Development and Evaluations) and the Evidence to Decisions framework was used to formulate recommendations. A series of multidisciplinary recommendations was formulated about the utilisation of pulmonary function tests, split lung function values, exercise tests, cardiologic testing, and the role of prehabilitation, sublobar resections, risk scores and comorbidities in selecting patients for curative intent treatment.

Introduction

Patient fitness is a critical factor influencing curative intent treatment of lung cancer. In 2009 the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) published guidelines on fitness for radical therapy in lung cancer patients, which focused mainly on surgical treatment due to the paucity of other published evidence on other oncological treatments [1]. In the meantime, there has been significant progress in all lung cancer treatment modalities. Perioperative outcomes after thoracic surgery have improved due to the widespread use of minimally invasive techniques and lung sparing resections which reduce surgical trauma without compromising oncological quality. In this direction, enhanced recovery programmes have been introduced to streamline and improve perioperative care with the aim of reducing hospital stay and further improving clinical outcomes [2–8]. Radiotherapy has also progressed with the application of intensity-modulated radiotherapy and stereotactic body radiotherapy (SBRT) in selected cases of early stage lung cancer [9]. The development of immune checkpoint inhibitors and targeted therapies has led to a substantially more integrated systemic treatment with surgery and radiotherapy [10–12]. All this progress is underpinned by patient empowerment. Its role in informed and shared decision-making has become increasingly important and should therefore be considered when discussing risk and benefit of a curative intent treatment. These developments contribute to a better prognosis but their combined use and interchangeability in the treatment sequence pose additional risks for side-effects, and therefore appropriate patient assessment and selection is required for any single/multimodality treatment.

Following the publication of the ERS/ESTS guidelines in 2009 [1] and the American College of Chest Physicians (ACCP) guidelines published in 2013 [13], no further guidelines on this topic have been published, except for a consensus document from an American Association for Thoracic Surgery expert panel which addressed the assessment of high-risk patients for lobectomy in stage I non-small cell lung cancer (NSCLC) [14].

The implementation of all novel oncological/surgical approaches in clinical practice needs to be linked with updated guidance on fitness assessment prior to treatment. Therefore, ERS and ESTS agreed to produce a new guideline addressing this unmet need. Compared to the previous guidelines published in 2009, a more robust methodology was applied, the scope of the guidelines was expanded to non-surgical treatments and newly published evidence has been included.

Methods

This section provides a summary of the applied methodology. Supplement A gives detailed information on the methodological process (section A1) as well as the PICO (population, intervention, comparison and outcomes) and narrative questions (section A2).

Scope and purpose of the document

This joint guideline was developed by the ERS and the ESTS. It follows the previous guideline from 2009 [1]. The objective of this guideline is to provide guidance on fitness evaluation and functional work-up in candidates for curative intent treatment for early stage lung cancer. This document is intended to be used by all specialists contributing to the lung cancer pathway.

Composition of the task force panel

This task force consisted of a multidisciplinary team of experts from different countries, led and chaired by A. Brunelli, G. Hardavella and R.M. Huber. The panel consisted of experts in the fields of respiratory medicine, radiation and medical oncology, thoracic surgery, cardiology, radiology, anaesthesiology and physiotherapy. In addition to ERS and ESTS, the following organisations were contacted to select experts in their respective specialty: European Society of Cardiology (Riccardo Asteggiano); European Society of Anaesthesiology and Intensive Care and European Association of Cardiothoracic Anaesthesiology and Intensive Care (Nandor Marczin); and European Society for Radiotherapy and Oncology (Corinne Faivre-Finn and Dirk De Ruyscher). The panel included also patient representatives from the lung cancer patient advisory group of the European Lung Foundation (ELF), who had voting rights and participated as active panel members. The task force was supported interchangeably by two ERS guideline methodologists, who consulted the panel throughout the entire process.

Formulation of questions and selection of outcomes

This document was developed according to the ERS methodology for clinical practice guidelines [15]. Two types of questions were addressed. Questions in the PICO format were answered using systematic searches, risk of bias assessment and certainty of evidence assessment. Narrative questions, which were meant to complement the PICO questions and were not comparative, were answered using systematic searches and narrative synthesis of evidence [15, 16]. GRADE (Grading of Recommendations Assessment, Development and Evaluation) Evidence to Decision (EtD) frameworks were used for discussion of both question types. Research questions were initially proposed by the chairs and were unanimously approved by the panel.

The panel selected the patient relevant outcomes which were agreed by the patient representatives. They rated their importance for clinical decision-making, using three levels of importance: 1) critical, 2) important but not critical, and 3) of limited importance for clinical decision-making [17]. Outcomes rated as critical and important were analysed and reported in this document.

Literature searches and evidence synthesis

A librarian from Université Libre de Bruxelles (Brussels, Belgium) designed the search strategies in collaboration with the methodology working group (T. Berghmans, T.G. Blum, A. Brunelli, G. Hardavella and R.M. Huber). The literature searches were conducted in the first quarter of 2021 using Ovid Medline for all questions, and additionally SciVerse Scopus database for PICO questions and APA PsycInfo through the Ebsco interface for narrative question 2a. As this follows the previous guideline [1], studies published since 2009 were searched. Relevant studies published before 2009 and utilised in the previous guidelines were also used to form the evidence base of this project and considered in the EtD frameworks. No language filters were used. Searches were updated in October 2022 and June 2024. Search strategies are shown in supplement A.

Screening for relevant studies was performed by two reviewers independently against predefined inclusion/exclusion criteria, in two phases (title/abstract and full text screening), using Covidence (www.covidence.org). Differences between reviewers were resolved by discussion or by a third reviewer. Systematic reviews, randomised controlled trials and observational studies (with more than 40 participants) were considered for inclusion. The screening results are presented using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (supplement A) [18]. Data extractions were done by at least two task force members per PICO or narrative question. The evidence synthesis incorporated all relevant study characteristics and results. As meta-analyses were not possible, due to large clinical and statistical differences between studies, a narrative evidence synthesis approach was used instead.

Assessment of quality of evidence and strength of the recommendations

For all PICO questions, risk of bias in observational studies was assessed using the QUIPS (Quality in Prognosis Studies) tool [19] (of note: no randomised controlled trials were detected for any of the four PICO questions). The certainty of evidence was assessed with GRADE, taking into consideration risk of bias, inconsistency, indirectness, imprecision and publication bias of included evidence [20]. GRADE has four levels of certainty of evidence (very low, low, moderate and high), representing the degree of

confidence we have in effect estimates to support a recommendation [20]. As the guideline dealt with prognostic questions, we followed GRADE guidance and assigned high certainty of evidence as the starting point even for non-randomised studies [21].

For deciding on direction and strength of recommendations, EtD frameworks were used [22, 23], taking into account the balance between benefits and harms, certainty of the evidence, patient values and preferences, health equity, costs, feasibility and acceptability. Strong recommendations are presented as “we recommend”. Conditional recommendations are presented as “we suggest”. The panel decided on the recommendations with voting. Recommendations were agreed only when a consensus of >90% was achieved. Disagreements were resolved by discussion.

Conflict of interest management

All task force members signed a confidentiality agreement and declared potential conflicts of interest following ERS rules.

Results

This section provides all recommendations as well as an executive summary for the four PICO and seven narrative questions of this clinical practice guideline. Supplement B lists the underlying GRADE evidence profiles and EtD frameworks.

PICO Question 1: Should D_{LCO} testing be used in lung cancer patients undergoing radical treatment (surgery and/or immunochemoradiotherapy) for risk stratification of mortality, length of stay, morbidity and quality of life following treatment (compared to not using it)?

Recommendations

1) The panel recommends performing pre-operative measurement of carbon monoxide lung diffusion capacity (D_{LCO}) to define the pre-operative risk of post-operative mortality and complications, as well as a baseline test for follow-up in lung cancer patients who are evaluated for lung cancer surgery (Strong recommendation for the intervention, low certainty of evidence).

Remark: The panel suggests the D_{LCO} categories $\geq 80\%$, 60–79%, 40–59% and $<40\%$ to stratify the pre-operative mortality and morbidity risks as normal, mild, moderate and high, respectively.

2) The panel suggests performing pre-operative measurement of D_{LCO} after completion of induction therapy to re-define the pre-operative risk of post-operative mortality and complications in lung cancer patients who are re-evaluated for lung cancer surgery (Conditional recommendation for the intervention, very low certainty of evidence).

Remark: Although evidence on the clinical relevance of certain D_{LCO} thresholds/categories is limited, $D_{LCO} < 80\%$ suggests a higher risk for post-operative mortality/morbidity.

3) The panel suggests performing pre-operative measurement of D_{LCO} to define the pre-treatment risk of respiratory impairment and to serve as a baseline test for follow-up in lung cancer patients being considered for concurrent chemoradiotherapy and radiotherapy $\pm$ chemotherapy (Conditional recommendation for the intervention, very low certainty of evidence).

Remark: Evidence supporting the clinical relevance of specific D_{LCO} thresholds or categories in this setting is limited.

Summary of evidence and overall certainty of evidence

We selected 75 observational studies out of the 1730 initially identified abstracts [4, 24–97]. Due to substantial heterogeneity of the body of evidence relating to treatment modalities, we formed four subgroups (1: surgical resection irrespective of neoadjuvant or adjuvant therapy; 2: neoadjuvant therapy followed by surgical resection; 3: concurrent chemoradiotherapy; 4: radiotherapy $\pm$ chemotherapy) which allowed clinically rational pooling of data. Varying D_{LCO} thresholds precluded meaningful meta-analyses. Thus, for each reported D_{LCO} threshold, their related effects per outcome were narratively assessed then an overall effect was estimated for each of the outcomes. The overall certainty of evidence was rated as very low for subgroups 1, 2 and 4, and low for subgroup 3.

Desirable effects

In the surgical subgroup (53 studies) [4, 24–75], despite the narrative assessment of included studies per outcome and the variation of applied D_{LCO} thresholds, D_{LCO} values below a certain threshold indicated

poorer mortality and morbidity rates, poorer overall survival, reduced quality of life and increased length of stay, yet with varying effect strengths (supplement B, table 1).

In the subgroup of patients with neoadjuvant therapy followed by surgical resection (five studies) [76–80], lower D_{LCO} values were associated with poorer 30-, 90-day and overall mortality, as well as respiratory morbidity (supplement B, table 2).

In the two remaining subgroups based on concurrent chemoradiotherapies (eight studies) [81–88] and radiotherapy $\pm$ chemotherapy (nine studies) [89–97] lower D_{LCO} values were associated with a small–moderate reduction of overall survival as well as a moderate increase of the risk of radiation pneumonitis (supplement B, tables 3 and 4).

Undesirable effects

No harms for measurement were identified in the 75 studies included [4, 24–97].

Justification of recommendations

1) The recommendation for D_{LCO} testing as part of evaluation for lung cancer surgery is based on 53 observational studies of varying sizes (65–13 376 patients) [4, 24–97]. Few studies applied multivariate analyses taking into account confounding factors (predictive or prognostic variables). The recommendation is strong despite the very low certainty of evidence as all studies show an association between low values of D_{LCO} and post-operative adverse events. Yet no substantial harms became evident or are foreseen by us related to performance of D_{LCO} measurements. One large multicentre study (13 376 patients) demonstrated significantly increasing absolute 30-day mortality and cardiopulmonary morbidity rates in the suggested D_{LCO} categories $\geq 80\%$, 60–79%, 40–59% and $<40\%$, allowing us to stratify for both pre-operative risks accordingly [26].

2) The recommendation for D_{LCO} testing as part of re-evaluation for lung cancer surgery after completion of induction therapy is based on five observational studies of small to medium size (21–1001 patients) [76–80]. Not all studies applied multivariate analyses taking into account confounding factors (predictive or prognostic variables). The recommendation is conditional due to the very low certainty of evidence. Yet no substantial harms became evident or are foreseen by us related to performance of D_{LCO} measurements. The largest study (1001) patients indicated significantly increased 30-day mortality and overall/respiratory morbidity for post-induction $D_{LCO} < 80\%$, prompting us to suggest the threshold of $D_{LCO} < 80\%$ accordingly [76].

3) The recommendation for D_{LCO} testing as part of pre-therapeutic evaluation before initiation of radiotherapy in lung cancer therapy is based on eight and nine small to medium-sized observational studies in lung cancer patients with concurrent chemoradiotherapy (112–557 patients) [81–88] and radiotherapy $\pm$ chemotherapy (31–483 patients) [89–97], respectively. Few studies applied multivariate analyses accounting for confounding factors (predictive or prognostic variables). The recommendation is conditional due to the very low certainty of evidence. Yet no substantial harms became evident or are foreseen by us related to performance of D_{LCO} measurements. There are insufficient data to define a D_{LCO} threshold below which radiotherapy would be contraindicated.

Additional remarks and practical considerations

D_{LCO} measurement is a well-established pulmonary function test aiming to describe gas exchange at rest. While D_{LCO} has been recommended as an essential first step beside forced expiratory volume in 1 s (FEV_1) in the risk stratification algorithm of the 2009 ERS/ESTS guidelines [1], D_{LCO} is still not regularly assessed in the routine pre-operative setting in many places.

The panel considers D_{LCO} measurements to be an essential part of pre-operative and pre-radiation risk stratification strategies. D_{LCO} measurements are commonly available in respiratory medicine services and lung cancer services; they represent rapid and safe tests at reasonable costs. Qualified technicians are required to ensure satisfactory performance of D_{LCO} testing.

Recommendations for future research

Despite limited certainty and varying strengths of evidence relating to our predefined outcomes, we are confident to suggest the integration of D_{LCO} measurements into pre-radiotherapy risk evaluation algorithms. The role of D_{LCO} measurement should be further investigated in the various radiotherapy settings and the context of multimodality treatment including chemotherapy and immunotherapy, and it should be considered in a wider clinical context.

Future research needs to support the current thresholds with better data deriving from both population-based clinical cancer registries as well as specialised respiratory medicine and lung cancer services.

PICO Question 2a: Should predicted post-operative FEV₁ be measured in lung cancer patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy), for risk stratification of mortality, length of stay, morbidity and quality of life following treatment (compared to not using it)?
Recommendations

1) The panel suggests assessing predicted post-operative FEV₁ (ppoFEV₁) to define the pre-operative risk of post-operative mortality and complications in lung cancer patients who are evaluated for lung cancer surgery (Conditional recommendation for the intervention, very low certainty of evidence).

Remark: The panel suggests the ppoFEV₁ categories $\geq 60\%$, 40–59% and $<40\%$ to stratify the pre-operative mortality and morbidity risks as normal, moderate and high, respectively.

2) The panel suggests assessing ppoFEV₁ *after completion of induction therapy to re-define* the pre-operative risk of post-operative mortality and complications in lung cancer patients who are *re-evaluated* for lung cancer surgery (Conditional recommendation for the intervention, very low certainty of evidence).

Remark: Although evidence on the clinical relevance of certain ppoFEV₁ thresholds/categories is limited, ppoFEV₁ $<60\%$ suggests a higher risk for post-operative mortality/morbidity.

Summary of evidence and overall quality of evidence

We selected 26 observational studies out of the 1730 initially identified abstracts [24, 26, 27, 29, 30, 37, 41, 44, 46, 49, 54, 56–58, 71, 72, 74, 77, 98–105]. Due to substantial heterogeneity of the body of evidence relating to treatment modalities, we formed two subgroups (1: surgical resection irrespective of neoadjuvant or adjuvant therapy; and 2: neoadjuvant therapy followed by surgical resection) which allowed clinically rational pooling of data. Varying ppoFEV₁ thresholds precluded meaningful meta-analyses. Thus, for each reported ppoFEV₁ threshold, their related effects per outcome were narratively assessed and then an overall effect estimated for each of the outcomes. The overall certainty of evidence was rated as very low and low for subgroups 1 and 2, respectively.

Desirable effects

In the surgical subgroup (25 studies), despite the narrative assessment of included studies per outcome and the variation of applied ppoFEV₁ thresholds, ppoFEV₁ values below a certain threshold indicated higher mortality and morbidity rates as well as poorer overall survival and reduced quality of life, yet with varying effect strengths (supplement A, table 5) [24, 26, 27, 29, 30, 37, 41, 44, 46, 49, 54, 56–58, 71, 72, 74, 98–105].

In the subgroup of patients with neoadjuvant therapy followed by surgical resection (one study), similar benefits of ppoFEV₁ were only reported and seen for overall and respiratory morbidity (supplement B, table 6) [77].

Undesirable effects

No harms in ppoFEV₁ measurement were identified in any of the 26 studies included [24, 26, 27, 29, 30, 37, 41, 44, 46, 49, 54, 56–58, 71, 72, 74, 77, 98–105].

Justification of recommendations

1) The recommendation for ppoFEV₁ assessment as part of evaluation for lung cancer surgery is based on 25 observational studies of varying sizes (50–13 376 patients) [24, 26, 27, 29, 30, 37, 41, 44, 46, 49, 54, 56–58, 71, 72, 74, 98–105]. Few studies applied multivariate analyses integrating confounding factors (predictive or prognostic variables). The recommendation is conditional due to the very low certainty of evidence. Yet no substantial harms became evident or are foreseen by us related to ppoFEV₁ assessments. One large multicentre study (13 376 patients) demonstrated significantly increasing absolute 30-day mortality and cardiopulmonary morbidity rates in the suggested ppoFEV₁ categories $\geq 80\%$, 60–79%, 40–59% and $<40\%$, allowing us to stratify for both pre-operative risks accordingly [26].

2) The recommendation for ppoFEV₁ assessment in re-evaluation for lung cancer surgery after completion of induction therapy is based on one small-sized observational study (66 patients) [77]. No multivariate analyses were performed. The recommendation is conditional due to the very low certainty of evidence. Yet no substantial harms became evident or are foreseen by us related to performance of ppoFEV₁

assessment. Due to limited data in this small study, the suggested threshold $\text{ppoFEV}_1 < 80\%$ to indicate a higher risk for post-operative mortality/morbidity is based on a conservative estimate by us.

Additional remarks and practical considerations

The calculation of ppoFEV_1 is a well-established spirometry-based parameter to estimate post-operative forced expiratory pulmonary function at rest. While ppoFEV_1 has been recommended as an essential second step (if FEV_1 and/or D_{LCO} are impaired) in the risk stratification algorithm of the 2009 ERS/ESTS guideline [1], ppoFEV_1 is not regularly assessed in the routine pre-operative setting. The panel considers the calculation of ppoFEV_1 to be an essential part in pre-operative risk stratification strategies and it should be included in the standard of care in respiratory medicine and lung cancer services, as it represents a rapid and safe measurement.

Recommendations for future research

Despite limited certainty and varying effect strengths of evidence relating to our predefined outcomes, we suggest the integration of ppoFEV_1 measurements into pre-therapeutic surgical risk evaluation.

Future research needs to shed light on the implementation of split function in radiotherapy settings. Further research is required into consolidating the current thresholds with better data deriving from both population-based clinical cancer registries, as well as specialised respiratory medicine and lung cancer services.

PICO 2b: Should predicted post-operative D_{LCO} be measured in lung cancer patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy), for risk stratification of mortality, length of stay, morbidity and quality of life following treatment (compared to not using it)?

Recommendation

1) The panel suggests assessing predicted post-operative D_{LCO} (ppoD_{LCO}) to define the pre-operative risk of post-operative mortality and complications in lung cancer patients who are evaluated for lung cancer surgery (Conditional recommendation for the intervention, very low certainty of evidence).

Remark: The panel suggests the ppoD_{LCO} categories $\geq 60\%$, 40–59% and $< 40\%$ to stratify the pre-operative mortality and morbidity risks as normal, moderate and high, respectively.

2) The panel suggests assessing ppoD_{LCO} after completion of induction therapy to re-define the pre-operative risk of post-operative mortality and complications in lung cancer patients who are re-evaluated for lung cancer surgery (Conditional recommendation for the intervention, very low certainty of evidence).

Remark: Although evidence on the clinical relevance of certain ppoD_{LCO} thresholds/categories is limited, $\text{ppoD}_{\text{LCO}} < 60\%$ suggests a higher risk for post-operative mortality/morbidity.

Summary of evidence and overall quality of evidence

We selected 24 observational studies out of the 1730 initially identified abstracts [24, 26, 29, 37, 41, 44–46, 49, 54, 56–58, 71, 72, 74, 77, 98, 100, 102, 103, 105–107]. Due to substantial heterogeneity of the body of evidence relating to treatment modalities, we formed two subgroups (1: surgical resection irrespective of neoadjuvant or adjuvant therapy; and 2: neoadjuvant therapy followed by surgical resection) which allowed clinically rational pooling of data. Varying ppoD_{LCO} thresholds precluded meaningful meta-analyses. Thus, for each reported ppoD_{LCO} threshold, their related effects per outcome were narratively assessed and then an overall effect estimated for each of the outcomes. From our predefined critical or important outcomes of interest, the following were addressed in the included studies: 30-day, 90-day and 1-year mortality, overall survival, overall morbidity, respiratory morbidity and various other types of morbidity, as well as periprocedural quality of life. The overall certainty of evidence was rated as very low and low for subgroups 1 and 2, respectively.

Desirable effects

In the surgical subgroup (23 studies), despite the narrative assessment of included studies per outcome and the variation of applied ppoD_{LCO} thresholds, ppoD_{LCO} values below a certain threshold almost always indicated poorer mortality and morbidity rates, as well as poorer overall survival and reduced quality of life, yet with varying effect strengths (supplement B, table 8) [24, 26, 29, 37, 41, 44–46, 49, 54, 56–58, 71, 72, 74, 98, 100, 102, 103, 105–107].

In the subgroup of patients with neoadjuvant therapy followed by surgical resection (one study), similar benefits of ppoD_{LCO} were only reported and seen for overall and respiratory morbidity [77].

Undesirable effects

No harms were identified for any of both subgroups with a total of 24 studies included [24, 26, 29, 37, 41, 44–46, 49, 54, 56–58, 71, 72, 74, 77, 98, 100, 102, 103, 105–107].

Justification of recommendations

1) The recommendation for ppoD_{LCO} assessment as part of evaluation for lung cancer surgery is based on 23 observational studies of varying sizes (50–13 376 patients) [24, 26, 29, 37, 41, 44–46, 49, 54, 56–58, 71, 72, 74, 98, 100, 102, 103, 105–107]. Few studies applied multivariate analyses exploring confounding factors (predictive or prognostic variables). The recommendation is conditional due to the very low certainty of evidence. Yet no substantial harms became evident or are foreseen by us related to ppoD_{LCO} assessments. One large multicentre study (13 376 patients) demonstrated significantly increasing absolute 30-day mortality and cardiopulmonary morbidity rates in the suggested ppoD_{LCO} categories ≥80%, 60–79%, 40–59% and <40%, allowing us to stratify for both pre-operative risks accordingly [26].

2) The recommendation for ppoD_{LCO} assessment in re-evaluation for lung cancer surgery after completion of induction therapy is based on one small-sized observational study (66 patients) [77]. No multivariate analyses were performed taking into account confounding factors (predictive or prognostic variables). The recommendation is conditional due to the very low certainty of evidence. Yet no substantial harms became evident or are foreseen by us related to performance of ppoD_{LCO} assessment. Due to limited data in this small study, the suggested threshold ppoD_{LCO} <80% to indicate a higher risk for post-operative mortality/morbidity is based on a conservative estimate by us.

From a clinical perspective, we are confident in both recommendations.

Additional remarks and practical considerations

The calculation of ppoD_{LCO} is an established lung function-based parameter. Although ppoD_{LCO} has been recommended as an essential second step (if FEV₁ and/or D_{LCO} are impaired) in the risk stratification algorithm of the 2009 ERS/ESTS guideline [1], ppoD_{LCO} is not regularly assessed in the routine pre-operative setting. The panel considers ppoD_{LCO} assessment to be an essential part of the pre-operative risk stratification.

Recommendations for future research

Despite limited certainty and varying effect of strengths of evidence relating to our predefined outcomes, we suggest the integration of ppoD_{LCO} measurements into pre-therapeutic surgical risk evaluation; however, prospective registries are advised.

Future research needs to shed light on the implementation of split function in radiotherapy/chemoradiotherapy and neoadjuvant settings with the view to consolidate and validate specific cut-offs relating to increased overall and lung cancer-specific mortality. Further research is required into consolidating the current thresholds with better data deriving from population-based clinical cancer registries, as well as specialised respiratory medicine and lung cancer services.

PICO Question 3: Should field exercise tests (6-min walk test/shuttle walk test, stair climbing test, BODE score) be used in lung cancer patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy) for risk stratification of mortality, length of stay and quality of life following treatment (compared to not using them)?

Recommendation

1) The panel suggests using one low technology test (6-min walk test/shuttle walk test, stair climbing test, BODE score) to define the risk of early mortality and complications in lung cancer patients who will undergo surgery (Conditional recommendation for the intervention, very low quality of evidence). The panel cannot suggest any specific cut-off to define patients at very high or very low mortality/morbidity risk.

Remarks: Although no specific thresholds can be recommended due to lack of evidence, 6-min walk test or shuttle walk test distance above 400 m and a stair climb height of more than 10 m suggest a lower surgical risk.

There is no available data for stratifying lung cancer patients before radical radiotherapy or multimodality treatment options.

The panel suggests that patients with poor performance in a low technology test should be referred to a formal cardiopulmonary exercise test (CPET) to better define their surgical risk and possibly improve their fitness for radical treatment.

No recommendation can be made about the predictive role of low technology tests in patients who will undergo radiotherapy, due to lack of data.

The BODE score is a multidimensional scoring system in COPD patients based on body mass index, airflow obstruction (FEV_1), dyspnoea, and exercise (6-min walk test) [108]. Due to inclusions of the other non-field exercise test (FET) parameters, we appraised it separately.

Summary of evidence and overall quality of evidence

30 studies (21 prospective, nine retrospective studies) were selected out of the 2071 initially identified abstracts [67, 71, 109–136], which were appraised separately relating to 6-minute walk test/shuttle walk test, stair climbing test and BODE score. In all studies, FETs were performed before radical surgery and none before radiotherapy. No subgroups were defined. The following outcomes were addressed by the selected studies: early mortality (30- or 90-day, in-hospital, 1-year mortality/survival), post-operative complications (pulmonary, cardiac, cardiopulmonary, any toxic events and some specific complications such as atrial fibrillation or prolonged air leak), hospital and intensive care unit (ICU) stay duration. All outcomes were considered critical. The overall certainty of evidence was rated as low.

Undesirable effects

No harms were identified for any of both subgroups in the 30 studies included [67, 71, 109–136].

Justification of recommendation

Although the evidence consists of small-sized studies with few multivariate analyses and valid concerns about bias, inconsistency and imprecision risks, and heterogeneity and the low quality of the studies not allowing for defining a specific cut-off, 14 studies found a statistically significant inverse relationship between mortality and acceptable FET results. The odds ratio of mortality ranged between 1.23 and 6.27, showing a lower risk of early mortality (30-day, 90-day, in-hospital, or 1-year) in patients with good results compared to those with poor test results. 24 studies [71, 109, 110, 114–126, 128, 129, 132, 135, 137–140] suggest that patients with good results have a lower risk of post-operative complications (OR 1.1–84.9). However, there is heterogeneity in the results due to differences in testing methods, threshold values and subgrouping analysis across the studies. No test helps predicting a specific complication (supplement B, tables 10–12), hence justifying referral of poor performers at FET to a more formal CPET to better define their fitness.

Additional remarks or practical considerations

FETs are simple, low-cost technology tests that can be easily performed in any clinical setting during a consultation. Trained personnel are required to conduct 6-min walk test and shuttle walk tests, as well as standardisation, e.g. stair height, for the stair climbing test.

Recommendations for future research

Comparative trials are necessary to confirm the validity of FETs and determine the best cut-off values associated with increased risk of post-operative mortality, morbidity and quality of life in radically treated lung cancer patients. Furthermore, FETs should be compared with more complex tests, such as CPET, to determine their relative effectiveness. Additionally, comparative data before radical (chemo-)radiotherapy and combined treatment modalities are needed.

PICO Question 4: Should laboratory exercise tests ($\dot{V}_{O_{2max}}$ or $\dot{V}_E/\dot{V}_{CO_2}$ measured at CPET) be used in lung cancer patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy) for risk stratification of morbidity, mortality or impaired quality of life following treatment (compared to not using them)?

Recommendation

1) The panel suggests using CPET in lung cancer patients with altered pulmonary function and suboptimal results from low-technology tests performed before surgery to predict the risk of early post-operative mortality and complications (Conditional recommendation for the intervention, very low certainty of evidence).

Remarks: In many studies, $\dot{V}_{O_{2max}}$ and $\dot{V}_{O_{2peak}}$ are used interchangeably. $\dot{V}_{O_{2max}}$ is considered an index of cardiovascular fitness and is measured in millilitres per minute per kilogram of body weight ($mL \cdot min^{-1} \cdot kg^{-1}$). It refers to the maximum amount of oxygen consumed during maximal exercise. $\dot{V}_{O_{2peak}}$

is also measured in millilitres per minute per kilogram of body weight ($\text{mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$). It is considered a performance index and refers to the highest oxygen consumption achieved during a specific exercise test. When analysed separately, both measures can provide different insight into patient fitness. In pre-operative testing $\dot{V}_{\text{O}_{2\text{peak}}}$ is measured.

Due to the limited number and quality of studies, the panel cannot recommend any specific parameter (such as $\dot{V}_{\text{O}_{2\text{max}}}$, $\dot{V}_{\text{O}_{2\text{peak}}}$, $\dot{V}_{\text{O}_2}$ as % of predicted values, $\dot{V}_E/\dot{V}_{\text{CO}_2}$ slope) or specific cut-offs for defining patients at very high or low risk of mortality/morbidity.

$\dot{V}_{\text{O}_{2\text{peak}}}$ below $12\text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ or $\dot{V}_E/\dot{V}_{\text{CO}_2}$ slope at an anaerobic threshold greater than 40 can suggest a high surgical risk.

There is lack of data for risk stratification prior to radical radiotherapy or multimodality treatment options.

Summary of evidence and overall quality of evidence

44 studies (29 prospective, 15 retrospective) and four systematic reviews/meta-analyses were selected out of the 2071 initially identified abstracts [46, 69, 74, 75, 109, 130, 141–178].

In all studies, all CPET exercise tests were performed before radical surgery and none before radiotherapy. Due to substantial heterogeneity of the body of evidence relating to treatment modalities, we formed two subgroups (1: surgical resection irrespective of neoadjuvant or adjuvant therapy; and 2: concurrent chemoradiotherapy) which allowed clinically rational pooling of data. The selected studies addressed the following outcomes: early mortality (30- or 90-day, in-hospital, 1-year mortality/survival), post-operative complications (pulmonary, cardiac, cardiopulmonary, any toxic events and some specific complications such as atrial fibrillation or prolonged air leak), hospital and ICU stay duration. All outcomes were considered critical. The overall quality of evidence was rated as low.

Undesirable effects

No harms were identified for any subgroups in the 44 studies included.

Justification of recommendation

Although the evidence consists of multiple heterogeneous small-sized studies with few multivariate analyses and concerns about bias, inconsistency and imprecision risks, most of the studies found a lower risk of early mortality (30-day, 90-day, in-hospital and 1-year) [59, 60, 65, 67, 70, 73, 79, 80, 82–83, 85, 87, 91, 94, 98] and complications [25, 59–66, 68–71, 73, 74, 77–85, 87, 89–92, 94, 96–98, 100] in patients with higher values of performance at CPET. The highest level of evidence for the relationship between CPET and mortality is observed with $\dot{V}_E/\dot{V}_{\text{CO}_2}$ slope confirmed in two multivariable analyses suggesting that a lower $\dot{V}_E/\dot{V}_{\text{CO}_2}$ slope is associated with a lower mortality risk as an indicator of better aerobic capacity and ventilator efficiency.

Additional remarks or practical considerations

Patients with potential cardiovascular risk factors (such as a history of cardiovascular disease or abnormal ECG results) should be assessed before CPET. Combining pulmonary and cardiovascular testing for some high-risk patients can benefit a more comprehensive evaluation; however, it is essential to standardise the testing process to ensure that the results can be accurately compared and interpreted.

CPET requires specific devices and trained staff to perform the test and interpret the results. CPET access may be difficult in low income countries, especially in rural and remote areas.

Recommendations for future research

Randomised studies and high-quality prospective registries are needed to define the optimal parameters and thresholds for CPET and compare it to low technology testing methods, such as the 6-min walk test and stair climbing. This information would determine the most reliable and cost-effective method for assessing patients' exercise capacity. More data is required to determine the utility of CPET in the context of radical (chemo-)radiotherapy and other combined treatment modalities.

Narrative questions

All narrative questions are presented as executive summaries. Detailed results for each of the underlying narrative reviews are reported in the corresponding GRADE EtDs in supplement B.

Narrative question 1: Which measures should be used to minimise the cardiovascular risk in NSCLC patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy)?

Recommendation

1) The panel suggests that patients with NSCLC who are potential candidates for curative intent treatment and present a history or have some evidence of suspect cardiovascular diseases (general heart disease, atrial fibrillation, coronary artery disease, left ventricular heart failure, right ventricular dysfunction, valvular heart disease, patent foramen ovale and pulmonary hypertension), should undergo a cardiology evaluation. Depending on the outcome, further diagnostic tests should be completed where appropriate (Conditional recommendation, very low certainty of evidence, stemming from narrative review).

Remarks: 1) The cardiology evaluation should be performed according to cardiology guidelines applicable to the respective institution.

2) The cardiology evaluation should be performed during the standard work-up process, aiming to minimise any delay of treatment initiation

3) The cardiology evaluation should be performed considering patient needs and preferences.

Brief summary of the narrative review

We selected 29 studies [179–207] out of the 178 initially identified abstracts consisting of 16 prospective, five prospective diagnostic/observational studies, six reviews and two guidelines. Our narrative review assessed: 1) general heart disease [179–182], 2) cardiovascular risk scores, risk factors and biomarkers [183–194], 3) atrial fibrillation [195], 4) coronary artery disease [196], 5) heart failure [197–199], 6) right ventricular dysfunction [200–202], 7) valvular heart disease/patent foramen ovale [203], and 8) pulmonary hypertension [204–207]. None of the studies justified specific conclusions regarding specific considerations going beyond our general suggestion to perform a cardiology evaluation in patients with a suspicion or history of cardiovascular diseases relating to any of these eight subtopics.

The systematic use of pre-operative risk scores as well as the cardiology evaluation may help to reduce morbidity and mortality following surgery and radiotherapy with curative intent. Patients at high risk and with evidence of cardiovascular diseases should undergo more extensive pre-operative evaluation and closer post-operative monitoring.

Additional invasive investigations should only be considered in patients with positive non-invasive screening tests appraising also potential adverse events.

Narrative question 2

Narrative question 2 was divided into subsections a–g, to assess the overall narrative question: which other factors should be taken into consideration for selection of NSCLC patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy)?

Narrative question 2a: What is the predictive impact of subjective factors (clinician gestalt/eyeballing and patient-reported outcomes) for selection of NSCLC patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy)?

Recommendations

1) The panel suggests being more rigorous about collecting health-related quality of life (HRQoL) data before and after curative treatments (surgery or SBRT). The appropriate questionnaires must be chosen to measure patient-reported outcomes (PROs). Particularly, the preferred patient-reported outcome measure (PROM) tools must be applicable at baseline and at follow-up visits. Follow-up visits should extend up to 12 months post-surgery and up to 2 years post-SBRT at regular intervals for accurate longitudinal PRO assessment (Conditional recommendation, low certainty of evidence, stemming from narrative review).

2) The panel suggests using cancer-specific internationally validated tools such as EORTC QLQ-C30, EORTC QLQ-LC29 and the National Institutes of Health-sponsored Patient Reported Outcome Measurement Information System (PROMIS) to assess quality of life after curative treatment (Conditional recommendation, low certainty of evidence, stemming from narrative review).

3) The panel suggests to assess the effect of acute side-effects on HRQoL within 3 months of treatment and severe symptoms (symptoms that are grade 3 and above according to Common Terminology Criteria for Adverse Events) with appropriate questionnaires as patient-reported symptoms should be managed

properly to hasten recovery time after definitive treatment (Conditional recommendation, low certainty of evidence, stemming from narrative review).

Remarks: 1) The assessment of PROs before radical treatment for lung cancer has the potential to identify predictors of outcomes which are not captured by traditional objective parameters traditionally used to assess fitness.

2) Tailored PRO tools, timing of assessment and strategies to increase the completion rate should be considered according to the population of interest.

3) By integrating PRO assessment into clinical practice, physicians can better identify patients at high risk of decline in HRQoL domains, such as emotional and physical functioning. This can enable the implementation of targeted psychological and physical support programmes tailored to benefit these patients.

Brief summary of narrative review

Eight out of 29 studies assessed the predictive impact of pre-treatment HRQoL on short-term outcomes [68, 72, 73, 208–212].

Studies were heterogeneous regarding applied tools (EORTC QLQ-C30, EORTC QLQ-LC13, SF-36, PROMIS), assessment time-points and outcomes. Pre-operative HRQoL functions measured by PROs may identify surgical patients at risk for longer post-operative length of stay and increased complications [73, 208, 209]. Interestingly, pre-operative HRQoL scores in early-stage COPD patients were not significantly associated with post-operative complications after lung cancer surgery in the included study [68].

Studies utilising different tools indicated that regular post-interventional evaluations of physiological, psychological and social impairments bear the potential to improve HRQoL in the further course of lung cancer patients after thoracic surgery or SBRT.

Narrative question 2b: What is the predictive impact of risk scores and nomograms, nutritional status and frailty for selection of NSCLC patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy)?

Recommendations

Risk scores and nomograms

1) The panel suggests that none of the current risk scores or risk nomograms on an individual basis has a role for patient selection for radical treatment (radiotherapy and/or surgery) (Conditional recommendation against, low certainty of evidence, stemming from narrative review).

2) The panel suggests EuroLung 2 risk score as a good tool to be used for comparison in surgical trials or benchmarking assessment. (Conditional recommendation, low certainty of evidence, stemming from narrative review).

Remarks: Risk modelling for post-operative morbidity and 30-day mortality has only moderate predictive value. Final decisions on surgical treatment should not be made based on these models alone. Other variables should also be considered.

Nutritional status

3) The panel suggests to evaluate the nutritional status of lung cancer patients before any type of treatment (Conditional recommendation, low certainty of evidence, stemming from narrative review).

Remarks: For nutritional status evaluation, using either the Nutritional Risk Index or Nutritional Risk Score can be considered targeting patients who are underweight (body mass index $<18.5 \text{ kg}\cdot\text{m}^{-2}$), who have suffered unintentional loss of 10% or more of their body weight, or who are >70 years of age.

Frailty

4) The panel suggests that frailty should be evaluated and taken into consideration when selecting lung cancer patients for any type of treatment (Conditional recommendation, low certainty of evidence, stemming from narrative review).

Remarks: Regarding frailty, the use of the frailty phenotype assessment (Fried's Frailty Phenotype) can be considered for patients >60 years of age.

Brief summary of narrative review

Risk scores and nomograms

We included two systematic reviews [213, 214] and six observational studies [183, 215–219] in our narrative review. 22 risk models assessed the post-operative mortality risk incorporating different parameters in lung cancer patients [213]. Validations and external evaluations were performed in series of patients operated before 2016 and beyond when minimally invasive surgery was not routinely applied.

In the context of radiotherapy, limited but detailed evidence elaborated a small number of variables predicting the development of radiation pneumonitis (prevalence of 15–40% of patients receiving concurrent chemoradiation) which include dose–volume parameters (especially V20), lower lobe tumour location, and treatment with carboplatin/paclitaxel [214]. Nevertheless, given the limitations, none of the risk scores seems currently applicable in routine lung cancer surgery and radiotherapy. Yet EuroLung 2 showed a good adjustment to observed 30 days mortality, justifying its usage in clinical trials.

Nutritional status

Eight studies [220–227] and one systematic review [228] were selected out of the systematic literature search. Malnutrition influences outcomes after chemotherapy treatments [220]. A pilot study using three different immunonutritional supplements for 7 to 14 days prior to surgery showed improvement in immunonutritional parameters [226]. A reduction greater than 22% of the baseline prognostic nutritional index predicted poorer overall survival in one study [227], while another study highlighted fewer post-operative complications in patients receiving nutritional supplements [225].

Frailty

We included two systematic reviews [14, 229] and three observational studies [230–232]. In a recently published meta-analysis, frailty is strongly associated with adverse health outcomes in elective cancer surgery [229]. A recent consensus paper from the American Association for Thoracic Surgery identified the most important factors considered determining high risk in lung cancer resections, in which frailty ranked second in relative importance [14]. Frailty can be assessed using Fried's frailty criteria [230]. The use of other metrics for frailty assessment (Modified Frailty Index, Risk Analysis Index) is more useful at a population level than at an individual patient level [231, 232].

Narrative question 2c: What is the predictive impact of planned extent of surgical resection (e.g. sublobar parenchymal sparing resections, lobectomy) for selection of NSCLC patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy)?

Recommendation

1) The panel suggests that in high-risk patients, the overall feasibility of a sublobar resection may influence the selection of patients for surgery (Conditional recommendation, low certainty of evidence, stemming from narrative review).

Remarks: 1) There is insufficient data available on the immediate post-operative lung function loss between lobectomy and the various sublobar resection types.

2) Current studies represent patients of mixed fitness levels, but with largely non-compromised physiology and lung function. There is insufficient data available on the role of segmentectomy in patients with compromised cardiorespiratory reserve.

3) Subjective measures of changes in dyspnoea scales or functional status at these early to mid-term time periods (PROMs) may represent a more important outcome. There is insufficient literature available reporting on these outcomes.

4) There is likely to be a difference in the degree of lung function preserved by each anatomical segmentectomy. Further heterogeneity results when considering bi- and multi-segmental resections in various conformations. There is insufficient data available on this topic.

Brief summary of narrative review

We selected two randomised controlled trials [2, 8] and two observational studies for this narrative review [233, 234]. The implementation of lung cancer screening programmes across Europe will cause an increase in the detection of small or minimally invasive lesions, also in compromised patients. More patients will present with multiple lung nodules. Lung sparing procedures have the appeal of allowing for subsequent curative treatments by preserving lung parenchyma and, potentially, lung function. Findings from two large

randomised controlled trials performed in fit patients have shown that sublobar resections are at least similar to lobectomies in terms of overall survival [2, 8].

A small reduction in perioperative morbidity and mortality appears to be associated with sublobar resections in the high-risk group of patients [233]. The evidence is inconsistent across study designs. However, current studies represent patients of mixed fitness levels, but with largely non-compromised physiology and lung function.

Sublobar resections seemed to offer a variable degree of functional preservation, as measured by spirometry at 6 to 12 months post-operatively compared to baseline. In addition, a recent trial revealed that patients undergoing sublobar resection have an increased ability to tolerate subsequent treatment procedures, ultimately leading to improved survival [8]. Recent evidence suggests that segmentectomy is associated with reduced risk of patient-reported post-operative dyspnoea deterioration in long term survivors after minimally invasive curative lung resection, pointing to a better HRQoL [234].

Narrative question 2d: What is the predictive impact of pulmonary rehabilitation for selection of NSCLC patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy)?

Recommendations

1) The panel suggests that prehabilitation has a role in preparing patients for tumour-specific treatments of lung cancer, as it can decrease the incidence of post-operative pulmonary complications in high-risk patients, and therefore might increase the number of patients eligible to undergo surgery (Conditional recommendation, moderate certainty of evidence, stemming from narrative review).

2) The panel suggests that post-operative rehabilitation has a role in the after care of patients who underwent tumour-specific treatments of lung cancers, as it can improve functional recovery in selected patients with persisting functional limitations, including those who followed prehabilitation (Conditional recommendation, moderate certainty of evidence, based on narrative review).

Brief summary of narrative review

The presented evidence on the effects of pre- and post-operative rehabilitation interventions is based on five recent systematic reviews of randomised controlled trials [235–239] and one randomised controlled trial [240]. There is consistent evidence that patients who are at high risk of developing post-operative complications and taught pre-operatively by a physiotherapist on how to perform breathing exercises after surgery or who strengthen their respiratory muscles before surgery with a loaded resistive breathing device can halve their risk of developing complications after major surgery. Additionally, post-operative length of hospital stay may be reduced [235, 237]. Combined respiratory muscle and exercise training can also improve (functional) exercise capacity with largest improvements in those presenting with lowest exercise capacity [235, 237]. Exercise training increases exercise capacity and quadriceps muscle force following lung resection for NSCLC [236]. Post-operative exercise training can significantly improve the quality of life of patients undergoing lung surgery [236, 238]. Only one adverse event (hip fracture) was reported in the intervention group of one randomised controlled trial evaluating post-operative interventions [236]. Patients valued respiratory prehabilitation including breathing exercises [240]. The optimal FITT-PV parameters (frequency, intensity, type, timing, progression and volume) for different patient profiles remain uncertain both for pre- and post-rehabilitation interventions due to insufficient evidence and large heterogeneity between studies.

Narrative question 2e: What is the predictive impact of age for selection of NSCLC patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy)?

Recommendation

1) The panel suggests that patient age alone should not be used as an independent predictive factor to affect the decision process for treatment modalities in radical lung cancer treatment settings (Conditional recommendation against, low certainty of evidence, stemming from narrative review).

Remarks: The evaluation of age in combination with current performance status prior to radical treatment, comorbidities and TNM should be considered as a whole to recommend for or against radical treatment approaches in elderly patients ensuring efficacy and safety.

Brief summary of narrative review

45 out of 369 publications were selected for the narrative review [70, 172, 241–283]. Definitions of age cut-offs in the elderly varied across the selected studies, which used cut-offs at 65 years [247], 70 years [70, 241, 242, 244, 246, 248, 250, 252–254, 260, 264, 267, 269, 273, 276–283], 75 years [243, 249, 255,

258, 259, 262, 263, 265, 270, 271, 275] and 80 years [245, 272, 274]. Regarding radical treatment modalities, most studies address surgical resection [70, 241, 243–247, 257, 259, 260, 263–268, 273, 278, 279, 282], few radiotherapy [242, 249, 252, 254, 255, 261] and fewer chemotherapy [249, 253] in the elderly.

Surgery

Older age does not seem to independently impact on surgical outcomes (morbidity, mortality, survival) when patients are properly selected [245, 248, 250, 275, 279, 280] and minimally invasive approaches are used [247, 260] while poorer D_{LCO} [70] and pre-operative American Society of Anesthesiologists Physical Status [283], greater extent of resections and in particular right-sided pneumonectomy [47, 247, 273, 281], the TNM staging [283], and comorbidity [251, 256, 260] negatively affect outcomes. Only one study found that age was a predictor of death within the early post-operative period [269].

The elderly tend to have longer recovery periods than younger patients. While one study showed a similar length of hospital stay in elderly compared to younger patients [251], a large proportion of them (up to 24%) are transferred to specialised care facilities after operation [260] as they fail to make a complete recovery and show a decreased tendency to achieve the pre-operative level of quality of life compared to younger patients [277].

Chemotherapy

Induction chemotherapy followed by major lung resection can be performed with acceptable short-and long-term results in appropriately selected elderly patients with toxicities and mortality rates that are comparable to those of younger patients [253, 261, 282]. Chemotherapy relapse patterns seem to be similar between younger and older patients [261]. Only one study reported more grade 4 toxicities in the elderly [276].

Radiotherapy

Age does not seem to be an independent predictive factor for radiotherapy-related toxicities [252] and overall survival [255] while these outcomes correlated with comorbidities [252] and performance status [261]. Elderly patients undergoing SBRT for early-stage NSCLC appear to have similar risk of toxicity and rate of efficacy as in younger patients. These findings support the use of SBRT in appropriately selected elderly patients [262].

Chemoradiotherapy

The elderly experienced more toxicities as well as worse mortality and overall survival when receiving concurrent chemoradiotherapy in trials [278] and routine care [249] in comparison to younger patients.

Narrative question 2f: What is the predictive impact of performance status and sarcopenia for selection of NSCLC patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy)?

Recommendations

Performance status

1) The panel suggests that assessment of performance status and its documentation can have an important role in the selection of patients being considered for radical treatment of lung cancer (Conditional recommendation, low certainty of evidence, stemming from narrative review).

Remarks: The panel cannot provide a performance status threshold for an absolute contraindication to radical treatment, but healthcare providers should recognise the increased risk of perioperative mortality and morbidity associated with any Eastern Cooperative Oncology Group (ECOG) performance status >0, and in particular with ECOG performance status ≥ 2 .

Sarcopenia

2) The panel suggests that the assessment of sarcopenia by computed tomography (CT) scan can have a promising role as a semi-quantitative tool to directly assess muscle mass, which could be complementary to the overall frailty phenotype (Conditional recommendation, low certainty of evidence, stemming from narrative review).

Remarks: There is considerable variation regarding the assessment tools for sarcopenia and reference race- and gender-adjusted cut-off values, the patient population studied and the relevant surgical procedures and outcomes, such as prognosis and post-operative complications, in the published reports. Thus, further validation, methodological refinement and larger studies are required to guide clinical practice.

Brief summary of narrative review

Performance status

The ECOG [284] and the Karnofsky scale [285] are widely implemented performance status tools in oncology to both predict prognosis and determine patient fitness to undergo anti-cancer therapies, primarily for systemic therapies. Our systematic literature search detected 11 eligible studies [269, 286–295]. Study cohorts receiving radical therapies were mainly composed of patients with performance status 0/1. Only a small number of studies enrolled small numbers of participants with performance status 2/3 [286, 288, 294]. The impact of performance status on outcomes was ambiguous. While larger datasets indicate increased perioperative morbidity and mortality in performance status ≥ 1 [269, 286, 291, 292, 295] or in performance status ≥ 2 in another study [293], data from single or multicentre retrospective cohorts showed differing trends.

Sarcopenia

Sarcopenia is common in NSCLC patients and is considered an independent risk factor for post-operative complications and poor prognosis after lung resection [296]. 17 publications reporting on the impact of sarcopenia on short-term post-operative outcomes in lung cancer were included [296–312], of which 16 were retrospective studies [297–312] and one was a systematic review with meta-analysis [296]. Studies used different sarcopenia diagnostic tools, software and cut-off values. Most of the studies use abdominal CT scan at the level of the third lumbar vertebra (L3), by taking either the psoas muscle mass index (cross-sectional area of the psoas muscle/height; $\text{cm}^2 \cdot \text{m}^{-2}$) [297–300, 308, 309, 312] or skeletal muscle index (cross-sectional area of skeletal muscle/height; $\text{cm}^2 \cdot \text{m}^{-2}$) [297–300, 308, 309, 312].

10 studies found poorer post-operative outcomes associated with sarcopenia, namely higher post-operative complication [297–299, 301–303, 307–309], increased 30-day mortality [303, 304], longer hospital [298, 302, 304, 308] and ICU stay [302], as well as shorter 1-year overall and disease-free survival [311].

Narrative question 2g: What is the predictive impact of different comorbidities (other than cardiovascular diseases) for selection of NSCLC patients, candidates for radical treatment (surgery and/or immunochemoradiotherapy)?

Recommendations

- 1) The panel suggests that the risk of surgery or radiotherapy is increased in patients with comorbidities and physicians need to be cautious if Charlson Comorbidity Index is increasing when providing surgery or radiotherapy with curative intent (Conditional recommendation, low certainty of evidence, stemming from narrative review).
- 2) The panel suggests that patients with non-dialysed chronic kidney disease seem not at an increased risk of surgery in early-stage NSCLC. Nevertheless, an additional risk is observed in those patients >75 years old (Conditional recommendation, low certainty of evidence, stemming from narrative review).
- 3) The panel suggests that patients with lung cancer and cirrhosis have an increased risk of complications and liver decompensation after surgery (Conditional recommendation, low certainty of evidence, stemming from narrative review).
- 4) The panel suggests that based on the available literature, no recommendation can be proposed for curative intent treatment in patients with autoimmune diseases and early lung cancer (Conditional recommendation, very low certainty of evidence, stemming from narrative review).
- 5) The panel suggests that the risk of post-surgical complications in HIV patients with early-stage NSCLC is dependent on CD4 count, the HIV viral load and the optimal antiviral therapy (highly active antiretroviral therapy). The decision must take into account on the potential detrimental long-term prognosis related to HIV status (Conditional recommendation, very low certainty of evidence, stemming from narrative review).
- 6) Based on the available literature, no recommendation can be made for or against chemoradiotherapy or definitive radiotherapy in HIV patients (Conditional recommendation, very low certainty of evidence, stemming from narrative review).
- 7) The panel suggests adapting HIV therapy while planning chemotherapy to avoid detrimental interactions (Conditional recommendation, low certainty of evidence, stemming from narrative review).

- 8) The panel suggests that stroke or cerebrovascular disease are not associated with a detrimental impact on mortality, while more post-surgical complications are observed (Conditional recommendation, low certainty of evidence, stemming from narrative review).
- 9) The panel suggests performing a pre-operative work-up to assess the risk of a cerebrovascular incident during surgical procedure (Conditional recommendation, low certainty of evidence, stemming from narrative review).
- 10) The panel suggests that diabetes is associated with an increased risk for post-surgical complications. Adequate diabetes control and vascular assessment are recommended before surgery to reduce post-operative complications (Conditional recommendation, low certainty of evidence, stemming from narrative review).
- 11) The panel suggests recommending definitive radiation to unresectable or inoperable NSCLC patients with diabetes despite an increase in radiation pneumonitis (Conditional recommendation, low certainty of evidence, stemming from narrative review).
- 12) The panel suggests that thoracic surgery in solid organ transplant recipients is associated with potential increase in early mortality and risk of respiratory failure but with adequate long-term survival (Conditional recommendation, low certainty of evidence, stemming from narrative review).
- 13) The panel suggests that patients with interstitial lung disease (ILD) are at increasing risk of complications after thoracic surgery and/or radiotherapy (Conditional recommendation, low certainty of evidence, stemming from narrative review).
- 14) The panel suggests considering SBRT as the treatment of choice, with RFA reserved for cases where SBRT is unavailable, contraindicated, or as a salvage treatment following SBRT. Final decisions should take into account the benefit/risk ratio for each option (Conditional recommendation, low certainty of evidence, stemming from narrative review).

Brief summary of narrative review

Comorbidities are frequent [313] and may occur concomitantly in a substantial number of lung cancer patients [314]. Our systematic literature search retrieved 133 publications [43, 47, 98, 183–185, 205, 274, 291, 303, 306, 315–436]. We assessed the predictive impact of comorbidities globally in the Charlson Comorbidity Index (28 studies) [98, 205, 303, 306, 315–338] as well as specifically in kidney (eight studies) [47, 183, 339–344], liver (six studies) [291, 345–349], autoimmune (three studies) [350–352], viral (nine studies, all on HIV) [353–361], and neurological diseases (five studies) [184, 341, 362–364], diabetes (18 studies) [185, 274, 343, 365–379], and diseases going along with immunosuppression (two studies) [380, 381] as well as ILD with radiotherapy (13 studies; two systematic reviews) [382–396] and surgery (36 studies; nine systematic reviews) [43, 326, 352, 386, 396–436]. The main characteristics and results of the retrieved series are reported in supplement B (tables 25–33). The evidence focuses mostly on surgery, while studies on radiotherapy, considering conventional or hypofractionated schedules, are scarce apart from in ILD. Overall, patients with comorbidities have an increased risk of early complications (in the year after surgery and/or radiotherapy), even though the impact of comorbidities is inconsistent across various series, probably due to the low number of patients, selection biases and variable definitions of specific comorbidities. Particularly, ILD patients are at increased risk of exacerbations with relevant mortality subsequent to surgery or radiotherapy (regardless if SBRT or conventionally fractionated radiation). However, this should not preclude considerations for locally ablative therapies in these patients.

The data suggest that comorbidities should be critically reviewed, weighing benefits and harms when considering curative surgery or radiotherapy in lung cancer patients. Lung cancer patients with specific conditions such as dialysis, post-transplantation, HIV or ILD should be treated in lung cancer services with the possibility of direct collaboration with these comorbidity-specific disciplines (table 1).

Good practice statement about smoking cessation

The panel suggests that actively smoking patients who are considered for radical lung cancer treatment should either receive a brief smoking cessation intervention or be given access to a structured smoking cessation programme pre-therapeutically (Good practice statement).

Brief summary of underlying evidence

Smoking can cause, among others, lung cancer and COPD. Quitting smoking at or around diagnosis improves overall survival of lung cancer patients [437]. Patients who quit smoking approximately 4 weeks

TABLE 1 Definition of high-risk patients for surgery

Risk factors	Stratification
ppoD _{LCO} <40%	Relative
CPET: $\dot{V}_{O_{2peak}}$ <12 mL·kg ⁻¹ ·min ⁻¹	Relative
CPET: $\dot{V}_E/\dot{V}_{CO_2}$ slope >40	Absolute
High cardiovascular risk	Absolute
Pulmonary hypertension	Absolute
Impaired performance status (ECOG ≥2)	Absolute
Interstitial lung disease	Relative, if stable; almost absolute, if progressive
Dialysis, hepatic failure	Relative
Severe immunosuppression	Relative
Severe autoimmune disease	Relative
Organ transplant	Relative
HIV	Relative

The presence of at least one absolute risk factor or a minimum of two relative risk factors defines a high-risk patient for surgery. For high-risk patients, consider alternative non-surgical curative treatments and management in highly specialised centres with experience in multidisciplinary support. The definitions and thresholds of the different risk factors were derived from our narrative literature search and review. ppoD_{LCO}: predicted post-operative diffusing capacity of the lung for carbon monoxide; CPET: cardiopulmonary exercise test; $\dot{V}_{O_{2peak}}$: peak oxygen uptake; $\dot{V}_E$: minute ventilation; $\dot{V}_{CO_2}$: carbon dioxide production; ECOG: Eastern Cooperative Oncology Group.

before any surgery have a reduced risk of post-surgical complications [438]. Thoracic surgery is prone to post-operative pulmonary complications, which can also be reduced by quitting smoking [439]. Smoking cessation seems to be of benefit even with shorter intervals to surgery [66, 440]. The risk reduction from smoking cessation seems also to be relevant with contemporary surgical and perioperative approaches [441].

We suggest including smoking cessation as a risk-modifying procedure in perioperative management.

Discussion

The previous ERS/ESTS guidelines evaluating fitness for radical treatment of lung cancer were published in 2009. From that publication, the management of NSCLC has rapidly evolved with the improvement of perioperative care and the introduction of novel surgical and non-surgical strategies (including radiotherapy and systemic anti-cancer treatment). In this context, ERS and ESTS agreed to update the previous guidelines with the latest evidence. Compared to the previous guidelines, a more robust methodology was applied, the scope of the guidelines was expanded to also include non-surgical treatments, and newly published evidence has been included. The relevance of a multidisciplinary approach and including comorbidities in the evaluation for the most suitable treatment is emphasised.

Based on the latest literature search, the current guidelines confirmed that pulmonary function tests, and in particular FEV₁ and D_{LCO}, should be measured in all surgical candidates. Split lung function should be calculated for both FEV₁ and D_{LCO} based on the number of functioning segments to be resected.

A novel recommendation compared to the previous guidelines is to repeat the pulmonary function tests (FEV₁ and D_{LCO}) after completion of a neoadjuvant systemic treatment.

Similar to the 2009 guidelines and the ACCP guidelines, we recommend the utilisation of a low technology test prior to lung resection and the referral to a formal CPET in case of poor performance during the low technology tests (*i.e.* shuttle walk test or stair climbing test). Due to the heterogeneity of the publications, it was difficult to define a clear-cut high-risk threshold. In any case, we suggest that a shuttle walking distance or 6 min walking distance shorter than 400 m and a $\dot{V}_{O_{2peak}}$ lower than 12 mL·min⁻¹·kg⁻¹ measured at CPET should be regarded as associated with increased risk of post-operative adverse events.

Recent literature has shown the relevance of the inefficiency slope ($\dot{V}_E/\dot{V}_{CO_2}$ slope) measured during CPET as a parameter associated with post-operative risk of mortality and respiratory complications, especially when greater than 40.

We confirm the importance of a cardiologic evaluation before surgery and, in case of cardiologic risk factors, specialist input should be requested to determine the need for further tests.

TABLE 2 Definition of high-risk patients for radiotherapy

Risk factors	Stratification	Notes
D_{LCO} <40%	Relative	Conditional to size of the radiation field and exposure and the presence of other risk factors; increased risk for impaired respiratory function in combination with immunotherapy
High cardiovascular risk	Relative	Risk varies according to size of the radiation field, dose and anatomical location; increased risk for radiation pneumonitis in combination with immunotherapy
Impaired performance status (ECOG ≥ 2)	Relative	Risk varies depending on the presence of other risk factors
Interstitial lung disease	Relative, if stable; absolute, if progressive	Increased risk of radiation pneumonitis
The definitions and thresholds of the different risk factors were derived from our narrative literature search and review. D_{LCO} : diffusing capacity of the lung for carbon monoxide; ECOG: Eastern Cooperative Oncology Group.		

One important new aspect of this task force is the relevance given to PROs. The panel is suggesting being more rigorous in collecting PROMs before and after treatment.

Another new recommendation compared to existing guidelines is the evaluation of the nutritional status and frailty of lung cancer patients before any type of treatment.

In recent years the role of sublobar resections has been popularised and this task force believes that in high-risk patients their overall feasibility may influence the selection of patients for surgery.

Among the novel aspects of the current project is the analysis of the impact of prehabilitation in the selection of patients for curative treatment. Since this intervention has a role in improving physical function and decreasing the incidence of post-operative pulmonary complications, it might increase the number of patients who are eligible to undergo surgery.

Based on a narrative review of the systematically collected evidence we propose definitions of high-risk patients for surgery, radiotherapy and systemic anti-cancer treatment (tables 1, 2 and 3) and a patient centred work-up algorithm (figures 1, 2 and 3). We hope these elements will represent useful guidance for

TABLE 3 Definition of high-risk patients for systemic anti-cancer treatment

Risk factors	Stratification	Notes
D_{LCO} <40%	Relative	Deterioration of respiratory function with some chemotherapeutic substances and with immune pneumonitis
High cardiovascular risk	Relative	Higher risk with the occurrence of immune-related carditis; other chemotherapeutic agents can induce cardiac toxicity, <i>i.e.</i> adriamycin (heart failure, rarely arrhythmia), high dose cyclophosphamide (heart failure), taxanes (arrhythmia)
Impaired performance status (ECOG ≥ 2)	Relative	Depending on the type of drug and regimen
Interstitial lung disease	Relative, if stable; almost absolute, if progressive	Risk of immune-related pneumonitis with immune therapy and acceleration of interstitial lung disease; other chemotherapeutic agents can also induce pneumonitis
Dialysis, hepatic failure	Relative	Pharmacodynamics altered, depending on the drug and regimen
Hepatic failure	Relative	Depending on the level of hepatic failure: Child–Pugg A, probably minor; Child–Pugg B, at risk and must be discussed with the hepatologist; Child–Pugg C, avoid any systemic treatment
Severe immunosuppression	Relative	Increased risk of infections; conditional to the presence of other risk factors
HIV	Relative	Immunotherapy can safely be given in patients with controlled disease and correct CD4 count; the infectious risk is increased with chemotherapy as well as drug interactions between HIV therapy and some chemotherapeutic agents
For systemic treatment we intend only a treatment for local/locoregional non-small cell lung cancer/small cell lung cancer with intended curative treatment, as we did not look at stage IV or palliative therapies. The definitions and thresholds of the different risk factors were derived from our narrative literature search and review. D_{LCO} : diffusing capacity of the lung for carbon monoxide; ECOG: Eastern Cooperative Oncology Group.		

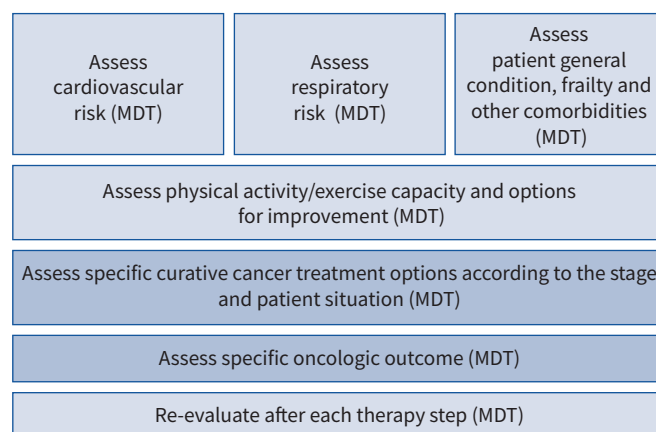


FIGURE 1 General fitness evaluation flow-chart for curative treatment of non-small cell lung cancer. The patient's values and preferences should always be taken into account in the shared decision-making process. MDT: multidisciplinary team.

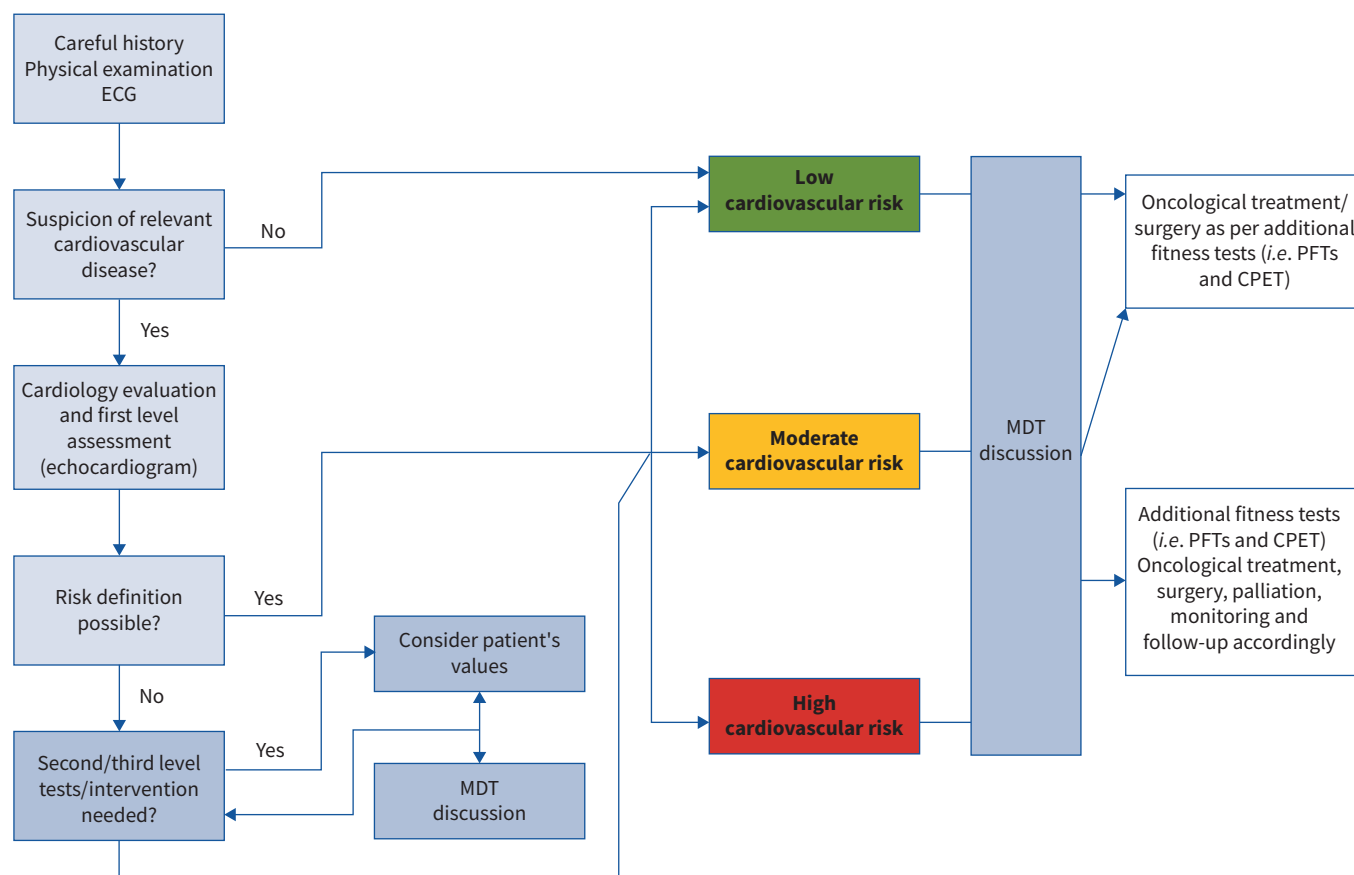


FIGURE 2 Algorithm for evaluating cardiovascular risk for curative treatment of non-small cell lung cancer. Algorithm was developed considering the recommendations and remarks arising from the evidence review performed for the narrative question, along with an educated judgement derived from clinical practice. MDT: multidisciplinary team; PFT: pulmonary function test; CPET: cardiopulmonary exercise test.

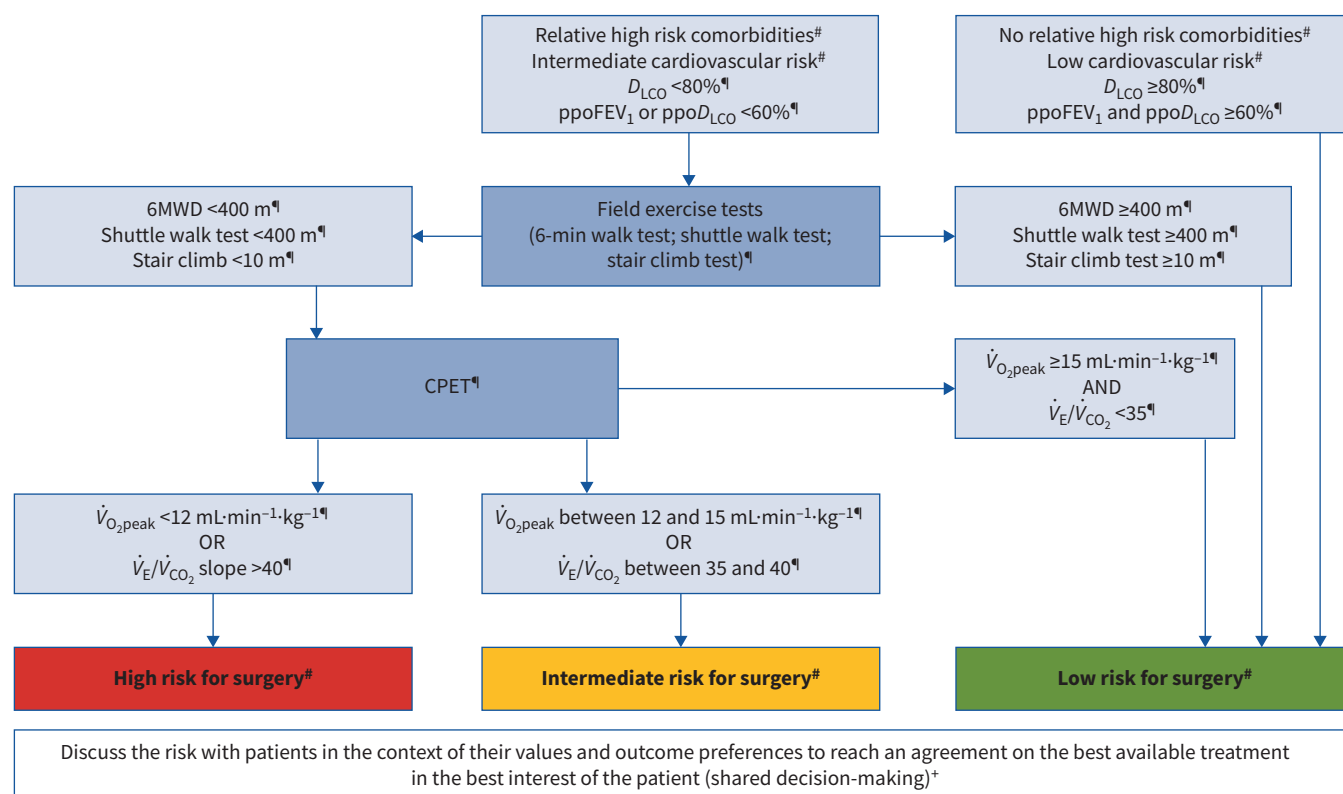


FIGURE 3 Algorithm for evaluating cardiorespiratory fitness for surgical treatment of non-small cell lung cancer. Algorithm was developed considering the recommendations and remarks arising from the evidence review performed for the PICO ([¶]) and narrative questions (⁺), along with an educated judgement derived from clinical practice ([#]). D_{LCO} : diffusing capacity of the lung for carbon monoxide; $ppoD_{LCO}$: predicted post-operative D_{LCO} ; $ppoFEV_1$: predicted post-operative forced expiratory volume in 1 s; 6MWD: 6-min walk distance; CPET: cardiopulmonary exercise test; $\dot{V}_{O_{2peak}}$: peak oxygen uptake; $\dot{V}_E$: minute ventilation; $\dot{V}_{CO_2}$: carbon dioxide production.

practising clinicians involved in the management of patients with NSCLC. The algorithms should be used as a general guide only and patients must be evaluated and risk-assessed on an individual basis.

Conclusions

In conclusion, we think the current guidelines represent an up-to-date evidence-based guidance for practising clinicians involved in the curative treatment of NSCLC. It expands the previous guidelines published more than 15 years ago by way of a more holistic and patient-centric approach.

This document was endorsed by the ERS Executive Committee on 19 August 2025, the European Society of Thoracic Surgeons on 13 August 2025, the International Association for the Study of Lung Cancer on 19 August 2025, the European Society for Radiotherapy and Oncology on 29 September 2025, and the European Society of Anaesthesiology and Intensive Care on 30 September 2025.

The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and the patient's caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

A lay summary of this document is available at <https://europeanlung.org/en/information-hub/guidelines/the-benefits-and-risks-of-lung-cancer-treatments/>

Conflict of interest: A. Brunelli reports consultancy fees from AstraZeneca, BMS, Ethicon, MSD, Medtronic and Roche, payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca, BMS, Ethicon, MSD, Medtronic and Roche, and a leadership role with the European Society of Thoracic Surgeons. R.M. Huber reports participation on a data safety monitoring board or advisory board with Janssen Germany, Merck Germany, Boehringer Ingelheim, Sanofi Germany, Novocure and AstraZeneca, and leadership roles with IASLC and Ludwig-Maximilians-Universität (LMU) ethics committee. T. Berghmans reports consultancy fees from Inhatarget, payment or honoraria for lectures, presentations, manuscript writing or educational events from Bayer, Janssen, Merck, BMS, Daiichi-Sankyo and Roche, support for attending meetings from Takeda and Johnson & Johnson, participation on a data safety monitoring board or advisory board with Bayer, Janssen, Merck, BMS, Daiichi-Sankyo and Roche, and leadership roles with ELCWP (President) and EORTC Lung Cancer Group (Treasurer). A. Frille reports grants from the MetaRot programme supported by the Federal Ministry of Education and Research (BMBF), Germany, Mitteldeutsche Gesellschaft für Pneumologie (MDGP) e.V., Medical Faculty, University of Leipzig and Novartis Foundation, and support for attending meetings from the European Respiratory Society (ERS). M. Rodriguez reports consultancy fees from AstraZeneca and Johnson & Johnson, payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca, Johnson & Johnson and Intuitive/Abex, support for attending meetings from Intuitive/Abex and Medtronic, and stock (or stock options) with Intuitive and Medtronic. L. Depypere reports consultancy fees from Medtronic and Ethicon, and support for attending meetings from BD. T. Batchelor reports consultancy fees from AstraZeneca and BMS, and payment or honoraria for lectures, presentations, manuscript writing or educational events from Intuitive, Johnson & Johnson and Medtronic. D. De Ruyscher reports grants from AstraZeneca, BMS, Beigene, Philips and Olink, and participation on data safety monitoring or advisory boards with AstraZeneca, BMS, Beigene, Philips, Olink and Eli-Lilly. C. Faivre-Finn reports grants from AstraZeneca, Merck and Elekta, consultancy fees from AstraZeneca, payment or honoraria for lectures, presentations, manuscript writing or educational events from Guy's and St Thomas NHS Hospital, and support for attending meetings from AstraZeneca, Elekta and Merck. B. Nagavci acted as ERS methodologist (2020–2022). N. Novoa reports grants from University of Toronto (lung transplant project) and payment or honoraria for lectures, presentations, manuscript writing or educational events from Medela, Medtronic, AstraZeneca and Johnson & Johnson. C. Pompili reports consultancy fees from Roche, payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca, BMS and Johnson & Johnson, and support for attending meetings from AstraZeneca and Medela. J. Rawlinson reports support for attending meetings from British Thoracic Oncology Group, EORTC MCCR workshop (with AACR/ESMO), UKIO, Queen Mary University London, UK LC clinical expert group and ERS/ELF, expenses or honoraria related to patient representative work from Nottingham University Hospital/Optellum study, UCL lung cancer PPI group, University of Birmingham ICRB and Oxford cancer PPI group, and is a member of the SOLACE science and ethics board and evaluation group. T. Tonia acts as ERS Methodologist. W.H. van Geffen reports a leadership role with NVALT (Dutch Society of Respiratory Physicians) and is local PI for trials run by his department funded by Roche, Novocure and MSD. E.J. Caruana reports payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca, AtriCure and MSD. U. Mansmann reports grants from European Community and BMBF, German Government. V. Fallet reports consultancy fees from Pfizer, MSD, BMS, AstraZeneca, Takeda, Janssen, Regeneron, Sanofi and Amgen, payment or honoraria for lectures, presentations, manuscript writing or educational events from Pfizer, MSD, BMS and AstraZeneca, and support for attending meetings from Pfizer, AstraZeneca, IsisMedical, Janssen and Takeda. The remaining authors have no potential conflicts of interest to disclose.

Support statement: This work was supported by the European Respiratory Society (TF-2020-07) and the European Society of Thoracic Surgeons. Funding information for this article has been deposited with the Open Funder Registry.

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