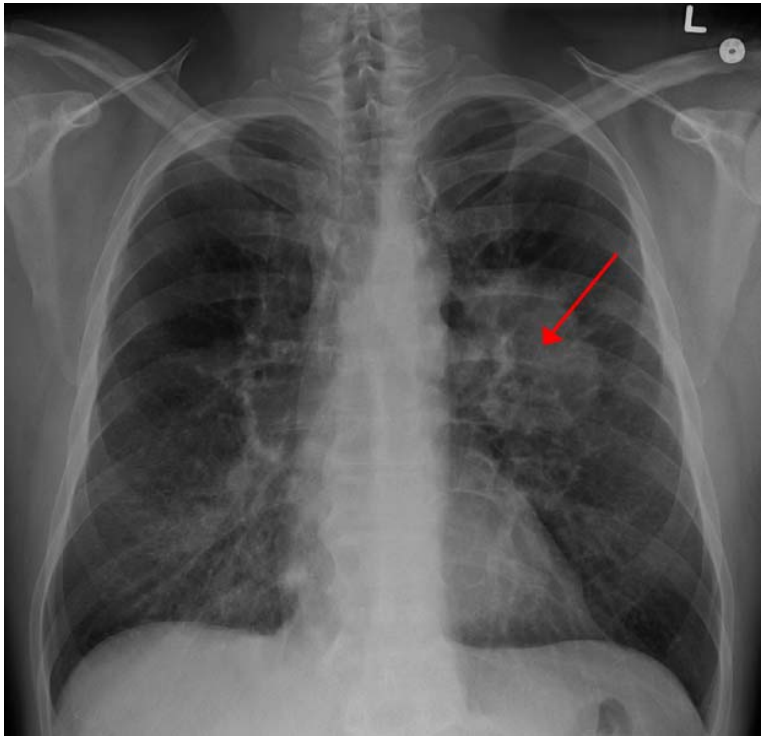
KCE REPORT 206

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SMALL CELL AND NON-SMALL CELL LUNG CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP



KCE REPORT 206
GOOD CLINICAL PRACTICE

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ISABELLE WAUTERS, JO ROBAYS, LEEN VERLEYE, KIRSTEN HOLDT HENNINGSEN, FRANK HULSTAERT, THIERRY BERGHMANS, WALTER DE WEVER, YOLANDE LIEVENS, PATRICK PAUWELS, SIGRID STROOBANTS, PAUL VAN HOUTTE, JAN VAN MEERBEECK, PAUL VAN SCHIL, BIRGIT WEYNAND, JACQUES DE GRÈVE

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COLOPHON

Title:	Small Cell and Non-Small Cell Lung Cancer: Diagnosis, Treatment and Follow-up
Authors:	Isabelle Wauters (UZ Leuven), Jo Robays (KCE), Leen Verleye (KCE), Kirsten Holdt Henningsen (KCE), Frank Hulstaert (KCE), Thierry Berghmans (Institut Bordet, Bruxelles), Walter De Wever (UZ Leuven), Yolande Lievens (UZ Gent), Patrick Pauwels (UZ Antwerpen), Sigrid Stroobants (UZ Antwerpen), Paul Van Houtte (Institut Bordet, Bruxelles), Jan Van Meerbeeck (UZ Antwerpen), Paul Van Schil (UZ Antwerpen), Birgit Weynand (CHU Mont Godinne, Yvoir), Jacques De Grève (UZ Brussel).
Reviewers:	Sabine Stordeur (KCE), Joan Vlayen (KCE)
Stakeholders:	Matteo Cappello (ULB), Paul De Leyn (UZ Leuven), Lore Decoster (Belgian Society for Medical Oncology), Ingel Demedts (Belgische Vereniging voor Pneumologie), Christophe Deroose (Société Belge de Médecine Nucléaire), Dirk De Ruysscher (Belgische Vereniging van Radiotherapie en Onocologie), Roland Hustinx (Société Belge de Médecine Nucléaire), Bart Ilsen (UZ Brussel), Thierry Pieters (Société Belge de Pneumologie), Myriam Remmelink (Belgian Society of Pathology), Vincent Remouchamps (Collège des Médecins en Radiothérapie), Karin Rondia (Fondation Contre le Cancer), Elisabeth Van Eycken (Stichting Kankerregister), Erik Verbeken (Belgian Society of Pathology), Johny Verschakelen (Royal Belgian Society of Radiology).
External validators:	Harry Groen (University Medical Center Groningen), Johan Vansteenkiste (UZ Leuven - Gasthuisberg), Bert Aertgeerts (KU Leuven)
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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
95%CI	95% Confidence Interval
AE	Adverse event
ALK	anaplastic lymphoma kinase
Bev	Bevacizumab
CHART	Continuous Hyperfractionated Accelerated Radiotherapy
CISH	Chromogenic In Situ Hybridization
COPD	Chronic Obstructive Pulmonary Disease
CP-EBUS	Convex Probe Endobronchial Ultrasound
CPET	Cardiopulmonary Exercise Testing
CPG	Clinical practice guideline
CRT	(concurrent) Chemoradiation
CT	Computer Tomography
CWU	Conventional work-up
DLCO	Diffusion capacity of the lung for CO
EBUS	Endobronchial Ultrasound
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
ESTS	European Society of Thoracic Surgeons
EUS	Endoscopic Ultrasound
FEV1	Forced expiratory volume in 1 second
FISH	Fluorescence In Situ Hybridization
FNAC	Fine Needle Aspiration Cytology
GDG	Guideline development group
Gy	Gray
HR	Hazard ratio
IPDMA	Individual patient data meta-analysis
ITT	Intention to treat
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog

KPS	Karnofsky performance status
LOS	Length of stay
LN	Lymph Node(s)
M+	Metastasis
MAs	Meta-analyses
M/F	Male/Female
MR(I)	Magnetic Resonance (Imaging)
NCI	National Cancer Institute
NICE	National Institute for Health and Clinical Excellence
NIH	National Institute of Health
NOS	Not Otherwise Specified
NPV	Negative Predictive Value
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PET	Positron Emission Tomography
PFS	Progression free survival
ppo	Predicted postoperative
PPV	Positive Predictive Value
PS	Performance status
Pt(s)	Patient(s)
QoL	Quality of Life
RCT	Randomized Controlled Trial
ROSE	Rapid On Site Evaluation
RR	Relative risk
RTOG	Radiation Therapy Oncology group
SBRT	Stereotactic body radiation therapy
SCC	Squamous Cell Carcinoma
SCLC	Small cell lung cancer

SD	Standard Deviation
SEN	Sensitivity
seq	Sequential
SPE	Specificity
TBNA	Transbronchial Needle Aspiration
TKI	Tyrosine-kinase inhibitor
TLCO	Transfer factor of the lung for carbon monoxide
TTNA	Transthoracic needle aspiration
USA	United States of America
V20	Volume of lung receiving at least 20 Gy
VATS	Video-Assisted Thoracic Surgery
VCO2	Ventilation to CO2

SCIENTIFIC REPORT

1. INTRODUCTION

The development of care pathways is one of the main items within the Belgian National Cancer Plan 2008-2010 and one of the tasks of the College of Oncology. KCE collaborates with the College of Oncology and provides scientific support in the development of clinical practice guidelines. Up to this date guidelines were jointly developed on breast cancer, colorectal cancer, testicular cancer, pancreatic cancer, upper gastrointestinal cancer and cervical cancer.

The present guideline aims to formulate, on the basis of scientific evidence, recommendations relative to the diagnosis, staging and treatment of non-small cell (NSCLC) and small cell lung cancer (SCLC).

The guideline was developed by KCE in collaboration with a multidisciplinary group of experts selected by the College of Oncology (referred to as the external experts group). The composition of the external experts group was as follows:

Isabelle Wauters, Respiratory oncology, University Hospitals Leuven, and coordinator of the External Experts Group

Thierry Berghmans, Medical Oncology, Bordet Institute, ULB, Brussels

Walter De Wever, Radiology, University Hospitals Leuven

Yolande Lievens, Radiotherapy, UZ Ghent

Patrick Pauwels, Pathology, UZ Antwerp

Sigrid Stroobants, Nuclear Medicine, UZ Antwerp

Paul.Van Houtte, Radiotherapy Bordet Institute, ULB, Brussels

Jan Van Meerbeeck, Thoracic Oncology, MOCA, UZ Antwerp

Paul Van Schil, Thoracic Surgery, UZ Antwerp

Birgit Weynand, Pathology, CHU Mont Godinne, UCL, Yvoir

Jacques De Grève, Medical Oncology, UZ Brussels and Chairman of the Working party Manuals of the College of Oncology

1.1. Background

In Belgium, lung cancer is the second most frequent malignancy in males and the third most frequent in females.[1] In 2010, age-standardised incidence rate was 82.5 per 100 000 person years in males and 30.6 per 100 000 person years in females in 2010.[2]

As for mortality, it is the leading cause of cancer death in males and the second in females. More than half of the patients die within the first year after diagnosis. 5-year relative survival is as low as 14.6% in males and 19.5% in females. In both males and females, lung cancer presents most often in advanced stages. 27.7% of cases with known stage are stage III and 46% stage IV in males. For females percentages for stage III and IV are 24.7% and 49.9% respectively.[1]

1.2. Scope and target patient population

This study aims to develop a clinical practice guideline (CPG) on lung cancer. The CPG will cover a broad range of topics: staging, treatment of non-small cell lung cancer, treatment of small cell lung cancer and follow-up. The specific clinical questions (paragraph 2.3) were the result of a scoping review of existing guidelines and consecutive discussion within the external expert group.

Screening for lung cancer, diagnosis and more specifically the subject of 'single pulmonary nodule' will not be covered in this guideline, nor are mesothelioma and carcinoid tumors.

1.3. Remit of the guideline

1.3.1. Overall objectives

This guideline provides recommendations based on current scientific evidence both for the diagnosis, treatment and follow-up of patients with lung cancer. It is intended to empower clinicians to always use these recommendations in the context of individual patient values and preferences, and to make appropriate decisions regarding all aspects of disease management, tailored to the patient.

1.3.2. Target users of the guideline

This guideline is intended to be used by health care professionals involved in the care of lung cancer patients across the cancer care continuum. It could also be of particular interest for patients and their family practitioners, for hospital managers and policy makers.

The guidelines are based on clinical evidence and may not always be in line with the current criteria for RIZIV – INAMI reimbursement of diagnostic and therapeutic interventions. The RIZIV – INAMI may consider adaptation of reimbursement/financing criteria based on these guidelines.

1.4. Statement of intent

Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of patients with lung cancer.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline should be fully documented in the patient's file at the time the relevant decision is taken.

1.5. Funding and declaration of interest

The KCE is a federal institution which is financed for the largest part by INAMI – RIZIV, but also by the Federal Public Service of Health, food chain safety and environment, and Federal Public Service of social security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of the guidelines is paid by KCE budget, the sole mission of the KCE is providing scientifically valid information. The KCE has no interest in companies/institutions (commercial or not, e.g. hospital, university), associations (e.g. professional association, syndicate), individuals or organisations (e.g. lobby group) on which the guidelines could have a positive or negative impact (financial or other).

All experts involved in the guideline development or the peer-review process completed a declaration of interest form. The information of possible conflicts of interest is published in the colophon of this report. All members of the *KCE Expert Team* make yearly declarations of interest and further details of these are available on request.

2. METHODOLOGY

2.1. Introduction

The KCE guideline is drawn up according to highly codified principles, based on scientific information regularly updated from the international literature. KCE analyses clinical practices in current use on the basis of existing recommendations. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

2.2. General approach

The present clinical practice guideline (CPG) was developed by adapting (inter)national CPGs to the Belgian context.

This approach was structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers. The ADAPTE methodology generally consists of three major phases (www.adapte.org):

1. Set-up Phase: Outlines the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources).
2. Adaptation Phase: Assists guideline developers in moving from selection of a topic to identification of specific clinical questions; searching for and retrieving guidelines; assessing the consistency of the evidence therein, their quality, currency, content and applicability; decision making around adaptation; and preparing the draft adapted guideline.
3. Finalization Phase: Guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

In general, and whenever necessary, included guidelines were updated with more recent evidence.

In summary, recent evidence-based guidelines of high quality were searched and summarized and served, together with more recent evidence, as basis to formulate the recommendations.

2.3. Clinical questions

A list of possible research questions was prepared by KCE based on recent international guidelines

The selection of research questions was made by the external experts group during an initial experts meeting at KCE on 3 May 2012.

This guideline addresses the following clinical questions:

1. Which diagnostic and staging techniques are needed for patients with NSCLC or SCLC?
2. What are the best treatment options for patients with early stage NSCLC (stage cI-II, selected stage cIIIA cT3N1)?
3. What are the best treatment options for patients with locally advanced NSCLC (stage cIIIA-cIIIB)?
4. What are the best treatment options for patients with metastatic and recurrent NSCLC?
5. How should the follow-up of patients treated for NSCLC be organized?
6. What are the best treatment options for patients with limited stage SCLC?
7. What are the best treatment options for patients with extensive stage SCLC?

2.4. Literature search and selection criteria

2.4.1. Search strategy

In order to identify published clinical practice guidelines (CPGs) on lung cancer, OVID Medline, the National Guideline Clearinghouse (guideline.gov) and Guidelines International Network (www.g-i-n.net) were searched for both national and international CPGs (Appendix 1.1.1).

A test search in OVID Medline for guidelines on lung cancer (2001-2011) revealed more than 1000 hits. It was consequently decided to deploy restrictions on language (English, Dutch, French) and date (2009 – current date). All searches for guidelines were run on 20 February 2012. Based on title and abstract, and after removal of duplicate guidelines, a total of 23 guidelines were retained for full-text evaluation. Of these 18 guidelines were excluded for the following reasons:

14 guidelines were excluded based on methodology i.e. the guideline was either consensus based or did not provide recommendations.

2 guidelines were excluded due to incomplete literature search or no reporting of search strategy.

2 guidelines were excluded because the guideline did not fulfil the criteria for language and/or publication date.

5 guidelines were retained for an evaluation of the methodological quality (see 2.4.1)

Source	Year	Title	Standardised Methodology Score	Final appraisal
National Institute for Health and Clinical Excellence (UK)[3]	2011	The diagnosis and treatment of lung cancer (update)	100%	Recommended
ASCO (Azzoli et al.) [4]	2009	American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer	100%	Recommended
	2011	2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer		
Cancer Care Ontario[5]	2010	First-line Systemic Chemotherapy in the Treatment of Advanced Non-Small Cell Lung Cancer	97%	recommended
Vereniging Integrale kankercentra[6,7]	2011	Niet-kleincellig longcarcinoom. Landelijke richtlijn, Versie: 2.0	85%	recommended
	2011	Kleincellig longcarcinoom. Landelijke richtlijn, Versie: 1.0		

The update search for peer-reviewed articles included a search in OVID Medline, EMBASE, CENTRAL and the Cochrane Database of Systematic Reviews. For diagnostic and staging research questions, the search was not limited to specific study designs with an aim to include diagnostic accuracy studies. Searches were run between April, 2012 and January, 2013. For search strategy and results on the article search, see appendix 1.1.2.

The identified studies were selected based on title and abstract and grouped according to main topic covered by one researcher. For all possible eligible studies, the full-text was retrieved fur further selection. In case no full-text was available, the study was not taken into account for the final recommendations.

2.5. Quality appraisal

2.5.1. Clinical practice guidelines

The AGREE II instrument was used to evaluate the methodological quality of the identified CPGs (www.agreetrust.org). Each of the 5 identified CPGs was scored by two independent researchers (JR and KHH or JR and FH) and discussed in case of disagreement. Based on an overall assessment – taking into account the AGREE scores – all 5 high quality CPGs were finally selected. However, only two of these five guidelines cover both lung cancer diagnostic, staging and treatment. Thus, three guidelines were selected for their lung cancer guidelines relating to treatment only.

2.5.2. Systematic reviews and peer-reviewed articles

The quality of the systematic reviews was assessed using the Dutch Cochrane checklist (www.cochrane.nl). Retrieved diagnostic studies were assessed for the risk of bias with the QUADAS-2 tool. For critical appraisal of randomized controlled trials, the Cochrane Collaboration's Risk of Bias Tool was used Critical appraisal of peer-reviewed articles was performed by a single KCE expert. In case of doubt, a second KCE expert was consulted.

2.6. Data extraction and evidence summary

For every clinical question, the evidence base and recommendations were extracted from each of the selected guidelines and summarized in text form. The update consisted of recent systematic reviews and primary studies. For each systematic review, the search date, publication year, included studies and main results were extracted. For primary studies, the following data were extracted: publication year, study population, study intervention, outcomes and results.

2.7. Statistical analysis

When new RCTs were found in addition to an existing meta-analysis, or in case subgroup analysis was needed for certain topics, meta-analysis was performed using Review Manager Version 5.

For progression-free survival (PFS) and overall survival (OS), a hazard ratio (HR) was extracted from the reported analyses. We used the extraction methods following Parmar et al.[8] All meta-analyses were performed using a generic inverse variance method, unless otherwise stated.

Heterogeneity was statistically assessed using χ^2test and I^2 statistic. If heterogeneity was present, a random-effects model was used instead of a fixed-effect model. Possible reasons for heterogeneity were explored post-hoc. Sensitivity analysis was performed by removing outliers from the analysis.

2.8. Grading of evidence

For therapeutic interventions, the quality of evidence was evaluated using the GRADE methodology. A level of evidence was assigned to the body of evidence supporting each conclusion using the GRADE system (Table 1).[9]

GRADE for guidelines was used, meaning that the evidence across all outcomes and across studies for a particular recommendation was assessed. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating was initially considered to be of high level. The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.[10]

The general principles used to downgrade the quality rating are summarized in Table 2. Decisions on downgrading with -1 or -2 points were based on the judgement of the assessors. Reasons for (no) downgrading were summarized in the GRADE profiles.

Observational studies are by default (based on the GRADE system) considered to be of low level of evidence However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:

   Large, i.e. relative risk (RR) >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level

   Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient: The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

For therapeutic interventions for which conducting clinical trials involving a control group that does not receive this intervention is not considered an option for ethical reasons, no grading of the level of evidence was performed. Such therapeutic interventions were considered standard care.

Due to current methodological limitations of the GRADE system for diagnostic tests, GRADE was not applied to the recommendations on diagnosis.[11]

Table 1 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Table 2 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations[12]	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency[13]	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down. If the body of evidence included only a single study, rating was downgraded with -1 points as consistency of results cannot be judged and there is no proof that results are reproducible. The only exception was the availability of one large multicentre trial without heterogeneity across sites.
Indirectness[14]	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision[15]	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. If the CIs included both appreciable benefit and appreciable harm, quality of evidence was downgraded by 2 levels. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias[16]	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication was also suspected if results came from small, positive industry-sponsored trials only.

2.9. Formulation of recommendations

Based on the retrieved evidence, draft recommendations were prepared by KCE experts (JR, LV, KHH), and sent for review to the external experts group selected by the College of Oncology. The evidence and the recommendations were discussed during meetings between KCE experts and the group of external experts. These meetings were held at KCE on 5 July, 4 October, 13 December 2012, 21 February, 28 March and 18 April 2013. FH coordinated the project for KCE and IW for the College of Oncology.

2.10. External review

Professional associations that were directly implicated by the guideline were asked by the College of Oncology to appoint two representatives to act as an external reviewer of the draft guideline. The following associations were invited.

1. Belgian Society of Medical Oncology - Belgische Vereniging voor Medische Oncologie - Société Belge d'Oncologie Médicale (BSMO)
2. Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie-Oncologie (BVRO - ABRO)
3. Belgian Society of Surgical Oncology (BSSO)
4. Royal Belgian Society of Surgery
5. Royal Belgian Radiological Society - Koninklijke Belgische vereniging voor Radiologie - Société Royale Belge de Radiologie (RBRS)
6. Belgische Genootschap voor Nucleaire Geneeskunde - Société Belge de Médecine Nucléaire
7. Belgian Society of Pathology - Belgische Vereniging Anatomopathologie - Société Belge d'Anatomopathologie
8. Belgische Vereniging voor Pneumologie
9. Domus Medica (Vereniging van huisartsen)
10. Société Scientifique de Médicine Générale (SSMG)

No representative was appointed by the two general practitioner associations. Patient organisation representatives were also invited but only a single representative participated. Stakeholders received the list of recommendations and good clinical practice points April 30th, two weeks prior to the stakeholder meeting on May 14th, 2013. As a preparation of the meeting all invited stakeholders were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'not in domain of expertise', '4' indicating 'somewhat agree', and '5' indicating 'completely agree'. In case a stakeholder disagreed with the recommendation (score '1' or '2'), (s)he was asked to provide appropriate evidence. Scores were received from 11 stakeholders, representing societies of medical oncology, pneumology, surgery, radiotherapy, radiology, nuclear medicine and pathology. The discussion at the face-to-face meeting with the stakeholders and the development group on May 14th 2013 focussed on the recommendations and good clinical practice points for which there was a need for clarification of the language or at least one disagreement score ('1' or '2'). (see appendix 5). Based on this discussion a final draft of the recommendations was prepared. In Appendix 6, an overview is provided of the comments of the stakeholders and the action taken based on the discussion at the meeting. In addition, we added to the table the number of scores '4' or '5', the total number of scores ('1', '2', '4' or '5'), and the calculated % of 'agree'-scores (score '4' and '5').

Additionally, patient representatives from the 'Vlaamse liga tegen kanker' and the 'Fondation contre le cancer' were invited to review the draft recommendations for a patient perspective, considering the following questions:

- Are there considerations from the patients' perspective that we missed in formulating our recommendations?
- Do we need to add information that allows to make clear choices when doctors discuss treatment options with patients?
- Are all recommendations relevant, or can we omit some of them?

2.11. Validation and updating of the guideline

2.11.1. Validation process

The guideline was reviewed prior to its publication by 3 independent validators (see colophon), making use of the Agree II checklist. The validation process was chaired by the Belgian Centre for Evidence Based Medicine (CEBAM). The validation of the report results from a consensus or a voting process between the validators.

3. DEFINITIONS

In this guideline, lung cancer staging according to the International Union Against Cancer, 7th edition is used as summarized in Table 3 and Table 4..

Table 3 – TNM Classification of Lung Tumours - International Union Against Cancer 7th edition

T – Primary Tumour	
T1	Tumour 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus) T1a Tumour 2 cm or less in greatest dimension T1b Tumour more than 2 cm but not more than 3 cm in greatest dimension
T2	Tumour more than 3 cm but not more than 7 cm; or tumour with any of the following features: Involves main bronchus, 2 cm or more distal to the carina Invades visceral pleura Associated with actelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung T2a Tumour more than 3 cm but not more than 5 cm in greatest dimension T2b Tumour more than 5 cm but not more than 7 cm in greatest dimension
T3	Tumour more than 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; OR tumour in the main bronchus less than 2 cm distal to the carina but without involvement of the carina, OR associated atelectasis or obstructive pneumonitis of the entire lung or separate tumour nodule(s) in the same lobe as the primary
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary

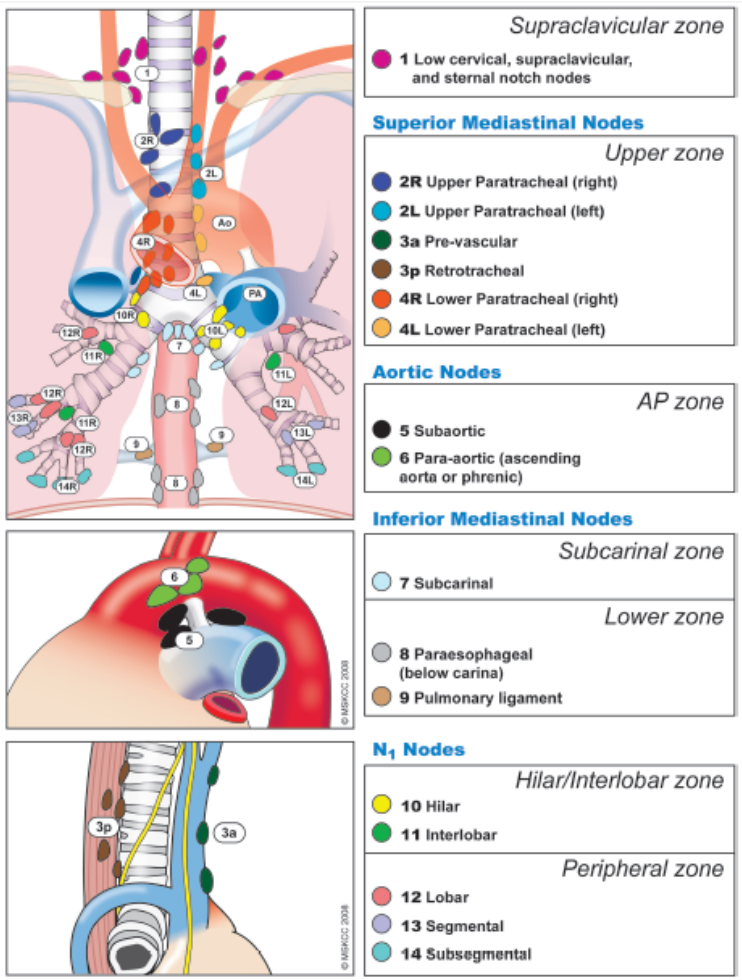
N – Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes
M- Distant metastases	
M0	No distant metastases
M1	Distant metastases M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or pleural or pericardial effusion M1b Distant metastasis

Table 4 – Lung cancer staging according to International Union Against Cancer (UICC), 7th edition

Stage	TNM		
Stage 0	Tis	N0	M0
Stage IA	T1a,b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a,b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,b, T2a,b	N2	M0
	T3	N1,N2	M0
	T4	N0,N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M0

Lymph node stations

Figure 1 The IASLC lymph node map shown with the proposed amalgamation of lymph nodes into zones (Memorial Sloan-Kettering Cancer Center, 2009).



Definitions to describe intraoperative lymph node assessment according to the European Society of Thoracic Surgeons (ESTS)[17]

Selected lymph node biopsy: in this procedure, one or multiple suspicious lymph node(s) are biopsied. This is only justified to prove N1 or N2 disease in patients in whom resection is not possible (exploratory thoracotomy).

Sampling: sampling is the removal of one or more lymph nodes guided by preoperative or intraoperative findings which are thought to be representative. Systematic sampling means a predetermined selection of the lymph node stations specified by the surgeon.

Systematic nodal dissection: all the mediastinal tissue containing the lymph nodes is dissected and removed systematically within anatomical landmarks. It was recommended that at least three mediastinal nodal stations (but always subcarinal) should be excised as a minimum requirement. Besides the mediastinal nodes, the hilar and the intrapulmonary nodes are dissected as well.

Lobe-specific systematic node dissection: in this procedure, the mediastinal tissue containing specific lymph node stations are excised, depending on the lobar location of the primary tumour.

Extended lymph node dissection: in this procedure, bilateral mediastinal and cervical lymph node dissection is performed through median sternotomy and cervicotomy.

Adjuvant chemotherapy or radiotherapy: treatment given after treatment with curative or radical intent, in an attempt to improve the cure rate.

Neo-adjuvant chemotherapy (also called induction chemotherapy): chemotherapy given before planned surgery or radiotherapy in patients with potentially curable disease at presentation.

Treatment with curative intent or radical treatment: the aim of the therapy is to achieve long-term survival without evidence of recurrence.

Sleeve lobectomy: surgery to remove a lung tumour in a lobe of the lung and a part of the main bronchus (airway). The ends of the bronchus are rejoined and any remaining lobes are reattached to the bronchus. This surgery is done to save part of the lung.

4. DIAGNOSIS AND STAGING

4.1. General considerations

The NICE guideline on lung cancer recommends as general principle to choose investigations that give the most information about diagnosis and staging with the least risk for and burden to the patient. The work up for diagnosis and staging needs to be a logic and sequential process. Staging is based on the TNM 7 classification. This staging system is used for NSCLC, SCLC and carcinoid tumours.

The recommendations presented below need to be seen as minimal recommendations. As for all guidelines the clinician also needs to take into account co-morbidities and their possible impact on treatment decisions. In some cases the local availability of diagnostic techniques may also be important in the trade-off between delays in diagnostic workup and the use of certain more advanced or technically demanding techniques.

Although diagnosis and staging are separate issues they are in reality intertwined. In particular, the CT scan is often used for both at the same time. Diagnosis of stage IV disease on CT permits to limit further imaging and invasive staging. A correct staging determines prognosis and therapeutic options.

Pathological confirmation of the diagnosis is highly recommended. In exceptions where histology cannot be obtained, documentation of the evolution of the lesion has to be considered.

The choice of the sampled lesion – primary tumour, lymph node or metastatic lesion- is however guided by the presentation of the disease. In locally advanced tumours an accurate evaluation of the lymph nodes is mandatory. In case of a solitary dubious metastatic lesion that would exclude the patient from treatment with radical intent, the lesion should be pathologically confirmed to exclude false positive lesions.

We grouped the recommendations using a 3 tier approach:

- Tier 1: parameters to be considered in every patient at presentation
- Tier 2: investigations to confirm the diagnosis and to evaluate the extent of the disease
- Tier 3: investigations conducted in patients considered for a treatment with curative intent

Throughout the diagnostic and staging process, patients should repeatedly be informed in detail about his/her disease, and the effects and side-effects of the various treatment options. In view of the poor prognosis of the majority of patients, attention should be given to timely obtaining the patient's wishes with regard to the planning of care for advanced disease and for palliative care.

We do not discuss solitary pulmonary nodules as a separate entity but refer to the Fleischner criteria.[18, 19] This is due to the complexity in deciding the appropriate management strategies for these lesions. We do not address the issue of screening.

For SCLC the IASLC also proposed to apply the seventh edition of the TNM classification because of better prognostic discrimination. Previously The Veteran's Administration Lung Cancer Study Group (VALSG) in the USA divides patients into limited and extensive disease. Limited disease was defined as tumour tissue that could be encompassed in a single radiation port and extensive disease was defined as any tumour that extended beyond the boundaries of a single radiation port. In 1989, the International Association for the Study of Lung Cancer (IASLC) revised the VALSG staging system and defined limited disease as tumour tissue confined to one hemithorax with regional lymph node metastasis including both ipsilateral and contralateral hilar, supraclavicular and mediastinal nodes, as well as ipsilateral pleural effusion. In most clinical trials with limited disease, patients with contralateral hilar or supraclavicular lymphadenopathy as well as malignant pleural or pericardial effusions have been excluded.

Most of the patients with SCLC have metastatic disease at diagnosis. When the tumour is limited to one hemithorax and can be encompassed by a safe radiation field extensive staging is advised. PET/CT has a high sensitivity to detect extracranial metastases and for precise defining of the radiation field and should be considered in patients where the intent of therapy is curative.

4.2. Diagnosis and staging of lung cancer

4.2.1. Suspicion of lung cancer

Clinical presentation

Lung cancer can either be suspected based on the clinical presentation of the patient or following an incidental finding during a radiological examination for another purpose.

NICE gives a set of criteria for referral for a chest X-ray. These criteria, presented below, were developed by the British Thoracic society and are based on expert opinion:

Haemoptysis or any of the following unexplained or **persistent** (that is, lasting more than 3 weeks) symptoms or signs:

- cough
- chest/shoulder pain
- dyspnoea
- weight loss
- chest signs
- hoarseness
- finger clubbing
- features suggestive of metastasis from a lung cancer (for example in brain, bone, liver or skin)
- cervical/supraclavicular lymphadenopathy.

Urgent referral is needed when following symptoms are present:[20]

- persistent haemoptysis in a smoker or ex-smoker older than 40 years
- signs of superior vena cava obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure)
- stridor

The Dutch guideline merely refers to existing clinical handbooks, without going deeper into the topic.

Imaging

Both the Dutch guideline and NICE recommend to start the diagnostic procedure with a CT. This CT of the thorax should be a high-dose, multi-detector CT with intravenous contrast, covering the supraclavicular area to the adrenal glands. The upper abdomen should be scanned in the portal phase. To achieve maximal diagnostic information, CT should be performed at deep inspiration and interruption of breathing.

The NICE guideline[3] states that chest MRI should not routinely be used to assess the stage of the primary tumour and should only be performed when it is necessary to assess the extent of disease for patients with superior sulcus tumours.

4.2.2. Pathological confirmation of the primary tumour

NICE gives different recommendations depending on the location of the lesion (central or peripheral lesions**).** However, different definitions of central and peripheral lung lesions are used in the literature**.**

Central and peripheral lesions

Often, central lung tumours are defined as tumours located in the inner one-third of the lung parenchyma and peripheral tumours as located in the lateral two-thirds of the lung.[21]

The **Radiation Therapy Oncology Group** (RTOG) defines a central tumour as a tumour within two centimetre of the proximal bronchial tree.[22]

NICE applies the following definitions:[3]

Peripheral primary tumours are those within the lung parenchyma and which may abut the pleura. Where they occur without other features of more advanced malignancy such as mediastinal lymphadenopathy, specific diagnostic techniques apply, in particular transthoracic needle biopsy or immediate resection.

Central primary tumours are those that are in close proximity to, or directly invading the mediastinum. There is usually endobronchial tumour, although there may also be submucosal disease or associated lymphadenopathy. Within this category is included gross mediastinal lymphadenopathy with obvious malignant features, contiguous with the main primary tumour.

For peripheral primary tumours NICE recommends to offer CT- or ultrasound-guided transthoracic needle biopsy in those cases where treatment can be planned on the basis of this test.

For central primary tumours they recommend to offer fibre-optic bronchoscopy to patients with central lesions on CT where nodal staging does not influence treatment.

However, sampling of the primary tumour may not always be needed. For example, NICE recommends to first sample enlarged lymph nodes in preference of primary tumours. The argument given is that both the diagnostic and staging information needed should be obtained with as few sampling procedures as possible.

Esophageal ultrasound (EUS) and endobronchial ultrasound (EBUS) have a role in sampling primary lung tumours not accessible using above methods;

For lesions that cannot be sampled but that show progression primary resection in fit patients will show the tumour type.

These recommendations were based on evidence presented hereafter; the recommendation to do biopsies only when treatment can be based on this test is based on expert opinion.

NICE identified fifteen studies varying from poor to high quality examining the accuracy of bronchoscopy ± biopsy and EBUS in diagnosing malignancy in patients with suspected lung cancer. The reference standard was the final diagnosis. They found for bronchoscopy ± biopsy and EBUS sensitivities ranging between 8.9-100%, specificities ranging between 44-100% and overall accuracies ranging between 50-95%. They also found nine studies that varied in quality from poor to moderate examining the accuracy of transthoracic needle aspiration (TTNA) in the diagnosis of malignancy in patients with suspected lung cancer, with sensitivities ranging between 85.5-92.2%, specificities ranging between 41.67-100% and overall accuracies of TTNA ranging between 77.2-94%.

Seven studies were found examining the accuracy of EUS ± fine needle aspiration (FNA), FNA and other biopsies in diagnosing malignancy in patients suspected of having lung cancer. These studies varied in quality from poor to moderate. The sensitivities, specificities and overall accuracies of EUS ± FNA, FNA and other biopsies ranged between 62.5-94.3%, 95-100% and 75.5-96.5%, respectively.

The Dutch guideline did not specifically address the role of EUS and EBUS in the diagnosis of a primary tumour. For the diagnosis histology is preferred. In order to avoid mistakes both for EUS and EBUS it is important to have a sufficient number and proportion of tumor cells sampled.

Update for pathological diagnosis of primary pulmonary lesions

One systematic review was assessed with the Dutch Cochrane tool for systematic reviews of diagnostic tests and included studies judged to be of high quality.

Steinfort 2010 [23] did a high quality systematic review with meta-analysis of studies that examined endobronchial ultrasound-transbronchial lung biopsy (EBUS-TBLB) with various guidance tools (guide sheath, fluoroscopy, none) for the diagnosis of primary pulmonary lesions (PPL). Inclusion criteria for the systematic review were:

1. radial probe EBUS for diagnosis of PPL;
2. diagnoses confirmed pathologically or by close clinical follow-up for at least 6 months used as the reference standard; and
3. enrolled at least 30 patients.

They found a pooled sensitivity of 73 % (95%CI 70%–76%) and a specificity of 100 % (95%CI 99%–100%) and a positive likelihood ratio of 26.84 (CI 12.60–57.20) and a negative likelihood ratio of 0.28 (0.23–0.36).

There was a high level of heterogeneity (I^2 72%) in the estimation of the sensitivity. Sensitivities ranged from 49% to 88% with 2 outliers under 70%. Exploration of this heterogeneity showed that average lesion size and prevalence of malignancy were contributing factors but this did not explain everything. Subgroup analysis taking into account these factors had only a limited effect on the estimations. These findings are also in line

with the guidelines and confirm the fact that a negative EBUS-TBNA is not sufficient to exclude a malignancy.

Conclusions

In addition to the standard practice based on bronchoscopy, estimations of the sensitivity of TTNB, EBUS and EUS plus needle aspiration vary between studies, so a negative result cannot exclude a malignancy.

4.2.3. Evaluation of distant metastasis

At the time of diagnosis, approximately one third to 40% of patients has distant metastases. Imaging is pointed at particular symptoms and the most frequent localisations of metastases: liver, adrenal glands, brain and skeleton.[3, 7] A first screening for metastases is included in the diagnostic CT-scan of the chest, which should include the supraclavicular region, the whole liver and adrenal glands. Diagnosis of stage IV disease on CT permits to limit further imaging and invasive staging.

4.2.3.1. PET-CT

The Dutch guideline concludes that PET-scan is suitable for the detection of distant metastases. Unexpected metastases are detected in 10 to 20% of patients by PET-CT. The accuracy of FDG-PET to detect adrenal metastasis larger than 15mm is approximately 100%.[7]

Pathological confirmation should be obtained for solitary FDG positive lesions.[3, 7]

4.2.3.2. Bone scan

FDG-PET is the preferred investigation for the detection of bone metastases, with a higher diagnostic accuracy than bone scintigraphy.[7]

However, as the PET-CT may not always include the head and the lower extremities, one should perform additional imaging if signs of possible bone metastasis outside the included body area are present.

4.2.3.3. Brain imaging

It is estimated that the incidence of brain metastases on imaging is between 0 and 10% in NSCLC patients without neurological examination findings. The incidence of brain metastases is positively related to T and N stage. If the primary lesion is more advanced than T1N0M0, MR with contrast can identify asymptomatic metastases in the brain in 22% of patients with NSCLC and surgical resectable thoracic disease.[21]

The Dutch guideline[7] advises to perform a PET-CT and an MRI of the brain in all clinically stage III lung cancer patients as the detection of brain metastases has therapeutic consequences if combination therapy is considered. Due to the high background activity in the brain, a PET-scan is not a suitable investigation for the detection of brain metastases.

Also the NICE guideline[3] recommends to consider MRI or CT of the head in patients selected for treatment with curative intent, especially in stage III disease. For patients with features suggestive of intracranial pathology, they suggest CT of the head followed by MRI if normal or MRI as an initial test.

In cases where no signs suggestive of brain metastases are present and a high quality CT scan of the brain, with IV contrast, is present, an additional MRI is not warranted (expert opinion).

Update

No recent evidence on the use of brain imaging for lung cancer patients was identified in the literature.

Conclusions

Diagnosis of stage IV disease based on conventional workup allows to limit further imaging and invasive staging.

PET-CT detects unexpected distant metastases in 10-20% of patients with newly diagnosed or suspected lung cancer.

PET-CT is more accurate for the detection of bone metastases compared with bone scintigraphy.

PET-scan has insufficient diagnostic accuracy for the detection of brain metastases.

Appropriate brain imaging (CT or MRI with IV contrast) should be performed in patients selected for treatment with curative intent, especially in stage III disease.

4.2.4. Mediastinal staging for patients otherwise eligible for treatment with curative intent

In patients considered eligible for surgery based on imaging, precise mediastinal staging is warranted to exclude N2 or N3 disease, both contra-indications for primary surgery. If N2 or N3 disease is confirmed by mediastinal staging procedures, patients are referred for combined treatment modalities.

4.2.4.1. PET-CT for mediastinal staging

The NICE guideline[3] contains two recommendations on the effectiveness of PET-CT i.e. to ensure all patients potentially suitable for treatment with curative intent are offered PET-CT before treatment. The evidence base for these recommendations consists of a diagnostic study on PET-CT of moderate quality (sensitivity range: 96-98%, specificity range:68-87%) and staging studies on PET-CT for T-staging (2 studies of moderate quality, sensitivity range: 77.3-96,1 %), N-staging (10 studies ranging from high to low quality, sensitivity range 47-98.4%, specificity range 37.5-100%) and overall M-staging (2 studies of moderate quality, sensitivity range 65,5-84,1%, specificity range: 94,5-97,7%).

Moreover, the NICE guideline offers two recommendations on PET-CT with respect to the sequence of investigations i.e. for mediastinal lymph node assessment in NSCLC. The guideline recommends to offer PET-CT as the preferred first test after CT showing a low probability of mediastinal malignancy (lymph node < 10 mm maximum short axis on CT) for patients who are suitable for treatment with curative intent. Secondly, it is recommended to offer PET-CT or EBUS-guided TBNA, or EUS-guided FNA, or non-ultrasound guided TBNA as a first test for patients with an intermediate probability of mediastinal malignancy (lymph nodes between 10 -20 mm maximum short axis on CT) who are potentially suitable for treatment with curative intent. The evidence base for these recommendations comes from an economic model by NICE developed to assess cost-effectiveness of PET-CT, TBNA, EBUS, mediastinoscopy and neck ultrasound in clinically relevant sequences. Published literature on test accuracy was included in the model.

The Dutch guideline[7] recommends PET-CT to all patients potentially suitable for treatment with curative intent, in line with NICE. They recommend proceeding to pathological confirmation when either PET-CT is positive or CT shows mediastinal lymph nodes of more than 1 cm or the primary tumour is close to the mediastinum. This is based on 7 validation studies, showing sensitivities for PET-CT ranging from 40 to 92% and specificities ranging from 70 to 98 %. There were also 3 RCTs comparing PET with PET-CT where 2 of the RCT showed that PET-CT had a significant impact in avoiding unnecessary thoracotomies. PET-CT can only be used for staging if the primary tumour takes up FDG. The assertion that when the primary tumour is close to the mediastinum one should proceed to histological sampling is based on expert opinion.

The main difference between the Dutch and NICE guidance is the fact that the Dutch guideline recommends to proceed directly to thoracotomy without pathological confirmation if PET-CT is negative and lymph nodes are on CT smaller than 1 cm, whereas the NICE guideline leaves this open to the judgment of the clinician. The Dutch guideline however explicitly states that this recommendation is based on expert opinion.

Update

One RCT and two observational studies, all with a low risk of bias, were included. These recent studies provide conclusions that are in line with the conclusions in the guidelines.

The RCT[24] compares staging with PET-CT followed by an invasive diagnostic procedure (conventional work up, CWU) with the diagnostic procedure (CWU) alone and finds a sensitivity of PET-CT of 75% (95%CI 59-86%) compared with CWU of 59% (95%CI 41-74%). Specificity of PET-CT in the study is 100% (95%CI 94-100%) compared with CWU 98% (95%CI 91-100%). One observational study[25] assesses the accuracy of PET-CT in mediastinal staging compared with invasive staging and finds a PET-CT sensitivity of 70% (95%CI 48-85%) and a specificity of 94% (95%CI 88-97%). Finally, one observational study[26] on patients with a negative FDG PET-CT scan finds a negative predictive value (NPV) of mediastinal staging by FDG-PET-CT of 85.6% (95%CI 77-91%) thus a relatively high number of false negatives.

Conclusions

A PET-CT scan is a useful first step for the staging of NSCLC and to assess whether there is lymph node involvement (N-staging: sensitivity ranges 47-98.4%, specificity ranges 37.5-100%).

A PET-CT scan, suggesting lymph node metastasis, has a considerable risk of being false positive. A false positive PET-CT has a consequence that a curable patient is denied potentially curative treatment, hence lymph node involvement has to be pathologically confirmed when radical treatment is considered.

Negative PET result for lymph nodes combined with lymph nodes smaller than 1 cm on CT has a high negative predictive value provided that the primary tumour takes up FDG, is not close to the mediastinum and in the absence of hilar adenopathies.

Other considerations

The CT system in a PET-CT scan is usually a modern multi-slice helical design, identical to any stand-alone CT scanner. This is typically referred to as a “diagnostic” quality scanner; that is, the scanner is capable of generating routine CT scans, as well as scans with altered acquisition settings used specifically for attenuation correction of the PET data. These CT-based attenuation correction scans are usually lower dose and lower quality than a “diagnostic” CT scan.

While a CT-based attenuation correction scan is used for attenuation correction and fused PET-CT image display, it typically should not be used for other purposes. A “diagnostic” quality CT, however, could be used for attenuation correction and image fusion as well as stand-alone decisions based on the CT, radiation treatment planning, if acquired in proper radiotherapy position, or other uses. If no additional CT scan is needed, it seems sensible to use a low-dose CT-based attenuation correction scan with the PET acquisition. If a diagnostic CT is needed, then one could conceivably use this CT for the PET attenuation correction, thus avoiding the radiation dose from a separate CT-based attenuation correction scan.

The role of PET-CT as a prognostic indicator or in assessing response to tumour was not within scope of this guideline.

4.2.4.2. Echo-endoscopy for mediastinal staging

According to the Dutch guideline,[7] endoscopic techniques (EBUS and/or EUS) are the preferred invasive approach for staging of the mediastinal lymph nodes rather than surgical procedures. If lymph node metastases are suspected on PET-CT and N2-3 disease is not confirmed by EBUS or EUS, cervical mediastinoscopy or parasternal mediastinotomy is indicated.

For EBUS-TBNA, the recommendation is based on three systematic reviews. Pooled sensitivity is reported between 88% (95%CI 79-94%) and 93% (91-94%). Pooled specificity is reported as approximating 100% but it must be noted that the vast majority of studies does not verify positive results. A systematic review including 18 studies investigating EUS-FNA reports a pooled sensitivity to detect N2-N3 disease of 83% (95%CI 78-87%). For both techniques, the sensitivity is lower if patients are not selected based on positive PET-CT scan results. The only study with complete verification of EUS-FNA results is the study by Micames et al. [7]

They report false positive results in 2% of the total study population. For N2-N3 disease, sensitivity, specificity, PPV and NPV are 76% (95%CI 56-90%), 97% (95%CI 90-99%), 92% (95%CI 73-99%) and 90% (95%CI 82-96%) respectively in that study. Complete endoscopic assessment with combined EBUS and EUS-FNA results in a higher sensitivity and NPV than use of a single technique. Sensitivity and NPV of the combined technique are 96% and 95% respectively.

The NICE guideline[3] recommends evaluation of PET-CT positive mediastinal nodes by mediastinal sampling for which EBUS and EUS are to be considered as initial staging technique. Negative results obtained by EBUS-TBNA and/or EUS-guided FNA should be confirmed by surgical staging if clinical suspicion of N2-3 malignancy is high. The EBUS recommendations are based on four systematic reviews with meta-analysis and six prospective studies with stated sensitivity between 46-94.9% and specificity between 66.7-100%. Two meta-analyses and five prospective studies examining EUS-FNA reported sensitivity between 50-87% and specificity between 97-100%.

Update

Four prospective and one retrospective cohort studies were included. These studies report a sensitivity between 64-95% and a NPV between 83-93% for EBUS. For combined EBUS and EUS, the reported sensitivity ranged between 71.8-94% and the NPV ranged between 86.6-96.1%.

Additionally, one health technology assessment based on a randomized controlled trial was recently published by Sharples et al.[27] Two hundred and forty-one patients were randomized to mediastinal staging by mediastinoscopy or by combined EBUS and EUS followed by mediastinoscopy if no nodal disease was found. Both sensitivity and NPV improved with the use of endoscopic techniques (94% versus 79% and 93% versus 86% respectively). Overall complication rate was also reduced by 1% and the number of non-curative thoracotomies was significantly lower if combined EBUS-EUS was performed first (7% versus 18%, p=0.02). Based on NHS UK parameters, the EBUS-EUS strategy was slightly more effective.

In the trial, EBUS and EUS were performed in a systematic fashion with sampling of all enlarged lymph nodes and mapping of at least paratracheal, subcarinal and paraesophageal mediastinal nodes. EUS and EBUS are complementary techniques. EUS permits access to mediastinal lymph node groups 2L, 4L,7,8L/R, 9L/R, whereas EBUS gives access to mediastinal lymph node stations 2R/L, 4R/L and 7.

Conclusions

The diagnostic accuracy of combined EBUS and EUS is higher than when a single technique is used.

The use of combined EBUS and EUS for staging of mediastinal lymph nodes, followed by mediastinoscopy in case of inconclusive or negative cytology, results in a higher sensitivity and NPV for nodal disease than the use of mediastinoscopy alone.

The use of combined EBUS and EUS for staging of mediastinal lymph nodes, followed by mediastinoscopy in case of inconclusive or negative cytology, results in a higher reduction of non-curative thoracotomies compared with mediastinal staging with mediastinoscopy alone.

Other considerations

It must be noted that the majority of studies considered all positive results of endosonography and mediastinoscopy as true positive without further pathological confirmation. As such, specificity and PPV are not reported in the evidence tables.

Although systematic and standardized reporting of adverse events (AEs) after EBUS or EUS is rare in published evidence, both are considered low risk procedures.

Furthermore, as discussed above, EBUS and EUS can also be useful for the diagnosis and evaluation of central lung tumours and hilar adenopathies. This clinical advantage of EBUS and EUS in this indication is not reflected in accuracy studies for staging purposes.

4.2.4.3. Mediastinoscopy for mediastinal staging

The Dutch guideline[7] considers mediastinoscopy as a valid method to detect mediastinal lymph node metastases if at least five lymph node stations were biopsied. A biopsy should be taken from at least two ipsilateral stations, one contralateral station and lymph node station number seven. It is recommended to offer cervical mediastinoscopy or parasternal mediastinotomy for all patients with a primary lung cancer with suspicious lymph nodes on PET-CT and no (distant) metastases detected on imaging or EBUS/EUS. Mediastinoscopy can be abandoned in patients with a PET-CT negative for metastases and suspicious lymph nodes if the primary tumour has positive uptake on PET-scan and is not a central tumour next to the mediastinum and in the absence of hilar adenopathies.

The NICE guideline[3] considers it more disputable if an additional assessment of the mediastinum by mediastinoscopy is necessary if EBUS/EUS is negative, as patients with only microscopic lymph node metastases may benefit from surgery. Based on expert opinion, they advise to confirm negative results obtained by EBUS-guided and/or EUS-guided FNA by mediastinoscopy if clinical suspicion of mediastinal malignancy remains high.

Update

Three studies, of which two studies were described in the evidence tables on endoscopic staging techniques,[27, 28] were included (Table 14).

The randomized study of Sharples et al is discussed above (paragraph 4.2.4.2).

In a prospective cohort study of 159 patients, Yasufuku et al. reported a sensitivity and specificity for mediastinoscopy of 79% and 100% respectively. Reported sensitivity and specificity of EBUS was 81% and 100% in the same patient cohort.

Gunluoglu et al.[29] report on a cohort of 185 NSCLC patients without distant metastasis. One hundred and sixty-eight patients had a central tumour or clinical T3-4 stage or a primary tumour with low uptake on PET-scan or suspicious lymph nodes on PET- or CT-scan and underwent mediastinoscopy. Reported sensitivity is 84% (95%CI 70-92%) and NPV 94% (95%CI 88-97%).

Conclusions

In lung cancer patients without distant metastases and suspicious mediastinal lymph nodes on PET-CT or a central lung tumour or a primary lung tumour without FDG uptake, mediastinoscopy can detect lymph node metastases with a sensitivity of 79-84% and a negative predictive value of 86-94%.

Other considerations

Results of both EBUS-EUS and mediastinoscopy are operator dependent.[30] The available expertise may influence local decision making.

The study of Sharples et al.[27] included mainly Belgian patients. In this study, surgical staging by mediastinoscopy after negative endosonography was able to detect lymph node metastasis in 6 out of 65 patients. This would correspond to a NNT of 11 to avoid one non-curative thoracomotomy. Another six patients had a false negative mediastinoscopy and underwent thoracotomy in spite of locally advanced disease.

It must be kept in mind that every additional step in the staging process can lead to treatment delay.

Recommendations

All patients suspected of lung cancer should have their history taken including smoking history, have a full clinical examination including assessment of performance status and fitness and have basic blood tests. Throughout the diagnostic and staging process, patients should be informed in detail and repeatedly about their disease and the treatment options.

The work-up for diagnosis and staging needs to be a logical and sequential process. In a patient suspected of lung cancer, either on clinical grounds or following a chance finding during a radiological examination for another purpose, we recommend a three-tier approach.

Tier 1: parameters to be considered in every patient at presentation

Offer urgent chest X-ray to patients presenting with haemoptysis or any of the following unexplained or persistent (that is, lasting more than 3 weeks) symptoms or signs:

- **cough**
- **chest/shoulder pain**
- **dyspnoea**
- **weight loss**
- **chest signs**
- **hoarseness**
- **finger clubbing**
- **features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin)**
- **cervical/supraclavicular lymphadenopathy.**

Moreover, offer urgent referral to a lung cancer multidisciplinary team (usually the lung specialist) if any of the following are present:

- **persistent major haemoptysis in a smoker or ex-smoker older than 40 years**
- **signs of superior vena cava obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure)**
- **stridor.**

Tier 2: investigations to confirm the diagnosis and to evaluate the extent of the disease in view of a possible treatment:

- **Offer a high-quality diagnostic CT of the thorax with a multi-detector CT with intravenous contrast, covering the supraclavicular area, liver and the adrenal glands.**
- **Pathological confirmation is highly recommended. In exceptions where histology cannot be obtained, documentation of the evolution of the lesion has to be considered.**
- **If metastasis is suspected on CT-scan, biopsy any enlarged mediastinal nodes (≥10 mm maximum short axis on CT) or other metastatic lesions in preference to the primary lesion in order to maximize the information on disease stage and because this may impact on treatment.**
- **The primary tumour can be biopsied using CT- or ultrasound-guided transthoracic needle biopsy, (EBUS guided) fibreoptic bronchoscopy**

depending on presentation, local availability and expertise when treatment can be planned on the basis of this test. Performing a PET-CT prior to the biopsy can be considered.

Tier 3: investigations conducted in patients considered for treatment with curative intent:

- Offer PET-CT to all patients potentially suitable for treatment with curative intent in order to look for metastases.
- A solitary suspected (metastatic) lesion on PET-CT scan must be confirmed pathologically as a false positive PET-CT has a consequence that a patient is denied lifesaving treatment with curative or radical intent.
- Do not offer bone scintigraphy to NSCLC patients if a PET-scan has been performed and all relevant body parts are included.
- Offer CT or MRI of the brain with IV contrast to NSCLC patients selected for treatment with curative intent, especially in stage III disease.
- Chest MRI may be considered for some very specific other clinical situations.
- If distant metastases are excluded, proceed to pathological confirmation of lymph node metastasis
  - when PET-CT of the lymph nodes is positive (in case of a PET positive primary tumour) or
  - if CT shows mediastinal lymph nodes of more than 1 cm or
  - if the primary tumour is close to the mediastinum or
  - when hilar adenopathies are present.

  Such patients should be offered invasive mediastinal staging. The preferred approach is combined EBUS and EUS, followed by mediastinoscopy if no lymph node metastasis is found by EBUS or EUS.

  Otherwise proceed directly to thoracotomy.

Good clinical practices

To allow adequate diagnostic and predictive examination and to avoid re-biopsy for additional tests. tissue sampling should be maximized whenever feasible and deemed clinically safe.

Endobronchial Ultrasound Transbronchial Needle Aspiration (EBUS-TBNA) and Endoscopic Ultrasound Fine Needle Aspiration (EUS-FNA) should be performed in a systematic fashion with sampling of all enlarged lymph nodes and at least mapping of ipsilateral and contralateral paratracheal stations (number 4L/R) and the subcarinal station (number 7).

When performing mediastinoscopy for mediastinal staging of lung cancer, at least five lymph node stations should be explored and at least three sampled, including one ipsilateral, one contralateral station and lymph node station number 7 (subcarinal).

Attention should be given to timely obtaining the patient's wishes (advance care planning) with regard to the planning of care for advanced disease and for palliative care.

4.3. Pathology

Pathology investigations for diagnosis and staging purposes (often obtained using fine needle aspiration or biopsy) are to be distinguished from the analysis of the surgical specimen of a resected tumour.

4.3.1. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma[31]

To address advances in oncology, molecular biology, pathology, radiology, and surgery of lung adenocarcinoma, an international multidisciplinary classification was sponsored by the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society.[31] This new adenocarcinoma classification is needed to provide uniform terminology and diagnostic criteria, especially for bronchioloalveolar carcinoma (BAC), the overall approach to small non-resection cancer specimens, and for multidisciplinary strategic management of tissue for molecular and immuno-histochemical studies. Recommendations for key questions were graded by strength and quality of the evidence according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. A list of these recommendations is provided in Appendix 4.

4.3.2. Pathological sub-classification and molecular tests using Fine Needle Aspiration Cytology (FNAC) samples

As most lung cancer patients present at diagnosis in an advanced unresectable stage, cytology samples obtained by EBUS or EUS guided FNA are often the only available materials to perform all diagnostic and predictive tests. Concern has risen about the suitability of those samples for subtyping of the histopathological diagnosis and accuracy of predictive tests such as epidermal growth factor receptor (EGFR) mutation analysis.

The problem of limited availability of tissue is discussed in the NICE guideline.[3] As no guiding evidence was found in the literature, a questionnaire was filled out by three histopathologists to provide expert opinion. These experts agree that discrimination between adenocarcinoma and non-adenocarcinoma is possible in approximately 80% of cytology samples if standard immunocytochemistry is applied. They stress the need for sufficient material and advise the use of immunocytochemistry and the use of cell blocks if possible.

Update

Four studies were included. Billah et al.[32] and Santis et al.[33] report on mutation analysis on cytology samples. Billah et al. considered samples containing less than 40% tumour cells insufficient for analysis. The specimen insufficiency rate was 6.2% overall and 4% for the EBUS samples.[32] In the study by Santis et al.[33], a complete EGFR mutation analysis was achieved in 95.4% and KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) mutation analysis was successful in 98.4%.

Nizolli et. al.[34] and Tournoy et al.[35] investigated the agreement between pathological subtyping on cytology samples and histology samples (biopsies or surgical specimens). They report both an agreement of approximately 75% with an increased number of cases of NSCLC not otherwise specified (NOS) diagnosed on cytology.

Conclusions

Histopathological subtype can reliably be diagnosed on cytology samples in 75% of cases. The diagnosis NSCLC-NOS is more frequent in cytology samples than in (surgical) biopsies.

Mutation analysis, such as EGFR mutation analysis, can successfully be performed in more than 90% of cytology samples.

Other considerations

If samples obtained by FNA are insufficient, procedures to obtain additional biopsies for pathological diagnosis can introduce morbidity. This must weighed against the advantage of additional testing.

4.3.3. Pathological sub-classification: use of immunohistochemistry

Non-small cell lung cancer is not a final diagnosis included in the WHO classification of lung cancer but includes squamous cell carcinoma (SCC), adenocarcinoma and large cell lung cancer. The differentiation between different types has become important for treatment decision e.g. choice of chemotherapy agents.[7] Based on a Dutch study, the Dutch guideline advises to use a diagnostic panel of assays consisting of mucin stain, cytokeratine 7, TTF1 and p63. With the use of this panel, 80% of tumours show a staining pattern clearly differentiating between SCC and adenocarcinoma. The remaining 5-20% is classified as NSCLC-NOS.

Update

Ocque et al.[36] showed in a retrospective study that the use of immunohistochemical studies resulted in increased diagnostic accuracy for adenocarcinoma (56% [44/78] from 2000-2004 vs 83.2% [154/185] after 2005) but not for squamous cell carcinoma (77% [57/74] before 2004 versus 73.9% [82/111] from 2005-2010). Adenocarcinoma showed high expression of cytokeratin (CK)7 (146/146 [100%]), thyroid transcription factor-1 (131/152 [86.2%]), surfactant A (29/36 [81%]), and periodic acid–Schiff with diastase (69/86 [80%]). All squamous cell carcinomas were positive for CK5/6 and p63.

Rekhtman et al.[37] studied whole-tissue sections of resected adenocarcinoma and squamous cell carcinoma (n=315) with markers commonly used to identify adenocarcinoma (TTF-1) and squamous cell carcinoma (p63, CK5/6, 34betaE12), and prospectively validated the devised algorithm in morphologically unclassifiable small biopsy/cytology specimens (n=38). Analysis of whole-tissue sections showed that squamous cell carcinoma had a highly consistent immunoprofile (TTF-1-negative and p63/CK5/6/34betaE12-diffuse) with only rare variation. In contrast, adenocarcinoma showed significant immunoheterogenetity for all 'squamous markers' (p63 (32%), CK5/6 (18%), 34betaE12 (82%)) and TTF-1 (89%). As a single marker, only diffuse TTF-1 was specific for adenocarcinoma whereas none of the 'squamous markers,' were entirely specific for squamous cell carcinoma. In contrast, co-expression profiles of TTF-1/p63 had only minimal overlap between adenocarcinoma and squamous cell carcinoma, and there was no overlap if CK5/6 was added as a third marker. They concluded that a two-marker panel of TTF-1/p63 is sufficient for subtyping of the majority of tumours as adenocarcinomas versus squamous cell carcinoma, and addition of CK5/6 is needed in only a small subset of cases.

Pelosi et al[38] jointly evaluated semiquantitatively preoperative biopsies and the corresponding surgical specimens from 63 consecutive non small cell carcinomas, for cytokeratins 5/6 and 7, p63, thyroid transcription factor-1, and vimentin immunoreactivity. Surgical specimens were the gold standard for morphology and IHC. They found that 59 of 63 (94%) lesions were correctly classified by IHC on biopsy compared with 53 of 63 (84%) by revised morphology, with the predictive positive value being 97% for squamous cell carcinoma, 88% for adenocarcinoma, and 100% for sarcomatoid and adenosquamous carcinoma.

Terry et al.[39] assessed the expression of 9 markers (p63, TTF1, CK5/6, CK7, 34bE12, Napsin A, mucicarmine, NTRK1, and NTRK2) on 200 cases of adenocarcinoma and 225 cases of squamous cell carcinoma in tissue microarray format to mimic small tissue specimens. They found that the single best marker to separate adenocarcinoma from squamous cell carcinoma is p63 (for squamous cell carcinoma: sensitivity 84%, specificity 85%). Logistic regression analysis with the area under the curve for a test panel as outcome identifies p63, TTF1,CK5/6, CK7, Napsin A, and mucicarmine as the optimal panel with bias-corrected ROC AUC (Receiver Operator Characteristics Area Under the Curve) for the 6-marker panel is 0.941, compared with 0.938 for all 9 markers and 0.843 for p63 alone to separate adenocarcinoma from squamous cell carcinoma.

Tsuta et al.[40] examined the value of 10 antibodies for IHC in 150 squamous cell carcinoma cases (53 well-, 51 moderately, and 46 poorly differentiated cases) and 159 adenocarcinoma cases (49 well-, 52 moderately, and 58 poorly differentiated cases). In all squamous cell carcinoma and adenocarcinoma cases, p63 was the most sensitive marker for squamous cell carcinoma (98.7%), followed by high-molecular-weight (HM) cytokeratin (CK) (97.3%), CK5/6 (93.3%), Sox2 (80%), thrombomodulin (79.3%), desmocollin-3 (72.7%), S100A7 (70.7%), S100A2 (63.3%), and glypican-3 (46.7%). Desmocollin-3 was the most specific marker for squamous cell carcinoma (100%), followed by CK5/6 (98%), Sox2 (95.5%), glypican-3 (92.4%), S100A7 (86.8%), thrombomodulin (79.9%), S100A2 (64.6%), p63 (51.6%), and HMCK (33.3%). Thyroid transcription factor-1 (TTF-1) expression was observed in

87.4% of adenocarcinoma cases and 2.0% of squamous cell carcinoma cases. When analyzing only poorly differentiated tumours, HMCK was the most sensitive marker for squamous cell carcinoma (100%), followed by p63 (97.8%), CK5/6 (87.0%), Sox2 (71.7%), thrombomodulin (58.7%), desmocollin-3 (52.2%), S100A2 (50%), glypican-3 (45.7%), and S100A7 (45.7%). Desmocollin-3 was the most specific marker for poorly differentiated squamous cell carcinoma (100%), followed by CK5/6 (98.3%), glypican-3 (94.8%), Sox2 (94.8%), S100A2 (81%), S100A7 (75.9%), thrombomodulin (72.4%), p63 (48.3%), and HMCK (36.8%). They used classification and regression tree analysis and concluded that the combination of CK5/6 and TTF-1 was the best immunohistochemical marker panel for the differentiation between squamous cell carcinoma and adenocarcinoma.

Conclusions

The update confirms the value of immunohistological markers, but evidence is conflicting on the optimal panel of tests

Other considerations

Decision analysis would be useful here to determine the optimal panel.

4.3.4. Molecular techniques to guide targeted treatment

Additional molecular tests should only be performed if results are important to guide treatment decisions. This is a rapidly evolving field.

4.3.4.1. EGFR mutations

The Dutch guideline[7] identified a meta-analysis published by Dahabreh et al. in 2010.[41] In the meta-analysis, a true positive test was defined as a patient harbouring an EGFR mutation showing a complete or partial response to EGFR TKI monotherapy. A true negative test was defined as a patient with wild-type EGFR showing no response to EGFR TKI monotherapy. For EGFR mutations, the pooled sensitivity was 78% (95%CI 74-82%) and pooled specificity was 86% (95%CI 82-89%) for predicting response to EGFR TKIs. Based on available data, they estimated response probability. In patients treated with EGFR TKI monotherapy, survival appears to be improved in patients with EGFR copy gain, although it is not clear if this represents a prognostic effect or a true predictive effect for EGFR TKI monotherapy[42] In the context of EGFR TKI therapy selection, the analysis of EGFR mutation analysis is preferred over EGFR gene copy number or KRAS mutation analysis.[7] Although EGFR activating mutations are found mainly in adenocarcinomas, they can also be found in mixed SCC/adenocarcinoma types of non-small cell lung cancer.[7]

Clinical factors such as gender, race and smoker versus non-smoker cannot replace EGFR mutation analysis.[7]

Update

One small, retrospective study by Sholl et al.[43] investigated the predictive value of EGFR mutation analysis, gene copy number analysis by both FISH and CISH and protein expression analysis by immunohistochemistry was included. EGFR mutation analysis appeared the most sensitive and specific assay to predict response to EGFR TKI monotherapy with a sensitivity of 92% and a specificity of 76% (confidence interval not stated). The results have to be interpreted with caution as the 40 patients were selected retrospectively based on known EGFR mutation status.

A recent comprehensive genomic characterization of squamous cell lung cancer identified an activating EGFR mutation in only 1.1% of squamous cell lung cancers. All pathology samples were reviewed by an group of experts in lung cancer pathology.[44] It cannot be excluded these are mixed tumour types. Also Rekhtman et al. found no EGFR or KRAS mutations in 95 biomarker-verified SCC of the lung.[45]

There is a rapid increase in knowledge of the tumour biology, leading to targeted treatments.

EGFR, KRAS, and ALK (anaplastic lymphoma kinase) mutations are almost always mutually exclusive (i.e. mutations of only 1 of the 3 genes occur within any individual tumour).

An early on release version of guidelines on molecular testing for selection of lung cancer patients for EGFR and ALK TKIs was identified while finalizing our guidelines.[46]

4.3.4.2. KRAS test

KRAS testing is currently not required for diagnostic work-up but this may change in the future as inhibitors of this pathway are in advanced clinical development.

4.3.4.3. ALK rearrangement test

Rearrangements of the gene encoding anaplastic lymphoma kinase (ALK) have been linked to abnormal cell proliferation. Up to 5% of NSCLC patients show the ALK rearrangement EML4-ALK, which arises from fusion between the 5′ end of the EML4 gene and the 3′ end of the ALK gene on chromosome 2p23. ALK rearrangement is more frequent in younger patients, never or light smokers with non-squamous NSCLC (mainly adenocarcinoma) whose tumours lack EGFR (and KRAS) mutations. Patients with ALK rearrangements do not benefit from EGFR-specific tyrosine kinase inhibitor therapy but are more likely to respond to the ALK inhibitor crizotinib. The recent guidelines[46] recommend screening for ALK using immunohistochemistry and to confirm positivity by FISH testing (there is an FDA-approved FISH test). Several ALK IHC stainings are available, that may be used to screen patients. In case of positivity FISH is performed. The interpretation of a FISH ALK test can be difficult.

Conclusions

EGFR mutation analysis has a higher sensitivity and specificity for predicting response to EGFR TKI monotherapy compared to EGFR gene copy assessment, immunohistochemistry or KRAS mutation analysis.

Other considerations

Analysis of a predictive factor is in daily practice only valuable if the result of the test changes clinical decision making. For practical implications of EGFR mutation analysis, we refer to the chapter on treatment of NSCLC.

EGFR mutation analysis should be performed using a well-validated and robust method. Comparison of existing methods and sample requirements are out of the scope of this document. KCE report 20 recommends the laboratory performing molecular tests (e.g. EGFR tests) for clinical management should be ISO 15189 accredited for this test and participate to external quality assurance (EQA) programs. These EQA programs should be organized by the national EQA organization (the Institute for Public Health, IPH).[47]

Pathology and molecular testing

Recommendation

Biopsy or surgical resection specimen are preferred for histology and molecular analyses.

In case no biopsy or surgical resection specimen is available, use samples obtained by FNA for determination of histology subtype and the performance of molecular techniques.

For pathological subclassification (in case morphology is not sufficient), use a diagnostic panel of assays that can consist amongst others of mucin stain, cytokeratine 5/6 cytokeratin 7, TTF1 and p63; other assays (e.g. p40) are emerging in this rapidly evolving field. The extent of the immunohistochemistry panel should remain limited to keep enough sample for additional molecular testing.

As response to EGFR targeted therapy depends on the presence of activating EGFR mutations, tests for these mutations should be offered to patients with non-squamous NSCLC or never/light smokers with mixed squamous/non-squamous cell carcinoma, potentially eligible for EGFR targeted therapy.

If no activating EGFR mutation is present, an ALK rearrangement test should be done to identify patients potentially eligible for crizotinib treatment.

Good clinical practices

Cell blocks should be prepared and immunocytochemistry should be applied on cytology samples whenever needed.

All molecular tests, such as EGFR mutation analysis and the ALK rearrangement test should be performed using a well-validated and robust method. A high proportion of tumor cells in the specimen is important for the test performance.

4.4. Diagnosis and evaluation of solitary pulmonary nodule (SPN)

Diagnosis and evaluation of solitary pulmonary nodes is out of scope of the guidelines, we refer to the Fleischner criteria[19] and the updated version specifically for the management of subsolid pulmonary nodules.[18] The most sensitive factor in the follow-up is tumor growth at 3D reconstructions especially of the solid part of the tumor.

Table 5 – The Fleischner criteria for follow-up and management of subcentimeter nodules[19]

Recommendations for Follow-up and Management of Nodules Smaller than 8 mm Detected Incidentally at Nonscreening CT

Nodule Size (mm)*	Low-Risk Patient†	High-Risk Patient‡
≤4	No follow-up needed§	Follow-up CT at 12 mo; if unchanged, no further follow-up‖
>4–6	Follow-up CT at 12 mo; if unchanged, no further follow-up‖	Initial follow-up CT at 6–12 mo then at 18–24 mo if no change‖
>6–8	Initial follow-up CT at 6–12 mo then at 18–24 mo if no change	Initial follow-up CT at 3–6 mo then at 9–12 and 24 mo if no change
>8	Follow-up CT at around 3, 9, and 24 mo, dynamic contrast-enhanced CT, PET, and/or biopsy	Same as for low-risk patient

Note.—Newly detected indeterminate nodule in persons 35 years of age or older.

* Average of length and width.

† Minimal or absent history of smoking and of other known risk factors.

‡ History of smoking or of other known risk factors.

§ The risk of malignancy in this category (<1%) is substantially less than that in a baseline CT scan of an asymptomatic smoker.

‖ Nonsolid (ground-glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma.

Table 6 – The Fleischner criteria for follow-up and management of subcentimeter and subsolid nodules[18]

Recommendations for the Management of Subsolid Pulmonary Nodules Detected at CT: A Statement from the Fleischner Society

Nodule Type	Management Recommendations	Additional Remarks
Solitary pure GGNs		
≤5 mm	No CT follow-up required	Obtain contiguous 1-mm-thick sections to confirm that nodule is truly a pure GGN
>5 mm	Initial follow-up CT at 3 months to confirm persistence then annual surveillance CT for a minimum of 3 years	FDG PET is of limited value, potentially misleading, and therefore not recommended
Solitary part-solid nodules	Initial follow-up CT at 3 months to confirm persistence. If persistent and solid component <5 mm, then yearly surveillance CT for a minimum of 3 years. If persistent and solid component ≥5 mm, then biopsy or surgical resection	Consider PET/CT for part-solid nodules >10 mm
Multiple subsolid nodules		
Pure GGNs ≤5 mm	Obtain follow-up CT at 2 and 4 years	Consider alternate causes for multiple GGNs ≤5 mm
Pure GGNs >5 mm without a dominant lesion(s)	Initial follow-up CT at 3 months to confirm persistence and then annual surveillance CT for a minimum of 3 years	FDG PET is of limited value, potentially misleading, and therefore not recommended
Dominant nodule(s) with part-solid or solid component	Initial follow-up CT at 3 months to confirm persistence. If persistent, biopsy or surgical resection is recommended, especially for lesions with >5 mm solid component	Consider lung-sparing surgery for patients with dominant lesion(s) suspicious for lung cancer

Note.—These guidelines assume meticulous evaluation, optimally with contiguous thin sections (1 mm) reconstructed with narrow and/or mediastinal windows to evaluate the solid component and wide and/or lung windows to evaluate the nonsolid component of nodules, if indicated. When electronic calipers are used, bidimensional measurements of both the solid and ground-glass components of lesions should be obtained as necessary. The use of a consistent low-dose technique is recommended, especially in cases for which prolonged follow-up is recommended, particularly in younger patients. With serial scans, always compare with the original baseline study to detect subtle indolent growth.

5. TREATMENT OF NSCLC

5.1. Treatment of early stage NSCLC (stage cI-II selected stage cIIIA cT3N1)

5.1.1. Criteria for operability

Operability centres on the development of criteria according to the patient's cardiopulmonary function and other co-morbidities and needs to be distinguished from resectability, which is the possibility to obtain complete resection of the tumour. NICE provides recommendations on operability i.e. on the process of selecting patients who will be able to tolerate surgery. The NICE recommendation applies to patients with NSCLC as well as SCLC, although it is acknowledged that fewer of the patients with SCLC will have this treatment form.[3]

Risk Assessment for operative mortality and postoperative morbidity

The NICE guideline[3] recommends that clinicians consider using a global risk score such as "Thoracoscore" to estimate the risk of death and to ensure the patient is aware of the risk before giving consent for surgery. This recommendation is based on a review of various risk models that found the Thoracoscore to be one of the better predictors of postoperative outcomes.

NICE provides a number of new recommendations regarding risk assessment for cardiovascular morbidity:

- To avoid surgery within 30 days of myocardial infarction.
- To seek a cardiology review in patients with an active cardiac condition, or three or more risk factors according to the Revised Cardiac Risk Index (RCRI) (see Appendix 4), or poor cardiac functional capacity.[48]
- To offer surgery without further investigations to patients with two or fewer risk factors according to the Revised Cardiac Risk Index (RCRI) and good cardiac functional capacity.
- To optimize any primary cardiac treatment and begin secondary prophylaxis for coronary disease as soon as possible.
- In the perioperative period to continue anti-ischaemic treatment including aspirin, statins and beta-blockers.
- If a patient has a coronary stent, perioperative anti-platelet treatment should be discussed with a cardiologist.
- To consider revascularisation before surgery for patients with chronic stable angina and conventional indications for revascularisation.

The NICE recommendations on risk assessment are based on a review of the evidence for a variety of risk scores consisting largely of retrospective analyses and some prospective. The population studied also included patients with benign disease and non-lung cancer thoracic surgery. It was noted that there was an absence of independent risk model validation in lung cancer patients. Included in the NICE review are also two recently published comprehensive guidelines on functional evaluation of lung resection candidates [49] [50] that were reviewed with particular attention to areas of controversy (Figure 2).

The Dutch guideline only recommends consulting a cardiologist in case of suspected increase in cardiovascular risk but does not give more specific recommendations. They consider age above 70 to be a risk factor but not an a priori reason to withhold surgery.

Update

A large retrospective study in 1073 lung cancer patients, published in 2011 by Takamochi et al., [51] aimed to identify predictors of morbidity after pulmonary resection in younger versus elderly patients (<70 years or ≥70 years). The analysis is based on clinical and pathological data and concludes that co-morbidities, including hypertension (P <0.001), ischemic heart disease (p=0.002), and renal insufficiency (p=0.001) were more frequently observed in the elderly group in comparison to the younger group. There were no statistical differences in the rates of overall morbidity and 30-day mortality between the younger and elderly groups (36% vs. 42% and 0.3% vs. 0.5%, respectively).

The univariate analysis showed that gender (95% CI 1.39-2.77, p<0.001), smoking status(95% CI 1.35-2.65, p<0.001), the presence of hypertension(95% CI 1.10-2.29, p=0.014), % forced expiratory volume in 1 sec (FEV1) (95% CI 1.64-3.70, p<0.001), % Diffusion capacity of the lung for CO (DLCO) (95% CI 1.06-2.17, p=0.022), the extent of pulmonary resection (95% CI 2.33-9.75, p<0.001), mediastinal lymph node dissection (MLD) (95% CI 1.98-6.25, p<0.001), clinical stage (95% CI 0.39-0.86, p=0.006) and histological cell type (95% CI 1.37-3.05, p<0.001) were significantly associated with morbidity in the group <70 years. In the group >70 years the following parameters were all found to be significant risk factors for morbidity: gender (95% CI 1.44-3.38, p<0.001), smoking status (95% CI 1.43-3.33, p<0.001), the presence of diabetes mellitus (95% CI 1.07-3.38, p=0.028), hypertension (95% CI 1.27-2.89, p=0.002), serum creatinine level (95% CI 1.35-5.05, p=0.004), % forced expiratory volume in 1 sec (FEV1) (95% CI 1.34-3.12, p<0.001),%DLCO (95% CI 1.26-3.00, p=0.003),and histological cell type (95% CI 1.08-2.65, p=0.022),

The study provides an exploratory analysis suggesting that perioperative management should take co-morbidity of elderly into account, but provides insufficient evidence for the development of recommendations.

Conclusion

It is advisable to develop a general risk assessment tool that can improve the ability to stratify the risk of various postoperative events before lung surgery is performed.

Recommendations
Perform a preliminary cardiologic evaluation for risk stratification according to the Revised Cardiac Risk Index (RCRI).
Patients with an active cardiac condition, a newly suspected cardiac condition, RCRI ≥ 3 or poor cardiac functional capacity should be carefully evaluated with a non-invasive cardiac test to optimize primary cardiac treatment or secondary prophylaxis, if any.
For patients already on acetylsalicyclic acid, statins and/or beta-blockers, the treatment should be continued in the peri-operative period.
Patients with an RCRI ≤ 2 and good cardiac functional capacity can proceed to respiratory function evaluation.
Consider using a global risk score to estimate the risk of death and ensure the patient is aware of the risk before giving consent to surgery.

Figure 2 – Algorithms from European Respiratory Society/European Society of Thoracic Surgeons

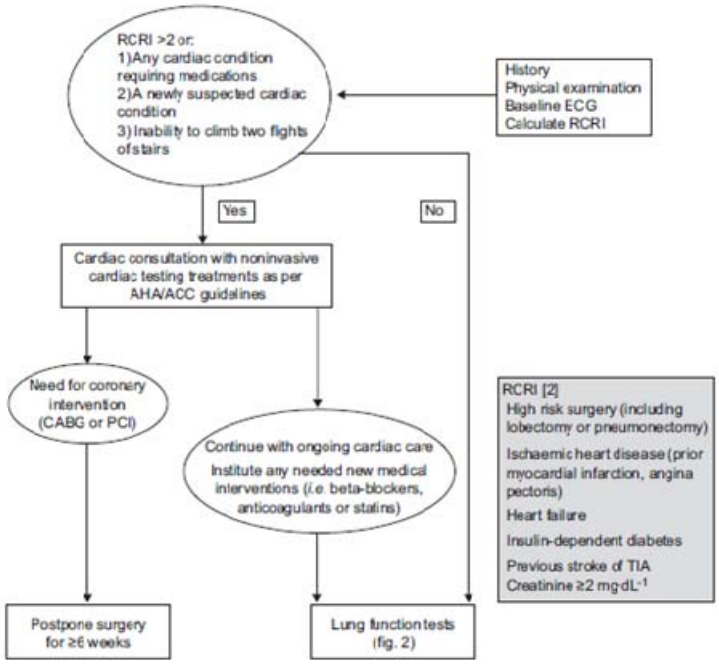
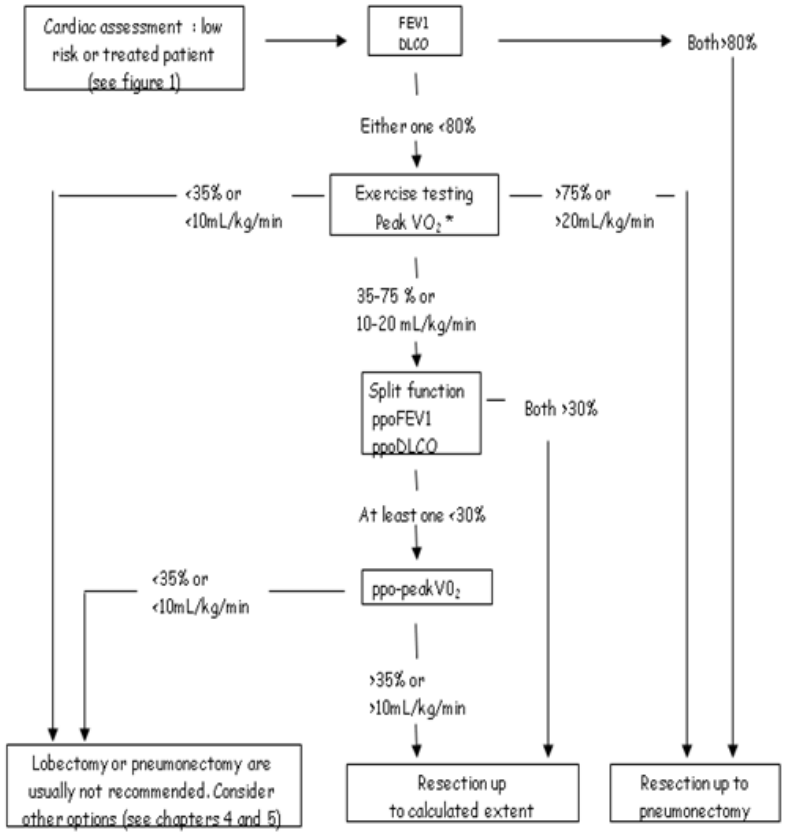


FIGURE 1. Algorithm for cardiac assessment before lung resection in lung cancer patients. For American College of Cardiology Foundation/American Heart Association (AHA/ACC) guidelines see [2–6]. CABG: coronary artery bypass graft; PCI: primary coronary intervention; TIA: transient ischaemic attack.



*: if not available, CPET can be replaced by stair climbing (see chapter 2-3); however if altitude reached at stair climbing < 22m, cardiopulmonary exercise test with peakVO2 measurement is highly recommended

5.1.1.1. Assessment of lung function and exercise testing

NICE recommends performing spirometry in all patients being considered for surgery. DLCO or TLCO (Diffusing capacity or Transfer factor of the lung for carbon monoxide) are similar tests and should be measured if breathlessness is disproportionate or there is other lung pathology (e.g. lung fibrosis). If the patient has a FEV1 within normal limits and good exercise tolerance, surgery should be offered. Patients with predicted postoperative FEV1 or TLCO below the recommended limit of 30% should be offered the option of undergoing surgery if they accept the risk of dyspnoea and associated complications. When considering surgery a segment count to predict postoperative lung function should be performed. The NICE recommendations on FEV1 and T_LCO stem from a large number of studies with varying results. A large number of these studies suggest that FEV1 is predictive of postoperative complications and/or mortality but a relatively large number of studies contradictory find that FEV1 is not predictive of postoperative outcomes. For studies on DLCO the same situation exist, where a number of studies find DLCO to be predictive of postoperative complications and/or mortality and a similar amount of studies find DLCO not to be predictive of postoperative outcomes. The NICE guideline group recognized the value of normal lung function as a predictor of good outcome and reflected this in the recommendations. Since evidence did not show a reliable lower limit of lung function a consensus statement was made by the guideline development group on this issue.

The Dutch guideline recommends considering all patients with a preoperative FEV1 and TLCO above 80 % without effort related dyspnoea as having a normal lung function. If these criteria are not fulfilled a predicted postoperative (ppo) FEV1 and TLCO should be calculated with the help of a perfusion scan. If ppo FEV1 and ppo TLCO are less than 40 % they recommend a VCO2max assessment, a VCO2max > 15 ml/kg/min should result in normal surgical risk when performing only a lobectomy and a VCO2max > 20 ml/kg/min should result in a normal surgical risk when performing only a pneumonectomy. A VCO2max < 10 ml/kg/min should be considered a very high risk (see Figure 3 for visual presentation of these recommendations) High risk and very high risk is not a contra-indication for surgery however but should be discussed with the patient. These recommendations are base on observational studies and expert opinion.

NICE recommends considering using a shuttle walk test, using a distance walked of more than 400 m as a cut-off for good function, to assess fitness of patients with moderate to high risk of postoperative dyspnoea. Additionally, NICE recommends considering cardiopulmonary exercise testing to measure VO2max and assess lung function in patients with moderate to high risk of postoperative dyspnoea, using more than 15 ml/kg/minute as a cut-off for good function. Finally it is recommended by NICE that a clinical oncologist specializing in thoracic oncology should determine suitability for radiotherapy with curative intent, taking into account performance status and co-morbidities.

The NICE recommendations on exercise testing are based on a small number of studies that were of variable quality and difficult to compare. Few of these studies addressed the issue of a lower limit before operative risk become unacceptable. Recommendations were confined to the use of cardiopulmonary exercise testing (CPET) to clarify whether borderline patients are likely to have good outcomes and for other less complex exercise test to be considered, with only one having an adequate evidence-based cut-off.

The Dutch guideline did not consider exercise testing apart for VO2max discussed above.

Update

No additional studies on FEV1 (or its derivate ppo FEV1) or DLCO (or ppo DLCO) performed without cardiopulmonary exercise testing were identified.

3 studies were included on exercise testing:

A study by Brunelli et al.[52] on 225 candidates for lobectomy or pneumonectomy, who underwent preoperative CPET, aims to verify the role of ventilatory efficiency/VCO2 slope in predicting respiratory complications after lung resection. The stepwise logistic regression analysis and bootstrap analysis, showed that ventilatory efficiency/VCO2 slope was the strongest predictor of respiratory complications including pneumonia, atelectasis requiring bronchoscopy, respiratory failure, adult respiratory distress syndrome, pulmonary oedema, and pulmonary embolism. Compared with patients with a lower ventilatory efficiency/VCO2 slope, those patients with a ventilatory efficiency/VCO2 slope exceeding 35 had a threefold higher rate of respiratory complications (22% vs. 7.6 %,

p=0.004) and a 12-fold higher rate of mortality (7.2% vs. 0.6%, p=0.01). The association of ventilatory efficiency with the risk of respiratory complications occurred both in patients with (p=0.03) and without (p=0.02) moderate to severe chronic obstructive pulmonary disease (COPD).

A study by Torchio et al. [53] on 145 COPD patients submitted to lung resection for NSCLC aims to verify ventilatory efficiency, expressed as VCO2 production ratio i.e. ventilatory efficiency/VCO2 slope, and assessed during CPET was able to predict morbidity and mortality. The logistic regression analysis (best fitted model with risk of death and risk of severe cardiopulmonary complications as dependent variables) showed that ventilatory efficiency/VCO2 slope to be the only independent predictor of mortality (OR: 1.24z=2.77; p < 0.007) and VO2 peak to be the best predictor of cardiopulmonary morbidity (OR: 0.05, z=-2.39, p < 0.02). The authors fail to report a cut-off value for the ventilatory efficiency/VCO2 slope and statistical analysis of mortality is limited by the relatively small number of deaths (n=5).

A study by Campione et al. [54] on 99 patients with poor lung function who underwent high-tech CPET before pulmonary resection looks at whether there is a correlation between postoperative outcomes (cardiopulmonary complications and mortality) and a number of variables including body mass index, age, FEV1, maximum heart rate and oxygen pulse (ratio of VO_2 to heart rate). On the multivariate analysis they find a correlation between postoperative outcomes and body mass index (p=0.0019, R=0.3045), maximum heart rate (p=0.0007, R=0.3368) and oxygen pulse (p=0.0004, R=0.3561). On this basis the authors conclude that oxygen pulse represents the most accurate index for predicting postoperative complications, although the authors could not define a cut-off value. The logistic regression did not confirm that peak oxygen consumption can assist in stratifying the risk of postoperative complications after pulmonary resection.

Other considerations

A consensus decision was taken to approve the European Respiratory Society/European Society of Thoracic Surgeons algorithms on cardiac assessment and assessment of cardiopulmonary reserve within the Belgian context. The algorithm is extracted from a review published in July, 2012 [55]. (Figure 2)

Patients should be advised about smoking cessation.

Conclusion

Further studies are needed to verify the role of exercise testing in selection of patients for surgery

Recommendation
Patients should be advised to stop smoking.
Perform spirometry and DLCO in all patients being considered for surgery.
Patients with FEV1 and DLCO > 80 % are candidate for a radical treatment without further functional testing.
Cardiopulmonary exercise tests are indicated in all patients with FEV1 or DLCO < 80 % of normal values.
Peak VO2 (VO2 max) should be regarded as the most important parameter to measure exercise capacity and to predict postoperative complications.
Peak VO2 > 75 % or 20 ml/kg/min qualifies for pneumonectomy.
Peak VO2 < 35 % or 10 ml/kg/min indicates resection bears a high risk.
Evidence does not support a clear cut-off value for lobectomy.
Patients with borderline pulmonary function need an estimation of their residual lung function (anatomic segment calculation or imaging based) before surgery.
Patients with predicted postoperative FEV1 or TLCO below the recommended limit of 30% should only be offered surgery if they accept the risk of dyspnoea and associated complications. Other treatment options should be considered.

5.1.2. Primary surgery

Surgery is historically the standard treatment for medically fit patients with resectable early stage lung cancer.

NICE[3] recommends for tumours confined to a single lobe, a lobectomy as the preferred treatment for patients with NSCLC who are medically fit and suitable for treatment with curative intent. Postoperative mortality after lobectomy is lower compared to mortality following pneumonectomy. If surgery with curative intent is performed, hilar and mediastinal lymph node sampling or 'en bloc' resection should be performed. Recommendations are based on a Cochrane review from Manser et al.[56] Only one small, old study compares surgery with radiotherapy for tumours limited to thorax. Improved four-year survival was seen in the surgery group, but due to small numbers the result was imprecise (RR 3.27; 95%CI 0.74-14.42). Three studies included in the review compare complete mediastinal lymph node dissection with systematic sampling. Meta-analysis shows a significant reduction of death in the group undergoing complete mediastinal lymph node dissection (HR 0.63; 95%CI 0.51-0.78). Also the risk for any cancer recurrence was reduced (RR 0.79; 95%CI 0.66-0.95).

The Dutch guideline[7] starts with pointing out that the aim of all surgery should be to obtain macroscopically and microscopically complete resection. As lobectomy is associated with a lower postoperative mortality than pneumonectomy, lobectomy with systematic mediastinal lymphadenectomy is the recommended treatment for resectable tumours if the tumour is limited to one lobe. An additional wedge resection or bilobectomy can be performed if the tumour spreads to an adjacent lobe. In case of central tumours, pneumonectomy is a feasible option.

Update

The European Society of Thoracic Surgeons (ESTS) has published proposed definitions of the different procedures for intraoperative lymph node assessment, see chapter 3.

One RCT and one controlled prospective observational study compared mediastinal lymph node sampling with complete lymph node dissection.

In the ACOSOG group Z0030 trial, published by Darling et al.,[57, 58] 1111 patients with a T1 or T2 tumour and N0 or non-hilar N1 disease, were randomized intra-operatively if standardized lymph node sampling resulted in no lymph node metastases on frozen section. One group underwent no further mediastinal surgery, the other group continued with systematic mediastinal lymph node dissection. The median number of additionally removed lymph nodes in that group was 18. No significant difference in overall survival (HR 0.92; 95%CI 0.76-1.11; p=0.34) or disease-free survival (p=0.89) was seen. A prior report on postoperative morbidity and mortality showed no differences between the two study arms.[59]

The results of the ACOSOG Z0030 trial were not added to the meta-analysis due to substantial heterogeneity between the two largest trials (Wu 2002, Darling 2011). The conflicting results of these two trials can possibly be explained by one of the following reasons:

- Different study populations: more extensive preoperative mediastinal staging procedures in the study of Darling et al., only patients without lymph node metastases at the end of the sampling procedure were randomized. Pathological stage III was present in 3% and 6% respectively. In the study of Wu et al. the prevalence of pathological stage III was 48% in complete lymph node dissection arm and 28% in the sampling arm.
- Different surgical procedures: the sampling procedure in the study of Darling et al. was standardized and consisted of systematic palpation and removal of at least one lymph node for each lymph node station. In the study of Wu et al. lymph node sampling consisted of exploration by palpation and removal of suspicious lymph nodes only.
- Different use of adjuvant therapy: according to a personal communication of one of the authors of the study by Wu et al. reported in the Cochrane review, stage III patients in that study were referred for postoperative radiotherapy but compliance was about 30% in both arms. In the trial of Darling et al., in only 3.8% of patients additional lymph node metastases were detected by complete lymph node dissection. No data on adjuvant treatment were reported but according to the discussion in annex to the paper, adjuvant chemotherapy was not standard practice at the time of the study.

Conclusion

In patients with T1-T2, N0 or non-hilar N1 NSCLC who underwent rigorous pre- and intra-operative mediastinal staging (including lymph node sampling with no lymph node metastases on peroperative frozen section), a survival benefit from complete mediastinal lymph node dissection compared to systematic lymph node sampling could neither be demonstrated nor refuted (Darling 2011; low level of evidence).

In patients with resectable NSCLC who underwent minimal preoperative mediastinal staging, It is plausible that complete mediastinal lymph node dissection is associated with a survival benefit compared to systematic lymph node sampling (Wu 2002; low level of evidence).

In patients with resectable NSCLC, there are indications that there is no significant difference in 30-day mortality after systematic mediastinal lymphadenectomy compared to mediastinal lymph node sampling (Manser 2010, Darling 2011; low level of evidence).

Other considerations

The international Association for the study of Lung Cancer (IASLC) staging committee[60] defined complete resection (R0) as follows:

- Free resection margins proved microscopically.
- Systematic nodal dissection in its wider form or, if it is not performed, lobe-specific systematic nodal dissection. The latter implies dissection of intrapulmonary and hilar nodes and, at least, three mediastinal nodal stations defined depending on the lobar location of the primary tumour. The lymph node specimen should include at least six nodes, three removed from intrapulmonary and/or hilar stations and three removed from mediastinal stations, one of which must be the subcarinal station.
- There should be no extracapsular extension of tumour in nodes removed separately or those at the margin of the main lung specimen.
- The highest mediastinal node that has been removed must be negative.

In complete resection, therefore, there is no evidence, or even suspicion, of residual disease and a standardized nodal assessment has been performed.

This definition is based on prognostic information and consensus reached by experts in the field.

The aim of each surgery should be to achieve R0 resection as complete removal of all macroscopic and microscopic disease results in the best prognosis and informs about the need for adjuvant chemotherapy and or radiotherapy.

If only limited mediastinal staging has been performed, (lobe-specific) systematic mediastinal staging results in a significant survival benefit. The need for systematic mediastinal lymph node dissection to achieve these goals in T1-2, N0-1 patients who underwent rigorous mediastinal staging remains unclear. Also the benefit for patients who underwent rigorous pre-operative staging but no intra-operative sampling, the survival benefit is still unclear. However, as the 30-day mortality appears not to be affected, at least lobe-specific systematic node dissection is still recommended in the majority of patients.

5.1.2.1. Extended surgery: bilobectomy, sleeve lobectomy, pneumonectomy

As stated above, generally, the morbidity and mortality are increased after pneumonectomy compared to lobectomy. Two studies have shown a postoperative mortality rate between 6% and 8% after pneumonectomy versus 2 to 3% after lobectomy.[7] No further search to update these data was performed.

According to the Dutch guideline, a sleeve lobectomy is recommended if the tumour involves the bronchus, even if lung function permits a pneumonectomy. That recommendation is based on review showing better long term results after sleeve lobectomy compared to pneumonectomy. Also in terms of quality of life and cost effectiveness sleeve lobectomy is preferred.

According to NICE, more extensive surgery (bronchoangioplastic surgery, bilobectomy, pneumonectomy) should only be considered if needed to obtain clear surgical margins.

Update

Two systematic reviews comparing sleeve lobectomy with pneumonectomy for tumours involving the bronchial ostium and/or the pulmonary artery were found. One was only available as abstract and is not further discussed.[61] Conclusions are similar to the results of the meta-analysis of Shi et al.[62]

Shi et al. performed a meta-analysis on 19 studies that reported on the comparison of interest. Methodology and risk of bias of the included studies are not reported. There was a significant difference in the postoperative mortality, which favoured the sleeve lobectomy group (OR 0.50; CI 0.34-0.72). No significant difference was seen for postoperative complications (OR 1.17; 95%CI 0.82-1.67). The estimated combined HR for overall survival in 13 studies was 0.63 (95%CI 0.56-0.71) in favour of the sleeve lobectomy group. Primary studies were reviewed by KCE: all included studies were retrospective observational studies subject to selection bias.

Conclusion

There are indications that sleeve lobectomy for NSCLC tumours involving the bronchial ostium and/or the pulmonary artery is associated with reduced postoperative mortality and improves overall survival compared to pneumonectomy (Shi 2012, very low level of evidence).

There are indications that there is no significant difference in postoperative morbidity after sleeve lobectomy for NSCLC tumours involving the bronchial ostium and/or the pulmonary artery compared to pneumonectomy (Shi 2012, very low level of evidence).

Other considerations

No further evidence for tumours growing into an adjacent lobe was found. Similar to sleeve lobectomy, it is assumed that performing a bilobectomy and avoiding a pneumonectomy is preferred.

5.1.2.2. Limited resection: segmentectomy, wedge resection

NICE[3] proposes to consider lung parenchymal-sparing operations (segmentectomy or wedge resection) for patients with borderline fitness and smaller tumours (T1a-b, N0, M0) if a complete resection can be achieved. Supporting evidence consists of one RCT included in the Cochrane review that found no significant differences between the two groups in 5-year survival or the rate of death with cancer. However, the rate of recurrence per person/year was statistically significantly higher in the limited resection group than in the lobectomy group.

In the Dutch guideline,[7] the subject is more extensively discussed. In addition to the RCT mentioned in NICE, a non-randomized comparative study by Landreneau comparing wedge resection with lobectomy, is referred to. Results of the RCT are confirmed. Japanese studies have reported high 5-year survival rates with anatomical segmentectomy. Based on available data, the Lung Cancer Study group has suggested that sublobar resection may have a value if selectively used for small tumours without lymph node involvement, with favourable histological profile and assurance of adequate surgical margins. The Dutch guideline could not identify comparative data for sublobar resection and stereotactic radiotherapy for high risk patients.

Update

One systematic review and three non-randomized observational studies were identified in the recent literature (Table 21).

Fan et al.[63] performed a meta-analysis on published studies comparing sublobectomy with lobectomy. No critical appraisal of included studies was performed. The majority of studies are retrospective case series at high risk of selection bias. Overall survival and cancer-specific survival appeared to be significantly lower after sublobar resection (wedge resection or segmentectomy) compared to lobectomy (HR 1.26; 95%CI 1.07-1.47 and 2.07; 95%CI 1.14-3.77 respectively). For tumours smaller than 2 cm, a non-significant difference was noted (HR 0.81; 95%CI 0.39-1.17). Also when only the data for segmentectomy (wedge resection excluded) were compared with lobectomy, no significant difference on overall survival was seen (HR 1.09; 95%CI 0.82-1.40).

Wolf et al.[64] published a retrospective cohort study including 238 patients with NSCLC smaller than 2 cm without lymph node involvement or distant metastases. 154 patients (24 segmentectomies) underwent sublobar resection and 54 underwent lobectomy. 5-year survival was 59% after sublobar resection and 80% after lobar resection (p= 0.0027). Five-year recurrence-free survival 74% versus 87% respectively (p=0.0496). As patients who underwent sublobar resection were older and had worse pulmonary function, results may be biased by patient selection.

Cheng et al.[65] performed a non-randomized prospective controlled study including 184 elderly patients (≥ 70 years) who underwent segmental resection or lobectomy combined with regional lymph node dissection or selected lymph node dissection. Only patients with tumours smaller than 3 cm on CT scan were eligible. No significant differences in 1-, 3- or 5-year survival were seen, independent from their lung function at the time of diagnoses (FEV1 > or < than 1.5l).

Shirvani et al.[66] performed a large, population based comparative observational study, based on Surveillance, Epidemiology, and End Results (SEER) Medicare database in the USA. Patients of 66 years and older with NSCLC smaller than 5 cm treated with sublobectomy, lobectomy or stereotactic body radiation therapy (SBRT) were included. During the first 6 months, risk of mortality was lowest after SBRT. After these first 6 months, lobectomy was associated with a better overall survival compared to sublobectomy (adjusted HR 1.40; 95%CI 1.28-1.54) and compared to SBRT (adjusted HR 1.56; 95%CI 1.21-2.00). Due to the low number of patients in the SBRT, an additional propensity-score matched analysis was performed. Matched analysis shows no significant difference between SBRT and lobectomy in terms of overall survival (HR 0.71; 95%CI 0.45-1.12) or between SBRT and sublobectomy (HR 0.82; 95%CI 0.53-1.27).

The results of the studies of Wolf and Cheng could not be added to the meta-analysis as data reporting was insufficient. Data of Shirvani were not added as they confirm the overall conclusion of Fan et al.

Conclusions

There are indications that sublobar resection of stage I NSCLC is associated with shorter overall survival compared to lobectomy (Fan 2012, Wolf 2011;Cheng 2012, Shirvani 2012; very low level of evidence).

There is limited evidence that there is no significant difference in overall survival after sublobar resection or lobectomy for NSCLC tumours smaller than 2 cm (Fan 2012, Wolf 2011; very low level of evidence).

Other considerations

Currently available evidence does not support the use of sublobar resection for NSCLC but is likely subject to selection bias. There are indications that segmentectomy may be safe in selected cases with small tumours where appropriate margins can be obtained. However, awaiting the results of ongoing RCTs, sublobar resection is generally not recommended.

For patients who are judged to be unfit for lobectomy, more limited resection can be considered. However, stereotactic radiotherapy is an alternative for these patients (see 1.1.1). Treatment decisions should be discussed by a multidisciplinary team.

5.1.2.3. Video-assisted thoracic surgery (VATS)

The Dutch guideline[7] considers VATS lobectomy an acceptable procedure if performed by experienced surgeons. This recommendation is based on a meta-analysis including two small RCTs and nineteen observational studies. In that meta-analysis,[67] there is no difference between VATS and open surgery in terms of postoperative air leak, arrhythmia, pneumonia or mortality. An improved 5-year mortality rate of VATS was seen (p=0.04).

NICE[3] considers lobectomy, either open or thoracoscopic, to be the treatment of choice for patients with NSCLC suitable for treatment with curative intent but offers no further advise on the choice between an open or a thoracoscopic technique.

Update

The meta-analysis referred to in the Dutch guideline has been criticised because unadjusted observational studies at high risk for selection bias have been included.

Cao et al.[68] performed a meta-analysis including only propensity-matched observational studies. The small RCTs were not included because the used surgical techniques do not fulfil the current standards for VATS. Other observational studies were excluded in order to avoid selection bias as much as possible. Four studies were included. No significant difference in postoperative mortality was seen (RR 0.75; 95%CI 0.44-1.27) but overall peri-operative morbidity (RR 0.67; 95%CI 0.56-0.82) and length of hospital stay (SMD -0.37; 95%CI -0.51 to -0.22) were improved in patients treated with VATS.

Conclusion

An effect of video-assisted thoracic surgery on postoperative mortality compared to open surgery could neither be demonstrated nor refuted (Cao 2013, low level of evidence).

There are indications that video-assisted thoracic surgery is associated with reduced postoperative morbidity compared to open surgery (Cao 2013, low level of evidence).

There are indications that video-assisted thoracic surgery is associated with shorter hospital stay compared to open surgery (Cao 2013, low level of evidence).

Other considerations

Surgical skills for minimal invasive surgery vary among surgeons. If video-assisted surgery is performed, resection should correspond to the same oncological standards as in thoracotomy; R0 resection should be achieved and mediastinal lymph node dissection should be part of the procedure. This should be taken into account when published results of clinical trials are applied in clinical practice.

5.1.2.4. Minimal criteria for surgery and pathology report

The Belgian Society of Pneumology developed a template for both a surgery report and pathology report of surgical specimens in 2006 (www.collegeoncologie.be/files/files/Richtlijnen/NSCLC_V1.2007_2_12128470_nl.pdf)

Update

Surgery report

The Dutch guideline[7] considers it good practice to include the following information in the surgery report, based on (inter)national consensus and requirements for staging and treatment

- Approach and incision
- Localisation, size and growth patern of the tumour, distance to the carina
- Presence or abscence of satelite lesions or metastases
- Status of lymph node stations and methods of assessment
- Presence of pleural effusion
- Results of frozen section(s), if performed
- Distance of tumour to the resection margins, especially the bronchial resection margin
- Macroscopic radicality of the resection
- Conclusions of any ad hoc peroperative multidisciplinary consultation
- Complications
- Conclusions: procedure performed and intraoperative TNM classification

The Belgian guideline published in 2007 recommends to also report on treatment prior to surgery (chemotherapy, radiotherapy) and the clinical TNM classification. It is suggested to leave clips in situ in case of incomplete resection to guide postoperative radiotherapy.

Pathology report

According to the Dutch guideline[7], at least the following information should be reported in the pathology report:

- Size of the tumour
- Histological subtype (WHO classification)
- Involvement of the pleura
- Completeness of resection: surgical margins
- Absence or presence of lymph node metastases

In the Dutch guideline, it is recommended to use a formal checklist for reporting purposes.

In tumours of less than 3 cm that are close to the pleura an elastine (Gieson elastic) stain is recommended to assess pleural invasion in order to obtain an adequate staging of the tumour, allowing an upstaging from T1 to T2 in the new TNM classification. This recommendation is based on a systematic review that identified six prognostic studies on the value of pleural invasion and 4 supplementary prognostic studies.

Additionally, the Royal College of Pathologists in the UK issued a dataset for lung cancer histopathology reports in 2011, available on their website (http://www.rcpath.org/Resources/RCPath/Migrated%20Resources/Documents/G/G048DatasetLungApril11.pdf). It includes complete assessment of pleural invasion and reporting of the pTNM classification. A summary of the checklist for resection specimens can be found in 0.

Reporting of the three-dimensional size of the tumour can additionally be considered.

As a quality measure, the number of lymph nodes and precise location should be reported.

5.1.2.5. Volume-outcome for lung cancer surgery

The question as to whether there is a relationship between volume or surgeon specialty and outcomes in lung cancer surgery was raised by the guideline development group (GDG).

The NICE guideline[3] does not cover this topic.

According to the Dutch guideline[7], lung cancer surgery should only be performed in specialized centres that perform at least 20 procedures per year. Each specialized centre should have at least specialized chest physicians, radiation oncologists, thoracic surgeons, specialized nurses etc. to ensure continuity of care. The recommendation is based on a meta-analysis performed by the Dutch 'KWF kankerbestrijding',[69] showing that postoperative mortality (but not long term survival) is lower in high-volume hospitals. It appears that the number of cases treated by the multidisciplinary team is more important than the case-load per surgeon.

Update

One recent systematic review[70] and two recent observational studies[71,72] were identified. Additionally, a KCE report from 2009 looked at the volume of surgical interventions and its impact on the outcome, based on Belgian data [73].

- The systematic review, with a search date up to January 2011, identified 19 studies on the effect of procedural volume or surgeon specialty on outcomes. For hospital volume there was a variation across studies in cut-off values of the highest hospital volume strata (between 20 and 129.4 procedures annually) and the lowest volume strata (between 3.6 and 60 procedures annually). The systematic review concludes that there is a significant relationship in favour of high-volume hospitals for postoperative mortality (OR=0.7; 95%CI: 0.62-0.81) determined by a pooled estimated effect size. The effects for survival (OR: 0.93; 95%CI: 0.84-1.03) and high volume surgeons (OR:0.68; 95%CI:0.42-1.08) were not statistically significant. General surgeons had significantly higher mortality risk than general thoracic (OR=0.78; 95%CI: 0.70- 0.88) or cardiothoracic surgeons (OR =0.82; 95%CI: 0.69-0.96). A minimal annual volume of resections for lung cancer could not be identified.

- One large observational study from July 2011 looks at the impact of hospital volume on chest tube duration, length of stay and mortality after lobectomy. The study concludes that in-hospital mortality was significantly lower in high-volume group compared with low-volume group (0.48% vs 0.94%, OR=0.60, p=0.047), that chest tube removal occurred earlier in high-volume group compared with low volume group (mean=4 days vs 5.1 days, p<0.001) and that postoperative length of stay was shorter in the high-volume group than in the low-volume group (mean 11.5 days vs 15.9 days, p<0.001). The study has important limitations. There are difference in age and comorbidities (high-volume patients were generally younger and had less co-morbidities), hospital volume categories appear not to be predefined and the authors report some limitations to the database utilized, including a lack of validation on diagnosis and co-morbidities reported, a lack of information on important factors including cancer stage and smoking status and a low reporting participation rate from very low-volume hospitals.
- Another large observational study, based on routine data from 498.099 patients who underwent pneumonectomy, lobar, segmentectomy or nonanatomic wedge resection between 2003 and 2009, assess whether hospital educational status has an effect on outcomes including mortality, risk of complications and “failure to rescue”. The study concludes that the risk of any complication after segmentectomy or nonanatomic wedge resection was lower at thoracic residency teaching hospitals (TR) compared with general surgery residency hospitals (GSR) (p<0.001). Significant effects for were found for TR hospitals as well among pneumonectomy recipients, where TR hospitals reduced the adjusted odds ratio of failure to rescue by more than 25% compared with no surgery residency (p<0.001), and where TR hospitals were associated with a reduced mortality odds ratio of death by more than 30% compared with GSR hospitals (p<0.001). The adjustment model provided has insufficient data on patient risk factors. [72]
- A feasibility study performed at KCE in 2009 looked at the volume of surgical interventions and its impact on the outcome, based on Belgian data. This study performed an analysis to assess whether there is a volume outcome relationship for selected procedures including a relationship for lung cancer surgery. This analysis found an inverse relationship between hospital volume and mortality after surgery for lung cancer but it was not possible to summarize a threshold thus no recommendations could be established with respect to a minimal threshold. [73]

Conclusion

A recent systematic review concludes that high-volume hospitals are superior for postoperative mortality but did not find a significant effect for survival. A minimal annual volume of resections for lung cancer could not be identified. This conclusion is supported by a KCE report using Belgian data that finds an inverse relationship between hospital volume and mortality without being able to establish a minimal threshold volume. One large observational study concludes that pulmonary resections performed at thoracic residency hospitals in general have better outcomes for mortality, risk of complication and “failure to rescue”.

Primary surgery in early stage NSCLC (stage cI-II selected stage cIIIA cT3N1)

Recommendation	Strength of recommendation	Level of evidence
Patients with resectable NSCLC considered sufficiently fit, surgery aiming at complete resection (R0) is recommended. For tumours confined to a single lobe, a lobectomy is the preferred treatment.	strong	not assigned
In patients with resectable NSCLC undergoing surgery, at least lobe-specific systematic nodal dissection is recommended.	weak	moderate
For right sided tumours involving an adjacent lobe, a bilobectomy is recommended; for tumours involving the bronchial ostium and/or the pulmonary artery, a sleeve lobectomy is recommended rather than a pneumonectomy.	weak	very low
For fit patients with NSCLC limited to one lobe, sublobar resection (wedge resection or segmentectomy) is only recommended in the framework of a clinical trial.	strong	very low
For borderline fit patients with NSCLC limited to one lobe, treatment options such as wedge resection or segmentectomy, as well as radical radiotherapy (stereotactic radiotherapy is recommended), can be considered by a multidisciplinary team.	weak	very low
In patients with resectable NSCLC undergoing lobectomy, either VATS or open surgery can be considered. VATS should only be performed by surgeons who are sufficiently trained.	weak	low
Lung cancer surgery should be carried out in high-volume centres specialised in thoracic surgery.	weak	low

Good clinical practice
Before deciding to operate, the multidisciplinary team should consider whether tumour-free resection margins can be achieved and what postoperative quality of life can be expected for the patient.
The specimens should include at least six lymph nodes: three removed from intrapulmonary and/or hilar stations and three removed from mediastinal stations, one of which must be the subcarinal station.
Surgery reports and pathology reports should at least contain the minimal datasets as defined by (inter)national professional organizations; it should always include the surgical and pathological TNM classification.
When surgical specimens are examined pathologically, an elastin (von Gieson elastic) stain is recommended in tumours of less than 3 cm that are close to the pleura to assess pleural invasion. This way an adequate staging of the tumour can be performed, allowing an upstaging from T1 to T2 in the 7th edition of the TNM classification.

5.1.3. (Neo-)adjuvant chemotherapy and surgery

5.1.3.1. Adjuvant chemotherapy

NICE recommends to offer postoperative chemotherapy to patients with good performance status (WHO 0 or 1) and T1-3 N1-2 M0 NSCLC and to consider postoperative chemotherapy in patients with good performance status (WHO 0 or 1) and T2-3 N0 M0 NSCLC with tumours greater than 4 cm in diameter. They also recommend to offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy and to ensure eligible patients have the benefit of detailed discussion of the risks and benefits of adjuvant chemotherapy

They base their conclusions on five systematic reviews with meta-analyses (Auperin et al., 2010[74]; Berghmans et al.[75], 2005; Bria et al.[76], 2009; Hamada et al.[77], 2005; Hotta et al.[78], 2004), one meta-analysis of the five largest trials on cisplatin-based adjuvant chemotherapy (Douillard et al[79]., 2010), and four RCTs (Felip et al.[80], 2010; Ichinose et al[81]., 2003; Ou et al.[82], 2010, reporting on the same RCT as Wang et al.[83], 2007).

Auperin et al. [74] included individual-patient data from 8447 patients and found that surgery in combination with adjuvant chemotherapy was associated with longer survival (HR 0.86; 95%CI 0.81 to 0.92, p<0.001) than surgery alone. The results also suggest that patients who received adjuvant chemotherapy experienced longer recurrence-free survival with longer time to both loco-regional and distant recurrence, but it is unclear whether these analyses are marked by significant between-study heterogeneity and the results therefore cannot be fully evaluated. Berghmans et al.[75] (2007) included 7644 patients from 19 studies and found that adjuvant chemotherapy was associated with longer survival (HR 0.84; 95%CI 0.78 to 0.89).

The meta-analysis of Douillard et al.[79] was a pre-planned subgroup analysis of the Lung Adjuvant Cisplatin Evaluation (LACE) database published by Pignon et al.[84] The five largest trials on cisplatin-based adjuvant chemotherapy, gave a pooled hazard ratio of 0.80 (95%CI 0.70 to 0.91, p<0.001).

The Dutch guideline on the contrary recommends adjuvant chemotherapy containing cisplatin for stages II and III but not for stage I, basing themselves on the meta-analysis of Pignon et al., where survival benefit for patients in stage I is unproven (HR 1.01; 95%CI 0.78 to 0.1.30). They leave open what to do with tumours stage I > 4 cm.

The suggestion to consider adjuvant chemotherapy for stage I tumours larger than 4 cm is based on a subgroup analysis of the study of Strauss et al.[85]

Update

We added the RCT reported by Felip et al.[80], 2010 and Ou et al.[82] to the studies reported by Auperin et al[86] using the O – E and variance method for combining studies, extracting data following Parmar et al.[8] We could not include Ichinose et al. 2003[81] as the paper did not report the data with sufficient detail to use any extraction method.

Combined effect for OS differs only marginally from the meta-analysis by Auperin et al. (HR 0.87; 95%CI 0.81 to 0.92). Details on the updated meta-analysis are given in Appendix 3.3.1

Conclusion

It is plausible that adjuvant chemotherapy improves overall survival in patients with completely resected early stage NSCLC (R0 resection) compared to surgery alone (Song 2010, Felip 2010, moderate level of evidence)

Other considerations

In RCTs investigating the value of adjuvant chemotherapy, the following platinum-based chemotherapy agents were used[86]:

- Cisplatin, vindesine, ± mitomycin
- Cisplatin, vinblastin, ± mitomycin
- Cisplatin, etoposide
- Cisplatin, vinorelbine
- Cisplatin, doxorubicin, cyclophasphamide
- Cisplatin, mitomycin, ifosphamide
- Carboplatin, paclitaxel
- Cisplatin, tegafur ± mitomycin
- Cisplatin, vindesine, tegafur, uracil ± mitomycin
- Cisplatin, doxorubicin, tegafur, uracil

5.1.3.2. Neo-adjuvant chemotherapy

The NICE guideline advises not to offer neo-adjuvant chemotherapy to patients with NSCLC suitable for surgery outside a clinical trial. NICE identified two meta-analyses, Song et al.[87], which is an update of Burdet et al[88] and three RCTs. Meta-analysis including all data found that patients who had received neoadjuvant chemotherapy experienced longer overall survival than the patients given surgery alone (HR 0.84; 95%CI 0.77 to 0.92, p=0.0001), this benefit also remained when the analysis was restricted to stage III patients and corresponds to a modest 5 % increase in 5 year survival. However, there is considerable heterogeneity in the effects, with a number of studies showing no effect at all, the main argument of NICE not to recommend this intervention. The study data did not allow a pooling of data on side effects nor on quality of life.

The Dutch guideline does not discuss neo-adjuvant chemotherapy in patients suitable for surgery.

Update

Two additional publications on RCTs compared neo-adjuvant chemotherapy followed by surgery with surgery alone. Both trials were closed early as data emerged about the benefit of adjuvant chemotherapy and the surgery alone arm was no longer considered safe. The data of both RCT were included already included however in the meta-analysis of Song et al.

Pisters et.al.[89] randomized 354 patients to preoperative paclitaxel and carboplatin followed by surgery or surgery alone. Patients with clinical stage IB-IIIA NSCLC (excluding superior sulcus tumours and N2 disease) were included. Overall survival was improved in the neo-adjuvant arm, but results were not statistically significant (HR 0.79; 95%CI 0.60 to 1.06, p=0.11).

Scagliotti et.al.[90] compared surgery alone with surgery plus preoperative cisplatin and gemcitabine in 270 patients with stage IB to IIIA NSCLC. 3-year progression-free survival was improved with neo-adjuvant chemotherapy (36.1% versus 55.4%, p=0.002).

We added the data of Felip et al[80] to the meta-analysis of Song et al[87], as Song et al could not include the data at that time the review was made due to incomplete reporting. We used the extraction methods following Parmar et al.[8] Including those results did not change the estimated pooled effect on overall mortality. The HR rate reported by Felipe et al was close to the pooled estimate. I^2 may underestimate the heterogeneity here as there are a number of small studies that artificially lower I^2, (Q – k + 1)/Q, with k being the number of studies in the analysis), by inflating k while only increasing Q with a small amount due to the small study size.

Details of the meta-analysis are given in Appendix 3.5.1.

Conclusion

There are indications that neoadjuvant chemotherapy improves overall survival in patients with resectable early stage NSCLC

5.1.3.3. *Adjuvant versus neo-adjuvant chemotherapy*

There is currently no direct evidence from RCTs to inform about the value of neo-adjuvant chemotherapy versus postoperative adjuvant chemotherapy. An indirect comparison meta-analysis by Lim et al.[91] showed no evidence that there is a difference between them (HR 0.96, 95%CI 0.92 to 1.20, p=0.7). However, indirect comparison meta-analysis as a technique is considered as immature and requires more methodological research. We did not replicate the analysis with the recent studies. The analysis reveals considerable uncertainty as the confidence interval is compatible with an important difference on both sides.

Inspite of indications that survival outcomes after neoadjuvant or adjuvant chemotherapy are not different, the supporting evidence for adjuvant chemotherapy is considered more robust. Therefore, adjuvant chemotherapy is generally the prefered option. Multidisciplinary lung cancer teams can however consider neoadjuvant chemotherapy when immediate surgery is not possible.

Justification of the GRADE scores given.

The evidence profiles a made with GRADE Pro and further justification are given in Appendix 3.2.2 and Appendix 3.3.2.

(Neo)adjuvant chemotherapy in early stage NSCLC (stage cI-II, selected stage IIIA cT3N1 or unforeseen N2)

Recommendation	Strength of recommendation	Level of evidence
It is generally not recommended to offer neo-adjuvant chemotherapy to patients with NSCLC suitable for surgery outside a clinical trial. Exceptions should be discussed by a multidisciplinary team.	**weak**	**low**
After R0 resection, offer postoperative chemotherapy to patients with good performance status (WHO 0 or 1) and pT1-3 pN1-2 M0 NSCLC.	**strong**	**moderate**
Consider postoperative chemotherapy in patients with good performance status (WHO 0 or 1) and pT2 pN0 M0 NSCLC with tumours greater than 4 cm in diameter or pT3 pN0 M0 NSCLC. Options should be discussed by a multidisciplinary team.	**weak**	**low**
After R0 resection, adjuvant chemotherapy is not recommended for patients with tumours smaller than 4 cm and no lymph node involvement.	**strong**	**low**
For adjuvant chemotherapy, a two-drug combination with cisplatin is preferred. In randomized trials, the attempted cumulative cisplatin dose was up to 300 mg/m^2, administered in three to four cycles. The most frequently studied regimen is cisplatin-vinorelbine.	**strong**	**low**

5.1.4. Postoperative radiotherapy

The NICE guideline[3] does not give recommendations on postoperative radiation therapy after primary resection of NSCLC.

The Dutch guideline[7] recommends postoperative radiotherapy in case of positive resection margins after surgery. In case of unexpected pN2 or pN3 postoperative radiotherapy can be considered. Postoperative radiotherapy is not recommended in case of R0 resection and pN0-1 disease.

The recommendation for completely resected lung cancer is based on a meta-analysis of the PORT meta-analysis group, showing a 35% reduction in recurrent disease but no survival advantage in case of pN2 disease. In case of microscopic or macroscopic residual disease, postoperative radiotherapy is recommended as a retrospective study has shown a better 5-year survival rate than expected without radiotherapy (indirect evidence). Another study comparing postoperative radiotherapy with or without chemotherapy in patients with pN2 disease or macroscopic residual disease showed better recurrence-free survival in the combination arm.

Update

An update of the Cochrane review (Table 26) on postoperative radiotherapy for completely resected NSCLC was published in 2010.[92] Search date was January 2009. Combined results of the analysis based on individual patient data shows a detrimental effect of postoperative radiotherapy on overall survival (HR 1.17; 95%CI 1.02-1.34, p=0.02). Recurrence-free survival was also adversely affected by postoperative radiotherapy but that effect was not statistically significant (HR 1.09; 95%CI 0.95-1.25). Subgroup analyses for predefined factors shows no evidence that the effect of postoperative radiotherapy is different for any group of patients defined by age, sex or histology. Results for stage III disease (for the meta-analysis defined as any T-stage with N2,3 disease) show no clear evidence for neither a detrimental nor a beneficial effect of postoperative radiotherapy. For completely resected N2 disease, HR was 0.97; 95%CI 0.81 to 1.16.

No further RCTs on the use of postoperative radiotherapy in completely resected lung tumours were identified.

For incompletely resected lung tumours, only one additional case series reporting separate results for incompletely resected tumours was found.

The case series published by Ohguri et al.[93] reported on the results of post-operative radiotherapy for incompletely resected lung tumours. This small, retrospective series included 41 patients only, treated between July 1980 and December 2008. Two patients who refused to complete their radiotherapy treatment were excluded. Thirteen out of 41 patients received also adjuvant chemotherapy. For the 23 patients with microscopic residual tumour, rates of 5-year overall survival, local control and progression-free survival were 62%, 75% and 51% respectively. For the 18 patients with macroscopic residual tumour, the rates were 47%, 46% and 19% respectively.

Justification of GRADE scores

For progression-free survival in patients with completely resected tumours, the lack of blinding in the majority of studies was considered a sufficiently important limitation for downgrading the level of evidence. Although the confidence interval includes no effect and an appreciable harmful effect, level of evidence was not downgraded for imprecision as both conclusions would lead to a recommendation against post-operative radiotherapy.

The evidence for post-operative radiotherapy in case of N2 disease was based on subgroup analysis of individual patient data of the randomized trials and the CI included both appreciable benefit and harm. Level of evidence was downgraded for both reasons.

As the evidence for postoperative radiotherapy is based on small, retrospective case series of limited quality (no consecutive inclusion of patients based on predefined inclusion criteria) only, the level of evidence was considered to be of very low. No formal evidence profile was compiled.

Conclusion

It is plausible that post-operative radiotherapy has a detrimental effect on overall survival in patients with completely resected N0-1lung cancer (Cochrane PORT meta-analysis 2010, moderate level of evidence).

There are indications that post-operative radiotherapy has no beneficial effect on disease-free survival in patients with completely resected N0-1 lung cancer (Cochrane PORT meta-analysis 2010, low level of evidence).

A beneficial or harmful effect of post-operative radiotherapy on OS or PFS in lung cancer patients with completely resected N2 disease could neither be demonstrated nor refuted (Cochrane PORT meta-analysis 2010, very low level of evidence).

There is insufficient evidence to estimate the effect of post-operative radiotherapy on progression-free or overall survival in patients with incompletely resected lung cancer (IKNL 2011, Ohguri 2013, very low level of evidence).

Other considerations

Completely resected tumours

The Updated Cochrane meta-analysis contains 11 RCTs of which the majority was conducted in previous century. Surgery, staging, radiotherapy techniques and way of response assessment have considerably changed since. Toxicity, which may explain the detrimental effect of radiotherapy, has been reduced by the use of conformal techniques.[94] There is a lack of good clinical trial data to inform on the effect of postoperative radiotherapy using appropriate surgery and staging procedures. Especially for (subgroups of) N2 disease as currently defined, the possible benefit of postoperative radiotherapy remains an unanswered question as the risk for local recurrence is high and observational data suggest improved local control with the use of adjuvant radiotherapy[95] and/or chemotherapy. Also the optimal sequence of adjuvant radiotherapy and chemotherapy is still unclear. Studies have shown acceptable toxicity but so far no clear survival benefit for combined chemoradiation (no systematic search was performed on this subject).[96-98]

Microscopically incompletely resected tumours

The use of post-operative radiotherapy in case of a microscopically incompletely resected tumour has never been investigated in a randomized controlled trial. However, microscopic positive resection margins are a known high risk factor for loco-regional recurrence and published results after post-operative radiotherapy suggest a significant beneficial effect. This possible positive effect on local control must be weighed against the additional acute and long-term toxicity of radiotherapy and the unknown effect on overall survival. Also the effect of post-operative chemotherapy after a R1 resection has not been investigated in randomized controlled trials and it is not known wether post-operative radiotherapy and chemotherapy should be combined, and wether it is combined which sequence is the optimal. Trial data for stage III disease suggest to administer chemotherapy first, followed by radiotherapy.

Macroscopically incompletely resected tumours

If macroscopic disease is left in situ at the end of an operation, evidently further treatment is warranted. Similarly to patients with primarily unresectable disease, concurrent chemoradiation is preferred if the patient is sufficiently fit. As RCTs with less radical treatment are not feasible in this population, GRADE was not applied.[99]

Postoperative radiotherapy in resected early-stage NSCLC

Recommendation	Strength of recommendation	Level of evidence
The use of post-operative radiotherapy is not recommended in lung cancer patients with completely resected, pN0-1 disease.	**strong**	**moderate**
The use of post-operative radiotherapy can be considered in lung cancer patients with completely resected pN2 disease. Decisions should be discussed by a multidisciplinary team.	**weak**	**very low**
The use of post-operative radiotherapy can be considered in patients with microscopically incompletely resected lung cancer. Decisions should be discussed by a multidisciplinary team.	**weak**	**very low**
The use of post-operative (chemo)-radiation is recommended in patients with macroscopically incompletely resected NSCLC.	**strong**	**not assigned**

5.1.5. Primary radiotherapy

According to the NICE guideline[3], patients with stage I-II and stage III-N1 NSCLC who are not suitable for surgery should be offered an assessment by a radiation oncologist specialising in thoracic oncology for radiotherapy with curative intent. Patients who have poor lung function but are otherwise suitable for radical radiotherapy should still be offered radiotherapy, provided the volume of irradiated lung is small.

Based on an analysis of four studies by the Radiation Therapy Oncology Group (RTOG), the Dutch guideline also advises against elective irradiation of mediastinal lymph nodes, as it has no effect on recurrence pattern or median survival.

Other considerations

Tumour size and organs at risk should be considered by the radiation oncologist.[100]

For patients with T1-2 tumours in the periphery of the lung and unfit or unwilling to undergo surgery, stereotactic body radiation therapy (SBRT) is becoming an alternative for conventionally fractionated external beam radiotherapy (either 3D conformal or IMRT). There is now considerable non-randomised evidence supporting SBRT as superior to conventional RT with respect to local control and survival.[100-102]

Ongoing randomized controlled trials of SBRT versus surgery will determine their relative effectiveness. Currently, treatment options for borderline fit patients should be discussed by a multidisciplinary team.

Primary radiotherapy in early-stage NSCLC

Recommendation	Strength of recommendation	Level of evidence
Any early-stage NSCLC patient not eligible for surgery should be offered radical radiotherapy.	**strong**	**not assigned**
For patients with a T1-2 N0 tumour not eligible for lobectomy, alternative treatment options (such as limited resection or radiotherapy) should be discussed in a multidisciplinary team. If radiotherapy is considered, stereotactic body radiotherapy (SBRT) is recommended.	**strong**	**low**

Radiofrequency ablation is suggested as an alternative treatment option.[103] It is to be discussed in a multidisciplinary team. A literature review of this treatment option was not part of the scope of this report.

5.2. Treatment of locally advanced NSCLC (stage cIIIA-cIIIB)

5.2.1. Combined chemo-radiotherapy

The NICE guideline[3] considers chemo-radiotherapy an established approach to treatment with curative intent of patients with NSCLC where surgery is not suitable. Chemoradiotherapy should thus be considered for stage III NSCLC who are not suitable for surgery but potential benefit in survival and risk of additional toxicities should be well balanced. This recommendation is based on a Cochrane review showing increased PFS and OS with chemoradiation compared to radiotherapy alone at the cost of higher rates of acute oesophagitis, neutropenia and anaemia.

The Dutch guideline[7] summarizes three meta-analyses comparing radiotherapy alone with combined chemotherapy and radiotherapy. The addition of cisplatin-containing chemotherapy to radiotherapy results in a 4% increase of 2-year survival.

Update

One recent RCT by Atagi et al.[104] compared radiotherapy with or without daily low-dose carboplatin in elderly patients (older than 70 years old) with NSCLC. Improved OS and PFS with the combination therapy were confirmed. Median overall survival was 22.4 months in the chemoradiotherapy group and 16.9 months in the radiotherapy group respectively. We updated the Cochrane review with this; the result is reported in following table

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Overall survival	11	1807	Hazard Ratio (IV, Random, 95% CI)	0.71 [0.64, 0.79]
Treatment related deaths	15	2269	Risk Ratio (IV, Random, 95% CI)	0.70 [0.41, 1.20]
Acute pneumonitis	10	1373	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.48, 1.04]
Oesophagitis	18	2421	Risk Ratio (M-H, Random, 95% CI)	1.64 [1.22, 2.21]
Neutropenia	8	1031	Risk Ratio (M-H, Random, 95% CI)	5.24 [3.50, 7.83]
Anemia grade 3 to 4	6	1016	Risk Ratio (M-H, Random, 95% CI)	5.31 [1.86, 15.13]

5.2.1.1. *Radiotherapy: dose, fractionation, treatment planning*

The quality of delivered chemoradiation therapy is important to optimize disease-control and minimize toxic effects. The European Organisation for Research and Treatment of cancer (EORTC) has developed recommendations for the planning and delivery of high dose, high precision radiotherapy for lung cancer.[100] At least 3D, image-guided treatment planning is recommended, 4D-CT or respiration-correlated CT is strongly preferred.

For details on the recommendations for patient selection, planning CT and PET scanning, generating target volumes and treatment planning we refer to the original publication.

The Royal college of Radiologists in the UK[105] recommends to use one of the following regimens for patients offered radical radiotherapy:

- CHART – 54 Gy in 36 fractions over 12 consecutive days
- Conventional radiotherapy – 60-66 Gy in daily 2 Gy fractions over 6-6.5 weeks with (neo-adjuvant or) concurrent chemotherapy.

A meta-analysis of the Meta-analysis of Radiotherapy in Lung Cancer collaborative group[106] shows a significant benefit in overall survival from accelerated radiotherapy (60-66 Gy in 4 to 5 weeks) in nonmetastatic NSCLC patients, compared to conventional radiotherapy (five daily fractions of1.8-2 Gy per week and a minimal dose of 60 Gy) in case of non-concurrent schedules.

With current modern planning and delivery techniques, higher total doses can be achieved; however the clinical benefit remains unclear.

5.2.1.2. *Concurrent versus sequential chemoradiation*

The Dutch guideline[7] bases its recommendation to administer chemotherapy concurrently with radiotherapy rather than sequentially on a meta-analysis and five RCTs.

The Nice guideline[3] included a Cochrane meta-analysis published in 2010. It shows longer survival in the patients who had received concurrent chemoradiation compared to sequential chemoradiation but no differences in progression-free survival. Toxicity rates were higher in the concurrent treatment group for acute oesophagitis but not for other adverse events.

Update

The RTOG 9410 study published by Curran et al.[107] in 2011 compared two concurrent treatment schedules (with vinblastine-cisplatin and etoposide-cisplatin respectively) with sequential vinblastine-cisplatin and radiotherapy. Five-year survival was significantly higher for patients treated with concurrent vinblastine-cisplatin (16%; 95%CI 11-22%) compared to sequential vinblastine-cisplatin (10%; 95%CI 7-15%). Acute grade 3-5 non-hematologic toxic effects were higher with concurrent therapy than with sequential therapy but late effects were similar.

We updated the above mentioned Cochrane meta-analysis by O'Rourke with the data of Curran et al. and obtained the following result. Details are given in Appendix 3.6.1.

Following table summarizes the main results:

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
Overall survival	4	753	Hazard Ratio (IV, Random, 95% CI)	0.77 [0.67, 0.89]
Treatment related deaths	6	950	Risk Ratio (IV, Random, 95% CI)	2.02 [0.90, 4.52]
Acute pneumonitis	6	1335	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.47, 1.50]
Oesophagitis	6	1335	Risk Ratio (M-H, Random, 95% CI)	5.08 [2.66, 9.72]
Neutropenia	6	1335	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.96, 1.62]

Conclusion

Patients receiving chemoradiotherapy have a better survival than patients receiving radiotherapy alone but have more side effects, including oesophagitis, neutropenia and anaemia grade 3 to 4.

Patients receiving concurrent chemoradiotherapy have a better survival than patients receiving sequential chemoradiotherapy but have more oesophagitis.

Justification of GRADE scores

Details are given in the GRADE evidence profiles in Appendix 3.5.2 and Appendix 3.6.2.

The recommendation to consider chemoradiotherapy for patients with inoperable stage III NSCLC is based on moderate level of evidence. The evidence on the effect on survival is counterbalanced by evidence on its increased toxicity and the evidence is considered moderate because of inconsistency, with a number of studies and subgroup analysis in the Cochrane review showing no effect.

The recommendation to prefer concurrent to sequential chemoradiotherapy is also based on moderate level of evidence. The evidence on the effect on survival is counterbalanced by evidence on its increased toxicity and the evidence is considered moderate because of inconsistency, mainly in the estimation of toxicity.

Other considerations

Acute oesophagitis is the most important additional toxicity if chemoradiation is prescribed concurrently. The guideline development group consideres acute oesophagitis a manageable, acceptable toxicity in fit patients.

However, based on inclusion criteria of the most important trials on concurrent chemoradiation, De Ruysscher et al. noted that 59% of patients with locally advanced lung cancer are theoretically not eligible for concurrent therapy.[108] Less toxic alternatives, such as sequential chemotherapy and radiotherapy, are needed for these patients.

The following eligibility criteria were applied:

- Younger than 75 years old
- WHO PS 0-2
- Weight loss < 10% in the last 3 months
- FEV1 at least 40% of the age-predicted value
- Adequate cardiac, renal, hematological functions
- At least one comorbidity on a modified Charlson comorbidity index

5.2.2. Neoadjuvant treatment followed by surgery for stage cIIIA-N2 disease

NICE[3] does not formulate a specific recommendation on the use of surgery in patients with stage IIIA-N2 disease. Based on an extensive literature review (mainly based on the Cochrane review by Manser et al.[56]), they conclude that surgery is the treatment of choice for stage cI and cII by consensus given the long term survival after complete resection compared to the natural history of survival. For stage IIIA-N2, they conclude that RCTs could not demonstrate a particular advantage for surgery over chemoradiation but as survival in the surgical arms remained acceptable; it is considered an alternative to chemoradiation. For patients with non-bulky single zone N2 disease, they advise to consider these patients for trials of surgery with or without multimodality treatment.

The Dutch guideline[7] recommends concurrent chemoradiation as standard treatment for stage cIIIA NSCLC with N2 disease. However, for each individual patient, a multidisciplinary team should evaluate the possibility to achieve complete resection with lobectomy in case of proven down-staging of the lymph node disease. This recommendation is based on two RCTs[109,110] that show a lack of benefit for surgery after induction chemotherapy or radiotherapy. The advice to consider lobectomy in selected patients is based on a subgroup analysis of the study of Albain et al.[110]

The two RCTs mentioned in the Dutch guidelines are summarized in Table 30.

The EORTC study published by Van Meerbeeck et al.[109] in 2007 registered 582 patients, of whom 579 gave consent. All patients had unresectable stage IIIA-N2 NSCLC. 'Unresectable' was defined as any N2 involvement by a non-squamous carcinoma or right sided SCC with N2 disease exceeding level R4 or left sided SCC with N2 disease exceeding level 5 and 6. All patients received 3 cycles of induction chemotherapy. In case of response, patients were randomized between surgery or radiotherapy. Overall response rate was 61%. Overall survival and progression-free survival were not significantly different (HR 1.06; 95%CI 0.84-1.35 and HR 1.06; 95%CI 0.85-1.33 respectively) between the two treatment arms. In the radiotherapy arm, there was late grade 3/4 oesophageal and pulmonary and oesophageal fibrosis in 7% and < 1% of the patients respectively. In the surgery arm, 4% of the patients died within 30 days of surgery. 40% received postoperative radiotherapy. There was no information on the further treatment and outcome of patients without response on the induction chemotherapy.

The Cochrane review included two other small RCTs of low quality (unclear sequence generation and unclear allocation concealment) comparing induction chemotherapy followed by surgery or radiotherapy. The study of Johnstone et al. showed no significant difference for overall survival at four years (HR 0.8; 95%CI 0.45-1.42). In the study of Stathopoulos et al., 67 patients were randomized. A significant survival for chemotherapy plus surgery arm was seen (HR 0.39; 95%CI 0.19-0.81). Studies were not pooled due to clinical and statistical heterogeneity.

In the study of Albain et al.[110], patients received induction chemotherapy (cisplatin and etoposide) plus radiotherapy (45 Gy) followed by, if no progression, resection in one group or identical induction chemoradiation followed by radiotherapy to a dose of 61 Gy in the second group. Both groups received two additional cycles of chemotherapy. Randomization took place before the start of induction therapy. Patients were eligible if they had stage IIIA(pN2) NSCLC, evaluated by clinicians to establish that the cancer was potentially technically resectable. 76% of included patients had only one involved lymph node station. No significant difference in OS (HR 0.87; 95%CI 0.70-1.10) but PFS was significantly longer in the surgery group (HR 0.77; 95%CI 0.62-0.96). Mortality was 8% in the surgery group and 2% in the chemoradiation group. Subgroup analysis based on type of surgery was considered at high risk of selection bias.

Update

No additional RCTs comparing induction therapy followed by surgery with chemotherapy plus radiotherapy were identified in the literature.

Conclusion

In NSCLC patients with any N2 involvement by a non-squamous carcinoma or right sided SCC with N2 disease exceeding level R4 or left sided SCC with N2 disease exceeding level 5 and 6, induction chemotherapy followed by surgery in case of response results in equal OS and PFS as induction chemotherapy followed by radiotherapy in case of response (Van Meerbeeck 2007, Johnstone 2002, Stathopolous 1996, moderate/low level of evidence).

In patients with stage III NSCLC considered resectable, there are indications that induction chemoradiation followed by surgery improves PFS but not OS compared to induction chemoradiation followed by completion of radiotherapy (Albain 2009, low level of evidence).

Other considerations

The trial of Albain et al. included patients with stage IIIA-N2 disease considered technically resectable by a multidisciplinary team. In 76% of included patients only one lymph node station was involved. Median PFS appeared to be 2 months longer in the surgery group compared to the radiotherapy group, however its evaluation may be hampered by the radiological changes induced by the surgery. This possible advantage must also be balanced with overall long term morbidity and quality of life. Unfortunately,good quality data on these outcomes are lacking.

The use of neo-adjuvant chemotherapy followed by surgery in selected N2 disease is supported by the good survival results in patients with N1 disease and unexpected (minimal) N2 disease. The toxicity is acceptable and probably lower compared with concurrent chemoradiation.

However, the following needs to be considered:

- A meta-analysis[111] suggests no significant difference between preoperative chemotherapy or chemoradiation. The meta-analysis is based on four randomized studies, of which two small studies published in abstract only. These two small studies could not be included in the meta-analysis as insufficent data for stage IIIA patients were available. Meta-analysis of the two other randomized trials shows a HR of 0.93 (95%CI 0.54-1.62) for overall survival. Importantly, in the largest RCT of Thomas et al., all patients who were treated with preoperative chemotherapy and surgery received postoperative radiotherapy up to 54 Gy in case of negative resection margins. Another underpowered RCT published in 2012[112] did not find a statistically significant difference in overall survival (HR 0.77; 95%CI 0.42-1.41) between preoperative chemotherapy or chemoradiation.
- As concurrent chemoradiotherapy has been shown to be superior to sequential chemotherapy and radiotherapy, induction chemoradiotherapy may be preferable to ensure optimal prognosis in case no surgery is performed.
- If preoperative chemotherapy or chemoradiation is used, it is important that time needed for response assessment is as short as possible to avoid prolonged overall treatment time and repopulation of the tumour in case no surgery is performed and chemo(radiation) treatment is completed.In the study of Albain et al.n response assessment was performed seven days before completion of induction chemoradiation, so that radiotherapy could be continued without interruption in case no surgery was performed.[110] Observational studies have reported accelerated regrowth of non-small-cell tumours after induction chemotherapy, demonstrating the need to keep the interval between induction chemotherapy and further treatment as short as possible and no longer than 2-3 weeks.[113, 114]
- In a considerable proportion of patients, neoadjuvant chemotherapy does not result in mediastinal downstaging. In a case series published by Lorent et al, 60 out of 131 patients (35%) had stable disease or progressive disease when they were re-staged after induction chemotherapy. Of the 75 patients who underwent surgery, 19 (25%) had postoperative radiotherapy.[115]).

Treatment of stage cIII NSCLC

Recommendation	Strength of recommendation	Level of evidence
Chemoradiotherapy is recommended for patients with stage III NSCLC.	**strong**	**moderate**
Induction therapy followed by surgery can be considered in selected patients with stage IIIA-N2 disease considered resectable at the start of treatment. **Optimal treatment in patients with limited stage IIIA-N2 disease should be discussed by a multidisciplinary team taking into account resectability, response to induction treatment, and the availability of surgical expertise.**	**weak**	**low**
When patients are considered for chemoradiation, it is recommended to offer concurrent chemoradiation in preference to sequential therapy if no contra-indications are present.	**strong**	**moderate**
Induction therapy followed by surgery is not recommended in patients with stage IIIA-N2 disease considered unresectable at the start of treatment.	**strong**	**moderate**

Good clinical practice

If preoperative chemoradiation is used, timely response assessment should be performed such that the overall treatment scheme is not interrupted in case no surgery is performed.

If preoperative chemotherapy is used and surgery cannot be performed, the time interval between chemotherapy and radiotherapy should be kept as short as possible and not exceed 2-3 weeks.

5.2.3. Treatment of tumours involving the chest wall and sulcus superior tumours

Lung cancers that occur in the apex of the chest and invade apicl chest wall structures are called superior sulcus tumours or Pancoast tumours. As noted in the NICE guideline, the exact definition of Pancoast tumours is controversial. The American College of Chest Physicians defines a Pancoast tumour as follows: "A tumour can be classified as a Pancoast tumour when it invades any of the structures at the apex of the chest, including the most superior ribs or periosteum, the lower nerve roots of the brachial plexus, the sympathetic chain near the apex of the chest, or the subclavian vessels. These tumours are now divided into anterior, middle and posterior compartment tumours depending on the location of the chest wall involvement in relation to the insertions of the anterior an middle scalene muscles on the first rib. A syndrome of pain radiating down the arm is no longer a prerequisite for an apical tumour to be designated a Pancoast tumour."[116]

For tumours growing towards the chest wall, the Dutch guideline[7] recommends an en bloc resection. For tumours growing into the superior vena cava, the aortic adventitia, the diaphragm or the pericardium, surgery is considered possible in selected cases.

According to NICE[3], for patients with T3 NSCLC with chest wall involvement who are undergoing surgery, complete resection of the tumour should be the aim by either extrapleural or en bloc chest wall resection.

For Pancoast tumours, they advise to treat in the same way as other types of NSCLC: offer multimodality therapy according to resectability, stage of the tumour and performance status of the patients. Literature search to compare radiotherapy alone with neoadjuvant (chemo)radiation followed by surgery for Pancoast tumours could not identify any relevant study.

Observational studies often referred to have shown good results treating patients with a pancoast tumour with induction chemoradiation and surgical resection. For example, Rusch et al.[117] reported on 110 patients with a N0-1 sulcus superior tumour. Eighty percent underwent thoractomy after induction chemoradiation, in 76% complete resection was achieved. Postoperative mortality was limited to 1.8%. Five-yer survival was 44%. In a case series of 76 Japanese patients, a 5-year disease-free and overall survival of 45% and 56% respectively was achieved.[118]

De Leyn et al.[119] reported on 32 patients with a superior sulcus tumour or a central T4 tumour. Thirty patients completed induction therapy. Overall complete resectability was 78%. In 14 patients, a chest wall resection was necessary. 5-year survival in the intention-to-treat population was 74% (median follow-up 26.5 months).

Update

One recent case series reporting the results of surgery for NSCLC with metastatic pleural extension was found.

Mordant et al.[120] reported on 32 patients with NSCLC and malignant pleural extension treated with surgery between 1983 and 2006. Median survival was 15 months and a 5-year survival of 16% (95%CI 6.9-33.6%) was achieved, at the cost of a 90-day postoperative morbidity of 34% and mortality of 16%. 5-year survival was compared with a control group

consisting of patients found to have unresectable pleural disease at the time of surgery. 5-year survival in the control group was 0%.

Conclusion

There is insufficient evidence to evaluate the effect of surgery in the treatment of NSCLC tumours with chest wall involvement and sulcus superior tumours.

There is no evidence of a difference in outcome comparing primary chemoradiation with induction therapy followed by surgery as treatment of NSCLC tumours with chest wall involvement and sulcus superior tumours

Other considerations

Historically, long term survival has been achieved with surgical treatment (± neoadjuvant treatment) in selected patients with NSCLC tumours involving the pleura, chest wall and Pancoast tumours. However, no comparative data with contemporary chemoradiation are available in terms of survival or toxicity. As very good long term results can be achieved with R0 resection, the guideline development group is of the opinion that surgery should be considered in the majority of patients.

Tumours involving the parietal pleura or the chest wall, and sulcus superior tumours

Recommendation	Strength of recommendation	Level of evidence
Surgery should be considered for patients with NSCLC involving the parietal pleura or the chest wall if R0 resection is considered feasible.	**strong**	**very low**
Neoadjuvant chemoradiation followed by surgery and consolidation chemotherapy or radical chemoradiation can be considered for patients with sulcus superior NSCLC if R0 resection is considered feasible. Treatment decisions should be discussed by a multidisciplinary team with an experienced thoracic surgeon.	**strong**	**very low**

5.3. Treatment of metastatic (stage cIV) and recurrent NSCLC

5.3.1. Use of chemotherapy in general versus best supportive care (BSC).

According to the ASCO guideline of 2011(update of 2009)[4], evidence supports the use of chemotherapy in patients with stage IV NSCLC with ECOG/Zubrod PS of 0, 1, and possibly 2. This is based on a recent meta-analysis[74] that compared the efficacy of chemotherapy with BSC and showed a benefit to chemotherapy in reduction of risk of death and an increase in 1-year survival. The meta-analysis included 16 trials with a total of 2,714 patients; 12 trials used platinum-based regimens, and 13 reported the PS. The meta-analysis found that patients with a PS of 2 also received a benefit, although it was less than the benefit seen in patients with a PS of 0 to 1. In an RCT with 725 participants comparing chemotherapy plus BSC versus BSC alone, the most common grade 3 or 4 AEs were hematologic AEs, nausea, and vomiting. Rare but serious AEs included neurologic and renal toxicities.

The Dutch guideline[7] recommends to start chemotherapy as soon as possible based on a individual based meta-analysis of 2008[74] on 2714 patients showing a significant benefit of chemotherapy (HR, 0.77; 95% CI, 0.71 to 0.83; P =< 0.0001), equivalent to a relative increase in survival of 23% or an absolute improvement in survival of 9% at 12 months, increasing survival from 20% to 29%.

The update yielded no publications dealing with this question

5.3.2. What is the most effective first-line chemotherapy?

5.3.2.1. Receptor tyrosine kinase inhibitors (EGFR TKI) as first-line treatment of patients with advanced EGFR mutation positive NSCLC

The ASCO guideline[4] recommends the possible use of gefitinib as first line treatment of patients with advanced EGFR mutation positive NSCLC.

The Dutch guideline[7] recommends the use of a receptor tyrosine kinase inhibitors (either gefitinib or erlotinib) as first-line treatment of patients with advanced EGFR mutation positive NSCLC based on two randomised Japanese phase III studies where EGFR mutation positive patients were randomly allocated to either a EGFR TKI or chemotherapy and 5 RCT where the effect of EGFR TKI was measured in a subgroup analysis among EGFR mutation positive NSCLC. EGFR TKI as first line treatment is not recommended in unselected patients or patients that are EGFR mutation negative, based on subgroup analysis of 5 RCT.

In the update we found a high quality meta-analysis of Bria et al, pooling 3 studies where EGFR mutation positive NSCLC patients were randomly selected to either a EGFR TKI or chemotherapy and where a statistically significant effect was found on progression free survival (HR: 0,31 (95 % CI 0,17–0,55) p<0.0001) and response rate (HR: 2,30 (95 % CI 1,88–2,81) p<0,0001) but not on overall survival (HR: 0,97 (95 % CI 0,64–1,47) p= 0,88). The limited effect on overall survival despite the large effect on progression free survival would be due to the cross over design of the trials, where patients in the control group that progress get an EGFR TKI that effectively slows down progression as well. All studies in the meta-analysis were performed on Asian patients. A meta-analysis by Liu et al pooled randomised and non randomised studies and was excluded. Petrelli et al pooled first and second line studies and was also excluded.

Rosell et al undertook the open-label, randomized phase 3 EURTAC trial at 42 hospitals in France, Italy, and Spain. Eligible participants were adults (>18 years) with NSCLC and activating EGFR mutations and with no history of chemotherapy for metastatic disease. Patients either received oral erlotinib 150 mg per day or 3 week cycles of standard intravenous chemotherapy of cisplatin 75 mg/m^2 on day 1 plus docetaxel (75 mg/m^2 on day 1) or gemcitabine (1250 mg/m^2 on days 1 and 8). Carboplatin (AUC 6 with docetaxel 75 mg/m^2 or AUC 5 with gemcitabine 1000 mg/m^2) was allowed in patients unable to have cisplatin. The pre-planned interim analysis showed that the study met its primary endpoint; enrolment was halted, and full evaluation of the results was recommended. At data cut-off (26 January, 2011), median PFS was 9,7 months (95% CI 8,4-12,3) in the erlotinib group, compared with 5,2 months (4,5–5,8) in the standard chemotherapy group (hazard ratio 0,37, 95% CI 0,25–0,54; p<0,0001). Main grade 3 or 4 toxicities were rash (11 [13%] of 84 patients given erlotinib *vs.* none of 82 patients in the chemotherapy group), neutropenia (none *vs.* 18 [22%]), anaemia (one [1%] *vs* three [4%]), and increased amino-transferase concentrations (two [2%] *vs.* 0). Five (6%) patients on erlotinib had treatment-related severe adverse events compared with 16 patients (20%) on chemotherapy. One patient in the erlotinib group and two in the standard chemotherapy group died from treatment-related causes.

One publication of Zhou et al reported on the OPTIMAL study, an open-label, randomised phase 3 trial at 22 centres in China, whose results were already included in the meta-analysis of Bria et al.

5.3.2.2. Platinum vs. non platinum containing regimens

The ASCO guideline[4] of 2011 recommends a combination of two cytotoxic drugs for first line therapy in patients with a PS of 0 or 1. Platinum combinations are preferred over non-platinum combinations because they are superior in terms of response rate and marginally superior in OS. Meta-analyses (MAs) were published comparing platinum- with non–platinum containing regimens. The number of participants in the MAs ranged from 23 512 to 7633 patients, and the number of participants in the individual RCTs ranged from 28 117 to 1725 patients. The toxicities reported were higher with platinum agents. AEs specific to platinum include nephrotoxicity and GI problems. Twelve individual trials showed statistically significantly higher hematologic toxicities in platinum treatment arms, and seven trials showed significantly higher non-hematologic toxicities in platinum arms. Contraindications to platinum-based therapy include allergy to cisplatin or carboplatin, baseline hearing loss, renal insufficiency, intolerable nausea despite optimal emesis prophylaxis, intolerance to corticosteroids needed for emesis prophylaxis and patient refusal to take a platinum drug. ASCO considers that for these patients, non-platinum combinations are acceptable alternatives.

The Dutch guideline[7] also recommends platinum based regimens if tolerated by the patient, based on a meta-analysis showing a better tumour response (OR 1.62, 95 %CI 1.46 – 1.80) and a better 1-year survival (34 % vs. 29 %; OR 1.21, 95% CI 1.09– 1.35).

The update yielded no publications dealing with this question.

5.3.2.3. Cisplatin vs. Carboplatin

The ASCO guideline[4] considers the choice of either cisplatin or carboplatin acceptable. The evidence suggests that cisplatin combinations have a higher response rate than carboplatin and may improve survival when combined with third generation agents. Carboplatin is less likely to cause nausea, nephrotoxicity, and neurotoxicity than cisplatin but is more likely to cause thrombocytopenia.

This recommendation is based on a lack of consistent superiority of either agent in terms of OS, toxicity or quality of life across the literature. ASCO identified three MAs and nine individual RCTs that compared cisplatin with carboplatin in combination with a variety of other cytotoxic drugs. The participant size of the individual RCTs ranged from 15 343 to 1218 patients. Two literature-based MAs and one individual patient data MA (IPDMA) found significantly better response rates with cisplatin versus carboplatin. The three MAs and three individual trials found no significant differences in survival between cisplatin and carboplatin. In the MAs, cisplatin was superior to carboplatin in terms of survival in certain subgroups, including non-squamous NSCLC, and when combined with third-generation agents.

The Dutch guideline[7] on the contrary recommends cisplatin as a first choice combined with a third generation agents for non-squamous NSCLC based on a meta-analysis showing that carboplatin was associated with

12% higher relative hazard of death (HR: 1,12; 95%CI: 1,01-1,23) in the subgroup of non-squamous NSCLC although the effect is comparable when considering all (HR: 1,07; 95%CI: 0,99-1,15).

No additional evidence was found in the update.

5.3.2.4. Which doublet therapy?

The ASCO guideline[4] considers the choice of either cisplatin or carboplatin acceptable. Drugs that may be combined with platinum include the third-generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. Some cisplatin-based combinations lead to better outcomes than others. Observations that docetaxel/cisplatin was superior to vinorelbine/cisplatin in a general NSCLC population, that pemetrexed/cisplatin was superior to gemcitabine/cisplatin for patients with non-squamous NSCLC, and that gemcitabine/cisplatin was superior to pemetrexed/cisplatin for patients with squamous NSCLC were based on individual clinical trials or retrospective (although pre-planned) subgroup analyses. They consider that these data are not sufficient to narrow down the selection of a platinum-based doublet to only two choices based on efficacy alone, and assert that the clinician must often choose one chemotherapy regimen over another based on other factors, including drug schedule and AEs.

The Dutch guideline[7] also considered the evidence insufficient to recommend a specific schedule bud does not recommend the combination pemetrexed/cisplatin for patients with squamous NSCLC based on the data above. Third generation cytotoxic agents are superior to second generation, based on a Cochrane review.

5.3.2.5. Addition of Bevacizumab to doublet chemotherapy.

The ASCO guideline[4] considers the addition of bevacizumab to carboplatin plus paclitaxel in patients with advanced NSCLC as a reasonable clinical option under the following conditions: the patients should have a good performance status (ECOG 0-1), not have brain metastases, no dominant squamous cell histology or hemoptysis and have no history of bleeding diathesis or coagulopathy. The dose of bevacizumab should follow study ECOG 4599, at 15mg/kg.

This recommendation is based on the clinically and statistically significant results found in one clinical trial. It is unknown if the survival benefit of bevacizumab is exclusive to its use with paclitaxel and carboplatin, but bevacizumab is not recommended in combination with cisplatin and gemcitabine given the lack of survival benefit in the AVAiL trial. Despite this selected population, treatment related mortality appears higher in patients treated with bevacizumab, and the risk-benefit ratio in patients >70 years of age may be worse.

The Dutch guideline does not recommend the addition of a third cytostaticum to doublet, but asserts in line with ASCO that bevacizumab can be considered as an addition to carboplatin plus paclitaxel for non-squamous cell tumours.

Update

We found two systematic reviews on the subject, with a slightly different focus. Botrel et al 2011[121] pooled 4 trials, comprising 2200 patients. The appropriateness of these pooling can be questioned given the heterogeneity of the interventions, studies using the doublet carboplatin plus paclitaxel and the doublet cisplatin and gemcitabine are pooled here, resulting in considerable heterogeneity, which is subsequently treated with a random effects model. We excluded the second systematic review of Lima et al 2011 [122] because also studies including second line patients were pooled here. Starting from the search date of Botrel et al, we found two publications (Reck et al. 2010[123] and Niho 2012[124]) but dealing with the same trial results that were already pooled by Botrel et al.

Because we considered the pooling of Botrel et al. not justified we pooled the 2 studies on the addition of bevacizumab ourselves, details are given in appendix 5.3.2.5. The pooled estimate of the overall survival was 0.80 (95 % CI 0.69 to 0.94) and the pooled odds ratio for the response rate 0.65 (95 % CI 0.57 to 0.75).

Other considerations

The guideline development group decided not to make a recommendation on bevacizumab as it is neither registered nor reimbursed in Belgium for this indication.

5.3.2.6. *Addition of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) to doublet chemotherapy.*

The ASCO guideline[4] does not recommend using epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKI) with doublet chemotherapy regimens outside of clinical trials until future trials demonstrate the utility of their use in specific patient subgroups. They base their recommendation on 4 studies, which have found no benefit to adding an oral EGFR TKI to new, platinum-based doublet chemotherapy.

The Dutch guideline[7] takes the same line based on the 4 same studies.

In the update, we excluded a meta-analysis of Chen et al. who pooled studies that had considerable clinical and statistical heterogeneity.

5.3.3. *Second and third line chemotherapy*

ASCO[4] considers docetaxel, erlotinib, gefitinib, or pemetrexed is acceptable as second-line therapy for patients with advanced NSCLC with adequate PS when the disease has progressed during or after first-line, platinum-based therapy. These recommendations include both cytotoxic chemotherapy and targeted therapies and are based on nine new phase III RCTs, two new phase II RCTs, a new IPDMA, a new systematic review, and two subgroup analyses of phase III trials on second-line chemotherapy that showed overall benefit for docetaxel, erlotinib, gefitinib, or pemetrexed. Five new phase III RCTs, one phase II RCT, two retrospective analyses of clinical trials, one systematic review, and one IPDMA were on chemotherapy; one phase II RCT and one phase III RCT were on combination biologic therapy; and three phase III trials were on schedules of administration. Seven of the RCTs compared new treatment (with or without standard treatment) with standard treatment or compared new targeted agents with placebo. Pemetrexed was compared with docetaxel, erlotinib was compared with placebo, and gefitinib was compared with BSC/placebo and also with docetaxel. Study size ranged from 120 to 1,692 patients. The recommendation for docetaxel is supported by a systematic review. Of the eight new second-line RCTs on treatment, with primary efficacy end points, one showed a statistically significant benefit in OS, and four of them showed non-inferiority. Three trials were negative; two trials used combinations including bevacizumab plus erlotinib, and the other trial compared gefitinib versus placebo. Four studies compared different dosages or schedules of administration of docetaxel. The three trials comparing schedules of administration found that there was no survival advantage to weekly administration (compared with every-3-week administration); hematologic toxicities were generally significantly greater in the every-3-week schedule. In some of the studies that compared docetaxel with newer agents, AEs of docetaxel included neutropenia, febrile neutropenia, use of granulocyte colony-stimulating factor, diarrhoea, and alopecia. The most common AEs of erlotinib were rash and diarrhoea. In addition, a low incidence of interstitial lung disease was seen. Neutropenia, febrile neutropenia, and use of granulocyte colony-stimulating factor were seen less often after pemetrexed than after docetaxel. Common AEs of gefitinib were rash and diarrhoea; in addition, a low incidence of interstitial lung disease was observed.

The Dutch guideline[7] also considers docetaxel, erlotinib, gefitinib, or pemetrexed, acceptable as second-line therapy and does not recommend combination therapies in second line, based on a systematic review of Di Maio et al.

Both ASCO and the Dutch guideline recommend considering erlotinib as third line therapy for persons who did not receive either erlotinib or gefitinib before, based on one RCT that shows a small benefit.

While updating the guidelines, 3 systematic reviews were identified:

Qi et al 2012[125] compared docetaxel-based doublet with single-agent docetaxel in patients with histologically proven non-small-cell lung cancer. They found eight randomized clinical trials (totally 2126 patients). Meta-analysis showed that there was significant improvement in PFS (HR 0.81, 95%CI 0.69-0.96, p=0.013) and overall response rate (OR 1.42, 95%CI 1.13-1.80, p=0.03) in docetaxel-based doublet group, compared with docetaxel alone, though the pooled HR for overall survival (HR 0.93, 95%CI 0.80-1.07, p=0.308) showed no significant difference between the two groups. However, there were more incidences of grade 3 or 4 neutropenia (OR 1.2, 95%CI 1.00-1.45, p=0.05), thrombocytopenia (OR 4.53, 95%CI 1.75-11.75, p=0.002), and diarrhoea (OR 1.78, 95%CI 1.16-2.74, p=0.008) in docetaxel-based doublet group. With regard to the risk of grade 3 or 4 anaemia (OR 1.95, 95%CI 0.62-6.17, p=0.25), fatigue (OR 1.09, 95%CI 0.75-1.59, p=0.66), and nausea and vomiting (OR 1.75,

95%CI 0.78-3.91, p=0.17), there was no significant difference between the two groups.

Qi et al. 2012[126] compared pemetrexed-based doublet with single-agent pemetrexed as second-line treatment for advanced non-small-cell lung cancer and found five randomized clinical trials (totally 1186 patients). Meta-analysis showed that there was significant improvement in PFS (HR 0.82, 95% CI 0.71-0.95, p=0.007) and overall response rate (OR 2.39, 95%CI 1.58-3.62, P<0.001) in pemetrexed-based doublet group, compared with pemetrexed alone, though the pooled HR for overall survival (HR 0.89, 95%CI 0.76-1.04; p=0.129) showed no significant difference between the two groups. However, there were more incidences of grade 3 or 4 neutropenia (OR 2.3, 95%CI 1.4-3.77, p=0.001), thrombocytopenia (OR 6.41, 95%CI 2.57-16.0, P<0.001), and leucopenia (OR 2.45, 95% CI 1.13-5.34, p=0.024) in pemetrexed-based doublet group. With regard to the risk of grade 3 or 4 anaemia (OR 0.71, 95% CI 0.17-2.91, p=0.629) and fatigue (OR 1.47, 95%CI 0.92-2.35, p=0.104), there was no significant difference between the two groups. They concluded that pemetrexed-based doublet therapy didn't gain any benefit in survival but significantly improved PFS and better objective response rate (ORR) compared with single-agent pemetrexed as second-line therapy for advanced non-small-cell lung cancer. However, more incidences of grade 3 or 4 neutropenia, thrombocytopenia, and leucopenia were observed in pemetrexed-based doublet group.

Jiang et al.[127] compared gefitinib with docetaxel and identified four multicenter, randomized controlled trials involving 2257 patients with previously treated advanced NSCLC. The pooled HRs showed no significant difference in OS and PFS between the two groups (HR: 1.02, 95%CI 0.92–1.12, ; HR: 0.97, 95% CI: 0.88–1.07, respectively). Gefitinib significantly improved overall response rate (RR: 1.58, 95%CI 1.02–2.45,) and quality of life (QoL) (RR: 1.55, 95%CI 1.27–1.88, by Functional Assessment of Cancer Therapy-Lung and RR: 1.86, 95% CI: 1.43–2.42, by Trial Outcome Index, respectively). Gefitinib had fewer grade 3 or 4 neutropenia and fatigue (OR: 0.02, 95%CI 0.01–0.03, and OR: 0.47, 95%CI 0.32–0.70, respectively), but more grade 3 or 4 rash (OR: 2.87, 95% CI: 1.24–6.63,) than docetaxel. The grade 3 or 4 nausea, vomiting and diarrhoea and symptom improvement were comparable between the two drugs. They concluded that, although similar OS and PFS, gefitinib showed an advantage over docetaxel in terms of objective response rate, QoL and tolerability.

TITAN[128] was an international, randomised multicentre, open-label, phase 3 study that was done at 77 sites in 24 countries that was halted prematurely and was inconclusive.

Other considerations:

It is important to note that the studies on the effectiveness of gefitinib and erlotinib in second line were done in populations without knowledge of the EGFR mutation status. There is no proof that this expensive treatment has any effect in EGFR wildtype patients. Therefore the guideline development group decided not to follow NICE or the Dutch guidelines and not to recommend these drugs in EGFR wildtype patients.

At the demand of the guideline development group available information on subgroup analysis involving EGFR wildtype patients was put together and a preliminary meta-analysis was done.

In a number of studies that compared EGFR TKI with chemotherapy EGFR mutation status was measured, in most cases however this was only possible in a limited proportion of the patients in the trials.

The presence of EGFR mutations is an important treatment modifier for both EGFR-TKI and chemotherapy. According to the INTEREST study, twice as many EGFR mutation positive patients responded to chemotherapy as compared to EGFR mutation negative patients.

Kim et al. and Douillard et al.,[129, 130] in a preplanned analysis of the INTEREST study, prospectively analyzed available tumor biopsies to investigate the relationship between biomarkers and clinical outcomes, and compared the effect on overall survival and progression free survival of gefitinib with docetaxel in 253 EGFR mutation negative patients and 44 mutation positive patients. Based on the fact that the test for interaction was negative they claim no evidence for a difference in effect, however, a test for interaction lacks sensitivity, and the study was not sufficiently powered to detect this interaction. There was no effect on overall survival and a tendency favoring docetaxel for PFS.

The TITAN study,[128] in a subgroup analysis, compared the effect of erlotinib with chemotherapy, either premetrexed or docetaxel, in 11 EGFR mutation positive patients with 149 EGFR wild type patients. They make similar claims as in the INTEREST study that there is no evicence of a difference in effect, however, as in the INTEREST study, the test for interaction used lacked power.

A randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small cell lung cancer who have wild-type or mutant EGFR (the DELTA trial, only published as an abstract in Annual Meeting Proceedings online supplement to the June 20, 2013, issue of Journal of Clinical Oncology) looked at the effect in 198 wild type patients.

A dedicated 2nd line randomised phase III superiority trial in selected EGFR wild type patients (TAILOR, a study by an independent group of Italian investigators, only published as an abstract in Annual Meeting Proceedings online supplement to the June 20, 2013, issue of Journal of Clinical Oncology) compared docetaxel (n=110) with erlotinib (n=108) as 2nd line for EGFR wild type NSCLC in patients with PS 0-2 advanced NSCLC with disease progression after first line platinum-based doublet. They reported the effect on progression free survival but the data on overall survival were immature.

Finally, a subgroup analysis was done in a superiority study (HORG, reported by Karampeazis et al.[131]) where pemetrexed was compared with erlotinib in pre-treated patients with metastatic non–small cell lung cancer. Mutation status was determined only in a 121 out of 332 patients and the total number of EGFR mutations found was left unreported. Time to progression was reported but not the progression free survival.

A preliminary meta-analysis shows a pooled effect on progression free survival favoring chemotherapy and no effect on overall survival. This subgroup analysis should be treated with extreme caution, as in most studies only in a minority of patients EGFR status could be determined. However, the claims of the investigators that the effect is similar in EGFR mutated and non mutated patients is not supported by the facts, because the test for interaction used could not possibly have the power to detect this difference.

Figure 3 – Pooled (subgroup) effect on progression free survival in EGFR wildtype patients

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
DELTA	0.3646	0.1468	25.6%	1.44 [1.08, 1.92]
INTEREST	0.2151	0.1413	27.7%	1.24 [0.94, 1.64]
TAILOR	0.3577	0.1369	29.5%	1.43 [1.09, 1.87]
TITAN	0.2231	0.1791	17.2%	1.25 [0.88, 1.78]
Total (95% CI)			**100.0%**	**1.35 [1.16, 1.56]**

Heterogeneity: Chi² = 0.91, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 3.99 (P < 0.0001)

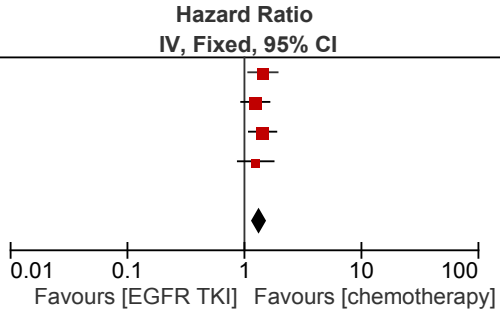
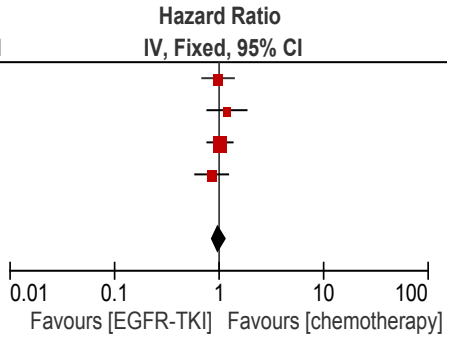


Figure 4 – Pooled (subgroup) effect on overall survival EGFR wildtype patients

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
DELTA	-0.0202	0.179	24.2%	0.98 [0.69, 1.39]
HORG	0.174	0.2221	15.7%	1.19 [0.77, 1.84]
INTEREST	0.0198	0.1435	37.7%	1.02 [0.77, 1.35]
TITAN	-0.1625	0.1863	22.4%	0.85 [0.59, 1.22]
Total (95% CI)			**100.0%**	**0.99 [0.84, 1.18]**

Heterogeneity: Chi² = 1.40, df = 3 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)



5.3.4. Crizotinib for the second line treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer

A horizon scanning report[132] identified one unpublished faze III trial (only abstract available, quality could not be assessed), Profile 1007, an ongoing international, multi-centre, open-label randomised trial with 237 recruiting study centres in Europe, North and South America, Asia and Australia investigating the efficacy and safety of crizotinib versus standard chemotherapy (pemetrexed or docetaxel) as second line treatment in patients with advanced NSCLC with a specific gene profile involving the ALK gene. 173 patients were randomly assigned to the intervention group consisting of 250 mg crizotinib orally twice daily, and 174 patients were allocated to the control arm receiving chemotherapy with either pemetrexed, 500 mg/m2 iv or docetaxel, 75 mg/m2 iv. The interim analysis after a median follow-up of about 12 months showed a statistically significant improvement (PFS) for the intervention group as determined per independent radiology radiology review (crizotinib group 7.7 months vs. chemotherapy group 3.0 months; HR 0.49 (95 % CI 0.37-0.64; p<0.0001)). In addition, the secondary endpoint objective response rate (ORR) was significantly better in the crizotinib group (65.3 % vs. 19.5 %; HR 3.4 (95 % CI 2.5-4.7; p<0.0001)). The median overall survival (OS) was with 20.3 months (crizotinib group) vs. 22.8 months (chemotherapy group) similar in both treatment arms, but results were still immature and may have been confounded by crossover (111 patients of the chemotherapy group crossed over to crizotinib outside the Profile 1007 trial).

5.3.5. Maintenance therapy

According to the Dutch guideline,[7] maintenance chemotherapy may be considered using either erlotinib or pemetrexed in patients who do not show progression of the tumour in first line therapy, and that it is important to take into account residual toxicity and patient preferences. Patients with an activating EGFR mutation should get an EGFR-TKI as maintenance therapy.

These recommendations are based on a meta-analysis of 13 RCTs showing an improvement of the progression free survival and a marginal improvement of the overall survival.

In the update a high quality systematic review and meta-analysis of Behera et al 2012 included twelve studies with a total of 4286 patients. However, in the systematic review studies with very different schedules were pooled and the appropriateness of some of these this pooling is debatable. Single agent maintenance therapy was superior in improving OS (HR 0.86; 95%CI 0.80–0.92; p=0.0003), this was done pooling switch and continuationmaintenance therapy, clinical implication of this pooling is unclear. There was no significant heterogeneity in the HRs of individual trials (p=0.92, I^2 < 0.05) but this is due to the relative important random uncertainty in the individual studies. Switch maintenance was found to be significantly better (HR 0.84; 95%CI 0.77–0.91; p=0.00026) whereas 'continuation' maintenance was not associated with a statistically significant survival benefit (HR 0.92; 95%CI 0.78–1.09; p=0.33). However, again it must be noted that pooled studies contained very different regimens and that the most important study, the PARAMOUNT study that evaluated maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer was not included as no data on overall survival are available until now (except from a interim analysis).

EGFR-targeted therapy, evaluated in 4 trials, was associated with a significant improvement in OS (HR 0.83; 95%CI 0.74–0.92; p=0.004) and PFS (HR 0.64; 95% CI 0.58–0.71, p < 0.0001).

This pooling can be considered as appropriate. A statistically significant improvement was seen in PFS in patients with maintenance therapy (HR 0.80; 95%CI 0.77–0.84; p < 0.0001). However, the study population was a mix of EGFR positive and negative patients. Lee et al,[133], in a subgroup meta-analysis, found a small benefit of EGFR-TKIs over placebo in the EGFR mutation negative subgroup (pooled HR 0.81; 95%CI 0.68-0.97, p=0.02) but the clinical implications of this is unclear, as EGFR test used in the primary studies may have lacked sensitivity. Switch maintenance was associated with significant improvement in PFS (HR 0.62, 95% CI 0.57–0.67; p<0.0001) whereas continuation maintenance showed a relatively modest improvement in PFS (HR 0.90, 95% CI 0.85–0.95; p=0.007). Cytotoxic agents were associated with significant improvement in PFS (HR 0.85; 95%CI 0.80–0.89; p<0.0001) and similar benefit was seen with EGFR-targeted maintenance therapy.

The ORR in the maintenance arm was 21.25% (7 trials; *n*=1520) as compared to 7% in control arm (6 trials, *n*=1110). In assessing AEs of grade 3 and above, 18% of the patients had toxicities in the maintenance arm (8 trials; *n* = 2006) and 5% of patients in the control arm (7 trials; *n*=1400).

A report of Paz-Ares et al 2012 concerning randomised controlled trial (PARAMOUNT) on the maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer was identified but the results (that are available for the moment) were already included in Behera et al 2012.

Other considerations

A major limitation of the evidence for maintenance therapy is the fact that there is no evidence on whether maintenance therapy is better than second line therapy after relapse. Therefore it is difficult to formulate conclusions on this issue.

Conclusion

Chemotherapy extends overall survival in patients with stage IV NSCLC with ECOG/Zubrod PS of 0 or 1; the effect in patients with a PS 2 is less clear.

Platinum combinations are preferred over non-platinum combinations because they are superior in response rate, and marginally superior in OS.

Compared to Cisplatin, carboplatin associated with 12% higher relative hazard of death (HR 1,12; 95%CI: 1,01-1,23) in the subgroup of non squamous NSCLC although HR is comparable (HR 1,07; 95%CI: 0,99-1,15) in the overall group.

Third generation cytostatica are superior to second generation.

Bevacizumab increases survival and progression free survival when added to carboplatin/paclitaxel but only increases progression free survival when added to cisplatin/gemcitabine.

Adding a EGFR TKI to doublet chemotherapy does not increase overall survival and has only a marginal effect on progression free survival.

Receptor tyrosine kinase inhibitors (EGFR TKI) as first-line treatment of patients with advanced EGFR-mutation positive NSCLC increases progression free survival and has less side effects, there is no evidence of an effect on overall survival, probably due to the cross over design used in the RCTs.

There is preliminary evidence from 1 fase III trial that crizotinib as second line treatment improves progression free survival but not overall survival in ALK-mutation positive NSCLC.

Second line chemotherapy has a statistically significant effect on overall survival in patients with advanced NSCLC and an adequate PS when the disease has progressed during or after first-line, platinum-based therapy.

Docetaxel or pemetrexed (only in non-squamous NSCLC) are acceptable as second-line therapy for patients with advanced NSCLC with adequate PS when the disease has progressed during or after first-line, platinum-based therapy as there is no evidence that one is superior to another. Erlotinib and gefitinib only have a proven effect in EGFR mutation positive NSCLC.

Combination second line therapies have a marginal effect on progression free survival compared to monotherapy but no proven effect on overall survival.

Maintenance therapy may have a beneficial effect on survival but it is unclear if this strategy has an advantage compared with second line therapy after relapse.

Justification of GRADE scores

Details are given in the GRADE evidence profiles in Appendix 3.8.

Treatment of metastatic (stage cIV) and recurrent NSCLC

Recommendation	Strength of recommendation	Level of evidence
The use of chemotherapy in patients with stage IV NSCLC with WHO/ECOG/Zubrod performance status (PS) of 0 or 1 and (based on clinical judgement) in some cases PS 2 is recommended.	**strong**	**high**
Maximal efforts should be made to determine the epidermal growth factor receptor (EGFR) mutation status, using a sensitive and validated method, in all non-squamous NSCLC or in never/very light smokers with mixed squamous/non-squamous NSCLC. It is recommended to use EGFR - tyrosine kinase inhibitors (EGFR TKI) as first-line treatment of patients with advanced EGFR mutation positive non-squamous NSCLC because of the better tolerance.	**strong**	**moderate**
If no EGFR TKI is given as first-line treatment in EGFR mutation positive NSCLC, a EGFR TKI should be offered thereafter, either as switch maintenance or at progression as second-line treatment.	**strong**	**moderate**
In the presence of the equipoise in efficacy for proven wild-type EGFR carriers, issues as residual and expected toxicity, patient preference and societal drug cost are of importance in the decision to administer second line treatment. Pending the publication of further data, the use of TKI's in second or third line should be restricted to either those patients in whom an activating EGFR mutation is present but was not yet treated with a TKI, or those patients who are not considered for further chemotherapy and whose EGFR mutational status could not be determined despite maximal efforts.	**strong**	**very low**
In patients with a WHO performance status of 0 or 1, evidence supports the use of a combination of two cytotoxic drugs for first-line therapy. Platinum combinations are preferred over non-platinum combinations	**strong**	**high**

because they are superior in response rate, and marginally superior in overall survival. Non-platinum therapy combinations are reasonable in patients who have contraindications to platinum therapy.		
In these patients, the choice of either cisplatin or carboplatin is acceptable. Drugs that can be combined with platinum include the third generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine.	weak	low
Pemetrexed is preferred to gemcitabine in patients with non-squamous NSCLC. Pemetrexed use should be restricted to non-squamous NSCLC in any line of treatment.	strong	low
It is recommended to offer second-line chemotherapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line therapy.	strong	moderate
Crizotinib is recommended as second-line therapy in ALK mutation-positive patients.	strong	low
The use of pemetrexed (only in non-squamous NSCLC) or docetaxel is acceptable as second-line therapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line, platinum-based therapy.	weak	very low
Maintenance therapy with pemetrexed can be considered after 4 cycles of chemotherapy in patients without disease progression.	weak	very low

Good clinical practice

It is recommended to offer radiotherapy for palliation of local symptoms to patients with NSCLC.

5.4. Follow-up

After an attempt to evaluate what is the most effective follow-up model for lung cancer, NICE[3] recommend to offer all patients an initial specialist follow-up appointment within 6 weeks of completing treatment to discuss ongoing care, and to offer regular appointments thereafter, rather than relying on patients requesting appointments when they experience symptoms. Additionally, NICE recommend to offer protocol-driven follow-up led by a lung cancer clinical nurse specialist as an option for patients with a life expectancy of more than 3 months and to ensure that patients know how to contact the lung cancer clinical nurse specialist involved in their care between their scheduled hospital visits. NICE do not specify the content of the specialist follow-up.

NICE base these recommendation on three retrospective studies of low quality and states that the paucity of evidence precludes firm evidence-based interventions within this area, and that although several studies identified had looked at specific intervention for follow-up none of these studies were of sufficient quality to allow for evidence based recommendations. The GDG consequently made a consensus recommendation regarding the timing of follow-up. Additionally, It is a research recommendation from NICE that RCTs should be conducted to examine the value of imaging and other interventions to monitor response and recurrent disease.

The Dutch guideline[7] on follow-up and after care recommend that the routine follow-up after surgical treatment of a patient with NSCLC consist of the following components:

- anamnesis
- physical examination
- possibly a chest X-ray

The Dutch further recommend that follow-up by imaging where disease progression can be determined is useful only if there is an active second or third-line treatment available, for tracking and tracing late side-effects.

The Dutch GDG recommends the following follow-up rate after surgical treatment:

- Within the first year after surgery: follow-up every 3 months (4 visits)
- In the second year after surgery: follow-up every 6 months (2 visits)
- Hereafter: follow-up once per year (1 visit) for at least 5 years

The Dutch recommendations build upon on a literature review on evidence-based follow-up care of the lung cancer patient that concludes that this care is straightforward with periodic anamnesis and physical examinations recommended to detect recurrence, that early chest radiographs to detect second primaries "may be reasonable" in small and non-small cell lung cancer patients and that routine use of CT scans, bone scans, brain imaging, and serum tumour markers is not recommended in lung cancer patients. The same review further states that many patients receive more extensive and expensive follow-up after treatment, despite the lack of curative options for recurrent lung cancer or evidence that earlier treatment of recurrence leads to better medical outcomes [134].

In the Dutch guideline this review is supported by several studies including four studies on cost-effectiveness concluding that follow-up is best done in a simple matter (anamneses, physical examination and optionally an X-ray or a low dose CT) and that an extended follow-up including CT (of lung and brains), PET, bronchoscopy with sputum cytology and tumour markers is not indicated unless the patient has symptoms or is participating in a clinical trial.

The Dutch guideline state that the frequency and duration of follow-up visits primarily are based on a judgment and the fact that most relapses and adverse events occur within two years after treatment.

Update

One recent systematic review of moderate quality examined whether follow-up after lobectomy for NSCLC with computed tomography (CT) scanning is of benefit in terms of survival [135].Five studies addressing this question were identified and included in this review and no consensus in literature was found. Three papers showed that CT scanning might improve the survival of patients by detecting local and distant recurrences at an earlier stage in asymptomatic patients (therefore allowing earlier interventions to take place) and one of these papers showed that detection by the use of low-dose CT or simultaneous chest CT plus positron emission tomography-CT led to a significantly longer duration of survival compared with detection by clinical suspicion (2.1 ± 0.3 versus 3.6 ± 0.2 years, p=0.002). The two remaining paper showed that follow-up with CT does not improve survival outcomes regardless of the site of recurrence. One of these studies showed that there was no clinically significant difference in survival whether patients were followed up using a strict CT

protocol compared with a symptom-based follow-up (median survival after recurrence: strict 7.9 months, symptom-based 6.6 months, p=0.219). The authors of the review conclude that further RCTs to assess survival outcomes of patients followed with a CT screening protocol versus a symptom-based follow-up is required to definitely comment on whether survival benefits are present.

Two additional primary studies were identified on the follow-up with PET or PET-CT but none of these studies provided outcomes on survival or QoL and were consequently not used as a basis for recommendations (evidence tables not provided). One of the studies looked at the effectiveness of PET scan in detecting distant metastasis in the long term follow-up of asymptomatic patients operated for NSCLC. The authors concluded that PET imaging appears to be a useful alternative to conventional imaging in asymptomatic patients (65 patients were included and PET scans detected metastasis in 7 patients with one PET scan was proven to be false positive) [136]. Another study looked at whether FDG-PET-CT scan at 3 months post-treatment could lead to early detection of progressive disease amenable for radical treatment in patients treated with curative intent with chemo-radiation. All patients underwent a planned FDG-PET-CT scan at 3 months after the start of radiotherapy. Of the 100 patients included, 24 patients had progressive disease after 3 months. 16/24 of these patients were symptomatic and in all these patients no curative treatment could be offered. Of the 8 asymptomatic patients 3 were potentially amenable for radical therapy (3 % of all patients)[137].

One retrospective study, published after the literature search, was identified by a member of the guideline development group.[138] This study analysed the feasibility and impact of a standardized intensive follow-up on outcomes in 162 patients with NSCLC, who had undergone complete surgical resection with curative intent. Patients with previous malignancy within 5 years before the NSCLC resection and patients who died within 30 days after the resection were excluded. The median OS following surgery was 38.5 months.

The univariate analysis of survival showed a significant association for the following measures: absense of symptoms at time of recurrence; HR (95%CI): 2.09 (1.33-3.28), p=0.001, the diagnostic procedure (physical examination and chest X-ray vs other): HR (95%CI):0.38 (0.24-0.60), p<0.0001 and gender (male/female): HR (95%CI): 0.48 (0.24-0.96), but not for age, histology, disease free survival and site of recurrence. The multivariate analysis showed a significant effect only for the diagnostic procedure (physical examination and chest X-ray vs other): HR (95%CI):0.37 (0.24-0.60), p<0.0001.

Conclusion

There is no consistent evidence on the benefit of systematically performing CT-scans in the follow-up of NSCLC patients after lobectomy in terms of overall survival. Despite the fact that the intervention is as yet unproven, it can be considered to perform a low dose CT once a year to detect second primary tumors in the follow-up of NSCLC patients after lobectomy.

Follow-up

Recommendation
Routine follow-up after treatment with curative intent of a patient with NSCLC consists of at least the following components: • **Anamnesis** • **Physical examination** • **Chest X-ray.**
Follow-up by imaging to detect disease progression is only recommended if there is an active second or third-line treatment available. Imaging may also be useful for tracking and tracing late side-effects.
The following rate for routine follow-up (including anamnesis, physical examination and chest X-ray) after radical treatment is suggested: • **During the first year after treatment: follow-up every 3 months (4 visits)** • **In the second year after treatment: follow-up at least every 6 months (2 visits)** • **Hereafter: follow-up at least once per year for at least 5 years after completing treatment** **The benefit of yearly follow-up with a low-dose CT scan for the detection of a second primary tumor is as yet unproven, but might be considered in patients in whom a second primary tumor would be treated with curative intent.**

6. TREATMENT OF SCLC

6.1. Treatment

6.1.1. Limited stage disease (broadly corresponding to T1-4, N0-3,M0)

6.1.1.1. What is the most effective first line treatment for patients with limited stage disease SCLC (broadly corresponding to T1-4, N0-3,M0)?

NICE[3] recommends to offer patients with limited-stage disease SCLC (broadly corresponding to T1-4, N0-3,M0) four to six cycles of cisplatin-based combination chemotherapy. It is unclear however on what they based their recommendation on as the Cochrane review they refer to does not find a difference. The Cochrane review pools newer and older studies, and in the older studies the standard of care would be considered suboptimal. This leads to considerable heterogeneity and the clinical implications of the meta-analysis is unclear. The Dutch guideline does the same recommendation but limits the number of cycles to a maximum of 4, mentioning but rejecting the results of the meta-analysis based on the above mentioned arguments. They base their conclusions on 2 meta-analyses and the RCT from the Norwegian Lung Cancer Study group.

NICE recommends to consider substituting carboplatin in patients with impaired renal function, poor performance status (WHO 2 or more) or significant co-morbidity, based on 2 RCTs. The Dutch guideline also considers that in some cases carboplatin can replace cisplatin, but is not more specific on the precise indications, based on one RCT.

NICE recommends to offer concurrent chemoradiotherapy to patients with limited-stage disease SCLC and a WHO performance status of 0 or 1 if they present with disease that can be encompassed in a radical thoracic radiotherapy volume. Start the radiotherapy during the first or second cycle of hemotherapy. Offer sequential radical thoracic radiotherapy to patients with limited-stage disease SCLC who are unfit for concurrent chemoradiotherapy but who respond to chemotherapy. This is based on 7 RCT comparing different radiation schemes, whose quality ranges from low to moderate. No studies compared however radiation with no radiation.

The Dutch guideline also recommends concurrent chemoradiotherapy as the preferred option if the patient is fit for this, based on a Cochrane meta-analysis pooling 7 trials that use d platinum chemotherapy concurrent with chest radiotherapy, observing significantly higher 2 and 5-year survival rates when chest radiotherapy (RT) was started within 30 days after the start of chemotherapy (2-year survival: HR: 0.73, 95% CI 0.57-0.94, p=0.01; 5-year survival: HR: 0.65, 95% CI 0.45-0.93, p=0.02).

The Dutch guideline[6] mentions that the best results are obtained using the 'Turrisi' fractionated schedule, however without formally recommending it. This is based on one RCT of Turrisi et al.[139] showing that twice-daily treatment beginning with the first cycle of chemotherapy significantly improved survival as compared with concurrent once-daily radiotherapy (p=0.04 by the log-rank test). After a median follow-up of almost 8 years, the median survival was 19 months for the once-daily group and 23 months for the twice-daily group. The survival rates for patients receiving once-daily radiotherapy were 41 percent at two years and 16 percent at five years. The estimated hazard ratio for death with once-daily treatment as compared with twice-daily treatment was 1.2 (95 percent confidence interval, 1.0 to 1.6). For patients receiving twice-daily radiotherapy, the survival rates were 47 percent at two years and 26 percent at five years. Acute grade 3 esophagitis was significantly more frequent with twice-daily thoracic radiotherapy, occurring in 27 percent of patients, as compared with 11 percent in the once-daily group (p<0.001).

Although there is no conclusive evidence on the optimal radiation scheme and he dose for chest radiotherapy is still under investigation, the guideline development group decided to propose expert opinion based guidance, proposing doses of 45 Gy in 3 weeks with two fractions a day or once daily fractions of higher doses of 60 Gy.

6.1.1.2. *Role of surgery in early-stage SCLC (T1-2a, N0, M0).*

NICE[3] recommends to consider surgery in patients with early-stage SCLC (T1-2a, N0, M0). This recommendation was based on two retrospective comparative studies (Badzio et al., 2004; Screiber et al., 2010). The Dutch guideline also recommends considering surgery, based on case series. Both guidelines state that it is difficult to take conclusion because of the very specific enrollment of the patients in the studies, including the fact that often the small cell tumour is a chance finding when exploring a solitary nodule. they state that it should be followed by adjuvant chemotherapy, but evidence for this is limited. The role of neo-adjuvant chemotherapy is unknown. The guideline development group however did not consider recommendations on surgery relevant.

6.1.1.3. *Maintenance chemotherapy in patients responding to induction chemotherapy*

NICE[3] does not recommend maintenance therapy for patients with limited disease outside of a clinical trial, based on 3 RCTs where different forms of[139] maintenance therapy were assessed but that were inconclusive. The Dutch guidelines does not deal with this issue separately.

6.1.1.4. *Prophylactic cranial irradiation*

NICE[3] recommends prophylactic cranial irradiation in patients with limited disease in fractions of 25 Gy. Their recommendation is based on a RCT of low quality showing an effect of prophylactic cranial irradiation and a moderate quality study of le Péchoux et al. 2009 and 2011[140, 141] showing that doses higher than 25 G do not prolong survival. The Dutch guideline makes the same recommendation, based on a individual based meta-analysis of Auperin et al, showing a benefit of 0.84 in overall survival (95 % confidence interval, 0.73 to 0.97; p=0.01) for the subgroup with limited disease that went into complete remission, in most primary studies assessed by chest X-ray, this implies that these patients would not be considered in complete remission with current imaging techniques.

The sensitivity of MRI to detect brain metastases has improved over time. The balance of benefit and harm of prophylactic cranial irradiation in patients who test negative for brain metastases using highly sensitive MRI remains a topic of research.

Conclusions

There are indications that platinum based chemotherapy added to chest radiotherapy extends overall and progression free survival.

There are indications that the best results are obtained with the Turrise scheme.

There is no conclusive evidence on the optimal schedule of the platinum based chemotherapy.

Concurrent chemoradiotherapy is more effective then sequential chemoradiotherapy.

There is limited evidence that surgery may be beneficial in early-stage SCLC (T1-2a, N0, M0), followed by adjuvant chemotherapy.

There is no proof that maintenance chemotherapy is beneficial in patients responding to chemotherapy.

There is evidence from one RCT and an individual based meta-analysis that prophylactic cranial irradiation in patients with limited disease prolongs survival.

There is evidence from one RCT that doses higher than 25 G do not prolong survival when applying prophylactic cranial irradiation.

6.1.2. Extensive stage disease small cell lung cancer (broadly staged as T1-4, N0-3, M1 a/b)

6.1.2.1. First line treatment for extensive stage disease small cell lung cancer (broadly staged as T1-4, N0-3, M1 a/b)

NICE[3] recommends to offer platinum-based combination chemotherapy to patients with extensive-stage disease SCLC (broadly corresponding to T1-4, N0-3, M1a/b – including cerebral metastases) if they are fit enough. It is not clear where this recommendation comes from, the 5 RCT identified and the Cochrane meta-analysis does not find a survival benefit. Combination therapies seem to be considered standard of care.

The Dutch guideline[6] also recommend platinum containing combination therapy, with the argument that is standard of care.

None does a recommendation concerning the choice between cisplatin and carboplatin.

Update

In the update we identified a the COCIS individual based meta-analysis of Rossi et al, showing that there is no statistically significant difference between Cisplatin and carboplatin containing regimens, median OS was 9.6 months for cisplatin and 9.4 months for carboplatin (hazard ratio [HR], 1.08; 95% CI, 0.92 to 1.27; p=.37). There was no evidence of treatment difference between the cisplatin and carboplatin arms according to sex, stage, performance status, or age. Median PFS was 5.5 and 5.3 months for cisplatin and carboplatin, respectively (HR, 1.10; 95% CI, 0.94 to 1.29; p=.25). ORR was 67.1% and 66.0%, respectively (relative risk, 0.98; 95% CI, 0.84 to 1.16; p=0.83). Toxicity profile was significantly different for each of the arms: hematologic toxicity was higher with carboplatin, and nonhematologic toxicity was higher with cisplatin. They pooled patients with limited disease and extensive disease though.

CONVERT, a multicentre, international, randomised, phase III trial open in Europe looking at optimisation of chemo-radiotherapy is ongoing.

NICE[3] also recommends to assess the patient's condition before each cycle of chemotherapy for extensive-stage disease SCLC (broadly corresponding to T1-4, N0-3, M1a/b) and offer up to a maximum of six cycles, depending on response and toxicity, based on the fact that no studies with more cycles were identified.

For patients with extensive-stage disease SCLC, thoracic radiotherapy should be considered after chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax. No evidence was given for this however. The Dutch guideline on the contrary does not recommend radiotherapy outside of a clinical trial, based one the phase III trial.

6.1.2.2. Maintenance chemotherapy in patients responding to induction chemotherapy

NICE[3] does not recommend maintenance therapy, outside a clinical trial, based on 3 RCTs where different forms of maintenance therapy were assessed but that were inconclusive. The Dutch guideline recommends the same, based on 4 RCTs, the same RCTs that were pooled by Bagi et al, 2011, see below.

Update

The update identified a systematic review of Bagi et al, 2011 that pooled 4 eligible trials, all of maintenance chemotherapy, including 498 patients. The median number of patients per arm was 27 (range=18-112). Induction chemotherapy lasted 6-8 cycles in 3 trials, and 4 cycles in 2 trials. Induction chemotherapy included cisplatin in 3 trials with either etoposide, irinotecan or ifosphamide. Maintenance chemotherapy was associated with a significantly longer PFS (HR 0.77, 95% CI 0.60 to 0.99; p 0.04), but not OS (HR 0.80, 95% CI 0.59 to 1.08; p=0.7). There were trends towards the effects on PFS being greater in trials using a platinum-based induction regimen (HR 0.64 v1.00, interaction p 0.09) and trials using 4 or fewer cycles of induction chemotherapy versus more than 4 cycles (HR 0.61 v0.99, interaction p=0.07). The appropriateness of the pooling is unclear on clinical ground as regimens differ considerably.

6.1.2.3. *Prophylactic cranial irradiation*

NICE[3] recommends prophylactic cranial irradiation in patients with extensive disease, their recommendation is based on one well-conducted RCT that found that PCI in patients with extensive disease SCLC conferred both an overall survival and a brain disease-free survival advantage relative to controls as well as a lower incidence of brain metastases (Slotman et al., 2007). The Dutch guideline[6] makes the same recommendation, based on the individual based meta-analysis of Aupérin et al, mentioned above (there the patients were a mix of limited and extended disease that went into complete remission, most of them only on X-ray, the effect in the subgroup with extended disease was not statisitically signifant) and the study of Slotman et al. Slotman reported a hazard ratio for the disease-free survival of 0.76 (95% CI 0.59 - 0.96) and a hazard ratio for overall survival of 0.68 (95% CI 0.52 - 0.88).[142]

Conclusions

There are indications that platinum based chemotherapy extends overall and progression free survival.

There is no proof that there is a difference between carboplatin and cisplatin containing regimens.

There is no conclusive evidence on the optimal schedule of the platinum based chemotherapy.

There is no proof that maintenance chemotherapy is beneficial in patients responding to chemotherapy.

There is evidence from one RCT that prophylactic cranial irradiation in patients with extensive disease prolongs survival.

6.1.3. *Second line treatment for patients with SCLC who relapse after primary treatment.*

Offer patients with relapsed SCLC, who are suitable for chemotherapy, treatment with an anthracycline-containing regimen or further treatment with a platinum-based regimen to a maximum of six cycles. They also inform patients whose disease has not responded to first-line treatment that there is very limited evidence that second-line chemotherapy will be of benefit. They base their recommendation on one RCT of low quality. The Dutch guideline[6] recommends chemotherapy, based on one RCT comparing the effect of metotrexate-doxorubicine with usual care and one comparing oral topetecan with usual care, both showing a statistically significant effect on overall survival. Both guidelines recommend to offer radiotherapy for palliation of local symptoms to patients with SCLC that has relapsed after first-line treatment, no evidence was given for this however.

Update

A meta-analysis by Riemsma et al was identified, showing that oral topotecan plus BSC has advantages over BSC alone in terms of survival (hazard ratio=0.61; 95% CI, 0.43 to 0.87) and quality of life (EQ-5D difference: 0.15; 95% CI, 0.05 to 0.25). it also showed that intravenous topotecan was at least as effective as cyclophosphamide, adriamycin and vincristine (CAV) in the treatment of patients with recurrent small-cell lung cancer and resulted in improved quality-of-life with respect to several symptoms. CAV was associated with significantly less grade 4 thrombocytopenia compared with IV topotecan (risk ratio=5.83; 95% CI, 2.35 to 14.42). Survival (hazard ratio=0.98; 95% CI, 0.77 to 1.25) and response (pooled risk ratio=1.04; 95% CI, 0.58 to 1.85) data were similar for the oral and IV topotecan groups. Symptom control was also very similar between the trials and between the oral and IV groups. Toxicity data showed a significant difference in favour of oral topotecan for neutropenia (pooled risk ratio=0.65; 95% CI, 0.47 to 0.89).

GRADE profiles and justification of GRADE scores are given in appendix 3.9

'Limited-stage disease' SCLC (broadly corresponding to T1-4, N0-3,M0)

Recommendation	Strength of recommendation	Level of evidence
It is recommended to offer patients with 'limited-stage disease' SCLC (broadly corresponding to T1-4, N0-3, M0) four to six cycles of platinum-etoposide combination chemoradiation.	strong	not assigned
'Limited-stage disease' SCLC is locoregional disease encompassed in a radical thoracic radiotherapy volume and broadly corresponds to T1-4, N0-3, M0. It is recommended to offer concurrent chemoradiotherapy (starting with cycle 1 or cycle 2) to WHO performance status of 0 or 1 patients with locoregional disease corresponding to a safe radiation volume ('limited-stage disease' SCLC). Start the radiotherapy during the first or second cycle of chemotherapy.	strong	high
The optimal dose schedule for chest radiotherapy is still under investigation The suggested doses for radiotherapy are 45 Gy in 3 weeks with two fractions a day or 60 Gy in once-daily fractions.	weak	very low
It is recommended to offer sequential radical thoracic radiotherapy to patients with 'limited-stage disease' SCLC (broadly corresponding to T1-4, N0-3, M0) who are no eligible for concurrent chemoradiotherapy but who respond to chemotherapy.	strong	not assigned
It is at present recommended to offer prophylactic cranial irradiation at a dose of 25 Gy in 10 fractions to patients with limited-stage disease SCLC and WHO performance status 2 or less, if their disease is in complete or partial remission after first-line treatment in order to improve survival and lower the risk of brain metastases. This benefit is to be reconfirmed with current techniques of staging such as PET/CT and brain MRI.	strong	low
It is recommended to offer maintenance therapy only in the context of a clinical trial.	strong	very low

Extensive disease SCLC (broadly corresponding to T1-4, N0-3, M1a/b – including cerebral metastases)

Recommendation	Strength of recommendation	Level of evidence
It is recommended to offer four to six cycles of platinum-etoposidecombination chemotherapy to patients with extensive-stage disease SCLC (broadly corresponding to T1-4, N0-3, M1a/b – including cerebral metastases) if they are fit enough.	strong	not assigned
It is recommended to offer maintenance therapy only in the context of a clinical trial.	strong	very low
It is recommended to offer prophylactic cranial irradiation to patients with extensive-stage disease SCLC and WHO performance status 2 or less, if their disease has not progressed on first-line treatment.	strong	high

Relapsed SCLC

Recommendation	Strength of recommendation	Level of evidence
It is recommended to offer patients with relapsed SCLC, who are suitable for chemotherapy, second-line treatment. Retreatment with first-line chemotherapy can be considered in chemotherapy-sensitive patients. These treatment decisions should be discussed by a multidisciplinary team.	**strong**	**low**

Good clinical practice
PET-CT can be useful in limited disease SCLC patients to detect extracranial metastases and to determine the extent of the radiation field.
Inform patients whose disease has not responded to first-line treatment that there is very limited evidence that second-line chemotherapy will be of benefit.

7. IMPLEMENTATION AND UPDATING OF THE GUIDELINE

7.1. Implementation

The implementation of this guideline will be conducted by the College of Oncology. An online implementation tool similar to the tools accompanying previous guidelines will be developed (www.collegeoncologie.be).

Additionally, the members of the guideline development group and consulted professional organisations agreed to facilitate the dissemination and implementation of this guideline e.g. during future scientific congresses and medical eduction programs.

7.2. Monitoring the quality of care

This guideline should be considered as a starting point to develop quality improvement programs that targets all caregivers concerned.

It can be used as a tool to support health policies to improve the quality of care, e.g. through the support of actions to increase caregivers' awareness and to improve their practice, or through the development (or revision) of sets of process and outcome quality indicators.

Illustration of clinical domains for indicators are:[143, 144]

- Histological confirmation rate
- Proportion of patients discussed at an MDT
- Proportion of stage I and II NSCLC patients with PS 0-1 who have their FEV1 absolute and FEV1% predicted recoreded
- Proportion of patients with stage III NSCLC receiving external beam radiotherapy to the thorax with concurrent chemotherapy
- Chemotherapy rates for patients with small cell lung cancer

KCE previously recommended to set up an integrative quality system in oncology, covering the development and implementation of clinical practice guidelines, the monitoring of the quality of care with quality indicators, feedback to health care providers and organisations and targeted actions to improve the quality if needed.[145]

7.3. Guideline update

The KCE processes foresee that the relevance of an update would be yearly assessed for each published guideline by the authors. Decisions are made on the basis of new scientific publications on a specific topic (e.g. Cochrane reviews, RCTs on medications or interventions). Potential interest for groups of health practitioners is also considered in this process.

This appraisal leads to a decision on whether to update or not a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

When important evidence becomes available, this will be mentioned on the website of the College of Oncology.

APPENDICES

APPENDIX 1. SEARCH STRATEGIES

Appendix 1.1.1. Search for guidelines

A test search in OVID Medline for guidelines on lung cancer (2001-2011) revealed more than 1000 hits. It was consequently decided to deploy restrictions on language (English, Dutch, French) and date (2009 – current date). All searches for guidelines were run on February 20th, 2012. Based on title and abstract, and after removal of duplicate guidelines, a total of 23 guidelines were retained for full-text evaluation. Of these 18 guidelines were excluded for the following reasons:

14 guidelines were excluded based on methodology i.e. the guideline was either consensus based or did not provide recommendations.

2 guidelines were excluded due to incomplete literature search or no reporting of search strategy.

2 guidelines were excluded because the guideline did not fulfil the criteria for language and/or publication date.

5 guidelines were retained for an evaluation of the methodological quality (see Table 9)

Table 7 – Search results guidelines lung cancer (same guidelines may be found in several databases)

Database	# of hits	# retrieved for full-text evaluation
OVID Medline	189	12
National Guideline Clearing House	184	17
G-I-N	48	9

Appendix 1.2.1. Search strategy diagnosis and staging

Date	April 17th, 2012
Database	Medline via OVID
Search Strategy	Population Search: 1 exp Lung Neoplasms/ 2 (lung adj (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chrondosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis or tumour$ or tumor$ or metast$)).ti,ab. 3 (NSCL or SCLC).ti,ab. 4 or/1-3 Diagnosis Search: 1 exp Radiography, Thoracic/ 2 exp Thorax/ and (X-Rays/ or Radiography/ or Tomography, X-Ray/) 3 ((chest or thora$) adj3 (x ray$ or x-ray$ or xray$ or radiograph$ or tomograph$)).mp. 4 CXR.mp. 5 exp Tomography, X-Ray Computed/ or Tomography Scanners, X-Ray Computed/ 6 (compute$ tomograph$ or ct).mp. 7 exp Radionuclide Imaging/ or ((radionuclide adj5 imag$) or scintiscan$ or scintigraph$).mp. 8 radiopharmaceuticals/ or fludeoxyglucose f 18/ or (radiopharmaceutical$ or FDG or Fludeoxyglucose or fluorodeoxyglucose or fluorodeoxyglucose or depreotide).mp. 9 ((positron or photon or gamma or scintillation) adj3 (emission or tomograph$ or camera$)).mp. 10 (CGC or PET or SPECT or NEOTECT or NEOSPECT or NEOTEC).mp. 11 Gamma Cameras/ 12 Diagnostic Imaging/ 13 exp Cytological Techniques/ 14 (Sputum/ or sputum$.mp.) and (Cytology/ or cytolog$.mp.) 15 (sputum adj5 (induced or modified)).mp. 16 bronchoscopy/ or bronchoscop$.mp. 17 bronchography/ or bronchograph$.mp. 18 Bronchoalveolar Lavage/ 19 (lavage or washing$ or brushing$).mp. 20 Cytodiagnosis/ 21 biopsy/ or biopsy, needle/ or biops$.mp. 22 ((transbronchial or transthoracic or fine or open or percutaneous) adj5 (biops$ or needle or puncture or aspiration)).mp. 23 (FNA or TTNA or TBNA).mp. 24 (pleural adj5 (tap or fluid or cytolog$ or effusion)).mp. 25 Thoracotomy/ or thoracotomy.mp. 26 Thoracoscopy/ or thoracoscopy.mp. 27 Mediastinoscopy/ or (mediastinoscopy or mediastinotomy).mp. 28 exp Video-Assisted Surgery/ 29 (video adj5 thora$).mp. 30 VATs.mp. 31 or/1-30 32 4 and 31 33 limit 32 to yr="2009 - current" Staging Search

	1 exp Tomography, X-Ray Computed/ or Tomography Scanners, X-Ray Computed/ 2 (compute$ tomograph$ or ct).mp. 3 exp Radionuclide Imaging/ or ((radionuclide adj5 imag$) or scintiscan$ or scintigraph$).mp. 4 radiopharmaceuticals/ or fludeoxyglucose f 18/ or (radiopharmaceutical$ or FDG or Fludeoxyglucose or fluorodeoxyglucose or fluorodeoxyglucose or depreotide).mp. 5 ((positron or photon or gamma or scintillation) adj3 (emission or tomograph$ or camera$)).mp. 6 (CGC or PET or SPECT or NEOTECT or NEOSPECT or NEOTEC).mp. 7 Gamma Cameras/ 8 exp Magnetic Resonance Imaging/ 9 ((magnetic adj1 resonance) or (MRI or NMRI)).mp. 10 (bone$ adj1 scan$).mp. 11 ultrasonography/ or endosonography/ 12 (EUS or EBUS or ultrasound or ultrasonograph$ or endosonograph$).mp. 13 biopsy/ or biopsy, needle/ or biops$.mp. 14 ((transbronchial or transthoracic or fine or open or percutaneous) adj5 (biops$ or needle or puncture or aspiration)).mp. 15 (FNA or TTNA or TBNA).mp. 16 Mediastinoscopy/ or (mediastinoscopy or mediastinotomy).mp. 17 exp Video-Assisted Surgery/ 18 (video adj5 thora$).mp. 19 VATs.mp. 20 Sentinel Lymph Node Biopsy/ 21 lymph node biopsy.mp. 22 or/1-21 23 neoplasm staging/ or TNM.mp. or stag$.mp. 24 (exp neoplasm metastasis/ or lymphatic metastasis/) and (exp Liver/ or exp Adrenal Glands/ or exp "Bone and Bones"/ or exp Brain/ or exp Mediastinum/ or exp Thoracic Wall/) 25 ((metastas?s or metastat$) adj2 (liver or adrenal or bone or brain or cerebral or mediastin$ or chest wall)).mp. 26 or/23-25 27 22 and 26 28 4 and 27 29 limit 28 to yr="2009 – current”
Note	Search was adapted for other databases

Table 8 – Search results diagnosis and staging

Database	# of hits
OVID Medline Diagnostic search	5915
OVID Medline Staging search	1323
EMBASE Diagnostic search	3597
EMBASE Staging search	451
Cochrane Diagnostic search	286
Cochrane Staging search	122

Appendix 1.2.2. Search strategies: criteria for operability

Date:	**August, 2012**
Database:	MEDLINE via OVID
Search Strategy:	Exercise --- 1 exp Lung Neoplasms/ (159740) 2 (lung adj (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chrondosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis or tumour$ or tumor$ or metast$)).ti,ab. (101292) 3 (NSCLC or SCLC).ti,ab. (17713) 4 1 or 2 or 3 (180809) 5 thoracotomy.mp. or Thoracotomy/ (18464) 6 pneumonectom$.mp. or Pneumonectomy/ (21228) 7 (resection adj3 (sleeve or extended or wedge or pulmonary or segmental or carinal or lung or chest wall)).tw. (13499) 8 (wedge biopsy or segmentectomy or lobectom$ or bi?lobar or bi?lobectom$).mp. (13639) 9 Thoracic Surgery/ or Thoracic Surgery, Video-Assisted/ or exp Thoracoscopy/ (18630) 10 Pulmonary Surgical Procedures.mp. or Pulmonary Surgical Procedures/ (418) 11 Lung/su [Surgery] (3822) 12 5 or 6 or 7 or 8 or 9 or 10 or 11 (70416) 13 4 or 12 (234477) 14 Exercise Test/ (46489) 15 (exercise adj test$).tw. (17506) 16 (climbing adj test$).tw. (130) 17 (shuttle adj walk$).tw. (264) 18 (shuttle adj test$).tw. (87) 19 (stair adj climb$).tw. (1040) 20 (walk adj test$).tw. (2519) 21 14 or 15 or 16 or 17 or 18 or 19 or 20 (54847) 22 13 and 21 (490) 23 limit 22 to yr="2010 -Current" (73)
Note	

Date:	**13 July 2012**
Database:	Embase
Search strategy	Exercise #18. 'lung tumor'/mj OR ('lung'/exp AND 'cancer'/exp OR 'lung'/exp AND alveolus AND 'cell'/exp AND 'carcinoma'/exp OR 'lung'/exp AND non AND small AND 'cell'/exp AND 'cancer'/exp OR 'lung'/exp AND squamous AND 'cell'/exp AND 'carcinoma'/exp OR 'lung'/exp AND small AND 'cell'/exp AND 'cancer'/exp) OR 'lung non small cell cancer'/exp OR 'lung non small cell cancer' OR 'lung small cell cancer'/exp OR 'lung small cell cancer' OR 'thoracotomy'/mj OR ('lung'/exp/mj AND 'resection'/exp/mj) OR ('resection'/mj AND (wedge OR pulmonary OR segmental OR carianal OR 'lung'/mj OR 'chest'/mj)) OR ('lung'/exp AND lobectomy OR temporal AND lobectomy) OR 'video assisted thoracoscopic surgery'/exp OR 'thoracic surgery'/exp OR ('lung'/exp OR lung AND ('surgery'/exp OR surgery)) AND ('exercise test'/exp OR ('climbing'/exp OR 'shuttle' OR 'walk' OR 'stair' AND 'test')) AND (2010:py OR

	2011:py OR 2012:py)
Note	

Date:	**August 2012**
Database:	MEDLINE via OVID
Search strategy	Risk Scores --- Disease search as for exercise combined with: 1 thoracic surgical procedure.tw. (1) 2 pulmonary surgery.tw. (8) 3 thoracic surgery.tw. (354) 4 thoracotomy.tw. (532) 5 pneumonectomy.tw. (178) 6 resection.tw. (7989) 7 1 or 2 or 3 or 4 or 5 or 6 (8771) 8 risk assessment.tw. (1597) 9 risk adjustment.tw. (60) 10 risk model.tw. (99) 11 risk score.tw. (344) 12 risk test.tw. (7) 13 risk analysis.tw. (271) 14 8 or 9 or 10 or 11 or 12 or 13 (2291) 15 postoperative complication$.tw. (1572) 16 hospital mortality.tw. (749) 17 (hospital adj (death or mortality)).tw. (816) 18 (risk-adjusted adj mortality).tw. (20) 19 perioperative.tw. (2400) 20 postoperative.tw. (11349) 21 (predict adj survival).tw. (72) 22 survival analysis.tw. (626) 23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (14175) 24 7 and 14 and 23 (9)
Note	

Date:	**1 August 2012**	
Database:	Embase	
Search strategy	Risk Scores --- #21. 'thorax surgery'/exp OR 'thorax surgery' OR 'lung surgery'/exp OR 'lung surgery' OR 'thoracotomy'/exp OR thoracotomy OR 'lung resection'/exp OR 'lung resection' OR (resection:ab,ti OR surg*:ab,ti AND (pulmonary:ab,ti OR lung:ab,ti OR thoracic:ab,ti)) AND ('postoperative complication'/exp OR 'postoperative complication' OR ('mortality'/exp OR mortality AND ('hospital'/exp OR hospital)) OR ('hospital'/exp OR hospital AND ('patient'/exp OR patient) AND near AND (death:ab,ti OR mortality:ab,ti)) OR ('risk'/exp OR risk AND assessment AND near AND ('mortality'/exp OR mortality)) OR ('perioperative period'/exp OR 'perioperative period' OR 'postoperative period'/exp OR 'postoperative period' AND near AND ('death'/exp OR death)) OR 'mortality'/exp OR mortality OR	141 1 Aug 2012

	('risk'/exp OR risk AND near AND ('mortality'/exp OR mortality)) OR (predict AND near3 AND ('survival'/exp OR survival)) OR 'survival analysis'/exp OR 'survival analysis') AND ('risk assessment'/exp OR 'risk assessment' OR ('risk'/exp OR risk AND near AND ('model'/exp OR model OR score OR 'analysis'/exp OR analysis OR test)) OR ('risk'/exp OR risk AND assessment AND near AND ('mortality'/exp OR mortality)) OR ('risk'/exp OR risk AND near AND ('mortality'/exp OR mortality))) AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [embase]/lim AND [2010-2013]/py
Note	

Date:	**August 2012**
Database:	MEDLINE via OVID
Search strategy	Spirometry --- Disease search as for exercise combined with: 11 exp Spirometry/ (17038) 12 FEV1*.tw. (15201) 13 dynamic lung volume*.tw. (84) 14 TLCO*.tw. (286) 15 (gas adj transfer*).tw. (638) 16 (transfer adj factor*).tw. (2250) 17 (CO transfer factor* or carbon?monoxide transfer factor*).tw. (31) 18 (DLCO* or KCO*).tw. (2174) 19 (full lung function* or full pulmonary function*).tw. (45) 20 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (34287) 21 4 and 20 (995) 22 10 and 20 (1292) 23 21 or 22 (1821) 24 limit 23 to yr="2010 -Current" (165)
Note	

Date:	**1 August 2012**
Database:	Embase
Search strategy	Spirometry --- #46. 'lung tumor'/exp OR 'lung tumor' AND [2010-2013]/py OR (lung:ab,ti AND (neoplasm*:ab,ti OR cancer*:ab,ti OR carcinoma*:ab,ti OR adenocarcinoma*:ab,ti OR angiosarcoma*:ab,ti OR chrondosarcoma*:ab,ti OR sarcoma*:ab,ti OR teratoma*:ab,ti OR lymphoma*:ab,ti OR blastoma*:ab,ti OR microcytic*:ab,ti OR carcinogenesis:ab,ti OR tumour*:ab,ti OR tumor*:ab,ti OR metast*:ab,ti) AND [embase]/lim) OR (nslc OR sclc AND [2010-2013]/py) AND ('spirometry'/exp OR spirometry AND [2010-2013]/py OR (dynamic AND ('lung'/exp OR lung) AND volume.tw AND [2010-2013]/py) OR (tlco AND [2010-2013]/py) OR 260 1 Aug 2012

	('gas diffusion'/exp OR 'gas diffusion' AND [2010-2013]/py) OR (co AND transfer AND factor AND [2010-2013]/py) OR ('carbon'/exp OR carbon AND monoxide AND transfer AND factor AND [2010-2013]/py) OR (dlco AND [2010-2013]/py) OR (kco AND [2010-2013]/py) OR (full AND ('lung'/exp OR lung) AND function AND [2010-2013]/py) OR (full AND pulmonary AND function AND [2010-2013]/py)) OR ('resection'/exp OR resection OR surg* AND near AND (pulmonary OR 'lung'/exp OR lung OR thoracic) OR ('thorax surgery'/exp OR 'thorax surgery' AND [2010-2013]/py) OR ('lung surgery'/exp OR 'lung surgery' AND [2010-2013]/py) OR ('thoracotomy'/exp OR thoracotomy AND [2010-2013]/py) OR ('pneumonectomy'/exp OR pneumonectomy AND [2010-2013]/py) AND ('spirometry'/exp OR spirometry AND [2010-2013]/py OR (dynamic AND ('lung'/exp OR lung) AND volume.tw AND [2010-2013]/py) OR (tlco AND [2010-2013]/py) OR ('gas diffusion'/exp OR 'gas diffusion' AND [2010-2013]/py) OR (co AND transfer AND factor AND [2010-2013]/py) OR ('carbon'/exp OR carbon AND monoxide AND transfer AND factor AND [2010-2013]/py) OR (dlco AND [2010-2013]/py) OR (kco AND [2010-2013]/py) OR (full AND ('lung'/exp OR lung) AND function AND [2010-2013]/py) OR (full AND pulmonary AND function AND [2010-2013]/py))) AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [embase]/lim AND [2010-2013]/py
Note	

Appendix 1.2.3. Search strategies surgery early stage NSCLC

Date	**7 March 2013**
Database	Medline via Ovid
Search strategy	1 Lung Neoplasms/ (150215) 2 (lung adj3 cancer$).ab,ti. (81761) 3 (lung adj3 neoplas$).ab,ti. (1750) 4 (lung adj3 carcin$).ab,ti. (22974) 5 (lung adj3 tumo$).ab,ti. (15425) 6 (lung adj3 malig$).ab,ti. (2469) 7 NSCLC.ab,ti. (14805) 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (175150) 9 Lung Neoplasms/su, th [Surgery, Therapy] (29382) 10 Thoracic Surgery/ (9942) 11 pulmonary surgical procedures/ or pneumonectomy/ (20034) 12 lobect$.tw. (11884) 13 surgical resection.tw. (24424) 14 9 or 10 or 11 or 12 or 13 (79851) 15 exp animals/ not humans.sh. (3778609) 16 meta-analysis.mp,pt. or review.pt. or search:.tw. (1899627) 17 randomized controlled trial.pt. (342617) 18 controlled clinical trial.pt. (85357) 19 randomized.ab. (245653) 20 placebo.ab. (136033)

	21 clinical trials as topic.sh. (162983) 22 trial.ti. (105168) 23 Lymph Node Excision/ (23177) 24 Lung Neoplasms/ (150215) 9. 25 (lung adj3 cancer$).ab,ti. (81761) 26 (lung adj3 neoplas$).ab,ti. (1750) 27 (lung adj3 carcin$).ab,ti. (22974) 28 (lung adj3 tumo$).ab,ti. (15425) 29 (lung adj3 malig$).ab,ti. (2469) 30 NSCLC.ab,ti. (14805) 31 24 or 25 or 26 or 27 or 28 or 29 or 30 (175150) 32 Lung Neoplasms/su, th [Surgery, Therapy] (29382) 33 Thoracic Surgery/ (9942) 34 pulmonary surgical procedures/ or pneumonectomy/ (20034) 35 Lymph Node Excision/ (23177) 36 lobect$.tw. (11884) 37 pneumonectomy.tw. (5681) 38 surgical resection.tw. (24424) 39 segmentectomy.tw. (1615) 40 wedge resection.tw. (2202) 41 lymph node sampling.tw. (469) 42 mediastinal lymphadenectomy.tw. (245) 43 sleeve resection.tw. (437) 44 sleeve lobectomy.tw. (302) 45 32 or 33 or 11or 12.mp. or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (74765) 46 31 and 45 (31913)
	47 exp animals/ not humans.sh. (3778609) 48 46 not 47 (30980) 49 meta-analysis.mp,pt. or review.pt. or search:.tw. (1899627) 50 randomized controlled trial.pt. (342617) 51 controlled clinical trial.pt. (85357) 52 randomized.ab. (245653) 53 placebo.ab. (136033) 54 clinical trials as topic.sh. (162983) 55 trial.ti. (105168) 56 49 or 50 or 51 or 52 or 53 or 54 or 55 (2488613) 57 48 and 56 (6191) 58 limit 57 to yr="2009 -Current" (1256)
Note	

Date	**7 March 2013**
Database	Embase via Embase.com
Search strategy	'lung non small cell cancer'/de AND [embase]/lim AND [2-10-2009]/sd OR (nsclc AND [embase]/lim AND [2-10-2009]/sd) AND ('thorax surgery' AND [embase]/lim AND [2-10-2009]/sd OR ('lymph node dissection' AND [embase]/lim AND [2-10-2009]/sd) OR (lobect* AND [embase]/lim AND [2-10-2009]/sd) OR (pneumonectomy AND [embase]/lim AND [2-10-2009]/sd) OR (surg* NEAR/3 resect* AND [embase]/lim AND [2-10-2009]/sd) OR (segmentectomy AND [embase]/lim AND [2-10-2009]/sd) OR (wedge AND resection AND [embase]/lim AND [2-10-2009]/sd) OR (lymph AND

	node AND sampling AND [embase]/lim AND [2-10-2009]/sd) OR (lymphadenectomy AND [embase]/lim AND [2-10-2009]/sd) OR (sleeve AND lobectomy AND [embase]/lim AND [2-10-2009]/sd) OR (sleeve AND resection AND [embase]/lim AND [2-10-2009]/sd)) AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [humans]/lim AND [embase]/lim AND [2-10-2009]/sd
Note	

Date	**7 March 2013**
Data base	Cochrane Library
Search strategy	#1 MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees #2 NSCLC in Trials #3 #1 or #2 from 2009 #4 MeSH descriptor: [Thoracic Surgery] explode all trees #5 surgical resection from 2009, in Trials #6 lobectom* in Trials #7 wedge resection in Trials #8 segmentectomy in Trials #9 sleeve resection #10 sleeve lobectomy #11 lymph node sampling #12 lymphadenectomy #13 MeSH descriptor: [Lymph Node Excision] explode all trees #14 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 #15 #3 and #14 from 2009
Note	

Appendix 1.2.4. Search strategies postoperative radiotherapy

Date	**7 February 2013**
Data base	Medline via Ovid
Search strategy	1 Lung Neoplasms/ (149058) 2 (lung adj3 cancer$).ab,ti. (80820) 3 (lung adj3 neoplas$).ab,ti. (1739) 4 (lung adj3 carcin$).ab,ti. (22775) 5 (lung adj3 tumo$).ab,ti. (15258) 6 (lung adj3 malig$).ab,ti. (2451) 7 NSCLC.ab,ti. (14562) 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (173679) 9 radiotherapy/ or chemoradiotherapy/ or radiotherapy, adjuvant/ or radiotherapy, computer-assisted/ or radiotherapy dosage/ or radiotherapy, image-guided/ (86258) 10 radiotherap$.ab,ti. (100727) 11 radiation.ab,ti. (205723) 12 9 or 10 or 11 (310835) 13 adjuvant.ab,ti. (77964) 14 post$operat$.ab,ti. (308751) 15 (complet$ adj3 resect$).ab,ti. (12259) 16 (incomplet$ adj3 resect$).ab,ti. (2321) 17 Neoplasm, Residual/rt, th [Radiotherapy, Therapy] (430) 18 Radiotherapy, Adjuvant/ (15596) 19 13 or 14 or 15 or 16 or 17 or 18 (396052)

	20 8 and 12 and 19 (2899) 21 limit 20 to yr="2009 -Current" (551)
Note	

Date	**7 February 2013**
Data base	Embase via Embase.com
Search strategy	'lung non small cell cancer'/exp AND [embase]/lim AND [2009-2013]/py OR ((lung NEAR/3 cancer*):ab AND [embase]/lim AND [2009-2013]/py) OR ((lung NEAR/3 neoplas*):ab AND [2009-2013]/py) OR ((lung NEAR/3 carcin*):ab AND [2009-2013]/py) OR ((lung NEAR/3 tumo*):ab AND [2009-2013]/py) OR ((lung NEAR/3 malig*):ab AND [2009-2013]/py) OR (nsclc:ab AND [2009-2013]/py) AND ('cancer radiotherapy' AND [embase]/lim AND [2009-2013]/py OR (radiother*:ab,ti AND [2009-2013]/py) OR (radiation:ab,ti AND [embase]/lim AND [2009-2013]/py)) AND ('cancer adjuvant therapy' AND [embase]/lim AND [2009-2013]/py OR (adjuvant:ab,ti AND [embase]/lim AND [2009-2013]/py) OR (post*operat*:ab,ti AND [2009-2013]/py) OR ((complet* NEAR/3 resect*):ab,ti AND [embase]/lim AND [2009-2013]/py) OR ((incomplet* NEAR/3 resect*):ab,ti AND [embase]/lim AND [2009-2013]/py)) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [embase]/lim AND [2009-2013]/py
Note	

Date	**7 February 2013**
Data base	Cochrane Library
Search strategy	#1 lung cancer #2 NSCLC #3 #1 or #2 #4 radiotherapy #5 radiation #6 #4 or #5 #7 adjuvant #8 post*operat* #9 complet* near/3 resected #10 incomplet* near/3 resected #11 #7 or #8 or #9 or #10 #12 #11 and #6 and #3 from 2009 to 2013, in Cochrane Reviews (Reviews only), Trials and Technology Assessments (Word variations have been searched)
Note	

Appendix 1.2.5. Search strategies combination treatment

This search strategy was designed as a combined search strategy for the following comparisons[3]:

- A: For patients fit for potentially curative (radical) radiotherapy: CHART versus radical RT versus sequential chemoradiation versus concurrent chemoradiation
- B: For patients with potentially operable NSCLC stage I-III (suitable for radical radiotherapy): surgery alone versus neoadjuvant chemotherapy then surgery versus surgery then adjuvant chemotherapy
- C: For patients with pancoast tumours: radiotherapy alone versus neoadjuvant chemoradiation then surgery versus neoadjuvant radiotherapy then surgery

Date	**12 July 2012**
Database	Medline via OVID
Search Strategy	1 pancoast$.tw. (490) 2 exp Pancoast Syndrome/ (612) 3 1 or 2 (740) 4 limit 3 to (yr="2010 -Current" and randomized controlled trial) (0) 5 exp Lung Neoplasms/ (158807) 6 (lung adj (neoplasm* or cancer or carcinoma* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcinogenesis or tumour* or tumor* or metast*)).ti,ab. (98653) 7 (NSCLC or SCLC).ti,ab. (17501) 8 5 or 6 or 7 (178790) 9 exp Radiotherapy Dosage/ or exp Radiotherapy/ or exp Radiotherapy, Computer-Assisted/ or exp Radiotherapy, High-Energy/ (126722) 10 exp Radiosurgery/ (7452) 11 exp Radiation Oncology/ (2197) 12 (radiotherap$ or radiat$ or CHARTWEL).tw. (288619) 13 9 or 10 or 11 or 12 (341117) 14 exp Combined Modality Therapy/ (184218) 15 (chemoradiotherapy or chemoradiation or chemo-radiotherapy or chemoradiotherapy).tw. (11179) 16 (multimodality or combind modality).tw. (5588) 17 (sequential or concurrent or concomitant).tw. (246641) 18 (radiotherap$ or radiat$ or chemotherap$).tw. (468003) 19 17 and 18 (17306) 20 exp Drug Therapy, Combination/ (236024) 21 exp Antineoplastic Combined Chemotherapy Protocols/ (94148) 22 exp Drug Therapy/ (986997) 23 exp Antineoplastic Protocols/ (94426) 24 exp Antineoplastic Agents/ (749080) 25 exp Radiotherapy Dosage/ or exp Radiotherapy/ or exp Radiotherapy, Computer-Assisted/ or exp Radiotherapy, High-Energy/ (126722) 26 exp Radiation Oncology/ (2197) 27 25 or 26 (127858) 28 22 or 23 or 24 (1562436) 29 27 and 28 (30605) 30 14 or 15 or 16 or 19 or 20 or 21 or 29 (402243) 31 exp Drug Therapy/ (986997) 32 exp Drug Therapy/ (986997) 33 exp Drug Therapy, Combination/ (236024) 34 23 or 24 (777651) 35 chemotherap$.tw. (229866)

36 exp Antineoplastic Combined Chemotherapy Protocols/ (94148)

37 32 or 33 or 34 or 35 or 36 (1648438)

38 (thoracotomy or thoracotomy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (18360)

39 (mediastinoscopy or mediastinoscopy).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (2444)

40 mediastinotomy.tw. (269)

41 chamberlain procedure.tw. (9)

42 (resection adj3 (sleeve or extended or wedge or pulmonary or segmental or carinal or lung or chest wall)).tw. (13412)

43 (wedge biopsy or segmentectomy or lobectom$ or bi?lobar or bi?lobectom$ or pneumonectom$).tw. (17411)

44 exp Pneumonectomy/ (19317)

45 thoracic surgery/ or thoracic surgery, video-assisted/ or exp thoracoscopy/ (18504)

46 exp Pulmonary Surgical Procedures/ (50879)

47 (VATS or (video adj5 thorac$)).mp. or thoracoscopy.tw. (7959)

48 ((mediastinal lymph node$ or mediastinum lymph node$) adj4 (sampling or clearance or resection or dissection or excision)).tw. (684)

49 exp Lymph Node Excision/ (31787)

50 (mediastinum or mediastinum).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (16241)

51 (mediastinal or VAMLA).mp. or (lymphadectomy adj2 (mediastin$ or intrapulmonary)).tw. (33790)

52 exp Surgical Procedures, Operative/ (2197517)

53 exp General Surgery/ (31919)

54 surg$.tw. (1132328)

55 exp Thorax/ (38416)

56 (thora$ or lung).mp. or mediastin$.tw. (731183)

57 Lung/ (166532)

58 exp Mediastinum/ (5985)

59 (operable or resectable).mp. or surg$.tw. (1137526)

60 52 or 53 or 54 (2735780)

61 55 or 56 or 57 or 58 (741217)

62 60 and 61 (195005)

63 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 59 or 62 (1296609)

64 exp Combined Modality Therapy/ (184218)

65 multimodality.mp. or combined modality.tw. (9029)

66 (adjuvant or neoadjuvant or neo-adjuvant or preoperative or pre-operative or postoperative or post-operative or sequential or concurrent or induction or concomitant).tw. (1000895)

67 chemotherap$.tw. (229866)

68 66 and 67 (58828)

69 64 or 65 or 68 (219718)

70 37 and 63 (136079)

71 63 and 69 (71267)

72 70 or 71 (160207)

73 8 and 13 (18542)

74 8 and 30 (22042)

75 8 and 72 (12908)

76 73 or 74 or 75 (37012)

77 limit 76 to (yr="2010 -Current" and randomized

	controlled trial) (288) 78 pancoast$.tw. (490) 79 exp Pancoast Syndrome/ (612) 80 78 or 79 (740) 81 limit 80 to (yr="2010 -Current" and randomized controlled trial) (0) 82 77 or 81 (288)
Note	

Date	**30 July 2012**
Database	EMBASE via Embase.com
Search Strategy	lung:ab,ti AND (neoplasm*:ab,ti OR cancer*:ab,ti OR carcinoma*:ab,ti OR adenocarcinoma*:ab,ti OR angiosarcoma*:ab,ti OR chrondosarcoma*:ab,ti OR sarcoma*:ab,ti OR teratoma*:ab,ti OR lymphoma*:ab,ti OR blastoma*:ab,ti OR microcytic*:ab,ti OR carcinogenesis:ab,ti OR tumour*:ab,ti OR tumor*:ab,ti OR metast*:ab,ti) AND ('multimodality cancer therapy'/exp AND [embase]/lim OR (chemoradiation:ab,ti AND [embase]/lim) OR ('chemo radiotherapy':ab,ti AND [embase]/lim) OR (radiochemotherapy:ab,ti AND [embase]/lim) OR (multimodality:ab,ti AND [embase]/lim) OR ('combined modality':ab,ti AND [embase]/lim) OR (radiotherap*:ab,ti AND [embase]/lim OR (radiat*:ab,ti AND [embase]/lim) OR (chemotherap*:ab,ti AND [embase]/lim) AND (sequential:ab,ti AND [embase]/lim OR (concurrent:ab,ti AND [embase]/lim) OR (concomitant:ab,ti AND [embase]/lim))) OR ('drug combination'/de AND [embase]/lim) OR ('antineoplastic agent'/exp AND [embase]/lim) OR ('radiation dose'/exp AND [embase]/lim OR ('radiation oncology':ab,ti AND [embase]/lim) AND ('antineoplastic agent'/exp AND [embase]/lim OR ('drug therapy'/exp AND [embase]/lim))) OR thoracotomy:ab,ti OR mediastinoscopy:ab,ti OR 'chamberlain procedure' OR ('resection'/exp OR resection AND near AND sleeve) OR ('resection'/exp OR resection AND near AND extended) OR ('resection'/exp OR resection AND extended) OR ('resection'/exp OR resection AND near0 AND extended) OR ('resection'/exp OR resection AND near3 AND sleeve OR extended OR wedge OR pulmonary OR segmental OR carinal OR 'lung'/exp OR lung OR 'chest'/exp OR chest AND wall AND tw.) OR (wedge AND ('biopsy'/exp OR biopsy) OR segmentectomy OR lobectom* OR pneumonectom* AND tw.) OR 'pneumonectomy'/exp OR pneumonectomy OR (thoracic AND ('surgery'/exp OR surgery) OR thoracic AND surgery, AND 'video assisted') OR (pulmonary AND surgical AND ('procedures'/exp OR procedures)) OR vats:ab,ti OR (mediastinal AND ('lymph'/exp OR lymph) AND node* OR 'mediastinum'/exp OR mediastinum AND ('lymph'/exp OR lymph) AND node* AND near4 AND sampling OR clearance OR resection OR dissection OR excision AND tw.) OR ('lymph'/exp OR lymph AND node AND ('excision'/exp OR excision)) OR mediastinum:ab,ti OR (mediastinal OR vamla:ab,ti AND 'lymphadenectomy'/exp) OR lymphadenectomy OR (surgical AND 'procedures'/exp AND [embase]/lim) OR (general AND 'surgery'/exp) OR (surg* AND tw)) AND [randomized controlled trial]/lim AND [2010-2013]/py

Note	

Appendix 1.2.6. Search strategies – Volume-outcome for lung cancer surgery

Date: January 18, 2012	Database: Ovid MEDLINE
Search Strategy:	1 (volume adj2 outcome).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (654) 2 (volume adj2 relat$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (7073) 3 (frequency adj2 relat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (8816) 4 (rate adj2 relat*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (10797) 5 "Length of Stay"/ (52290) 6 Intraoperative Complications/ (24499) 7 exp Mortality/ (255534) 8 exp Morbidity/ (328613) 9 exp Postoperative Complications/ (389494) 10 Patient Admission/ (17086) 11 Patient Discharge/ (16987) 12 Patient Readmission/ (6733) 13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (997843) 14 2 or 3 or 4 (26586) 15 13 and 14 (2989) 16 1 or 15 (3464) 17 limit 16 to humans (3269) 18 exp Lung Neoplasms/ (159748) 19 17 and 18 (84)
Note	Additionally a KCE report with Belgian data on volume-outcomes within lung cancer surgery was used (hand search)

Appendix 1.2.7. Search strategies surgery stage IIIA-N2 disease

Date	12 February 2013
Database	Medline via Ovid
Search strategy	1 Lung Neoplasms/ (149058) 2 (lung adj3 cancer$).ab,ti. (80820) 3 (lung adj3 neoplas$).ab,ti. (1739) 4 (lung adj3 carcin$).ab,ti. (22775) 5 (lung adj3 tumo$).ab,ti. (15259) 6 (lung adj3 malig$).ab,ti. (2451) 7 NSCLC.ab,ti. (14561) 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (173679) 9 Lung Neoplasms/su, th [Surgery, Therapy] (29197) 10 Thoracic Surgery/ (9921) 11 pulmonary surgical procedures/ or pneumonectomy/ (19928) 12 lobect$.tw. (11829) 13 surgical resection.tw. (24218) 14 9 or 10 or 11 or 12 or 13 (79397) 15 N2.tw. (21145) 16 (stage adj3 III$).tw. (29788)

	17 15 or 16 (50111) 18 8 and 14 and 17 (2983) 19 exp animals/ not humans.sh. (3754077) 20 18 not 19 (2981) 21 meta-analysis.mp,pt. or review.pt. or search:.tw. (1881898) 22 randomized controlled trial.pt. (338195) 23 controlled clinical trial.pt. (85043) 24 randomized.ab. (241810) 25 placebo.ab. (134534) 26 clinical trials as topic.sh. (162087) 27 trial.ti. (103477) 28 21 or 22 or 23 or 24 or 25 or 26 or 27 (2464650) 29 20 and 28 (857) 30 limit 29 to yr="2010 -Current" (118)
Note	

Date	**12 February 2013**
Database	Embase via Embase.com
Search strategy	'lung non small cell cancer'/exp AND [embase]/lim OR (lung NEAR/3 cancer AND [embase]/lim) OR (lung NEAR/3 neoplas* AND [embase]/lim) OR (lung NEAR/3 carcin* AND [embase]/lim) OR (lung NEAR/3 tumo* AND [embase]/lim) OR (lung NEAR/3 malig* AND [embase]/lim) OR (lung NEAR/3 metasta AND [embase]/lim) AND (n2 AND [embase]/lim OR (stage NEAR/3 iii* AND [embase]/lim)) AND ('lung resection' AND [embase]/lim OR ('lung lobectomy' AND [embase]/lim) OR (lobectom* AND [embase]/lim) OR (pneumonectomy AND [embase]/lim) OR (surg* NEAR/3 resect* AND [embase]/lim)) AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [humans]/lim AND [embase]/lim AND [2010-2013]/py
Note	

Date	**12 February 2013**
Database	Cochrane Library
Search strategy	#1 MeSH descriptor: [Lung Neoplasms] explode all trees #2 NSCLC #3 #1 or #2 #4 MeSH descriptor: [Pulmonary Surgical Procedures] explode all trees #5 lobect* #6 pneumonect* #7 surgical resection #8 #4 or #5 or #6 or #7 #9 N2 #10 stage near/3 III* #11 #9 or #10 #12 #3 and #8 and 11 from 2010 to 2013
Note	

Appendix 1.2.8. Search strategies – Follow-up

Date	2 April 2013
Database	MEDLINE via OVID
Search strategy	1 exp Lung Neoplasms/ (161789) 2 (lung adj (neoplasm$ or cancer$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chrondosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis or tumour$ or tumor$ or metast$)).ti,ab. (103338) 3 (NSCL or SCLC).ti,ab. (4637) 4 1 or 2 or 3 (183246) 5 exp Aftercare/ (6299) 6 (aftercare or after-care or follow-up or surveillance).m_titl. (88178) 7 ((post-treatment or posttreatment) adj1 evaluation$).mp. (323) 8 ((post-treatment or posttreatment) adj1 care).mp. (58) 9 ((post-treatment or posttreatment) adj1 monitoring).mp. (84) 10 5 or 6 or 7 or 8 or 9 (93319) 11 Radiography, Thoracic/ (24991) 12 tomography, x-ray computed/ or tomography, spiral computed/ (269765) 13 11 or 12 (288212) 14 4 and 10 and 13 (157) 15 limit 14 to (english language and humans and yr="2009 -Current") (58)
Note	Search focused on imaging (not a full update from the NICE strategy)

Date	2 April 2013
Data base	Embase
Search strategy	#2 AND #7 AND #11 AND [humans]/lim AND [english]/lim AND [embase]/lim AND [2009-2013]/py #2 AND #7 AND #11 #3 AND #10 'follow-up'/exp #5 OR #6 'positron emission tomography'/exp 'spiral computer assisted tomography'/exp 'aftercare'/exp OR aftercare AND [2009-2013]/py 'lung tumor'/exp OR 'lung tumor' AND [2009-2013]/py
Note	Search focused on imaging (not a full update from the NICE strategy)

APPENDIX 2. CRITICAL APPRAISAL

Table 9 – Critical appraisal of guidelines

Source	Year	Title	Standardised Methodology Score	Final appraisal
National Institute for Health and Clinical Excellence (UK)	2011	The diagnosis and treatment of lung cancer (update)	100%	Recommended
ASCO (Azzoli et al.)	2009	American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer	100%	Recommended
	2011	2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer		
Cancer Care Ontario	2010	First-line Systemic Chemotherapy in the Treatment of Advanced Non-Small Cell Lung Cancer	97%	recommended
Vereniging Integrale kankercentra	2011	Niet-kleincellig longcarcinoom. Landelijke richtlijn, Versie: 2.0	85%	recommended
	2011	Kleincellig longcarcinoom. Landelijke richtlijn, Versie: 1.0		

Appendix 2.1. Evidence tables

Appendix 2.1.1. Solitary lung nodule

The full text of 24 articles was acquired and examined. Only studies that assessed sensitivity and specificity with a gold standard were retained. Six diagnostic accuracy studies were retained for an assessment of the risk of bias with QUADAS-2 by 2 experts (JOR & KHH). Of those six studies, only two were considered to have a sufficient low risk of bias, the result of these concern the role of PET and are presented in the part on the assessment of solitary pulmonary lesions. One had a high proportion of tuberculosis lesions; a situation unlikely to occur in Belgium. Three studies had unclear or insufficient reference standards, mainly due to problems with the follow-up of negatives.

Additionally, one systematic review that examined endobronchial ultrasound-transbronchial lung biopsy (EBUS-TBLB) with various guidance tools (guide sheath, fluoroscopy, none) for the diagnosis of primary pulmonary lesions (PPL) was included and judged to be of high quality (assessed with the Dutch Cochrane tool for systematic reviews of diagnostic studies).

Table 10 – Evidence table: solitary lung nodule

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Grgic, 2010	Design: retrospective cohort (follow-up of negatives that did not undergo surgery) Sources of funding: not mentioned, there is a declaration that there is no conflict of interest Setting: Saarland university Medical Center, Homburg/Saar, Germany Sample size: 140 Duration:2 years follow-up	Eligibility criteria: patients with solitary pulmonary lesion Patients characteristics: 26 women and 114 men Prevalence of disease: 57 % malignancy	Index test(s) 18F-fluorodeoxyglucose (FDG) PET Reference standard: surgery + follow-up	Sensitivity: 96%(92–100%) Specificity: 55% (38–72%) PPV 79% (71–86%) NPV 92% (82–100%)	Effect size secondary outcome	Dropouts is presented as a survival analysis and difficult to estimate Results critical appraisal Low risk of bias.
Huang, 2010	Design: retrospective cohort (follow-up of negatives that did not undergo surgery) Sources of funding: not mentioned, there is a declaration that there is no conflict	Eligibility criteria: patients with solitary pulmonary lesion Patients characteristics: 26 women and 114 men Prevalence of disease: 57 %	Index test(s) modalities of PET using 18F-fluorodeoxyglucose, one with SUV quantification, attenuation controlled and non attenuation controlled Reference standard: surgery + follow-up	sensitivity of 100 % and a specificity of 64 % for SUV quantification sensitivity 91 % and a specificity of 59 % attenuation controlled PET sensitivity of 79 % and a specificity of 77 % non attenuation controlled	Effect size secondary outcome	small sample, no statistical inference Results critical appraisal Low risk of bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	of interest Setting: Saarland university Medical Center, Homburg/Saar, Germany Sample size: 140 Duration:2 years follow-up	malignancy		method		

Table 11 – Evidence table: systematic review on solitary lung nodule

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Steinfort, 2010	Design: SR and MA Sources of funding: Post-graduate research scholarship from the National Health and Medical Research Council of Australia Search date:december	Eligibility criteria: studies that examined EBUS for the diagnosis of PPLs. Inclusion criteria were: 1) radial probe EBUS for diagnosis of PPL; 2) diagnoses confirmed histologically or by close clinical follow-up for at least 6 months used as the reference standard; and 3) enrolled at	Index test(s): EBUS- TBLB (Endobronchial Ultrasound-Transbronchial Lung Biopsy with various guidance tools (guide sheath, fluoroscopy, none) Reference standard: surgery/clinical follow-up	results meta-analysis Sensitivity 0.73 (95% CI 0.70–0.76) Specificity 1.00 (95% CI 0.99–1.00) PPV na (different proportions malignang lesions) NPV na (different proportions malignang lesions) LR+26.84 (12.60–57.20) LR- 0.28 (0.23–0.36).	different sensitivities according to size Sensitivities ranging from 0.49 to 0.88 but most but only 2 outlyers are under 0.7	: Results critical appraisal High quality review High level of heterogeneity I2 72 % in sensitivities, exploration showd that average lesion size and prevalence of malignancy were factors but did not explain everyting. subgroup analysis taking into account these factors had a

	2009 Searched databases: Medline Included study designs: validation studies Number of included studies: 16	least 30 patients. Patient characteristics patients with Peripheral Pulmonary Lesions		limited effect on the estimations.

Appendix 2.1.2. Mediastinal staging: PET-CT

The full text of 21 articles was acquired and examined. Only studies that assessed sensitivity and specificity with a gold standard were retained. Eight diagnostic accuracy studies were retained for an assessment of the risk of bias with QUADAS-2 by 2 experts (JOR & KHH). One study did not evaluate PET-CT, one study was already included in the NICE guideline, one study only included a per node analysis and two studies were excluded due to a very high risk of bias. Three studies were included for the update on mediastinal staging by PET-CT.

Table 12 – Evidence table: mediastinal staging PET-CT

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of quality
Fischer, 2012	Design: RCT Sources of funding: Danish Cancer Society and the Danish Center for Health Technology Assessment Setting: Large University Hospital, Denmark Sample size: 189 Duration: not stated	Eligibility criteria: pt with a verified diagnosis of NSCLC who were considered operable Patient characteristics: PET-CT arm: Mean age 62 years (range 42-80), 54 % male. CWU arm: Mean age 64 years (38 -80) Prevalence of disease: NA	Index test(s) PET-CT followed by invasive diagnostic procedure (CWU) or diagnostic procedure alone (CWU) Reference standard: (CWU) mediastinoscopy	Sensitivity: CWU=59% (range 41-74). PET-CT (based on ITT analysis) = 73 % (range 59-86) Specificity: CWU=98% (range 91-100) PET-CT (based on ITT analysis) = 100 % (range 94-100)	Effect size secondary outcome: NA	Dropouts: n=14 Results critical appraisal: well-conducted RCT, drop-out is considerable
Darling, 2011	Design: prospective study of one arm from an RCT Sources of funding: Grants	Eligibility criteria: pt with chest CT and proven NSCLC who were randomized to the PET-CT and brain imaging arm of an RCT	Index test(s) PET-CT scan Reference standard: mediastinoscopy thoracotomy or	Sensitivity:70 % (95%CI 48-85%) Specificity: 94% (95%CI 88-97%) PPV: 64 % (95%CI 43-	Effect size secondary outcome: NA	Dropouts: one person dropped out prior to study investigation. 19 pt did not undergo thoracotomy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of quality
	from the Ontario Ministry of Health and Long Term Care and the CIHR Setting: PET-CT centres across Ontario, Canada. Pt recruited from tertiary and community hospitals in Ontario. Sample size: 170 Duration: pt enrolled between 2004-2007	(ELPET) Patients characteristics: Mean age: 67 Female 49%, Male 51%. 66 % ex-smokers, 28 % current smokers and 6 % never smokers	both	80%) NPV: 95% (95%CI 90-98%)		mainly due to upstaging with metastasis. 149 pt were included in analysis. Results critical appraisal: well conducted
Gomez-Caro, 2010	Design: prospective Sources of funding: not stated Setting: tertiary hospital, Barcelona, Spain Sample size:125 Duration:2007-2009	Eligibility criteria: histologically diagnosed with NSCLC, clinically staged as cNO and met the oncological and functional criteria for resectability Patients characteristics: Mean age: 66.5 Gender: 84% males, 16% females	Index test(s) A negative FDG PET-CT (and CT-scan) Reference standard: thoracotomy	NPV=85.6% (CI=77-91) FN=14.4%	Effect size secondary outcome: NA	Dropouts: no drop-out Results critical appraisal: well-conducted

Appendix 2.1.3. Mediastinal staging: EBUS-EUS

Based on title and abstract, 45 articles were retrieved. Three of the selected studies were already included in one of the guidelines and are not further discussed.[146-148] Retrospective studies with less than 200 patients, prospective studies with less 50 patients, studies without separate results for mediastinal lymph node staging or no 2x2 table were excluded. After further selection based on full text articles, six studies were critical appraised using the QUADAS-2 checklist. One health technology assessment based on a randomized controlled trial, four prospective and one retrospective cohort studies were included for the update.

Table 13 – Evidence table: mediastinal staging EBUS-EUS

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Cetinkaya, 2011[149]	Design: prospective cohort study Sources of funding: none Setting: single centre, Turkey Sample size: 52 pts Duration: Jan 2007-May 2009	Eligibility criteria: NSCLC patients suitable for operation according to metastatic screening with imaging, with suspicious LN on PET/CT Patients characteristics: M/V 45/7, median age 59.9y (range 53-67y) Prevalence of disease: 80%	Index test(s): EBUS FNAC Reference standard: mediastinoscopy ± thoracotomy	Sensitivity:95% NPV: 83%	No complications	Dropouts: none Results critical appraisal all positive results considered as true positive.
Sharples, 2012[27]	Design: RCT/HTA Sources of funding: NIHR Health Technology Assessment programme Setting: international (B, NI,	Eligibility criteria: known/suspected NSCLC with suspected mediastinal LN involvement otherwise eligible for surgery with curative	Index test(s) Arm 1: combined EUS and EBUS FNAC followed by surgical staging if negative Arm 2: surgical staging	Sensitivity Arm 1: 94% (95%CI 85-98%) Arm 2: 79% (95%CI 66-88%) p=0.02 NPV	**Overall complication rate** 6% in the surgical staging arm versus 5% in the EBUS-EUS arm. **Unnecessary**	Dropouts: arm 1: 1 pt had no thoracotomy after 2nd EUS. arm 2:1 pt had no surgical staging because of distant M+, 7 pts had no thoracotomy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	UK) multicentre Sample size: 241 pts Duration: February 2007-April 2009	intent Patients characteristics: average age 64.5y (SD 8.9y), majority male. Prevalence of disease: 49%	Reference standard: thoracotomy with systematic lymphadenectomy	Arm 1: 93% (95%CI 84-97%) Arm 2: 86% (95%CI 76-92%) p=0.18	**thoracotomy** in 18% of patients of surgical staging arm versus 7% in EBUS-EUS strategy (p=0.02) Better **QoL** during staging in the EBUS-EUS arm. EBUS-EUS strategy slightly more **effective** and less expensive.	Results critical appraisal low risk of bias. Positive results considered true positive.
Hwangbo, 2010[150]	Design: prospective cohort study. Sources of funding: none Setting: single centre, Korea Sample size: 150 pts Duration: August 2008 - March 2009	Eligibility criteria: NSCLC pts without M+ on PET-CT and brain-MRI and no LN M+ outside the mediastinum, medically and surgically considered operable Patients characteristics: M/V 113/37, median age 64.5y (range 34-80y) Prevalence of disease: 43.8%	Index test(s): EBUS + EUS performed in one session Reference standard: surgical confirmation of negative results	EBUS Sensitivity:84.4% NPV:93.3% EBUS + EUS Sensitivity:91.1% NPV: 96.1%	One serious complication after EBUS: lymph node abscess, resolved with antibiotics	Dropouts: 7 pts with negative EBUS-EUS had no surgical confirmation: 5 refused, one had benign disease and one patients appeared inoperable due to pleural M+ Results critical appraisal: patients without suspicious LN on PET-CT also included. Low risk of bias
Ohnishi, 2011[151]	Design: prospective cohort study. Sources of funding: none Setting: single	Eligibility criteria: newly diagnosed or suspected lung cancer with < T4 and M0 on imaging	Index test(s): PET-CT, combined EBUS and EUS Reference	EBUS Sensitivity: 64.1% (95%CI 48.4-77.3%) NPV: 83.5% (95%CI 74.2-89.9%)	Effect size secondary outcome	Dropouts: 5 patients refused surgery and are excluded from the analysis Results critical

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	centre, Japan Sample size:120 pts (115 EBUS-EUS) Duration: June 2008 – June 2010	considered eligible for curative surgery Patients characteristics: M/F 79/41 median age 69y (range 40-85y) Prevalence of disease:	standard: surgery	EUS Sensitivity: 48.7% (95%CI 33.9-63.8%) NPV: 78% (95%CI 68.5-85.3%) EBUS + EUS Sensitivity: 71.8% (95%CI 53.2-83.5%) NPV: 86.6% (95%CI 77.6-92.3%)		appraisal: patients without suspicious LN on PET-CT also included. Low risk of bias
Yasufuku, 2011[28]	Design: prospective cohort study Sources of funding: equipment loaned from Olympus medical systems Setting: Single centre, Canada Sample size: 159 pts Duration: July 2006 – August 2010	Eligibility criteria: pts with (suspected) NSCLC who required mediastinoscopy to determine suitability for lung cancer resection Patients characteristics: M/F 84/96 Prevalence of disease: 35%	Index test(s): EBUS TBNA Reference standard: all pts underwent mediastinoscopy followed by thoracotomy if no LN M+ detected by mediastinoscopy	EBUS Sensitivity: 81% Specificity: 100% PPV: 100% NPV: 91%	mediastinoscopy Sensitivity: 79% Specificity: 100% PPV: 100% NPV: 90% 4 pts with N2/N3 disease were missed by both EBUS and mediastinoscopy, 7 cases were missed by mediastinoscopy but diagnosed by EBUS and 6 cases the other way around	Dropouts: 31 pts did not proceed to EBUS due to advanced disease, decrease of LN size on FU imaging or patient withdrawal. 6 pts excluded after EBUS due to advanced disease. Results critical appraisal: Not all patients had PET-scan prior to EBUS. Patients without suspicious LN on PET-CT also included. Low risk of bias. All patients underwent mediastinoscopy even if EBUS was positive. Low risk of bias;

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Sanz-Santoz, 2012[152]	Design: retrospective (?) cohort study Sources of funding: Fondo de Investigacion Sanitaria and Fundacio Catalana de Pneumologia Setting: single centre, Spain Sample size: 296 pts Duration: 2005-2011	Eligibility criteria: pts diagnosed with NSCLC who did not show distant M+ at first examination (CT-scan) Patients characteristics: mean age 63y (SD ±10); 183 had nodal enlargement on CT-scan. Prevalence of disease: 60.5%	Index test(s): EBUS-TBNA Reference standard: mediastinoscopy and/or surgery	NPV:93% 38 pts with unsatisfactory EBUS not included in analysis	No clinically significant complications	Dropouts: 16/98 (16.3%) pts with negative EBUS did not undergo surgery because of impaired lung function or other co-morbidities Results critical appraisal: High numbers of dropouts, see above. Otherwise low risk of bias;

Appendix 2.1.4. Mediastinal staging: mediastinoscopy

Based on title and abstract, 26 articles were retrieved. Two of the selected studies were already included in one of the guidelines and are not further discussed.[153, 154] Retrospective studies with less than 200 patients, prospective studies with less 50 patients, studies without separate results for mediastinal lymph node staging or no 2x2 table were excluded. After further selection based on full text articles, two studies[29, 155] were critical appraised using the QUADAS-2 checklist, of which one was excluded.[155] Three studies, of which two studies were also included in the evidence tables on endoscopic staging techniques[27, 28], were included.

Table 14 – Evidence table: mediastinal staging mediastinoscopy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Sharples, 2012[27]	Design: RCT/HTA Sources of funding: NIHR Health Technology Assessment programme Setting: international (B, NI, UK) multicentre Sample size: 241 pts Duration: February 2007-April 2009	Eligibility criteria: known/suspected NSCLC with suspected mediastinal LN involvement otherwise eligible for surgery with curative intent Patients characteristics: average age 64.5y (SD 8.9y), majority male. Prevalence of disease: 49%	Index test(s) Arm 1: combined EUS and EBUS FNAC followed by surgical staging if negative Arm 2: surgical staging Reference standard: thoracotomy with systematic lymphadenectomy	Sensitivity Arm 1: 94% (95%CI 85-98%) Arm 2: 79% (95%CI 66-88%) p=0.02 NPV Arm 1: 93% (95%CI 84-97%) Arm 2: 86% (95%CI 76-92%) p=0.18	**Overall complication rate** 6% in the surgical staging arm versus 5% in the EBUS-EUS arm. **Unnecessary thoracotomy** in 18% of patients of surgical staging arm versus 7% in EBUS-EUS strategy (p=0.02) Better **QoL** during staging in the EBUS-EUS arm. EBUS-EUS strategy slightly more **effective** and less expensive.	Dropouts: arm 1: 1 pt had no thoracotomy after 2nd EUS. arm 2:1 pt had no surgical staging because of distant M+, 7 pts had no thoracotomy Results critical appraisal low risk of bias. Positive results considered true positive.
Yasufuku, 2011[28]	Design: prospective cohort study Sources of funding: equipment loaned from Olympus medical systems Setting: Single centre, Canada Sample size: 159	Eligibility criteria: pts with (suspected) NSCLC who required mediastinoscopy to determine suitability for lung cancer resection Patients characteristics: M/F 84/96	Index test(s): EBUS TBNA Reference standard: all pts underwent mediastinoscopy followed by thoracotomy if no LN M+ detected by mediastinoscopy	EBUS Sensitivity: 81% Specificity: 100% PPV: 100% NPV: 91%	mediastinoscopy Sensitivity: 79% Specificity: 100% PPV: 100% NPV: 90% 4 pts with N2/N3 disease were missed by both EBUS and mediastinoscopy,	Dropouts: 31 pts did not proceed to EBUS due to advanced disease, decrease of LN size on FU imaging or patient withdrawal. 6 pts excluded after EBUS due to advanced disease. Results critical

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	pts Duration: July 2006 – August 2010	Prevalence of disease: 35%			7 cases were missed by mediastinoscopy but diagnosed by EBUS and 6 cases the other way around	appraisal: Not all patients had PET-scan prior to EBUS. Patients without suspicious LN on PET-CT also included. Low risk of bias. All patients underwent mediastinoscopy even if EBUS was positive. Low risk of bias;
Gunluoglu, 2011[29]	Design: prospective cohort study Sources of funding: not stated Setting: single centre, Turkey Sample size: 185 pts Duration: 2007-2009	Eligibility criteria: NSCLC patients who have no distant metastasis with central tumour OR T3-4 OR LN > 1,5cm on CT OR primary tumour PET (-) OR LN (+) on PET Patients characteristics: M/V 149/19 Prevalence of disease: 29.2%	Index test(s) mediastinoscopy Reference standard: thoracotomy with systematic lymphadenectomy	Sensitivity: 84% (95%CI 70-92%) NPV: 94% (95%CI 88-97%)		Dropouts: 14 patientsin whom PET was performed with PET-fusion scanner were excluded. Two patients didn't have surgery and were also excluded Results critical appraisal: low risk of bias. No EBUS-EUS performed prior to mediastinoscopy.

Appendix 2.1.5. Histological sub-classification using FNAC samples

Based on title and abstract, 18 full-text articles were retrieved. Studies including fewer than 50 cases were excluded. All remaining observational studies describing the feasibility of histological sub-typing or molecular techniques were included. This amounted to four studies.

Table 15 – Evidence table: histological sub-classification and molecular tests using Fine Needle Aspiration Cytology (FNAC) samples

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Santis, 2011[33]	Design: retrospective cohort study Sources of funding: Biotechnology and biological Sciences Research Council, Department of Health (UK) and Experimental Cancer Medicine Centre Network Setting: single study, UK Sample size: 132 pts Duration: May 2009 – February 2011	Eligibility criteria: patients diagnosed with NSCLC using EBUS-TBNA (only non-squamous type included in second half of the study) Patients characteristics: 125 Caucasian, 4 Asian, 3 British Black Prevalence of disease: 10.3% EGFR mutations; 17.7% KRAS mutations	Index test(s): EGFR and KRAS mutation analysis using COLD-PCR Reference standard: repeat COLD-CPR on second cell block	EGFR: complete molecular analysis was available in 126/132 (95.4%) patients KRAS mutations: successful analysis in 130/132 (98.4%) of samples		Dropouts: NA Results critical appraisal: negative results (no mutation identified) are not confirmed on a second cell block. Results are not verified by assays performed on tissue blocks.
Nizzoli, 2011[34]	Design: retrospective cohort study Sources of funding: none	Eligibility criteria: NSCLC cases with concurrent or subsequent histological diagnosis	Index test(s): cytological diagnosis on TBNA or TTNA samples Reference standard:	Agreement between cytological and histological typing in 137/156 (88%) of cases not diagnosed as	FNAC allowed tumour typing in 85% of cases, 15% diagnosed as NSCLC-NOS	Dropouts: NA Results critical appraisal: the value of endoscopic biopsies as reference standard

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Setting: single centre, Italy Sample size: 186 cases Duration: 2000-2009		histological diagnosis on endoscopic biopsy (112 cases) or surgical specimen (74 cases)	NSCLC-NOS Agreement in 139/185 (75%) of cases if NSCLC-NOS cases are included		can be questioned
Tournoy, 2012[35]	Design: retrospective cohort study Sources of funding: none Setting: single centre, Belgium Sample size: 92 pts Duration: June 2004-July 2010	Eligibility criteria: Patients with FNA showing NSCLC and presence of a pulmonary or nodal biopsy sample that matched the same clinical episode	Index test: histological diagnosis on cytology sample Reference standard: histological diagnosis on biopsy	Agreement on squamous or non-squamous diagnosis in 70/92 (76% 95%CI 66-84%) Sensitivity FNA for SCC: 64% Sensitivity FNA for non-squamous: 88% PPV FNA for SCC: 82% PPV FNA for non-squamous: 72%	When further subtyping non-squamous carcinoma: less NSCLC-NOS on biopsy compared to cytology (0/92 versus 7/92, p=0.008)	Dropouts: NA Results critical appraisal: only 10% of patients undergoing endosonography had a matching biopsy sample. Only 25% of biopsies delivered by surgery, other samples obtained by bronchoscopy or transthoracic trucut biopsies
Billah, 2011[32]	Design: retrospective cohort study Sources of funding: none Setting: single centre, USA Sample size: 209 samples Duration: September 2009-April 2010	Eligibility criteria: lung cancer patients for whom cytology specimens were collected and submitted for molecular testing Patients characteristics: M/F 95/114, mean age 63y (range 29-91y) specimens: 99 EBUS-FNAs, 67 CT	Index test: EGFR or KRAS mutation testing Samples containing less than 40% tumour cells were considered insufficient.		Specimen insufficiency rate: 6.2% (EBUS specimens 4%)	Level of evidence: Dropouts Results critical appraisal: diversity of samples may not be representative for all clinical scenarios.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		guided FNAs, 27 pleural/pericardial effusions, 10 US guided FNAs, 1 bronchoalveolar lavage, 1 bronchial washing Prevalence of disease: 19.4% EGFR mutations, 23.6% KRAS mutations				

Appendix 2.1.6. Histology sub-typing by immunohistochemistry

Based on title and abstract, 18 full-text articles were retrieved. Studies including fewer than 50 cases were excluded. After quality assessment, 5 studies were retained.

Table 16 – Evidence table: histology sub-typing by immunohistochemistry

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Ocque, 2011[38]	Design: retrospective validation study Sources of funding: not mentioned but there is a declaration that they have no relevant relationships with commercial interest	Eligibility criteria: non small cell lung carcinoma of intermediate grade Patients characteristics: Median FU: surgery as gold standard	diverse histochemical tests on biopsy Comparator(s): Staging on surgically resected tumour	Increased diagnostic accuracy for adenocarcinoma (56% [44/78] from 2000-2004 vs 83.2% [154/185] after 2005) but not for squamous cell carcinoma (77% [57/74] before 2004 vs 73.9% [82/111] from 2005-2010). Adenocarcinoma showed high expression of		Results critical appraisal: sample recruitment somewhat unclear but unlikely to have caused bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Setting: US university hospital Sample size: 448 Duration: transversal			cytokeratin (CK)7 (146/146 [100%]), thyroid transcription factor-1 (131/152 [86.2%]), surfactant A (29/36 [81%]), and periodic acid–Schiff with diastase (69/86 [80%]). All squamous cell carcinomas were positive for CK5/6 and p63		
Rekhtman, 2011[37]	Design: prospective validation Sources of funding: not mentioned Setting: Memorial Sloan-Kettering Cancer Center, New York, NY, USA Sample size: 315 Duration:	Eligibility criteria: Non small cell lung cancers with morphologically unclassifiable small biopsy/cytology specimens	Intervention(s): p63, CK5/6 34betaE12 and TTF-1 on morphologically unclassifiable small biopsy/cytology specimens Comparator(s): Staging on surgically resected tumour	adenocarcinoma showed significant immunoheterogenetity for all 'squamous markers' (p63 (32%), CK5/6 (18%), 34betaE12 (82%)) and TTF-1 (89%). As a single marker, only diffuse TTF-1 was specific for adenocarcinoma whereas none of the 'squamous markers,' were entirely specific for squamous cell carcinoma. In contrast, co-expression profiles of TTF-1/p63 had only minimal overlap between adenocarcinoma and squamous cell carcinoma, and there was no overlap if CK5/6 was added as a third marker.		Results critical appraisal Somewhat unusual design but low risk of bias
Pelosi, 2011[38]	Design: transversal validation study Sources of funding: no sources of	Eligibility criteria: Patients characteristics: non small cell carcinomas	Index test(s) semiquantitatively preoperative biopsies tested for cytokeratins 5/6 and	They found that 59 of 63 (94%) lesions were correctly classified on biopsy compared with 53 of 63		Results critical appraisal low risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	support that require acknowledgement Setting: Milan, Italy Sample size:63		7, p63, thyroid transcription factor-1, and vimentin immunoreactivity Reference standard: the corresponding surgical specimens	(84%) by revised morphology, with the predictive positive value being 97% for squamous cell carcinoma, 88% for adenocarcinoma, and 100% for sarcomatoid and adenosquamous carcinoma.		
Terry, 2011[39]	Design: validation on known samples Sources of funding: not mentioned Setting: British Colombia, Canada Sample size: 200 cases of adenomacarcinoma and 225 cases of squamous cell carcinoma	Eligibility criteria: Patients characteristics: non small cell carcinomas	Index test(s) expression of 9 markers (p63, TTF1, CK5/6, CK7, 34bE12, Napsin A, mucicarmine, NTRK1, and NTRK2) on 200 cases of adenomacarcinoma and 225 cases of squamous cell carcinoma in tissue microarray format to mimic small tissue specimens. Reference standard: the corresponding surgical specimens	They found that the single best marker to separate adenocarcinoma from is p63 (for squamous cell carcinoma: sensitivity 84%, specificity 85%). Logistic regression analysis with the area under the curve for a test panel as outcome identifies p63, TTF1,CK5/6, CK7, Napsin A, and mucicarmine as the optimal panel with bias-corrected ROC AUC (Receiver Operator Curve Area Under the Curve) for the 6-marker panel is 0.941, compared with 0.938 for all 9 markers and 0.843 for p63 alone to separate adenocarcinoma from squamous cell carcinoma		Results critical appraisal is essentially an experimental study on known samples but the way it is done results in a low risk of bias
Tsuta, 2011[40]	Design: validation on known samples Sources of funding:	Eligibility criteria: Patients characteristics: non	Index test(s) expression of 10 markers 150 cases	Sensitivities: Marker for adencarcinoma		Results critical appraisal is essentially an

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	not mentioned Setting: Tokyo, Japan Sample size: 150 cases of adenocarcinoma and 159 cases of squamous cell carcinoma	small cell carcinomas	of adenocarcinoma and 159 cases of squamous cell carcinoma in tissue microarray format to mimic small tissue specimens Reference standard: the corresponding surgical specimens	p63 98.7% high-molecular-weight (HM) cytokeratin (CK) 97.3%, CK5/6 93.3% Sox2 80% thrombomodulin 79.3% desmocollin-3 72.7% S100A7 70.7% S100A2 63.3% glypican-3 46.7% marker for squamous cell carcinoma: Desmocollin- 100% followed by CK5/6 98% Sox2 95.5% glypican-3 92.4% S100A7 86.8% thrombomodulin 79.9% S100A2 64.6%, p63 (51.6%), and HMCK (33.3%). Thyroid transcription factor-1 (TTF-1) expression was observed in 87.4% of adenocarcinoma cases and 2.0% of squamous cell carcinoma cases. When analyzing only poorly differentiated tumours, HMCK was the most sensitive marker for squamous cell carcinoma (100%), followed by p63		experimental study on known samples but the way it is done results in a low risk of bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				(97.8%), CK5/6 (87.0%), Sox2 (71.7%), thrombomodulin (58.7%), desmocollin-3 (52.2%), S100A2 (50%), glypican-3 (45.7%), and S100A7 (45.7%). Desmocollin-3 was the most specific marker for poorly differentiated squamous cell carcinoma (100%), followed by CK5/6 (98.3%), glypican-3 (94.8%), Sox2 (94.8%), S100A2 (81%), S100A7 (75.9%), thrombomodulin (72.4%), p63 (48.3%), and HMCK (36.8%). They used classification and regression tree analysis and concluded that the combination of CK5/6 and TTF-1 was the best immunohistochemical marker panel for the differentiation between squamous cell carcinoma and adenocarcinoma.		

Appendix 2.1.7. Molecular tests: EGFR status

After a first selection based on title and abstract 8 articles were selected. After further assessment of the full texts and critical appraisal one article was included.

Table 17 – Evidence table: Molecular tests, EGFR status

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Sholl, 2010	Design: retrospective case-control Sources of funding: grant from National Institutes of Health, Bethesda Setting: single centre, USA Sample size: 40 cases Duration: NA	Eligibility criteria: patients with advanced NSCLC treated with erlotinib or gefitinib, assays obtained before start of TKI treatment Patients characteristics: M/F 14/26, median age 69y (range 35-91y)	Index test(s) EGFR DNA sequencing Reference standard: FISH, CISH, immunohistochemical analysis	Sensitivity DNA: 67% CISH: 41% FISH: 55% ImmunoH 10% cutoff: 74% Specificity DNA: 86% CISH: 57% FISH: 50% ImmunoH 10% cutoff: 50%-	Assay failure DNA: 0 FISH:3 CISH:3 ImmunoH: 8	Results presented for disease control (including response to treatment and stable disease)

Appendix 2.1.8. Criteria for operability

Based on title and abstract 29 articles were retrieved for full-text evaluation. On risk assessment, one study on risk assessment for post-operative morbidity was within scope. This large well-conducted retrospective study was included. On assessment of lung function no articles of sufficient quality were identified. On preoperative exercise testing, two studies were included.

Table 18 – Evidence table: criteria for operability

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Takamochi, 2011 [51]	Design: retrospective Sources of funding: Not stated Setting: Cancer Institute, Japan Sample size: 1073 Duration: Sept 1996 – Oct 2009	Eligibility criteria: Patients with NSCLC who underwent pulmonary resection at the institute within time period (see duration), no pt receiving induction therapy Patients characteristics: 677 males, 393 females Median age =65 years	Evaluation of risk factors for morbidity were evaluated independently in groups of younger (<70 years) and older (>70 years)	Risk factors for morbidity (defined as postoperative events e.g. pneumonia and arrhythmia): Younger group: % forced expiratory volume in 1 sec (FEV1)(95%CI 1.46-3.76, p<0.001), the extent of pulmonary resection (95% CI 2.59-15.3, p<0.001) and tumour histology (95% CI 1.17-3.01, p=0.009) Older group: smoking (95% CI 1.66- 4.65, p<0.001), hypertension (95% CI 1.24-3.52, p=0.005), renal insufficiency (95% CI 1.35-6.93, p=0.008) and % diffusing capacity of the lung to carbon monoxide		Multivariate analysis performed on identified risk factors alone Decision to perform surgery might be biased by individual surgeon or family wishes Large study, Well-conducted for retrospective study design

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				(DLCO) (95% CI 1.47-4.11, p=0.001)		
Brunelli, 2012 [52]	Design: prospective Sources of funding: not stated Setting: Division of thoracic surgery and cardiology, Ancona, Italy Sample size: 225 Duration: 2008-2010	Eligibility criteria: candidates for lobectomy or pneumonectomy Patients characteristics: Age average (SD)= 67.2 (9.8) Males no. (%)= 183 (81)	Preoperative (within 1 week before operation) symptom-limited CPET on a cycle ergonometer. Expired gases and volumes were analysed breath-by-breath, with a metabolic cart	Respiratory complications: RCs = 25 patients (11%). Pt had a significantly higher V˙e/V˙co2 slope compared with those without complications (34.8 vs 30.9, *p*=0.001). Mortality: mortality = 5 patients. Pt who died had a higher value of V˙e/V˙co2 slope than survivors (36.3 vs 31.2, *p* =0.07). Cardiac complications: patients with cardiac complications (mainly atrial fibrillation) did not have a significantly higher value of V˙e/V˙co2 slope compared with those without cardiac complications (31.8 vs 31.2, *p* =0.6).		a priori def, patients not selected on slope values no obvious selection bias data if not 95% complete, imputed by averaging non-missing values Not clear clinical implications
Torchio, 2010 [53]	Design: retrospective Sources of	Eligibility criteria: COPD patients referred for	CPET with gas-exchange measurement, using a treadmill with “Balke	Mortality prediction: Logistic regression analysis: V˙e/V˙co2 is		no cut-off defined for slope not reliable statistical analysis for mortality (5

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	funding: not stated Setting: Torino, Italy Sample size: 145 Duration: 2005-2007	preoperative evaluation and who performed a CPET before surgery because of a higher operative risk Patients characteristics: Age (years) 64.2 (SD=7.9) Gender (M/F) = 128/17	protocol". 12-lead electrocardiogram, heart rate and arterial blood pressure were obtained at rest and each minute during exercise. For breath-be-breath gas-exchange measurement a Sensor Medics Vmax 29C system was used	only independent mortality predictor (OR:1.24z=2.77; p<0.007). Morbidity (cardiopulmonary): VO2 peak is best predictor for cardiopulmonary complications (OR:0.05, z=-2.39, p<0.02)		patients) absence of a statistical test to prevent correlated variables (i.e. peak VO2 and VE=VCO2 slope Unclear clinical implications
Campione, 2010[54]	Design: retrospective analysis Sources of funding: not stated Setting: Thoracic Surgery Unit of S. Croce Hospital Sample size: 99 Duration: January 2003 – December 2007	Eligibility criteria: patient with non-small-cell lung cancer who underwent CPET and were scheduled for lung cancer surgery Patients characteristics: Age (years): Mean 67.39, SD± 8.08 80 % of pt had a history of tobacco use	A standard bicycle exercise ramp protocol with increments of 10 W x min^{-1} A 12-lead electrocardiogram was recorded (MAX-1) Blood pressure was recorded every minute with a cuff sphygmomanometer. VO_2 and VCO_2 and minute ventilation were measured by breath-by-breath gas analysis with a computerized metabolic cart	Multivariate analysis showed correlations between perioperative outcomes and: body mass index (p=0.0019, R=0.3045) maximum heart rate (p=0.0007, R=0.3368) oxygen pulse (p=0.0004, R=0.3561)		pt selected based on poor lung function relatively small sample size parts of statistical analysis not well described unclear clinical implications

Comprehensive search for publications on surgery published since 2009 resulted in 1316 citations. First selection based on title and abstract excluded 1263 articles.

Complete mediastinal lymphadenectomy versus lymph node sampling

Selection based on review of full texts, lead to the inclusion of one RCT comparing complete mediastinal lymphadenectomy with lymph node sampling as summarized in Table 19.

Table 19 – Evidence table: lymphadenectomy versus lymph node sampling - RCTs

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Darling 2011[57, 58]	Design: RCT Sources of funding: Setting: multicentre, USA Sample size: 1111 pts Duration: June 1999-February 2004	Eligibility criteria: clinically resectable T1 or T2 NSCLC with cytological or histological confirmation. ECOG PS < 3. N0 or N1 status after sampling of lymph nodes. Patients characteristics: median age 68 y (range 23-89), 52% male, 27% SCC, 42% adenoca 74-76% lobectomy, 4-5% pneumonectomy, 98% R0 resection Median FU: 6.5 years	Intervention(s): Mediastinal lymph node sampling Comparator(s): complete mediastinal lymph node dissection	Median OS: 8.1 years versus 8.4 years (p=0.34) 5-year DFS: 68% versus 67% (p=0.89)	Perioperative morbidity previously reported[59] No difference in median length of hospital stay (p=0.404) One or more complications occurred in 38% of patients in each group No difference in operative mortality (p=0.157)	Dropouts: not stated Results critical appraisal: unclear sequence generation, unclear allocation concealment, no blinding reported. No info on loss of follow-up.

Sleeve lobectomy

Based on full text selection, a further 5 citations were excluded. One recent systematic review was included, critical appraisal of primary studies was performed by KCE.

Table 20 – Evidence table: sleeve-lobectomy: Systematic Review

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Shi, 2012	Design: SR and MA Sources of funding: none stated Search date: October 2011 Searched databases: Pubmed, Embase Included study designs: observational studies Number of included studies: 19	Eligibility criteria: studies comparing short-term and long-term outcomes of sleeve lobectomy and pneumonectomy for NSCLC Patients characteristics: stage I-II-III included Median FU: not stated	Intervention: Sleeve lobectomy Comparator: pneumonectomy	Postoperative mortality: OR 0.50; 95%CI 0.34-0.72 Overall survival: HR 0.63; 95%CI 0.56-0.71	Postoperative complications: OR 1.17; 95%CI 0.82-1.67 Locoregional recurrences: 0.78; 95%CI 0.47-1.29	Results critical appraisal: no critical appraisal of included studies performed. Only observational studies included, majority at risk for selection bias, confounders insufficiently taken into account (review KCE) Statistical tests suggest no publication bias

Sublobectomy

Based on full text selection, a further 13 citations were excluded. One recent systematic review was included, critical appraisal of primary studies was performed by KCE. Also one prospective, non-randomized study and two retrospective case series were included.

Table 21 – Evidence table: sublobectomy – Systematic Review

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Fan, 2012	Design: SR and MA Sources of funding: PhD programs foundation of Ministry of Education of China Search date: August 2010 Searched databases: Pubmed Included study designs: 1 RCT, 23 observational studies Number of included studies: 24	Eligibility criteria: comparisosn lobectomy with sublobectomy (wedge resection or anatomic segmentectomy) in clinical stage I patients, reporting on OS or cancer-specific survival Patients characteristics: not stated Median FU: not stated	Intervention: Sublobectomy: wedge resection or anatomical segmentectomy Comparator: lobectomy	OS sublobectomy vs lobectomy Stage I: 1.26; 95%CI 1.07-1.47 ≤ 2cm: 0.81; 95%CI 0.39-1.71 OS segmentectomy vs lobectomy: Stage I: 1.09; 95%CI 0.85-1.40		Results critical appraisal: only pubmed searched, no critical appraisal performed. No publication bias detected. Only observational studies included, majority at risk for selection bias, confounders insufficiently taken into account (review KCE).

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Wolf, 2011	Design: retrospective case series Sources of funding: none reported Setting: single centre, USA Sample size: 238 pts Duration: 2000-2005	Eligibility criteria: all patients who underwent resection of tumours smaller than 2 cm. Pts who underwent neoadjuvant therapy, had other tumours, pure bronchialveolar carcinomas, had LN or distant metastases	Intervention(s): Sublobectomy (segmentectomy, wedge resection) Comparator(s): lobectomy	Any recurrence: 24% vs. 15% (p=0.1364) 5-y survival: 59% vs. 80% (p=0.0027) 5-y recurrence-free survival: 74% vs. 87% (p=0.0496)	No significant difference for morbidity and perioperative mortality.	Dropouts: unclear Results critical appraisal: consecutive inclusion of all eligible patients. Patients who had sublobar resection were older and had worse preoperative pulmonary function. Number loss of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		were excluded. Patients characteristics: median age 66-71 years, 40-42% male. Median tumour size 1.5 cm; squamous 15-21% Median FU: not stated				follow-up not stated. Duration follow-up unclear.
Cheng, 2012	Design: non-randomized prospective controlled study Sources of funding: National Natural Scientific Foundation of China, Province Natural Scientific Foundation of Hunan Setting: single centre, China Sample size: 184 pts Duration: September 1997-October 2006	Eligibility criteria: NSCLC pts age ≥ 70 years. FEV1 > 1.0l. No evidence of metastases on imaging. Stage I, peripheral tumours ≤ 3cm Patients characteristics: mean age 72.7 years (range 70-82 years), 81% male, 54% SCC. Median FU: not reported	Intervention(s): Segmentectomy + regional or selected lymph node dissection Comparator(s): lobectomy + regional or selected lymph node dissection	Pts with FEV < 1.5l 1-year survival: p=0.708 3-year survival: p=0.312 5-year survival: p=0.585 Pts with FEV1 ≥ 1.5l: 1-year survival: p=0.569 3-year survival: p=0.293 5-year survival: p=0.439	Patients undergoing segmentectomy + regional lymph node dissection had significantly better 3- and 5-year survival than patients who had segmentectomy + selected lymph node dissection	Dropouts: 8 patients (4.3%) lost of follow-up Results critical appraisal: no info on consecutive inclusion of patients. No blinding, no randomization. Insufficient correction for confounding. Duration of follow-up unclear.
Shirvani, 2012	Design: retrospective observational study Sources of funding: Cancer prevention & Research Institute of texas, Department of Health and Human	Eligibility criteria: ≥ 66 years without prior malignancy, with NSCLC, tumours ≤ 5 cm who underwent (sub)lobectomy or SBRT	Intervention(s): Sublobectomy, SABR Conventional RT Comparator(s): lobectomy	Risk of death 0-6 months: SBRT vs lobectomy: HR 0.48; 95%CI 0.38-0.63 Sublobectomy vs	Propensity score matched comparison SBRT with lobectomy: OS: HR 0.71; 95%CI 0.45-1.12 (=0.14) Propensity score	Dropouts: not stated (SEER database covers up to 98% of cases) Results critical appraisal: results adjusted for known

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Services NCI Setting: multicentre, USA Sample size: 10 923 pts Duration:2001-2007	Patients characteristics: 46% male, 18% 66-69y, 26% ≥ 80y. 40% tumour ≤ 2 cm. Median age 75 years. Median FU: not reported		lobectomy: HR 0.95; 95%CI 0.86-1.05 Risk of death > 6 months SBRT vs lobctomy: HR 1.56; 95%CI 1.21-2.00 Sublobectomy vs lobectomy: HR 1.40 ; 1.28-1.54	matched comparison SBRT with sublobectomy: OS: HR 0.82; 95%CI 0.53-1.27	confouders, however proportion of lymph nodes sampled differs between treatment groups.

VATS

Selection based on review of full texts, lead to the inclusion of one recent meta-analysis comparing VATS with open surgery. Results are summarized in Table 22.

Table 22 – Evidence table: video-assisted thoracic surgery (VATS) versus open thoracotomy – Systematic Review

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Cao, 2013	Design: SR and MA Sources of funding: none declared Search date: April 2012 Searched databases: Medline, CENTRAL, ACP journal Club, DARE Included study designs:	Eligibility criteria: 1:1 propensity score-matched with NSCLC who underwent VATS or open thoracotomy Patients characteristics: not reported Median FU: not reported, no long-term outcomes reported	Intervention: VATS Comparator: open surgery	Overall Perioperative mortality: RR 0.75; 95%CI 0.44-1.27 (p=0.28) Overall Perioperative morbidity: RR 0.67; 95%CI 0.56-0.82 (p<0.0001	Length of hospital stay: SMD -0.37; 95%CI -0.51 to -0.22 (p=<0.00001)	Results critical appraisal: comprehensive search but no critical appraisal of included (observational) studies. No precise data on used matching methods available.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	propensity score-matched comparative studies Number of included studies: 4 Included studies: Ilonen 2011 Park 2011 Paul 2010 Villamizar 2009					

Volume Outcome

Based on title and abstract, 9 full-text articles were retrieved. Of these, one recent systematic review was included together with one additional observational study, published after the end of search for the systematic review. Additionally, a KCE report using belgian data was found by hand-searching. Finally, the observational study by Bhamidipati [72] was identified by a member of the expert group (this study was published after our search).

Table 23 – Evidence table: Lung surgery: relationship between volume and outcome

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Von Meyenfeldt, 2012 [70]	Design: SR Sources of funding: Not stated Setting: NA Sample size: NA Duration: articles published between January 1, 1990 and January 20, 2011	Eligibility criteria: English studies on surgical treatment of lung cancer using primary data. Comparisons btwn providers (hosp or surgeons), no single-hosp or single-surgeon studies. Postoperative mortality or survival as outcome parameters +	Systematic review to evaluate of the effect of surgeon specialty and hospital or surgeon volume of lung resection on mortality and survival	Pooled estimated effect size significantly in favour of high-volume hospitals for postoperative mortality; OR=0.7 (95% CI: 0.62-0.81) Effect for survival: NS (OR: 0.93, 95% CI: 0.84-1.03)	A minimal annual volume of resections for lung cancer could not be identified	Clearly defined in and exclusion criteria Well-conducted analysis Quality appraisal of the individual studies is not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		distinct cut-off values for procedural volume or clearly defined specialty Patients characteristics: pt who underwent lung resection for cancer		High volume surgeons: NS (OR:0.68, 95% CI:0.42-1.08) General surgeons had significantly higher mortality risk than general thoracic (OR=0.78, 95%CI: 0.70- 0.88) or cardiothoracic surgeons (OR =0.82, 95% CI: 0.69-0.96)		
Otake, 2011 [71]	Design: observational cohort study Sources of funding: Funded by Grants-In-Aid for Research and Policy Planning and Evaluation from The Ministry of Health, Labour and Welfare, Japan Setting: data from the Japanese Diagnostic Procedure Combination Database Sample size: 19831 patients Duration: pt who	Eligibility criteria: pt who underwent lobectomy betwn July and December 2007 and 2008 Patients characteristics: Sex: Male 60.3 % Age (average, years): 67.5 (SD 10.5) Most common co-morbidities were hypertension (18.6 %), Chronic lung disease (14.2 %) and Diabetis Mellitus (11.4%)	Analysis of the effect of hospital volume on in-hospital mortality, duration of chest tube drainage and postoperative LOS. Hospitals were categorised in 4 groups (low, medium-low, medium-high and high) with appr equal number of patients in each group	In-hospital mortality was significantly lower in high-volume group compared with low-volume group (0.48 % vs 0.94%, OR=0.60, p=0.047)	Chest tube removal occurred earlier in high-volume group compared with low volume group (mean=4 days vs 5.1 days, p<0.001 Postoperative LOS was shorter in the high-volume group than in the low-volume group (mean 11.5 days vs 15.9 days, p<0.001)	A direct comparison of low and high-volume hospitals might not be appropriate due to baseline differences in age and comorbidities (high-volume patients were generally younger and had less co-morbidities) Appears that the grouping of hospitals was not pre-defined, categories are defined afterwards so that an approximately equal amount of patients are placed

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	underwent lobectomy between July and December in 2007 and 2008					within each category Authors report that the data has known limitations (lacks validation of diagnosis and co-morbidities, lacked information on important factors including cancer stage and smoking status) Participation rate from very low-volume hospitals on reporting to the database is low. Not clear whether other (less significant) outcomes could have been reported No reporting on specialty, extent of resident participation etc.
Bhamidipati, 2013 [72]	Design: retrospective study Sources of funding: data is retrieved from the NIS database that receive funding from AHRQ	Eligibility criteria: pt selected from the database if they underwent a pneumonectomy, lobar, segmentectomy, or nonanatomic wedge	Intervention: pneumonectomy, lobar, segmentectomy, or nonanatomic wedge resection (according to ICD-	Mortality (adjusted model based on case-mix): Pneumonectomy Adjusted OR (95% CI): TSR 0.33 (0.21-0.53), GSR 0.69	For pneumonectomy significant results for "failure to rescue" in favour of TR hospitals vs no surgery residency (p<.001)	Observational study with rutine data; adjusted model provides insufficient data on risk factors so results might be biased

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Sample size: 498099 patients Duration: patients evaluated in an all-payer inpatient database between 2003 and 209	resection (according to ICD-9-CM) Patient characteristics: Pneumonectomy recipients; N=22663 Lobar resection recipients; N=222586 Segmentectomy recipients; N=43851 Nonanatomic wedge resection recipients; N=208999	9-CM) performed at a thoracic residency (TR), general surgery residency (GSR), no surgery residency or no residency hospital	(0.47-0.99), NSR 0.64 (0.48-0.85) p <.001 (reference NR hospital) Lobar Adjusted OR (95% CI): TSR 0.83 (0.66-1.05), GSR 0.63 (0.50-0.79), NSR 0.95 (0.80-1.13), p <.001 (reference NR hospital) Segmentectomy TSR 0.65 (0.39-1.08), GSR 0.86 (0.58-1.28), NSR 0.99 (0.70-1.42), p=0.38 (NS), reference NR hospital Nonanatomic wedge TSR 0.76 (0.60-0.95), GSR 0.92 (0.75-1.13), NSR 0.98 (0.82-1.16), p=0.12 (NS), reference NR hospital	Complication were least likely to occur at TR hosptals (p<0.001)	

Appendix 2.1.10. Multi-modality treatment

Comprehensive search for publications on multi-modality treatment published since 2009 resulted in 533 citations. First selection based on title and abstract excluded 474 articles.

Adjuvant chemotherapy early stage NSCLC

Selection based on review of full texts, lead to the inclusion of three RCTs reporting on adjuvant chemotherapy in early stage lung cancer. Two were already included in previously reported meta-analyses.

Table 24 – Evidence table: Adjuvant chemotherapy early stage NSCLC

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Arriagada, 2010	Design: RCT Sources of funding: Eli-lilly-France, several cancer leagues and hospital research funds Setting: multinational Sample size: 1867 patients (early closure due to slow accrual) Duration: February 1995 – December 2000	Eligibility criteria: NSCLC stage I,II or III who had undergone complete resection. 18-75 years old. No previous other cancer, chemotherapy or radiotherapy. Patients characteristics: median age 59 y, 36% stage I, 24% stage II, 40% stage III Median FU: 90 months	Intervention: 3 or 4 cycles of cisplatin containing doublet chemotherapy Comparator: observation	Survival: HR 0.91; 95%CI 0.81-1.02 (p=0.10) Median survival 54 versus 45 months Absolute gain at 5 years 3.9% At 5y FU: HR of death 0.86; 95%CI 0.76-0.97 (p=0.01)	Disease-free survival HR 0.88; 95%CI 0.78-0.98 (p=0.02) Absolute gain at 5 years 4.3% Less benefit from chemotherapy in patients 70 years of older or those with WHO PS 2 No significant interaction with radiotherapy	Dropouts: survival status known for 96.8% Results critical appraisal: early closure for slow accrual, 3300 patients were required according to sample size calculation. No blinding.
Butts, 2010	Design: RCT Sources of funding: NCI Cananda, NCI USA and GSK	Eligibility criteria: completely resected T2N0, T1N1 or T2N1 NSCLC, ECOG PS 0 or 1	Intervention(s): Adjuvant vinorelbine + cisplatin Comparator(s):	Overall survival: HR 0.78; 95%CI 0.61 to 0.99 (p=0.04) Absolute improvement in 5-year survival for the	Adjusted disease-specific survival: HR 0.73; 95%CI 0.55 to 0.96 (p=0.03)	Dropouts: 33 patients lost of follow-up Results critical appraisal: no

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Setting: multinational, multicentre Canada & USA Sample size: 482 pts Duration: July 1994-April 2001	Patients characteristics: median age 60.9y, F/M 35%/65%, adenoca 53%, SCC 37%, no longer smoker: 84% Median FU: 9.3 years	observation	chemotherapy arm: 11% (67% versus 56%) Survival adjusted for prognostic factors: HR 0.79; 95%CI 0.62 to 1.00 (p=0.05) For stage II patients: HR 0.68; 95%CI 0.50 to 0.92 For stage IB patients: HR 1.03; 95%CI 0.70 to 1.52		blinding of caregivers and patients, unclear blinding of outcome assessors.
Felip, 2010	Design: RCT Sources of funding: Bristol Myers Squibb Setting: multicentre, multinational Europe Sample size: 624 pts Duration: April 2000 – March 2007	Eligibility criteria: stage IA > 2cm, IB, II or T3N1 NSCLC Median FU: not reported	Intervention(s): pre-operative or post-operative paclitaxel-carboplatin Comparator(s): surgery alone	3-year PFS pre-operative chemotherapy versus surgery alone: HR 0.92; 95%CI 0.81 to 1.04 (p=0.176) 3-year PFS post-operative chemotherapy versus surgery alone: HR 0.96; 95%CI 0.75 to 1.22 (p=0.74)		Dropouts: 5 pts with missing information not included in analysis Results critical appraisal: no blinding, no ITT.

Neo-adjuvant chemotherapy early stage NSCLC

Selection based on review of full texts, lead to the inclusion of two RCTs reporting on neoadjuvant chemotherapy in early stage lung cancer.

Table 25 – Evidence table: RCTs neo-adjuvant chemotherapy or chemoradiotherapy followed by surgery

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Scagliotti, 2012	Design: RCT Sources of funding: Eli Lilly Setting: multinational Europe Sample size: 270 pts Duration: September 2000-December 2004	Eligibility criteria: stage I (except T1N0), stage II or IIIA (T3N1 excluding superior sulcus) NSCLC. ECOG PS 0-1, predicted post-resection FEV1 of more than 1.0 litre. Patient characteristics: median age 61.8y, (range 37.6-79.8y). Stage 1: 132/270, stage II 128/270, stage III 10/270 Median FU:	Intervention(s): Preoperative cisplatin + gemcitabine followed by surgery Comparator(s): surgery alone	Overall survival: adjusted HR 0.63 (95%CI 0.43 to 0.92) in favour of the neo-adjuvant treatment. 3-year survival rates: 67.3% (95%CI 58.4% to 75.2%) for the neo-adjuvant arm versus 59.8% (95%CI 50.7 to 67.8%) Subgroup analysis shows no survival benefit in stage I/IIA disease and a significant survival benefit for stage IIB/IIIA patients	Serious adverse events possibly related to study drug or procedure was 12% in the neo-adjuvant arm versus 8% in the surgery alone arm. Complete resection occurred in 88% of patients in the neo-adjuvant arm and in 84% of the patients in the surgery alone arm. Perioperative morbidity was 3% and 4% respectively.	Dropouts: unclear Results critical appraisal: Unclear allocation concealment. Early closure due to positive results for adjuvant chemotherapy. No blinding.
Pisters, 2010	Design: RCT Sources of funding: PHS Cooperative Agreement Grants from the National Cancer Institute, Bristol-Myers Squibb Setting: Multicentre, USA & Canada Sample size: 354 patients Duration: October 1999 – June 2004	Eligibility criteria: Stage IB-IIIA NSCLC excluding superior sulcus tumours and N2 disease. Zubrod PS 0-1. Predicted post-resection FEV1 more than 1 litre. Patient characteristics: median age 64.5y (range 35-83), one third stage IIB/IIIA, two thirds stage IB/IIA Median FU: 64 months	Intervention(s): Paclitaxel-carboplatin followed by surgery Comparator(s): surgery alone	Overall survival: HR 0.79; 95%CI 0.60 to 1.06 in favour of the neo-adjuvant arm (p=0.11). PFS: HR 0.80; 95%CI 0.61 to 1.04 (p=0.10)		Dropouts: 17/354 ineligible patients excluded from analysis Results critical appraisal: Unclear allocation concealment. Early closure due to positive results for adjuvant chemotherapy. No blinding. No ITT analysis.

Postoperative radiotherapy

The Cochrane systematic review, already included in other guidelines was updated, updated results are summarized below.

Table 26 – Evidence table post-operative radiotherapy: systematic review (update)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
PORT Meta-analysis Trialist Group	Design: SR and MA based on individual patient data Sources of funding: Medical research council, UK. HNS R&D programme Search date: January 2009 Searched databases: Medline, Cancerlit Included study designs: RCT Number of included studies: 11 Included studies: Van Houtte 1966 Camps 1981 EORTC 08861 GETCB 04CB86 GETCB 05CB88 Italy 2002 Korea2007 LCSG 773 Lille 1985 MRC LU11 Debevec 1988	Eligibility criteria: histologically confirmed NSCLC, completely resected Patients characteristics: M/F 1980/362, 45,5% SCC, 17,6% adenoca, 31,7% unknown. Based on data from 4 trials, 26,8% had poor PS. Median FU: not stated	Intervention: Complete resection followed by radiotherapy Comparator: complete resection	Overall survival: HR 1.17; 95%CI 1.02-1.34 Recurrence-free survival: HR 1.09; 95%CI 0.95-1.25	OS stage 2: HR 1.26; 95%CI 1.04-1.52 OS stage 3: HR 0.99; 95%I 0.85-1.15 OS N2 disease: HR 0.97; 0.81-1.16	Results critical appraisal: All included studies adequate allocation concealment, no other information on quality of included studies Trials conducted over a period of 40 years, with changes in diagnosis, surgical staging, radiotherapy techniques and assessment of recurrence.

Search for RCTs and observational studies published since 2009 resulted in 876 citations. 866 citations were excluded based on title and abstract. After further selection based on full text, only one retrospective case series was included.

Table 27 – Evidence table: postoperative radiotherapy for incompletely resected lung tumours

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Ohguri 2012	Design: retrospective case series Sources of funding: none stated Setting: single centre, Japan Sample size: 43 pts Duration: July 1980-December 2008	Eligibility criteria: pathologically confirmed NSCLC, microscopically (R1) or macroscopically (R2) incompletely resected. Patients characteristics: 23 pts R1 resection, 18 pts R2 resection. Median age 66y (range 48-81 years). 31% received chemotherapy. Median FU: 24 months (1-127 months)	Intervention(s): Post-operative radiotherapy Comparator(s): NA	R1 group: Overall 5- year survival: 62% Local control: 75% Disease-free survival: 51% R2 group: Overall 5- year survival: 47% Local control: 46% Disease-free survival:19%	Acute toxicity ≥ grade 2 Neutropenia grade 3 in 1 pt Radiation pneumonia grade 3 in 1 pt Bronchial fistula grade 2 in one pt Radiation esophagitis grade2 in one pt Late toxicity Esophageal stenosis grade 3 in 1 pt Radiation pneumonia grade 2 in two pts	Dropouts: 2 pts who interrupted radiotherapy were excluded from the analysis Results critical appraisal: retrospective analysis with very small sample size, no matched comparison with no PORT

Chemoradiation

Selection based on review of full texts, lead to the inclusion of one RCT comparing sequential and concurrent chemoradiation, one RCT comparing radiotherapy with chemoradiation in elderly patients. Three RCTs comparing differenct schedules for chemoradiation were not further discussed.

Table 28 – Evidence table: RCTs sequential versus concurrent chemoradiation

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Curran, 2011 RTOG 9410	Design: RCT Sources of funding: Setting: multicentre USA & Canada Sample size: 610 pts Duration: July 1994-July 1998	Eligibility criteria: stage II, IIA or IIIB NSCLC, KPS > 70 and no more than 5% weight loss over 3 months before enrollment Patient characteristics: median age 61y. F/M 36%/64%. SCC 38%, adenoca 31%, large	Intervention(s): CRT A: vinblastine + cisplatin CRT b: etoposide + cisplatin Comparator(s): sequential chemotherapy & radiotherapy	OS CRT A versus seq: HR of death 0.81 ; 95%CI 0.66 to 0.996 (p=0.046) OS CRT A versus B: HR of death 0.93; 95%CI 0.75 to 1.14 (p=0.46) Median survival time: Seq arm: 14.6 months (95%CI 12.1-17) Concurrent A: 17.0	**Acute oesophagitis** **Seq: 4%** **CRT A: 22%** **CRT B: 45%** Acute pulmonary toxicity: higher in the sequential arm compared to concurrent treatments Granulocyte level	Dropouts: 5% ineligible patients not included in analysis. 2 pts lost of FU Results critical appraisal: no blinding, no ITT

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		cell 14% Median FU: 11 years		months (95%CI 14.0-20.2) Concurrent B: 15.6 months (95%CI 13-18)	depressions: higher in the treatment arm containing vinblastine	

Table 29 – Evidence table: RCTs radiotherapy versus chemoradiotherapy versus other chemoradiotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Atagi, 2012	Design: RCT Sources of funding: Ministry of health, Labour and Welfare of Japan Setting: multicentre, Japan Sample size: 200 Duration: Sept 2003-May 2010	Eligibility criteria: NSCLC ≥ 71 years old, unresectable stage IIIA or IIIB (except T3N1M0 disease, contralateral hilar nodes, atelectasis of the entire lung or malignant pleural or pericardial effusions), with a condition that precluded cisplatin therapy, measurable disease, no previous chemo or radiotherapy, PS 0-2 Patients characteristics: median age 77 years, 80% male, 90% history of smoking Median FU: 19.4 months for censored cases	Intervention(s): chemoradiotherapy with low-dose carboplatin Comparator(s): radiotherapy	Survival: HR 0.68 95%CI 0.47-0.98 (one-sided p=0.0179). Median overall survival 22.4 months in the chemoradiotherapy group and 16.9 months in the radiotherapy group	Progression-free survival: HR 0.66; 95%CI 0.49-0.90 (2-sided p=0.009) Median PFS 8.9 months (95%CI 7.4-10.6) after chemoradiotherapy and 6.8 months (95%CI 5.6-8.0) after radiotherapy More leucopenia, neutropenia or thrombocytopenia in the chemoradiotherapy group. 3 treatment-related deaths in the chemoradiotherapy group and 4 treatment-related deaths in the radiotherapy group	Dropouts: 3 ineligible patients excluded from analysis Results critical appraisal: analysis bases when 129 of 173 planned events occurred; One-sided test only.
Govindan, 2011	Design: phase II RCT Sources of	Eligibility criteria: inoperable stage IIIA or IIIB NSCLC, ECOG	Intervention(s): Pemetrexed, carboplatin and	Grade 3-5 haematological toxicity: 42% versus 28%	18-months OS: 58% (95%CI 46-74%) versus 54% (95%CI 42-70%)	Dropouts: none Results critical appraisal: unclear allocation

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	funding: NCI Setting: Multicentre, USA Sample size: 101 Duration: September 2005-January 2008	PS 0-1, weight loss < 10% in the past 3 months. PET-CT performed. No prior chemotherapy, radiotherapy or EGFR-targeting therapy. Patients characteristics: F/M 39%/61%, median age 66y (32-81). Adenoca 44%, SCC 35%, large cell 2% Median FU: 32 months (range 11.7-48.4)	thoracic radiation + cetuximab Comparator(s): Pemetrexed, carboplatin and thoracic radiation	Grade 3 non-haematological toxicity: 46% versus 6% Grade 4 non-haematological toxicity: 53% versus 9% Grade 5 non-haematological toxicity: 2 pts versus 3 pts.	Median failure-free survival: 12.6 months (95%CI 7.9-17.2 months) versus 12.3 months (95%CI 8.8-18.7 months)	concealment, no blinding. Phase II trial with toxicity as primary outcome.
Hoang, 2012	Design: RCT Sources of funding: NCI NIH, public health services Setting: multicentre, USA Sample size: 546 pts Duration: January 2000-October 2006	Eligibility criteria: stage IIIA or IIIB NSCLC with measurable disease. ECOG PS 0-1, use of two accepted and effective methods of contraception Patients characteristics: median age 63, F/M 39%/61%. Adenoca 37%, SCC 35%, large cell 5% Median FU: 61.8 months	Intervention(s): Thoracic radiation + paclitaxel-carboplatin + thalidomide (TPC) Comparator(s): Thoracic radiation + paclitaxel-carboplatin (PC)	Overall survival TPC 16.0 months PC 15.3 months (p=0.99) Progression-free survival: TPC 7.8 months PC 7.4 months (p=0.96	Response to treatment: TPC 38.2% PC 35.0% (p=0.47)	Dropouts: 43 randomized but ineligible patients not included in analysis. Results critical appraisal: unclear allocation concealment, no blinding, early closure based on interim analysis
Segawa, 2010	Design: RCT Sources of funding: none	Eligibility criteria: unresectable stage IIIA or IIIB NSCLC for	Intervention(s): Docetaxel-cisplatin (DC) +	2-year survival: favourable for the DC arm (p=0.059) Median survival time: DC	Progression-free survival tended to be greater in the DC arm	Dropouts: none Results critical appraisal: unclear

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Setting: Multicentre, Japan Sample size: 200 pts Duration: 2000-2005	which the radiation field did not exceed one half of the lung on the chest radiograph. ECOG PS 0-1. Patients characteristics: F/M 10%/90%, SCC 48.5%, adenoca 37.5%, large cell 5%	radiotherapy Comparator(s): mitomycin-vindesine-cisplatin (MVC) + radiotherapy	arm 26.8 months (95%CI 23.6 to 33.4 months) versus MVC arm 23.7 months (95%CI 15.9 to 33.2 months).	(p=0.065) Grade 3-4 hematologic toxicity was more frequent in the MVP arm (p=0.12) and radiation oesophagitis was more frequent in the DC arm (p=0.056).	blinding. Unplanned analyses performed.

Neoadjuvant therapy followed by surgery stage IIIA-N2 disease

Search for RCTs published since 2010 identified 315 citations after removal of duplicates. After first selection based on title and abstract, 8 remaining papers were evaluated by reading the full text. Finally, no publication was selected.

Table 30 – Evidence table: neoadjuvant therapy + surgery for resectable stage IIIA-N2 disease

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Van Meerbeeck, 2007	Design: RCT Sources of funding: NCI, Eli Lilly, Bristol-Myers Squibb, Aventis Setting: multicentre, Europe Sample size: 332 Duration: December 1994-december 2002	Eligibility criteria: Histological proof of unresectable stage IIIA-N2 NSCLC defined as follows: any N2 involvement by a non-squamous carcinoma OR right sided SCC with N2 disease exceeding level R4 OR left sided SCC with N2 disease exceeding level 5 and 6. Tumour and involved LN had to be measurable on CT scan. WHO PS 0-2 Patients	Intervention(s): 3 cycles induction chemotherapy followed by surgery in case of response Comparator(s): 3 cycles induction chemotherapy followed by radiotherapy in case of response	Overall survival: HR 1.06; 95%CI 0.84-1.35 Progression-free survival: HR 1.06; 95%CI 0.85-1.33 Toxicity: Radiotherapy: acute grade 3/4 esophageal and pulmonary toxic effects in < 1% and 4% respectively. Late pulmonary and esophageal fibrosis in 7% and < 1% respectively Surgery: 4% died within 30 days following surgery	Overall response rate for 579 registered patients: 61% Postoperative radiotherapy in 40% of patients surgery arm	Note: of the 582 registered patients, 247 off study before randomization due to PD, SD, death, toxicity, other Dropouts: none Results critical appraisal: see Cochrane review: unclear blinding. No info on treatment and outcome of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		characteristics: M/F 427/152, median age 61 y (range 29-78) Median FU: ± 6 years				registered patients without response to induction chemotherapy.
Albain, 2009	Design: RCT Sources of funding: NCI, Canadian Cancer Society Setting: multicentre USA, Canada Sample size: 396 pts Duration: March 1994 – November 2001	Eligibility criteria: stage IIIA(pN2) NSCLC, evaluated by clinicians to establish that N2 disease was present to the extent that concurrent chemoradiation was regarded as standard approach instead of definitive resection and that the cancer was potentially technically resectable Patients characteristics: M/F 64%/36%, median age 60y (range 31-78) Median FU: 22.5 months	Intervention(s): Induction concurrent chemoradiation followed by surgery if no progression Comparator(s): Induction concurrent chemoradiation followed by continued radiotherapy Patients received 2 cycles of consolidation chemotherapy	OS: HR 0.87; 95%CI 0.70-1.10 PFS HR 0.77; 95%CI 0.62-0.96	Toxicity: Grade 3/4 oesophagitis: 10% vs. 23% Grade 3/4 neutropenia: 38% vs. 41% Grade 3/4 respiratory complications: 9% vs. 14% 16 patients (8%) in the surgery group died of causes not attributable to cancer, included 10 patients who died within 30 days after thoracotomy. 4 patients (2%) in the radiotherapy group died of treatment-related causes	Results critical appraisal: see Cochrane review

Pancoast tumours and tumours extending into pleura and chest wall

Table 31 – Evidence table: Pancoast tumours and tumours extending into pleura and chest wall

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Mordant, 2011	Design: retrospective case series Sources of funding: none stated Setting: single centre, France Sample size: 70 (32+38) pts Duration: 1983-2006	Eligibility criteria: NSCLC with unexpected pleural metastatic extension during surgery Patients characteristics: 82.5% male, 90% smokers, mean age 61.4 years. 46% SCC, 38% adenocarcinoma Mean FU: 72.8 months	Intervention(s): Complete surgical resection of primary tumour, mediastinal lymph nodes and pleural metastatic nodules if pleural extension was limited Comparator(s): pleural biopsy alone if pleural extension was widespread (diffuse non-resectable carcinomatous pleuritis)	Intervention group: median survival: 15 months 5-year survival rate: 16% Control group: 5-year survival rate: 0%	90-day postoperative mortality intervention group: 16% 90-day postoperative morbidity intervention group: 34%	Dropouts: none Results critical appraisal: non-randomized, retrospective case series. Control group insufficiently comparable to intervention group, no adequate adjustment for confounders. Small sample size recruited during a long time interval.

Treatment metastatic disease

Table 32 – Evidence table: systematic review on Bevacizumab + doublet chemotherapy vs doublet chemotherapy alone

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Botrel, 2011	Design: SR and MA Sources of funding: not mentioned Search date:2011 Searched databases: MEDLINE, EMBASE, LILACS, and CENTRAL Included study designs: RCT Number of included studies: 16	Eligibility criteria: Patients with non-small cell lung cancer (NSCLC) previously untreated locally advanced or metastatic (IIIB, with supraclavicular lymph node metastasis or malignant pleural or pericardial effusion or IV). Table	Index test(s): Bevacizumat + doublet (platinum) chemotherapy Reference standard: doublet (platinum) chemotherapy	PFS: CT plus Bev 7.5 mg/kg (HR = 0.78, CI95% = 0.68–0.90; p=0.0005) Bev 15 mg/kg (HR = 0.72, CI95% = 0.65–0.80; p < 0.00001) with moderate heterogeneity (Bev 7.5 mg/kg: Chi2 = 1.43, df = 1 (p=0.23); I2 = 30% and Bev 15 mg/kg: Chi2 = 7.43, df = 3 (p=0.06); I2 = 60%). Overall survival in patients who received CT plus Bev 15 mg/kg (HR = 0.89, CI95% = 0.80–1.00; p=0.04), with moderate heterogeneity (Chi2 = 5.09, df = 3 (p=0.17); I2 = 41%). The random-effects model analysis for this endpoint did not confirme the difference seen in the fixed effects model analysis (HR = 0.90, CI95% = 0.76–1.07;p=0.23).	The response rate CT plus Bev 7.5 mg/kg (RR = 0.58; CI95% = 0.46–0.74; p < 0.00001) Bev 15 mg/kg (RR = 0.53; CI95% = 0.45–0.63; p < 0.00001) with moderate heterogeneity at dose of 15 mg/kg (Chi2 = 4.30, df = 3 (p=0.23); I2 = 30%). Severe haematologic toxicities (grade > 3), neutropenia and febrile neutropenia were more common among the patients that received Bev.	: Results critical appraisal High quality review The appropriateness of these pooling can be questioned given the heterogeneity of the interventions, studies using the doublet carboplatin plus paclitaxel and the doublet cisplatin and gemcitabine are pooled here, resulting in considerable heterogeneity, that is subsequently treated with a random effects model.

Table 33 – Evidence table: gefitinib or erlotinib versus chemotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Bria, 2011	Design: SR and MA Sources of funding: National Ministry of Health; Italian Association for CancerResearch (AIRC) Search date: October 2010 Searched databases: Medline (PubMed,www.ncbi.nlm.nih.gov/PubMed), American Society of Clinical Oncology(ASCO, www.asco.org), European Society for Medical Oncology (ESMO,www.esmo.org), Federation of European Cancer Societies (www.fecs.be),and World Lung Cancer Conference (WLCC, www.iaslc.org) Web site Included study designs: RCT Number of included studies: 5	Patients previously untreated patients with advanced or metastatic NSCLC	gefitinib or erlotinib versus chemotherapy	TKI significantly increased progression-free survival (PFS) [hazard ratio (HR) 0.45, 95% confidence interval (CI) 0.36–0.58, p<0.0001] When only the 3 prospective studies are taken into account HR is 0.31 (0.17–0.55)	overall response rate (ORR) (HR 2.08, 95% CI 1.75–2.46, p<0.0001)] over chemotherapy, while significantly decreasing neutropenia. No significant difference was observed in overall survival.	Hiigh quality review. Although there is heterogeneity it was explored by metaregression techniques.

Table 34 – Evidence table: gefitinib versus docetaxel

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Jiang, 2012[127]	Design: SR and MA Sources of funding: not mentioned Search date may 2009 Searched databases: medline, cochrane Included study designs: RCT Number of included studies: 4	Patients previously treated patients with advanced or metastatic NSCLC	gefitinib versus docetaxel	The pooled HRs showed no significant difference in OS and PFS between the two groups (HR = 1.02, 95% CI = 0.92–1.12, p=0.70; HR = 0.97, 95% CI = 0.88–1.07, p=0.57, respectively).	Gefitinib significantly improved overall response rate (RR = 1.58, 95% CI = 1.02–2.45, p=0.04) and QoL (RR = 1.55, 95% CI = 1.27–1.88, p=0.00) by Functional Assessment of Cancer Therapy-Lung and RR = 1.86, 95% CI = 1.43–2.42, p=0.00 by Trial Outcome Index, respectively). Gefitinib had fewer grade 3 or 4 neutropenia and fatigue (OR = 0.02, 95% CI = 0.01–0.03, p=0.00; and OR = 0.47, 95% CI = 0.32–0.70, p=0.00, respectively), but more grade 3 or 4 rash (OR = 2.87, 95% CI = 1.24–6.63, p=0.01) than docetaxel. The grade 3 or 4 nausea, vomiting and diarrhea and symptom improvement were comparable between the two drugs.	High quality review.

Table 35 – Evidence table: pemetrexed-based doublet versus single-agent pemetrexed

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Qi, 2012[126]	Design: SR and MA Sources of funding: not mentioned Search date may 2011 Searched databases: medline, embase cochrane Included study designs: RCT Number of included studies: 5	Patients previously treated patients with advanced or metastatic NSCLC	pemetrexed-based doublet versus single-agent pemetrexed	though the pooled HR for overall survival (HR 0.89, 95% CI 0.76–1.04; p=0.129) showed no significant difference between the two groups. difference between the two groups.	PFS (HR 0.82, 95% CI 0.71–0.95, p=0.007) and overall response rate (OR 2.39, 95% CI 1.58–3.62, p=0.000) in pemetrexed-based doublet group, compared with pemetrexed alone, However, there were more incidences of grade 3 or 4 neutropenia (OR 2.3, 95% CI 1.4–3.77, p=0.001), thrombocytopenia (OR 6.41, 95% CI 2.57–16.0, p=0.000), and leucopenia (OR 2.45, 95% CI 1.13–5.34, p=0.024) in pemetrexed-based doublet group. With regard to the risk of grade 3 or 4 anemia (OR 0.71, 95% CI 0.17–2.91, p=0.629) and fatigue (OR 1.47, 95% CI 0.92–2.35, p=0.104), there was no significant	High quality review.

Table 36 – Evidence table: docetaxel based doublet versus single-agent docetaxel

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Qi, 2012[125, 126]	Design: SR and MA Sources of funding: not mentioned Search date may 2011 Searched databases: medline, embase cochrane Included study designs: RCT Number of included studies: 4	Patients previously treated patients with advanced or metastatic NSCLC	docetaxel based doublet versus single-agent docetaxel	HR for overall survival (HR 0.93, 95% CI 0.80-1.07, p=0.308) showed no significant difference between the two groups PFS (HR 0.81, 95% CI 0.69-0.96, p=0.013) and overall response rate (OR 1.42, 95% CI 1.13-1.80, p=0.03) in docetaxel-based doublet	more incidences of grade 3 or 4 neutropenia (OR 1.2, 95% CI 1.00-1.45, p=0.05), thrombocytopenia (OR 4.53, 95% CI 1.75-11.75, p=0.002), and diarrhea (OR 1.78, 95% CI 1.16-2.74, p=0.008) in docetaxel-based doublet group. With regard to the risk of grade 3 or 4 anemia (OR 1.95, 95% CI 0.62-6.17, p=0.25), fatigue (OR 1.09, 95% CI 0.75-1.59, p=0.66), and nausea and vomiting (OR 1.75, 95% CI 0.78-3.91, p=0.17), there was no significant difference between the two groups.	High quality review.

Table 37 – Evidence table: Maintenance therapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Behera, 2012	Design: SR and MA Sources of funding: supported by NIH P01 CA116676 Search date 2011 Searched databases: medline, embase cochrane Included study designs: RCT Number of included studies: 12	Patients previously treated patients with advanced or metastatic NSCLC	Maintenance therapy versus placebo	OS (HR 0.86, 95%CI 0.80–0.92; p=0.0003). Switch maintenance: (HR 0.84, 95% CI 0.77–0.91; p=0.00026): 'continuation' maintenance was not associated with a statistically significant survival benefit (HR 0.92, 95% CI 0.78–1.09; p=0.33). cytotoxic agents OS (HR 0.89, 95% CI 0.80–0.98; p=0.018). EGFR-targeted therapy, OS (HR 0.83, 95% CI 0.74–0.92; p=0.004). PFS (overall) (HR 0.80, 95% CI 0.77–0.84; p<0.0001;). Switch maintenance (HR 0.62, 95%CI 0.57–0.67; p<0.0001) continuation maintenance (HR 0.90, 95% CI 0.85–0.95; *p*=0.007). Cytotoxic agents (HR 0.85, 95% CI 0.80–0.89; *p*<0.0001) EGFR-targeted (HR 0.64, 95% CI 0.58–0.71, *p*<0.0001).	The ORR in the maintenance arm was 21.25% (7 trials; *n* = 1520) as compared to 7% in control arm (6 trials, *n* = 1110). In assessing AEs of grade 3 and above, 18% of the patients had toxicities in the maintenance arm (8 trials; *n* = 2006) and 5% of patients in the control arm (7 trials; *n* = 1400).	High quality review. There was no significant heterogeneity in the HRs of individual trials (p=0.92, I2 < 0.05).

Table 38 – Evidence table: Follow-up

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Srikantharajah, 2012	• SR • Sources of Funding: The University Hospital of Poitiers • Search data: 1948 – March 2012 • Searched databases: PubMed and Cochrane Review database • Included study designs: observational studies • Number of included studies: 5	• Patients who have undergone lobectomy for non-small cell lung cancer	Follow-up with CT versus clinical suspicion	OS No consensus in literature 3 studies showed a possible effect on survival rates with CT-follow-up (one study significant: CT or PET-CT vs. clinical suspicion: 2.1±0.3 vs. 3.6±-0.2 years, p=0.002) Two studies showed no significant survival benefits with CT (one study: strict CT protocol 7.9 months vs. symptom-based follow-up 6.6 months, p=0.219)	Outcomes on cost-effectiveness, neurological symptoms and disease recurrence were not systematically considered	Selection criteria based on comparison (CT vs.?) is not explicitly stated, but appears to be clinical suspicion. Quality appraisal of included studies is not provided. Evidence level per study is provided but appears to be inconsistent with guideline provided in the study protocol.
Gourcerol, 2013 [138]	• Retrospective study • Sources of Funding: not stated • Sample size: 162 • Duration: January 1990 –	• Patients with NSCLC who had undergone a complete surgical resection with curative intent • Age (av. year old) 59 (range 31-81)	Patient follow-up for 3 years after surgery with the inclusion of the following procedures: physical examination, and chest X-ray every 3 months; chest CT scan, fiberoptic bronchoscopy, abdominal ultrasound, brain CT scan and bone	Survival: Median OS following surgery = 38.5 months In univariate analysis on survival factors significant association were found for absense of symptoms at time of	Recurrence: recurrence was detected by physical examination or chest x-ray in 47 patients (55.3%) and by another procedure in 38 patients (44.7%)	Small retrospective study Change in quality of CT scans and staging systems during study period

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	December 2007	• Male 147 (90.7%) • Female 15 (9.3%)	scan every 6 months During the next two years, physical examination and chest X-ray were performed every 3 months, and chest CT scan, fiberoptic bronchoscopy, abdominal ultrasound, brain CT scan, and bone scan were performed once a year	recurrence: HR (95%CI): 2.09 (1.33-3.28), p=0.001, the diagnostic procedure (physical examination and chest x-ray vs other): HR (95%CI):0.38 (0.24-0.60), p<0.0001 and gender (male/female): HR (95%CI): 0.48 (0.24-0.96). In multivariate analysis a significant effect was found for diagnostic procedure only: HR (95%CI):0.37 (0.24-0.60), p<0.0001		

Table 39 – Evidence table: small cell lung cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Rossi, 2012	Design: SR and individual basedMA Sources of funding: not mentioned Search date 2011 Searched databases: medline, embase Cochrane, Proceedings of the main international meetings (American Society of Clinical Oncology, EuropeanSociety for Medical Oncology, European Cancer Conference, and World Conference on Lung Cancer) Included study designs: RCT Number of included studies: Four eligible trials with 663 patients	Primary treatment SCLC	Cisplatin vs carboplatin	Median OS was 9.6 months for cisplatin and 9.4 months for carboplatin (hazard ratio [HR], 1.08; 95% CI, 0.92 to 1.27; P: 0.37). . Median PFS was 5.5 and 5.3 months for cisplatin and carboplatin, respectively (HR, 1.10; 95% CI, 0.94 to 1.29; P =0.25)	There was no evidence of treatment difference between the cisplatin and carboplatin arms according to sex, stage, performance status, or age. ORR was 67.1% and 66.0%, respectively (relative risk, 0.98; 95% CI, 0.84 to 1.16; P _.83). hematologic toxicity was higher with carboplatin, and nonhematologic toxicity was higher with cisplatin.	High quality review. Individual based analysis with exploration of sources of heterogeneity Pooling of limited and extensive disease.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Rossi, 2010	Design: SR and individual basedMA Sources of funding: not mentioned Search date 2008 Searched databases: medline, embase Cochrane, Included study designs: RCT Number of included studies: Four eligible trials with 663 patients	patients with extensive SCLC	maintenance therapy vw usuals care	OS (HR 0.93, 95% CI 0.87-1.00; p=0.05) PFS (HR 0.98, 95% CI 0.91-1.06; p=0.63PFS:	.	Pooling of heterogeneous studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Bagi, 2011	Design: SR and individual basedMA Sources of funding: not mentioned Search date 2008 Searched databases: medline, embase Cochrane, Included study designs: RCT Number of included studies: Four eligible trials with 663 patients	patients with e SCLC	maintenance therapy vw usuals care	HR 0.77, 95% CI 0.60 to 0.99; p 0.04), OS (HR 0.80, 95% CI 0.59 to 1.08; p 0.7).	.	Reanalysis of Rossi et al. Lung Cancer 2010 limiting the populations to patients with limited disease

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Riemsma, 2010	Design: SR Sources of funding: GSK Search date march 2009 Searched databases: MEDLINE, EMBASE, CDSR, CENTRAL, DARE, and HTA Included study designs: RCT Number of included studies: Four	Patients with relapsed SCLC	Topotecan vs usual care one study	Overall survival (hazard ratio = 0.61; 95% CI, 0.43 to 0.87)	quality of life (EQ-5 D difference: 0.15; 95% CI, 0.05 to 0.25). (hazard ratio [HR], 1.08; 95% CI, 0.92 to 1.27; P: 0.37).	High quality review.
			Topotecan vs cyclophosphamide, adriamycin and vincristine (CAV) one study	Overall survival (hazard ratio = 1.04 (0.78 to 1.40) Overall survival (hazard ratio = 0.98; (95% CI, 0.77 to 1.25)	Progression free survival (hazard ratio = 1.33 (0.79 to 2.25) response rate 1.02 (95% CI: 0.70, 1.49)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
			Oral vs IV topotecan 2 pooled studies			

APPENDIX 3. SUPPLEMENTARY METALANALYSES AND EVIDENCE REVIEWS

Appendix 3.1. Surgery

Appendix 3.1.1. Mediastinal lymphadenectomy

Table 40 – GRADE profile mediastinal lymphadenectomy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Overall survival T1-T2 N0 non-hilar N1 HR 0.92; 95%CI 0.76-1.11	1	0	0	-1	-1	0	3: intraoperative sampling with frozen section not routinely performed 4: CI includes clinical both appreciable benefit and no effect	Low
Overall survival minimal mediastinal staging HR 0.63; 95%CI 0.51-0.78	3	0	0	-1	0	0	3: preoperative mediastinal staging very limited, not to current standards	Moderate
30-day surgical mortality RR 0.56; 95%CI 0.23-1.35	4	0	0	-1	-1	0	3: possible indirectness due to specialized setting (surgeons) in clinical trials 4: low number of events	Moderate

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Appendix 3.1.2. Extended surgery: sleeve lobectomy

Table 41 – GRADE profile sleeve lobectomy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Overall survival HR 0.63; 95%CI 0.56-0.71	13	-1	0	0	0	0	1: observational studies, majority subject to selection bias, no adequate control of confounding	Very low
Postoperative mortality OR 0.50; 95%CI 0.34-0.72	18	-1	0	0	0	0	1: observational studies, majority subject to selection bias, no adequate control of confounding	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Appendix 3.1.3. Limited resection: segmentectomy, wedge resection

Table 42 – GRADE profile segmentectomy and wedge resection

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Overall survival HR 1.26; 95%CI 1.07-1.47 (Fan)	26	-1	0	0	0	0	1: observational studies, majority subject to selection bias, no adequate control of confounding	Very low
Overall survival tumours < 2 cm HR 0.81; 95%CI 0.39-1.71	7	-1	0	0	-1	0	1: observational studies, majority subject to selection bias, no adequate control of confounding 4: CI includes considerable benefit and considerable harm	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Appendix 3.1.4. Video-assisted thoracic surgery (VATS)

Table 43 – GRADE profile Video-assisted thoracic surgery (VATS)

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Peri-operative morbidity RR 0.67; 95%CI 0.56-0.82	4	0	0	0	0	0	1: no down-grading as propensity-matched observational studies	Low
Postoperative mortality RR 0.75; 95%CI 0.44-1.27	4	0	0	0	0	0	1: no down-grading as propensity-matched observational studies 4: no down-grading, absolute RD clinically not significant (low number of events)	Low
Length of hospital stay	3	0	0	0	0	0	1: no down-grading as propensity-matched observational studies	Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Appendix 3.1.5. Volume-outcome for lung cancer surgery

Table 44 – GRADE profile volume-outcome for lung cancer surgery

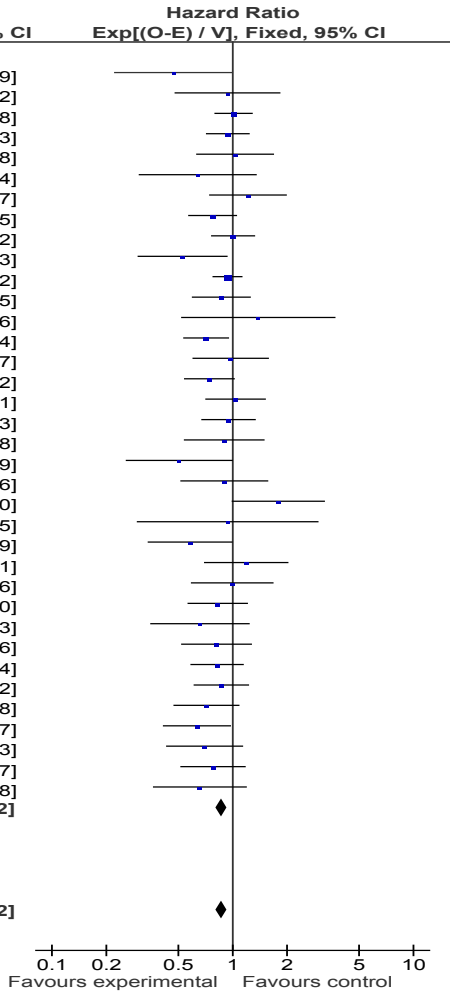
Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Postoperative mortality high- vs low-volume hospitals OR=0.7; 95% CI: 0.62-0.81	11	0	0	0	0	0	Observational studies starting from low level of evidence (no up or downgrading)	Low
Overall survival high- vs low-volume hospitals OR: 0.93; 95% CI: 0.84-1.03	7	0	0	0	0	0	Observational studies starting from low level of evidence (no up or downgrading)	Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Appendix 3.2. Should adjuvant therapy + surgery vs surgery be used for lung cancer?

Appendix 3.2.1. update meta-analysis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
6.1.1 New Subgroup								
ACTLC4a14	10	52	18	52	-5.22	6.92	0.8%	0.47 [0.22, 0.99]
ACTLC4b14	17	52	18	52	-0.58	8.75	0.9%	0.94 [0.48, 1.82]
ALPI1	143	310	144	308	0.83	71.37	7.7%	1.01 [0.80, 1.28]
ANITA1	102	231	113	232	-3.31	53.68	5.8%	0.94 [0.72, 1.23]
BLT1	34	69	32	67	0.51	16.34	1.8%	1.03 [0.64, 1.68]
BLT2	15	37	15	28	-3.13	7.01	0.8%	0.64 [0.31, 1.34]
BLT3	34	56	34	62	3.21	16.43	1.8%	1.22 [0.75, 1.97]
calgb9633	78	173	93	171	-10.91	42.59	4.6%	0.77 [0.57, 1.05]
felip 2010	102	210	109	210	0.273	53	5.7%	1.01 [0.77, 1.32]
FLCSG1	20	54	30	56	-7.79	12.21	1.3%	0.53 [0.30, 0.93]
IALT1	235	499	243	502	-7.96	119.34	12.9%	0.94 [0.78, 1.12]
IALT2	55	149	61	145	-4.19	28.96	3.1%	0.87 [0.60, 1.25]
IPCR Chiba28	11	15	7	14	1.33	4.07	0.4%	1.39 [0.52, 3.66]
JBR10	86	242	111	240	-16.64	49.07	5.3%	0.71 [0.54, 0.94]
JCOG9304	33	59	35	60	-0.43	16.94	1.8%	0.97 [0.61, 1.57]
JLCRG38	67	498	91	501	-11.72	39.49	4.3%	0.74 [0.54, 1.02]
JLCSSG31	59	111	52	98	0.98	27.38	3.0%	1.04 [0.71, 1.51]
LCSG801	66	140	71	143	-1.81	34.21	3.7%	0.95 [0.68, 1.33]
LSG853	29	94	32	94	-1.65	15.22	1.7%	0.90 [0.54, 1.48]
MINEO	14	33	21	33	-5.79	8.51	0.9%	0.51 [0.26, 0.99]
NJSGLCS37	24	109	27	110	-1.37	12.73	1.4%	0.90 [0.52, 1.56]
OLCSG1	27	41	21	42	6.59	11.36	1.2%	1.79 [1.00, 3.20]
OLCSG1b20	5	12	7	16	-0.19	2.93	0.3%	0.94 [0.30, 2.95]
OLCSG2a15	20	85	35	87	-7.44	13.73	1.5%	0.58 [0.34, 0.99]
OLCSG2b15	28	47	28	48	2.38	13.87	1.5%	1.19 [0.70, 2.01]
OLSCG1a20	30	163	28	158	-0.09	14.47	1.6%	0.99 [0.59, 1.66]
Ou 2010	60	79	51	71	-5.2504826	27.5675	3.0%	0.83 [0.57, 1.20]
PARK1	17	59	23	59	-4.15	9.95	1.1%	0.66 [0.35, 1.23]
PARK2	37	53	43	55	-4.1	19.87	2.2%	0.81 [0.52, 1.26]
SGACLC ACTLC129	68	154	75	152	-7.09	35.62	3.9%	0.82 [0.59, 1.14]
SGACLC ACTLC233	64	165	68	167	-4.8	32.88	3.6%	0.86 [0.61, 1.22]
WJSG2 (1+3)13	44	115	49	100	-7.66	22.94	2.5%	0.72 [0.48, 1.08]
WJSG2 (2+3)13	38	108	49	100	-9.79	21.49	2.3%	0.63 [0.42, 0.97]
WJSG335	27	109	40	116	-6.01	16.74	1.8%	0.70 [0.43, 1.13]
WJSG440	38	176	56	191	-5.87	23.38	2.5%	0.78 [0.52, 1.17]
Xu34	19	35	26	35	-4.67	11.18	1.2%	0.66 [0.37, 1.18]
Subtotal (95% CI)		**4594**		**4575**			**100.0%**	**0.87 [0.81, 0.92]**
Total events	1756		1956					
Heterogeneity: Chi² = 36.33, df = 35 (P = 0.41); I² = 4%								
Test for overall effect: Z = 4.40 (P < 0.0001)								
Total (95% CI)		**4594**		**4575**			**100.0%**	**0.87 [0.81, 0.92]**
Total events	1756		1956					
Heterogeneity: Chi² = 36.33, df = 35 (P = 0.41); I² = 4%								
Test for overall effect: Z = 4.40 (P < 0.0001)								
Test for subgroup differences: Not applicable								



Appendix 3.2.2. Evidence profile

Date: 2012-11-29
Question: Surgery + adjuvant chemotherapy for lung cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SURGERY PLUS ADJUVANT CHEMO	Control	Relative (95% CI)	Absolute		
New Outcome												
36	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	1756/4594 (38.2%)	1956/4575 (42.8%)	OR 0.87 (0.81 to 0.92)	34 fewer per 1000 (from 20 fewer to 51 fewer)	⊕⊕⊕O MODERATE	
								48.9%		35 fewer per 1000 (from 21 fewer to 52 fewer)		

[1] *mix of different stages in primary studies hampers interpretation*

We make a weak recommendation against the use of neo- adjuvant treatment outside a clinical trial because of risk of bias in the studies (early stoppings overestimate effect), heterogeneity (part of the studies show no effect, others do) and imprecision (Confidence interval compatible with clinically significant effect). There is also no direct comparison of adjuvant chemotherapy and neo-adjuvant chemotherapy and indirect comparison is inconclusive.

We make a strong recommendation in favour of postoperative chemotherapy to patients with good performance status (WHO 0 or 1) and T1-3 N1-2 M0 NSCLC, level of evidence was downgraded to moderate for indirectness, as studies contain a mix of stages where it is unclear if the evidence really concerns this target group.

We make a weak recommendation based on low level of evidence in favour of postoperative chemotherapy based in chemotherapy in patients with good performance status (WHO 0 or 1) and T2-3 N0 M0 NSCLC with tumours greater than 4 cm in diameter, as it was not possible to provide a precise estimate of the possible effect in this group.

We made a strong recommendation against postoperative chemotherapy after R0 resection, for patients with tumours smaller than 4 cm and no lymph node involvement. We consider the evidence as low because CI around the pooled estimate can includes both serious benefit and serious harm, morever it was based on subgroup analysis.

We make a weak recommendation based on low level of evidence in favour cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy as there is limited, indirect and heterogenuous evidence from the meta-analysis of Doullard et al.[79]

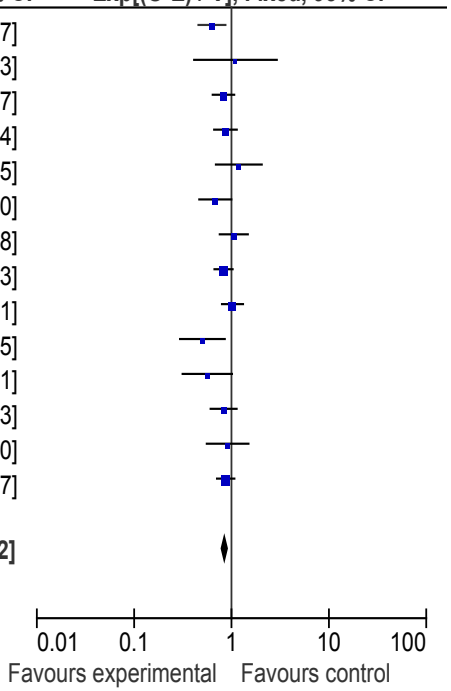
Appendix 3.3. Should neoadjuvant treatment + surgery vs surgery be used for lung cancer?

Appendix 3.3.1. Update meta-analysis

	Experimental		Control					Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
Ch.E.S.T.	56	141	43	129	-17.05	36.91	6.9%	0.63 [0.46, 0.87]	
Dautzenberg	8	13	8	13	0.38	4	0.7%	1.10 [0.41, 2.93]	
Depierre	110	179	123	176	-10.97	58.07	10.8%	0.83 [0.64, 1.07]	
felip 2010	99	199	109	210	-7.3124046	51.87980769	9.7%	0.87 [0.66, 1.14]	
JCOG	28	31	24	31	2.26	12.92	2.4%	1.19 [0.69, 2.05]	
Li	59	77	47	60	-10.03	26.2	4.9%	0.68 [0.46, 1.00]	
Liao	73	108	65	103	1.94	34.38	6.4%	1.06 [0.76, 1.48]	
lYao	154	234	171	222	-15.19	81.03	15.1%	0.83 [0.67, 1.03]	
MRC LU22	122	258	122	261	1.38	61	11.4%	1.02 [0.80, 1.31]	
rosell	25	30	30	30	-9.38	13.64	2.5%	0.50 [0.30, 0.85]	
Roth	19	28	27	32	-6.38	11.15	2.1%	0.56 [0.31, 1.01]	
S9900	95	180	101	174	-7.41	39.77	7.4%	0.83 [0.61, 1.13]	
Sorensen	28	44	35	46	-1.44	15.56	2.9%	0.91 [0.55, 1.50]	
Zhou	206	314	235	310	-12.24	89.77	16.7%	0.87 [0.71, 1.07]	
Total (95% CI)		**1836**		**1797**			**100.0%**	**0.84 [0.77, 0.92]**	
Total events	1082		1140						

Heterogeneity: Chi² = 15.93, df = 13 (P = 0.25); I² = 18%

Test for overall effect: Z = 3.95 (P < 0.0001)



Appendix 3.3.2. Evidence profile

Question: Should neoadjuvant treatment + surgery vs surgery be used for lung cancer?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Neoadjuvant treatment + surgery	Surgery	Relative (95% CI)	Absolute		
overall survival												
14	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	1082/1836 (58.9%)	1140/1797 (63.4%)	HR 0.84 (0.77 to 0.92)	64 fewer per 1000 (from 31 fewer to 95 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] *Early stoppings overestimate effect*
[2] *Part of the studies show no effect*
[3] *Confidence interval compatible with clinically significant effect*

Appendix 3.4. Adjuvant radiotherapy

Table 45 – GRADE profile post-operative radiotherapy

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Completely resected, all patients								
Overall survival HR 1.17; 95%CI 1.02-1.34 (p=0.02)	11	0	0	-1	0	0	3: old trials using outdated surgery, RT and staging	Moderate
Disease-free survival HR 1.09; 95%CI 0.95-1.25 (p=0.23)	11	-1	0	-1	0	0	1: no blinding in majority of studies 3: old trials using outdated surgery, RT and staging 4: no downgrading as no effect and harmful effect included in CI lead to same recommendation	Low
Completely resected, N2 disease								
Overall survival HR 0.97; 95%CI 0.81-1.16	11	0	0	-2	-1	0	3: subgroup analysis, old trials using outdated surgery, RT and staging 4: CI includes appreciable benefit and harm	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Appendix 3.5. Chemoradiotherapy versus radiotherapy alone

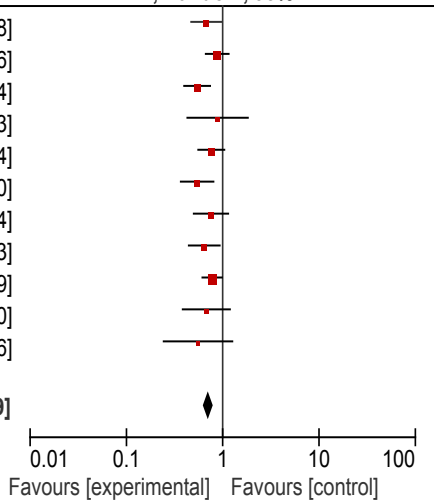
Appendix 3.5.1. Updated meta-analysis

Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	chemoradiation Total	radiotherapy alone Total	Weight	Hazard Ratio IV, Random, 95% CI
Atagi 2012	-0.38566	0.18844903	100	100	8.6%	0.68 [0.47, 0.98]
Blanke 1995	-0.13	0.14	104	111	15.6%	0.88 [0.67, 1.16]
Cakir 2004	-0.61	0.16	88	88	11.9%	0.54 [0.40, 0.74]
Clamon 1999	-0.12	0.37	130	120	2.2%	0.89 [0.43, 1.83]
Huber 2003	-0.27	0.16	99	113	11.9%	0.76 [0.56, 1.04]
Jeremic 1995	-0.61	0.2	52	61	7.6%	0.54 [0.37, 0.80]
Jeremic 1995 bis	-0.28	0.21	56	0	6.9%	0.76 [0.50, 1.14]
Jeremic 1996	-0.44	0.19	65	66	8.5%	0.64 [0.44, 0.93]
Schaake-Koning 1992	-0.25	0.12	217	114	21.2%	0.78 [0.62, 0.99]
Soresi 1988	-0.39	0.29	45	48	3.6%	0.68 [0.38, 1.20]
Yadav 2005	-0.59	0.42	15	15	1.7%	0.55 [0.24, 1.26]
Total (95% CI)			**971**	**836**	**100.0%**	**0.71 [0.64, 0.79]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.83$, df = 10 (P = 0.55); $I^2 = 0\%$

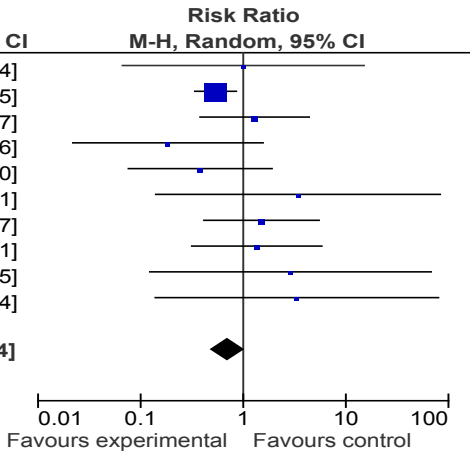
Test for overall effect: Z = 6.19 (P < 0.00001)



treatment related deaths

Study or Subgroup	chemoradiation Events	Total	radiotherapy alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Atagi 2005	1	23	1	23	2.0%	1.00 [0.07, 15.04]
Atagi 2012	20	96	38	98	59.5%	0.54 [0.34, 0.85]
Bonner 1998	5	32	4	33	9.7%	1.29 [0.38, 4.37]
Clamon 1999	1	130	5	120	3.2%	0.18 [0.02, 1.56]
Groen 1999	2	82	5	78	5.6%	0.38 [0.08, 1.90]
Huber 2003	1	99	0	113	1.5%	3.42 [0.14, 83.01]
Jeremic 1995	8	108	3	61	8.7%	1.51 [0.41, 5.47]
Jeremic 1996	4	65	3	66	6.9%	1.35 [0.32, 5.81]
Landgren 1974	1	26	0	25	1.5%	2.89 [0.12, 67.75]
Soresi 1988	1	45	0	50	1.5%	3.33 [0.14, 79.64]
Total (95% CI)		**706**		**667**	**100.0%**	**0.71 [0.48, 1.04]**
Total events	44		59			

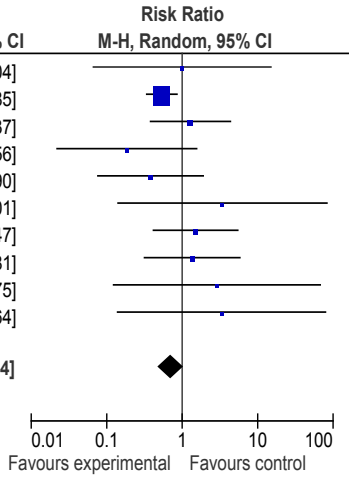
Heterogeneity: Tau² = 0.01; Chi² = 9.15, df = 9 (P = 0.42); I² = 2%
Test for overall effect: Z = 1.76 (P = 0.08)



acute pneumonitis

Study or Subgroup	chemoradiation Events	Total	radiotherapy alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Atagi 2005	1	23	1	23	2.0%	1.00 [0.07, 15.04]
Atagi 2012	20	96	38	98	59.5%	0.54 [0.34, 0.85]
Bonner 1998	5	32	4	33	9.7%	1.29 [0.38, 4.37]
Clamon 1999	1	130	5	120	3.2%	0.18 [0.02, 1.56]
Groen 1999	2	82	5	78	5.6%	0.38 [0.08, 1.90]
Huber 2003	1	99	0	113	1.5%	3.42 [0.14, 83.01]
Jeremic 1995	8	108	3	61	8.7%	1.51 [0.41, 5.47]
Jeremic 1996	4	65	3	66	6.9%	1.35 [0.32, 5.81]
Landgren 1974	1	26	0	25	1.5%	2.89 [0.12, 67.75]
Soresi 1988	1	45	0	50	1.5%	3.33 [0.14, 79.64]
Total (95% CI)		**706**		**667**	**100.0%**	**0.71 [0.48, 1.04]**
Total events	44		59			

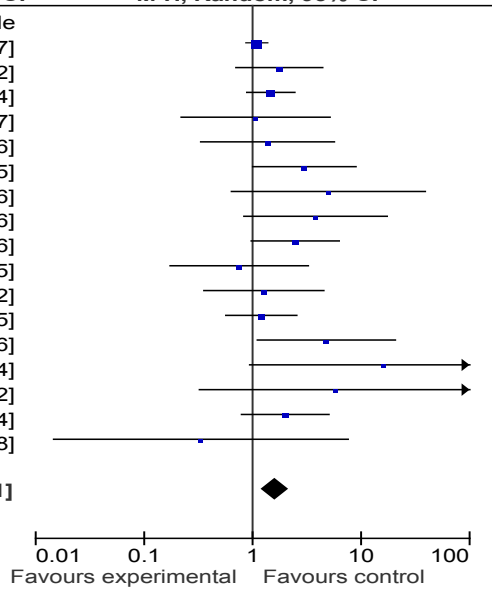
Heterogeneity: Tau² = 0.01; Chi² = 9.15, df = 9 (P = 0.42); I² = 2%
Test for overall effect: Z = 1.76 (P = 0.08)



Oesophagitis

Study or Subgroup	chemoradiation Events	Total	radiotherapy alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Atagi 2005	0	23	0	23		Not estimable
Atagi 2012	61	96	57	98	21.8%	1.09 [0.87, 1.37]
Ball once 1999	11	53	6	51	7.4%	1.76 [0.70, 4.42]
Ball twice 1999	24	50	15	46	14.5%	1.47 [0.89, 2.44]
Blanke 1995	3	104	3	111	3.1%	1.07 [0.22, 5.17]
Bonner 1998	4	32	3	33	3.7%	1.38 [0.33, 5.66]
Clamon 1999	13	130	4	120	5.7%	3.00 [1.01, 8.95]
Gouda 2006	5	20	1	20	1.9%	5.00 [0.64, 39.06]
Groen 1999	8	82	2	78	3.3%	3.80 [0.83, 17.36]
Huber 2003	13	99	6	113	7.2%	2.47 [0.98, 6.26]
Jeremic 1995	4	108	3	61	3.5%	0.75 [0.17, 3.25]
Jeremic 1996	5	65	4	66	4.5%	1.27 [0.36, 4.52]
Landgren 1974	10	26	8	25	9.6%	1.20 [0.57, 2.55]
Lu 2005	10	47	2	45	3.5%	4.79 [1.11, 20.66]
Manegold 2003	7	43	0	46	1.0%	16.02 [0.94, 272.34]
Schaake-Koning 1992	5	217	0	114	1.0%	5.80 [0.32, 104.02]
Trovo 1992	12	73	6	73	7.3%	2.00 [0.79, 5.04]
Yadav 2005	0	15	1	15	0.9%	0.33 [0.01, 7.58]
Total (95% CI)		**1283**		**1138**	**100.0%**	**1.64 [1.22, 2.21]**
Total events	195		121			

Heterogeneity: Tau² = 0.09; Chi² = 23.31, df = 16 (P = 0.11); I² = 31%
Test for overall effect: Z = 3.28 (P = 0.001)

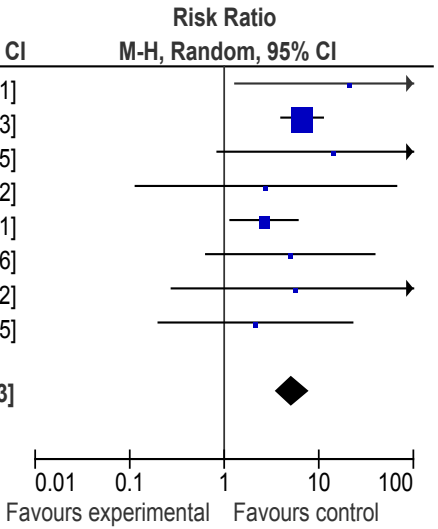


Neutropenia

Study or Subgroup	chemoradiation Events	Total	radiotherapy alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Atagi 2005	10	23	0	23	2.1%	21.00 [1.30, 338.51]
Atagi 2012	85	96	13	98	61.9%	6.67 [4.00, 11.13]
Ball once 1999	7	53	0	51	2.0%	14.44 [0.85, 246.55]
Ball twice 1999	1	50	0	46	1.6%	2.76 [0.12, 66.22]
Clamon 1999	20	130	7	120	23.8%	2.64 [1.16, 6.01]
Gouda 2006	5	20	1	20	3.8%	5.00 [0.64, 39.06]
Huber 2003	2	99	0	113	1.8%	5.70 [0.28, 117.32]
Manegold 2003	2	43	1	46	2.9%	2.14 [0.20, 22.75]
Total (95% CI)		**514**		**517**	**100.0%**	**5.24 [3.50, 7.83]**
Total events	132		22			

Heterogeneity: Tau² = 0.00; Chi² = 5.77, df = 7 (P = 0.57); I² = 0%

Test for overall effect: Z = 8.06 (P < 0.00001)

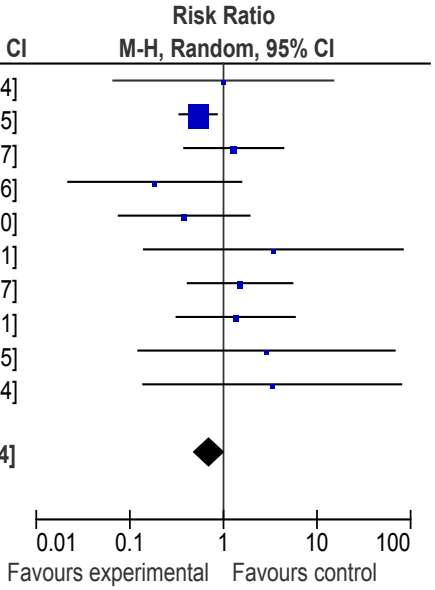


Anemia grade 3 to 4

Study or Subgroup	chemoradiation Events	Total	radiotherapy alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Atagi 2005	1	23	1	23	2.0%	1.00 [0.07, 15.04]
Atagi 2012	20	96	38	98	59.5%	0.54 [0.34, 0.85]
Bonner 1998	5	32	4	33	9.7%	1.29 [0.38, 4.37]
Clamon 1999	1	130	5	120	3.2%	0.18 [0.02, 1.56]
Groen 1999	2	82	5	78	5.6%	0.38 [0.08, 1.90]
Huber 2003	1	99	0	113	1.5%	3.42 [0.14, 83.01]
Jeremic 1995	8	108	3	61	8.7%	1.51 [0.41, 5.47]
Jeremic 1996	4	65	3	66	6.9%	1.35 [0.32, 5.81]
Landgren 1974	1	26	0	25	1.5%	2.89 [0.12, 67.75]
Soresi 1988	1	45	0	50	1.5%	3.33 [0.14, 79.64]
Total (95% CI)		**706**		**667**	**100.0%**	**0.71 [0.48, 1.04]**
Total events	44		59			

Heterogeneity: Tau² = 0.01; Chi² = 9.15, df = 9 (P = 0.42); I² = 2%

Test for overall effect: Z = 1.76 (P = 0.08)



Appendix 3.5.2. Evidence profile

Date: 2012-12-05
Question: chemoradiation versus radiotherapy alone for lung cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chemoradiation versus radiotherapy alone	Control	Relative (95% CI)	Absolute		
overall survival												
1	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	971/18 (5394.4%)	0%	HR 0.71 (0.64 to 0.79)	-[3]	⊕⊕⊕O MODERATE	CRITICAL
acute pneumonitis												
10	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	44/706 (6.2%)	59/667 (8.8%)	RR 0.71 (0.48 to 1.04)	26 fewer per 1000 (from 46 fewer to 4 more)	⊕⊕⊕O MODERATE	IMPORTANT
								4.5%		13 fewer per 1000 (from 23 fewer to 2 more)		
Oesophagitis												
18	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	195/1283 (15.2%)	121/1138 (10.6%)	RR 1.64 (1.22 to 2.21)	68 more per 1000 (from 23 more to 129 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								5.2%		33 more per 1000 (from 11		

										more to 63 more)		
Neutropenia												
8	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	132/514 (25.7%)	22/517 (4.3%)	RR 5.24 (3.5 to 7.83)	180 more per 1000 (from 106 more to 291 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								1.1%		47 more per 1000 (from 27 more to 75 more)		
Anemia grade 3 to 4												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	27/510 (5.3%)	3/506 (0.6%)	RR 5.31 (1.86 to 15.13)	26 more per 1000 (from 5 more to 84 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								0%		-		
Treatment related deaths												
15	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	none	31/1205 (2.6%)	44/1064 (4.1%)	RR 0.7 (0.41 to 1.2)	12 fewer per 1000 (from 24 fewer to 8 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] *compatible with serious harm or serious benefit*
[2] *subgroup analysis reveals considerable heterogeneity, part of it unexplained.*
[3] *Hazard rate, no baseline survival available*

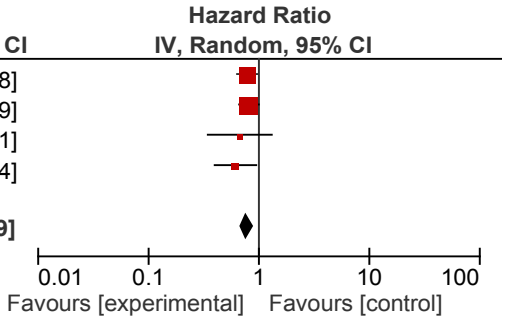
Appendix 3.6. Concurrent versus sequential chemoradiotherapy

Appendix 3.6.1. Updated meta-analysis

Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	concurrent Total	sequential Total	Weight	Hazard Ratio IV, Random, 95% CI
Curran 2003	-0.24	0.11	200	199	40.2%	0.79 [0.63, 0.98]
Curran 2011	-0.20825	0.103431	31	20	45.5%	0.81 [0.66, 0.99]
Fournel 2001	-0.4	0.34	100	101	4.2%	0.67 [0.34, 1.31]
Zatloukal 2003	-0.49	0.22	52	50	10.1%	0.61 [0.40, 0.94]
Total (95% CI)			**383**	**370**	**100.0%**	**0.77 [0.67, 0.89]**

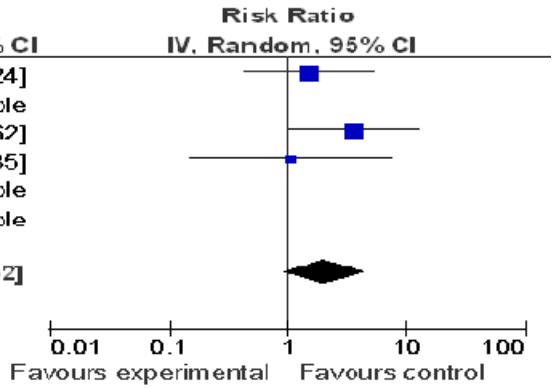
Heterogeneity: Tau² = 0.00; Chi² = 1.54, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 3.69 (P = 0.0002)



Treatment related deaths

Study or Subgroup	concurrent Events	Total	sequential Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Curran 2003	6	201	4	201	41.6%	1.50 [0.43, 5.24]
Curran 2011	0	0	0	0		Not estimable
Fournel 2001	10	93	3	100	41.0%	3.58 [1.02, 12.62]
Reinfuss 2005	2	84	2	89	17.3%	1.06 [0.15, 7.35]
Wu 2006	0	40	0	40		Not estimable
Zatloukal 2003	0	52	0	50		Not estimable
Total (95% CI)		**470**		**480**	**100.0%**	**2.02 [0.90, 4.52]**
Total events	18		9			

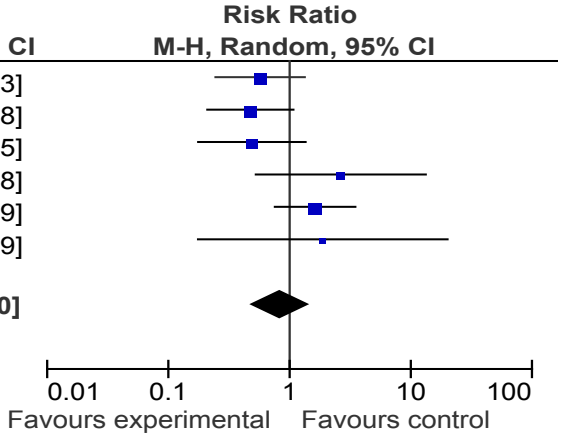
Heterogeneity: Tau² = 0.00; Chi² = 1.44, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)



Pneumonitis

Study or Subgroup	concurrent Events	Total	sequential Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Curran 2003	8	201	14	201	21.5%	0.57 [0.25, 1.33]
Curran 2011	8	193	17	195	22.2%	0.48 [0.21, 1.08]
Fournel 2001	5	93	11	100	17.8%	0.49 [0.18, 1.35]
Reinfuss 2005	5	84	2	89	9.7%	2.65 [0.53, 13.28]
Wu 2006	13	40	8	40	23.5%	1.63 [0.76, 3.49]
Zatloukal 2003	2	51	1	48	5.2%	1.88 [0.18, 20.09]
Total (95% CI)		**662**		**673**	**100.0%**	**0.84 [0.47, 1.50]**
Total events	41		53			

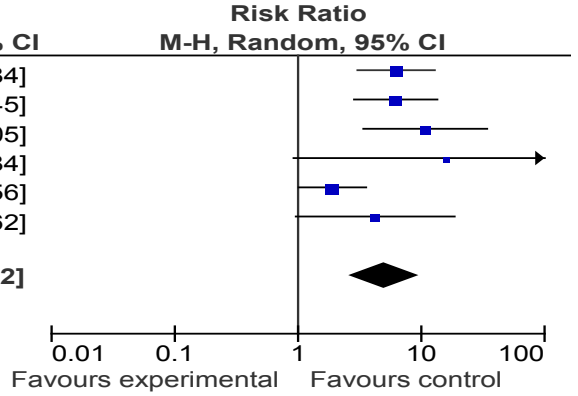
Heterogeneity: Tau² = 0.22; Chi² = 9.01, df = 5 (P = 0.11); I² = 45%
Test for overall effect: Z = 0.58 (P = 0.56)



Oesophagitis

Study or Subgroup	concurrent Events	Total	sequential Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Curran 2003	50	201	8	201	22.4%	6.25 [3.04, 12.84]
Curran 2011	43	193	7	195	21.5%	6.21 [2.86, 13.45]
Fournel 2001	30	93	3	100	15.7%	10.75 [3.40, 34.05]
Reinfuss 2005	7	84	0	89	4.4%	15.88 [0.92, 273.84]
Wu 2006	19	40	10	40	24.0%	1.90 [1.01, 3.56]
Zatloukal 2003	9	51	2	48	11.9%	4.24 [0.96, 18.62]
Total (95% CI)		**662**		**673**	**100.0%**	**5.08 [2.66, 9.72]**
Total events	158		30			

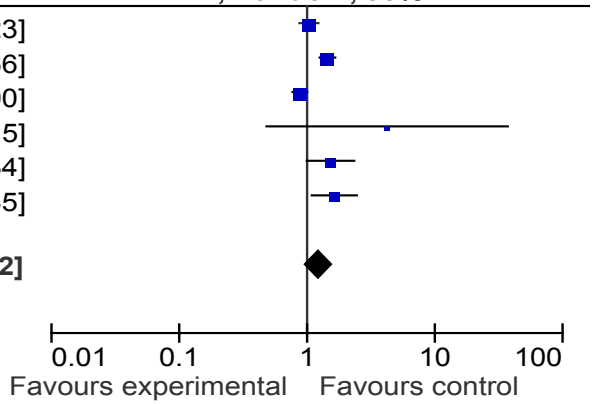
Heterogeneity: Tau² = 0.35; Chi² = 12.63, df = 5 (P = 0.03); I² = 60%
Test for overall effect: Z = 4.91 (P < 0.00001)



neutropenie

Study or Subgroup	concurrent Events	Total	sequential Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Curran 2003	117	201	113	201	22.2%	1.04 [0.87, 1.23]
Curran 2011	162	195	111	193	23.0%	1.44 [1.26, 1.66]
Fournel 2001	72	93	88	100	23.1%	0.88 [0.77, 1.00]
Reinfuss 2005	4	84	1	89	1.4%	4.24 [0.48, 37.15]
Wu 2006	26	40	17	40	14.9%	1.53 [1.00, 2.34]
Zatloukal 2003	33	51	19	48	15.5%	1.63 [1.09, 2.45]
Total (95% CI)		**664**		**671**	**100.0%**	**1.25 [0.96, 1.62]**
Total events	414		349			

Heterogeneity: Tau² = 0.07; Chi² = 35.94, df = 5 (P < 0.00001); I² = 86%
Test for overall effect: Z = 1.66 (P = 0.10)



Appendix 3.6.2. Evidence profile

Date: 2012-12-04
Question: Concurrent versus sequential chemoradiation for lung cancer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Concurrent versus sequential chemoradiation	Control	Relative (95% CI)	Absolute		
overall survival												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	383/0 (0%)	370/0 (0%)	HR 0.77 (0.67 to 0.89)	-	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		-		
acute pneumonitis												
6	randomised trials	no serious risk of	no serious inconsistency	no serious indirectness	serious[1]	none	41/662 (6.2%)	53/673 (7.9%)	RR 0.84 (0.47 to	13 fewer per 1000 (from 42	⊕⊕⊕O MODERATE	IMPORTANT

		bias							1.5)	fewer to 39 more)		
								7.8%		12 fewer per 1000 (from 41 fewer to 39 more)		
Oesophagitis												
6	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	158/662 (23.9%)	30/673 (4.5%)	RR 5.08 (2.66 to 9.72)	182 more per 1000 (from 74 more to 389 more)	⊕⊕⊕O MODERATE	CRITICAL
								3.8%		155 more per 1000 (from 63 more to 331 more)		
Neutropenia												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	none	414/664 (62.3%)	349/671 (52%)	RR 1.25 (0.96 to 1.62)	130 more per 1000 (from 21 fewer to 322 more)	□□□□ MODERATE	IMPORTANT
								49.4%		124 more per 1000 (from 20 fewer to 306 more)		

[1] *I2 60 %, unexplained and varying degree of harm*
[2] *compatible with serious harm*

Appendix 3.7. Neoadjuvant therapy plus surgery for stage IIIA-N2 disease

Table 46 – Neoadjuvant therapy followed by surgery for stage IIIA-N2 disease

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Induction chemotherapy followed by surgery versus radiotherapy								
Overall survival	3	0	-1	0	0	0	2: heterogeneity between studies	Moderate
Progression-free survival	1	0	-1	0	-1	0	2: single study 4: OIS not reached	Low
Induction chemoradiation followed by surgery versus completion of radiotherapy								
Overall survival	1	0	-1	0	-1	0	2: single study 4: OIS not reached	Low
Progression-free survival	1	-1	-1	0	-1	0	1: no blinding 2: single study 4: OIS not reached	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

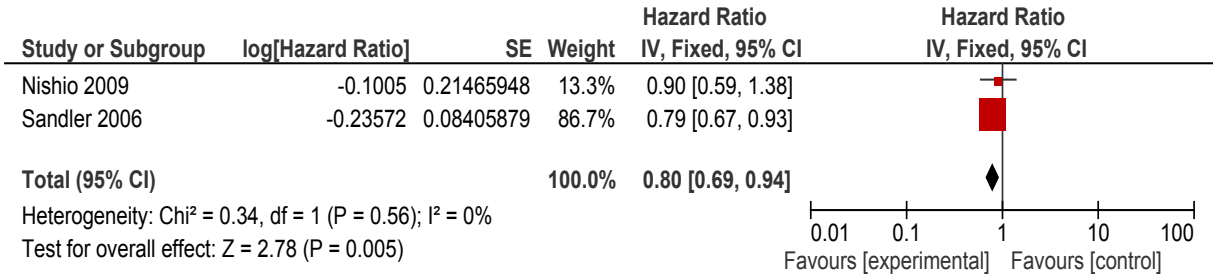
Appendix 3.8. Advanced stage

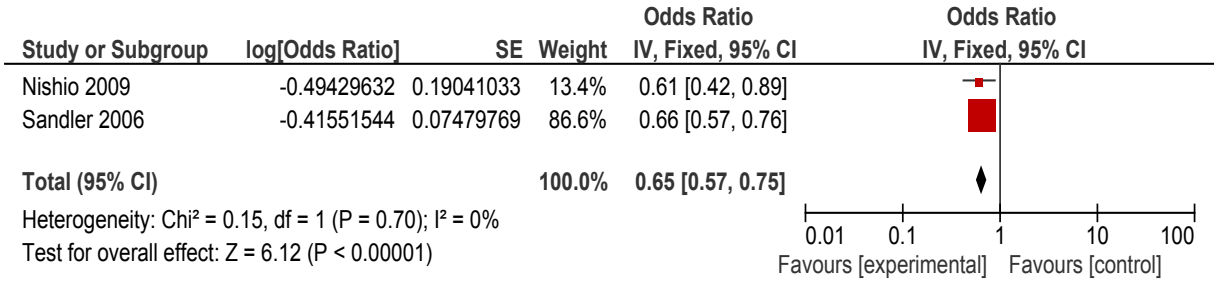
Table 47 – Use of chemotherapy.

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Use of chemotherapy in general versus best supportive care (BSC).								
Overall survival HR, 0.77; 95% CI, 0.71 to 0.83; P <or=.0001	16	0	0	0	0	0		High
Cisplatin versus carboplatin overall								
Overall survival HR: 1,07; 95% CI: 0,99-1,15	9	0	0	0	-1	0	4: confidence interval is compatible with decrease overall survival	Moderate
Cisplatin versus carboplatin non squamous								
Overall survival HR: 1,12; 95% CI: 1,1-1,25	9	0	0	0	-1	0	4: confidence interval is compatible with no clinically significant effect	Moderate
Adding bevacizumab to the combination carboplatin/paclitaxel in patients with non squamous carcinomas								
Overall survival HR: 0.80 [0.69, 0.94]	2	0	0	0	0	0		High
Progression free survival HR: 0.65 [0.57, 0.75]	2	0	0	0	0	0		High
Receptor tyrosine kinase inhibitors (EGFR TKI) as first-line treatment of patients with advanced EGFR-mutation positive NSCLC								
Overall survival HR: 0,97 (95 % CI 0,64–1,47) p= 0,88	2	0	0	0	-1	0	Downgraded for imprecision	Moderate

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Progression free survival HR: 0,31 (95 % CI 0,17–0,55) p<0.0001	2	0	0	0	0	0		High
Receptor tyrosine kinase inhibitors (EGFR TKI) as first-line treatment of patients with advanced EGFR-mutation positive NSCLC								
Overall survival median overall survival (OS) 20.3 months (crizotinib group) vs. 22.8 months	1	-1	0	0	-1	0	Downgraded for imprecision and the fact that results are preliminary/de facto early stopped due to large propoportion of cross over	Low
Progression free survival HR 0.49 (95 % CI 0.37-0.64; p<0.0001)	1	-1	0	0	0	-1	Downgraded due to the fact that results are preliminary/de facto early stopped due to large propoportion of cross over and the fact that there is only one study	Moderate

Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias





Justification of the GRADES given:

The recommendation on the use of chemotherapy in patients with stage IV NSCLC is a strong recommendation with a high level of evidence, based on a cochrane review and meta-analysis that shows the effect on survival.b

The recommendation to use receptor tyrosine kinase inhibitors (EGFR TKI) as first-line treatment of patients with advanced EGFR-mutation positive NSCLC because of the better tolerance (strong recommendation, moderate level of evidence). If tyrosine kinase inhibitors are not given in first line in mutated patient it should be given in second line (Strong recommendation, moderate level of evidence).

Here the level of evidence was downgraded to moderate because the studies could not demonstrate an effect on mortality, even if this was probably due to the cross over design in the primary studies.

In patients with performance status of 0 or 1, evidence supports using a combination of two cytotoxic drugs for first-line therapy. Platinum combinations are preferred over non-platinum combinations because they are superior in response rate, and marginally superior in overall survival. Non-platinum therapy combinations are reasonable in patients who have contraindications to platinum therapy (strong recommendation, high level of evidence). Level of evidence was considered high based on a based on a meta-analysis that shows the effect on survival.

The choice of either cisplatin or carboplatin is acceptable. Drugs that may be combined with platinum include the third generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine. The evidence suggests that cisplatin combinations have a higher response rate than carboplatin and may improve survival when combined with third-generation agents in patients with non squamous carcinomas (weak recommendation, moderatie level of evidence). Here the level of evidence was downgraded to low because of imprecision

Consider adding bevacizumab to the combination carboplatin/paclitaxel in patients with non squamous carcinomas (weak recommendation, moderate level of evidence). level of evidence was downgraded because of imprecision

It is recommended to give second line chemotherapy for patients with advanced NSCLC with adequate PS when the disease has progressed during or after first-line, platinum-based therapy (strong recommendation, high level of evidence). different RCTs showing an effect of different forms of chemotherapy, there are not poolable but consistent, so no downgrading was done

Appendix 3.9. Small cell lung cancer

Table 48 – Limited disease

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Use of chemotherapy in general versus best supportive care (BSC).								
Overall survival Divers studies not poolable	8	0	0	0	0	0		High
Concurrent versus sequential chemoradiotherapy								
One year survival:RR: 0.73, 95% CI 0.57-0.94, p=0.01; 5-year survival: HR: 0.65, 95% CI 0.45-0.93, p=0.02	7	0	0	0	0	0		High
Prophylactic cranial irradiation vs no prophylactic cranial irradiation								
Overall survival 0.84 (95 % confidence interval, 0.73 to 0.97; p= 0.01)	9	0	0	-1	-1	0	3: current brain imaging much more sensitive to detect possible metastasis compared to trials 4: CI includes clinical non-significant reduction in OS considering side effects	Low
Prophylactic cranial irradiation high dose versus low dose								
Overall survival HR 1.20 [1.00-1.44]; p=0.05	1	0	0	0	0	0		High

Limited disease

- It is recommended to offer patients with limited-stage disease SCLC (broadly corresponding to T1-4, N0-3,M0) four to six cycles of platinum -based combination chemotherapy (strong recommendation, no level of evidence). No level of evidence was provided for this indication as it is considered standard of care.
- It is recommended to offer concurrent chemoradiotherapy (starting with cycle 1 or cycle 2) to patients with limited-stage disease SCLC (broadly corresponding to T1-4, N0-3, M0) and a WHO performance status of 0 or 1 if they present with disease that can be encompassed in a radical thoracic radiotherapy volume. Start the radiotherapy during the first or second cycle of chemotherapy (strong recommendation, high level of evidence).
- It is recommended to offer sequential radical thoracic radiotherapy to patients with limited-stage disease SCLC (broadly corresponding to T1-4, N0-3, M0) who are unfit for concurrent chemoradiotherapy but who respond to chemotherapy.
- There is high level evidence that concurrent chemotherapy is results in a longer survival than sequential chemotherapy
- It is recommended to offer prophylactic cranial irradiation at a dose of 25 Gy in 10 fractions to patients with limited-stage disease SCLC and WHO performance status 2 or less, if their disease in complete remission after first-line treatment. Evidence was downgraded for imprecision as CI effect is compatible with clinically non significant effect and indirectness due to outdated assessment of complete remission.
- It is recommended to offer maintenance therapy only in the context of a clinical trial (weak recommendation very low level of evidence). There is no reliable evidence against or in favour of maintenance therapy.

Table 49 – Extensive disease disease.

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Prophylactic cranial irradiation vs no prophylactic cranial irradiation								
Overall survival 0.68; 95% CI, 0.52 to 0.88	1	0	0	0	0	0		High

- It is recommended to offer platinum-based combination chemotherapy to patients with extensive-stage disease SCLC (broadly corresponding to T1-4, N0-3, M1a/b – including cerebral metastases) if they are fit enough (strong recommendation, no level of evidence). No level of evidence was provided for this indication as it is considered standard of care.

Table 50 – Relapsed small cell lung cancer.

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
topotecan vs no chemotherapy								
Overall survival	1	0	0	0	0	-1	Only one industy sponsored study	moderate
Qualtiy of life Difference in rate of change EQ-5 D 0.15 (0.05 to 0.25) in favour of topotecan	1	0	0	0	0	-1	Only one industy sponsored study	moderate

APPENDIX 4. REVISED CARDIAC RISK INDEX

Revised Cardiac Risk Index
1. History of ischemic heart disease
2. History of congestive heart failure
3. History of cerebrovascular disease (stroke or transient ischemic attack)
4. History of diabetes requiring preoperative insulin use
5. Chronic kidney disease (creatinine > 2 mg/dL)
6. Undergoing suprainguinal vascular, intraperitoneal, or intrathoracic surgery
Risk for cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest: 0 predictors = 0.4%, 1 predictor = 1%, 2 predictors = 2.4%, ≥3 predictors = 5.4%

APPENDIX 5. GRADED RECOMMENDATIONS OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER/AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY INTERNATIONAL MULTIDISCIPLINARY LASSIFICATION OF LUNG ADENOCARCINOMA

Summary of Pathology Recommendations

1. We recommend discontinuing the use of the term “BAC” (strong recommendation, low-quality evidence).

2. For small (3 cm), solitary adenocarcinomas with pure lepidic growth, we recommend the term “Adenocarcinoma

in situ” that defines patients who should have 100% disease-specific survival, if the lesion is completely resected (strong recommendation, moderate

quality evidence). Remark: Most AIS are nonmucinous, rarely are they mucinous.

3. For small (3 cm), solitary, adenocarcinomas with predominant lepidic growth and small foci of invasion measuring 0.5 cm, we recommend a new concept of “Minimally invasive adenocarcinoma” to define patients who should have near 100%, disease-specific survival, if completely resected (strong recommendation, low-quality evidence). Remark: Most MIA are nonmucinous, rarely are they mucinous.

4. For invasive adenocarcinomas, we suggest comprehensive histologic subtyping be used to assess histologic patterns semiquantitatively in 5% increments,

choosing a single predominant pattern. We also suggest that individual tumours be classified according to the predominant pattern and that the percentages of the subtypes be reported (weak recommendations and low-quality evidence).

5. In patients with multiple lung adenocarcinomas, we suggest comprehensive histologic subtyping in the comparison of the complex, heterogeneous mixtures of histologic patterns to determine whether the tumours are metastases or separate synchronous or metachronousprimaries (weak recommendation, low-quality evidence).

6. For nonmucinous adenocarcinomas previously classified as mixed subtype where the predominant subtype consists of the former nonmucinous BAC, we recommend use of the term LPA and discontinuing the term “mixed subtype” (strong recommendation, low-quality evidence).

7. In patients with early-stage adenocarcinoma, we recommend the addition of “micropapillary predominant adenocarcinoma,” when applicable, as a major histologic subtype due to its association with poor prognosis (strong recommendation, low-quality evidence).

8. For adenocarcinomas formerly classified as mucinous BAC, we recommend that they be separated from the adenocarcinomas formerly classified as nonmucinous BAC and depending on the extent of lepidic versus invasive growth that they be classified as mucinous AIS, mucinous MIA, or for overtly invasive tumours “invasive mucinous adenocarcinoma” (weak recommendation, low-quality evidence).

9. For small biopsies and cytology, we recommend that NSCLC be further classified into a more specific type, such as adenocarcinoma or squamous cell carcinoma, whenever possible (strong recommendation, moderate quality evidence).

10. We recommend that the term NSCLC-NOS be used as little as possible, and we recommend it be applied only when a more specific diagnosis is not possible by morphology and/or special stains (strong recommendation, moderate quality evidence).

Clinical Recommendation

In patients with advanced lung adenocarcinoma, we recommend testing for EGFR mutation (strong recommendation, moderate quality evidence).

Remarks: This is a strong recommendation because potential benefits clearly outweigh harms. This recommendation assumes that correct classification by EGFR mutation status is associated with important benefit based on randomizedphase 3 clinical trials of EGFR-TKI therapy, which demonstrate a predictive benefit for response rate and PFS, but not overall survival, and subset analyses of multiple additional studies.

Radiology Recommendations

1. When an opacity in the lung adenocarcinoma spectrum is either a pure GGN or part-solid nodule with a predominant ground-glass component, we recommend that the term BAC no longer be used. These tumours should be classified by the new terms: AIS, MIA, and LPA (strong recommendation, low-quality evidence).

2. For overtly invasive adenocarcinomas previously classified as mucinous BAC, we recommend they be separated from nonmucinous adenocarcinomas and be classified as invasive mucinous adenocarcinoma (strong recommendation, moderate quality evidence).

Remark: At CT, this entity is usually solid or mostly solid,has frequent air bronchograms, shows a lobar or multilobar distribution, and frequently consists of multiple nodular or consolidative opacities (former term multicentric BAC).

APPENDIX 6. HISTOPATHOLOGY REPORTING PROFORMA FOR LUNG CANCER RESECTION SPECIMENS OF THE ROYAL COLLEGE OF PATHOLOGISTS (UK)

Histopathology reporting proforma for lung cancer resection specimens

Surname	Forenames	Date of birth	Sex
Hospital	Hospital no	NHS/CHI no	
Date of receipt	Date of reporting	Report no	
Pathologist	Surgeon/physician	Lab no	

Previous treatment (neoadjuvant chemotherapy/radiotherapy) Yes ☐ No ☐

Specimen type

Right lung	☐	VATS	☐
Left lung	☐	VATS converted to open	☐
		Open	☐
Single wedge resection	☐	Pneumonectomy (extra-pericardial)	☐
Multiple wedge resections	☐	Pneumonectomy (intra-pericardial)	☐
Segmentectomy	☐		
Lobectomy/bi-lobectomy	☐	Other ☐ (specify) ……	

Other surgical procedures

Sleeve resection ☐ Other (e.g. chest wall) ……

Macroscopic features

Main bronchus within 20 mm of carina (T3) (if known) ☐

Main bronchus more than 20 mm from carina (T2) ☐

Location of tumour: ……

Hilar/endobronchial/central ☐

Right upper lobe	☐	Right middle lobe	☐	Right lower lobe	☐
Left upper lobe	☐	Left lower lobe	☐	Not assessable	☐

Tumour size……mm (maximum dimension) Not assessable ☐

(T1a =<20 mm; T1b 21–≥30 mm; T2a 31–≤50 mm; T2b 51–≤70 mm; T3 >70 mm).

Distance of tumour (or stapled margin if completion lobectomy) from bronchial or medial resection margin: ……mm

Extent of atelectasis/obstructive pneumonia:	None/less than the two categories below ☐
	Involving hilar region but not whole lung (T2) ☐
	Involving whole lung (T3) ☐

Microscopic features

Histological type

Squamous cell carcinoma ☐ Large cell undifferentiated ☐ Small cell carcinoma ☐

Adenocarcinoma ☐

Adenocarcinoma-in-situ ☐

Minimally invasive adenocarcinoma (invasive component less than 5 mm) ☐

Predominant pattern ..... (lepidic, acinar, papillary, micropapillary, solid)

Mucinous ☐

Non-mucinous ☐

Mixed mucinous/non-mucinous (>10% of each) ☐

Combined tumours ☐ (specify .....)

Other tumour ☐ (specify, e.g. carcinoid, etc. .....)

Local invasion

Visceral pleura (T2) ☐

Parietal pleura/chest wall (T3) ☐

Mediastinal pleura (T3) ☐

Pericardium (T3) ☐

Diaphragm (T3) ☐

Great vessel (aorta, central pulmonary artery or vein) (T4) ☐

Atrium, heart (T4) ☐

Malignant pleural effusion (M1a) ☐

Satellite nodules

Satellite tumour nodules in same lobe (T3) ☐

Satellite tumour nodules in different ipsilateral lobe (T4) ☐

Satellite tumour nodules in contralateral lobe (M1a) ☐

Pleural invasion

PL0 (no pleural involvement) ☐

PL1 (breaching of the outer layer of the visceral pleura but no extension to the pleural surface) ☐

PL2 (breaching of the outer layer of the visceral pleura **and** extension to the pleural surface) ☐

PL3 (involvement of the parietal pleura) ☐

Lymph node spread

Ipsilateral hilar/intrapulmonary (node stations 10–14)	Submitted ☐	Involved (N1) ☐
Ipsilateral mediastinal (node stations 1–9)	Submitted ☐	Involved (N2) ☐
Contralateral mediastinal, hilar nodes	Submitted ☐	Involved (N3) ☐
Ipsilateral or contralateral scalene or supraclavicular nodes	Submitted ☐	Involved (N3) ☐

Margins

Bronchial	Clear ☐	Involved ☐	N/A ☐
Mediastinal	Clear ☐	Involved ☐	N/A ☐
Vascular	Clear ☐	Involved ☐	N/A ☐
Chest Wall	Clear ☐	Involved ☐	N/A ☐

Other pathology (non-core)

Emphysema No ☐ Yes ☐ Specify degree(mild/moderate/severe)

Interstitial fibrosis No ☐ Yes ☐ State cause (if known) .....

Other ☐ Details: .....

Metastases

Unknown (MX) ☐ Absent (M0) ☐ Present (M1a) ☐ (M1b) ☐

Details: .....

Ancillary data

Epidermal growth factor mutation Yes ☐ No ☐ Not assessed ☐

Other genetic data (specify) .....

Summary of pathological staging

(Select highest stage from above data; for synchronous primaries, use protocol above;
use prefix 'y' for resection during or following treatment and 'r' for recurrence after treatment)

...pT .....pN .....pM .....

Complete resection at all margins Yes ☐ No ☐

SNOMED code:

Comments .....

Signature .....

Date ...../...../.....

APPENDIX 7. STAKEHOLDER MEETING: SCORES OF DRAFT RECOMMENDATIONS AND GOOD CLINICAL PRACTICE POINTS AND ACTIONS TAKEN

REC / GCPP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recommendation (weak, strong)	GRADE Level of evidence (Very low to High)	Scores 4, 5 (= agree)	Scores 1, 2, 4, 5	% agree	Comments (required if 1 or 2)	Changes made
FINAL RECOMMENDATIONS NSCLC								
Diagnosis and staging of lung cancer								
REC	All patients suspected of lung cancer should have their history taken, including smoking history, have a full clinical examination including assessment of performance status and fitness and have basic blood tests.			6	6	100%		none
	In a patient suspected of lung cancer, either on clinical grounds or following a chance finding during a radiological examination for another purpose, we recommend a 3 step approach:			1	2	50%	Depends on the notion of 3 step: is this conceptual framework or a binding chronological shedule?	clarification
	Tier 1: parameters to be considered in every patient at presentation/diagnosis			1	1	100%		
REC	Offer urgent chest X-ray to patients presenting with haemoptysis, or any of the following unexplained or persistent (that is, lasting more than 3 weeks) symptoms or signs: cough, chest/shoulder pain, dyspnoea, weight loss, chest signs, hoarseness, finger clubbing, features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin), cervical/supraclavicular lymphadenopathy.			7	7	100%	what is the definition of "urgent" chest X-ray; should "ASAP" more appropriate	none
REC	Moreover, offer urgent referral to lung cancer multidisciplinary team (usually the chest physician) if any of the following are present: persistent major haemoptysis in a smoker or ex-smoker older than 40 years, signs of superior vena cava obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure), stridor.			7	7	100%	what is the definition of "urgent" chest X-ray; should "ASAP" more appropriate	none
	Tier 2: investigations conducted in patients likely to be offered some form of active treatment:			2	2	100%	I do not understand these tiers. Does that mean that mean that PET/CT is limited to tier 3? Performing invasive procedures before obtaining a metabolic evaluation seems counterproductive. Furthermore, the Fleischner recommendations include PET for solid lesions >8mm and are imentioned in the body of the text. Quid possibility of PET/CT wih diagnostic CT.	clarification
REC	Offer a high diagnostic CT of the thorax with a multi-detector CT with intravenous contrast, covering the supraclavicular area, liver and the adrenal glands.			7	7	100%		none
REC	Pathological confirmation is highly recommended. In exceptions where histology cannot be obtained, documentation of the evolution of the lesion has to be considered.			6	6	100%		none
REC	Biopsy any enlarged mediastinal nodes (>=10 mm maximum short axis on CT) or other metastatic lesions in preference to the primary lesion if determination of stage affects treatment.			5	6	83%	PET positive nodes shloud be biopsied as well, not just enlarged nodes	none
REC	In absence of suspected lymph nodes or metastases biopsy the primary tumour using CT- or ultrasound-guided transthoracic needle biopsy, (EBUS guided) fibreoptic bronchoscopy depending on presentation, local availability and expertise when treatment can be planned on the basis of this test.			6	6	100%	I would write "E(B)US guided" as EUS is also aoropriate	none

REC / GCPP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recommendation (weak, strong)	GRADE Level of evidence (Very low to High)	Scores 4, 5 (= agree)	Scores 1, 2, 4, 5	% agree	Comments (required if 1 or 2)	Changes made
	Tier 3: investigations conducted in patients in whom hitherto no metastases were found and clinically fit for a treatment with curative intent:							
REC	Offer PET-CT to all patients potentially suitable for treatment with curative intent in order to look for metastases.			7	7	100%		none
REC	A solitary suspected (metastatic) lesion on PET-CT scan must be confirmed pathologically as a false positive PET-CT has a consequence that a patient is denied lifesaving treatment with curative or radical intent.			7	7	100%		none
REC	Don't offer bone scintigraphy to NSCLC patients if a PET-scan has been performed and all relevant body parts are included.			7	7	100%	what means " relevant"? Bone scintigraphy can be useful to find the cause of non-oncological skeletal complaints. Rephrase as "Don't offer BS for staging ..."	none
REC	Offer CT or MR of the brain with IV contrast to NSCLC patients selected for treatment with curative intent, especially in stage III disease.			7	7	100%		none
REC	MR may be considered for some very specific other clinical situations, such as a sulcus superior tumour.			6	6	100%	Chest MR	clarification
REC	If distant metastases are excluded, proceed to pathological confirmation of lymph nodes when either PET-CT of the lymph nodes is positive or if CT shows mediastinal lymph nodes of more than 1 cm or if the primary tumour is abutting the mediastinum or when hilar adenopathies are present. Otherwise proceed directly to thoracotomy.			5	7	71%	PET is only valuable for mediastinal purpose in case of FDG uptake in the primary tumor; replace abutting to proximal	clarification
REC	NSCLC patients with suspicious lymph nodes on PET-CT who are considered eligible for a treatment with curative intent should be offered invasive mediastinal staging. The preferred approach is combined EBUS and EUS for mediastinal staging, followed by mediastinoscopy if no lymph node metastasis is found by EBUS or EUS.			6	7	86%	agree but more practiced before surgery than RT; In some cases, the evaluation must be performed by VATS. Especially for the station 5 and 6	none
GCPP	To allow adequate diagnostic and predictive examination, tissue sampling should be maximized whenever feasible and deemed clinically safe, in order to reduce the need for re-biopsy for additional studies.			6	6	100%		none
GCPP	EBUS-TBNA and EUS-FNA should be performed in a systematic fashion with sampling of all enlarged lymph nodes and at least mapping of ipsiplateral and contralateral paratracheal stations (number 4L/R) and the subcarinal station (number 7).			5	6	83%	all PET positive nodes that can be reached should be sampled as well	none
GCPP	When performing mediastinoscopy for mediastinal staging of lung cancer, at least five lymph node stations should be sampled including two ipsilateral, one contralateral station and lymph node station number 7 (subcarinal).			5	6	83%	If it is possible ! Sometimes, some lymph nodes are not anatomicaly present (for instance station 2L..)	modification
Pathology								
Pathological sub-classification and molecular tests using Fine Needle Aspiration Cytology (FNAC) samples								
REC	In lung cancer patients, use samples obtained by FNA for determination of histology subtype and the performance of molecular techniques if no biopsy or surgical resection specimen is available.			6	6	100%		none
REC	Cell blocks should be prepared and immunocytochemistry should be applied on cytology samples whenever needed.			6	6	100%		none
Pathological sub-classification: use of immunohistochemistry								
REC	For pathological subclassification (in case morphology is not sufficient), use a diagnostic panel of assays that can consist amongst others of mucin stain, cytokeratine 5/6 cytokeratin 7, TTF1 and p63, but other assays can emerge in this rapidly evolving field.			5	6	83%	The new recommendations is the preservation of tissue for molecular testings . So it if important to limit ancillary techniques and to realize only 2 tests if there is a doubt about the type of NSCLC : P63 and TTF1.Others tests are not necessary . P63?	clarification
Molecular techniques to guide targeted treatment								
REC	As response to EGFR targeted therapy depends on the the presence of activating EGFR mutations, tests for these mutations should be offered to patients with non-squamous NSCLC potentially eligible to EGFR targeted therapy.			7	7	100%		none
REC	If no activating EGFR mutation is present, a ALK rearrangement test should be done to find patients potentially eligible for crizotinib treatment.			7	7	100%		none
GCPP	All molecular tests, such as EGFR mutation analysis and the ALK rearrangement test should be performed using a well-validated and robust method.			7	7	100%		none

REC / GCPP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recommendation (weak, strong)	GRADE Level of evidence (Very low to High)	Scores 4, 5 (= agree)	Scores 1, 2, 4, 5	% agree	Comments (required if 1 or 2)	Changes made
Criteria for operability								
REC	Perform a preliminary cardiologic evaluation in order to risk stratify according to the Revised Cardiac Risk Index (RCRI).			4	5	80%	anamnesis, consultation cardiol enough?	none
REC	Patients with an active cardiac condition, a newly suspected cardiac condition, RCRI ≥ 3 or poor cardiac functional capacity should be carefully evaluated with non-invasive cardiac test to optimize any primary cardiac treatment or secondary prophylaxis.			5	5	100%		none
REC	For patients already on acetylsalicyclic acid, statins and beta-blockers the treatment should be continued in the peri-operative period.			4	4	100%		none
REC	Patients in need of coronary intervention (CABG or PCI) should postpone lung surgery for >= 6 weeks.			3	4	75%	6 weeks seems to be to long especially for stage III diseases	deletion
REC	Patients with an RCRI =< 2 and good cardiac functional capacity can proceed to respiratory function evaluation.			5	5	100%		none
REC	Consider using a global risk score to estimate the risk of death and ensure the patient is aware of the risk before giving consent to surgery.			5	5	100%		none
Assessment of lung function and exercise testing								
REC	Patients should be advised to stop smoking.			6	6	100%		none
REC	Perform spirometry and DLCO in all patients being considered for surgery.			5	5	100%		none
REC	Patients with FEV1 and DLCO > 80 % are candidate for a radical treatment without further functional testing.			5	5	100%		none
REC	Cardiopulmonary exercise tests are indicated in all patients with FEV1 or DLCO < 80 % of normal values.			3	5	60%	not evidence based; Is 6MWT also considered as a cardiopulmonary exercise? DLCO 80% in many patients	none
REC	Peak VO2 (VO2max) should be regarded as the most important parameter to measure exercise capacity and to predict postoperative complications.			5	5	100%		none
REC	Peak VO2 > 75 % or 20 ml/kg/ min qualifies for pneumonectomy.			5	5	100%		none
REC	Peak VO2 < 35 % or 10 ml/kg/min indicates a high risk for any resection.			5	5	100%		none
REC	Evidence does not support a clear cut-off value for lobectomy.			5	5	100%		none
REC	When considering surgery postoperative lung function should be estimated with the anatomic segment method.			4	4	100%		none
REC	Patients with borderline pulmonary function need an estimation of their residual lung function (segment calculation or imaging based) before surgery.			4	4	100%		none
REC	Patients with predicted postoperative FEV1 or TLCO below the recommended limit of 30% should only be offered surgery if they accept the risk of dyspnoea and associated complications.			4	5	80%	In this case, we can chose an alternative approach. If a limited resection is not possible, a non surgical treatment must be offered to the patient in order to maintain an acceptable level of quality of live	modification
REC	A multidisciplinary oncology team should determine suitability for radiotherapy with curative intent, taking into account performance status and co-morbidities.			5	5	100%		none
Primary Surgery								
Minimal criteria for surgery and pathology report								
GCPP	Surgery reports and pathology reports should contain minimal datasets as defined by (inter)national professional organisations, including the pTNM classification.			6	6	100%		none
GCPP	When surgical specimens are examined pathologically, an elastin (von Gieson elastic) staining is recommended in tumours of less than 3 cm that are close to the pleura to asses pleural invasion in order to obtain an adequate staging of the tumour, allowing an upstaging from T1 to T2 in the 7th edition of the TNM classification.			6	6	100%		none

REC / GCPP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recommendation (weak, strong)	GRADE Level of evidence (Very low to High)	Scores 4, 5 (= agree)	Scores 1, 2, 4, 5	% agree	Comments (required if 1 or 2)	Changes made
	Primary surgery early stage NSCLC (stage cI-II selected stage cIIIA cT3N1)							
REC	In patients with resectable NSCLC considered sufficiently fit, surgery aiming at complete resection (R0) is recommended. For tumours confined to a single lobe, a lobectomy is the preferred treatment (strong recommendation, standard of care).	strong	standard care	5	5	100%		none
REC	In patients with resectable NSCLC undergoing surgery, at least lobe-specific systematic nodal dissection is recommended (weak recommendation, moderate level of evidence).	weak	moderate	5	5	100%	At least !!!	none
REC	For (right sided) tumours involving an adjacent lobe, a bilobectomy is recommended; for tumours involving the bronchial ostium and/or the pulmonary artery, a sleeve lobectomy is recommended rather than pneumonectomy (weak recommendation, very low level of evidence).	weak	very low	5	5	100%		none
REC	For fit patients with NSCLC limited to one lobe, sublobar resection (wedge resection or segmentectomy) is not recommended outside the framework of a clinical trial (strong recommendation, very low level of evidence).	strong	very low	5	5	100%		none
REC	For borderline fit patients with NSCLC limited to one lobe, wedge resection or segmentectomy, as well as radical radiotherapy (preferably stereotactic radiotherapy for non central tumours), or radiofrequency ablation, can be considered after discussion by a multidisciplinary team (weak recommendation, very low level of evidence).	weak	very low	4	6	67%	adapted dose SBRT for central tumors	modication
REC	In patients with resectable NSCLC undergoing lobectomy, either VATS or open surgery can be considered. VATS should only be performed by surgeons who are sufficiently trained (weak recommendation, low level of evidence).	weak	low	5	5	100%		none
REC	Lung cancer surgery should be carried out in high volume specialist centres in thoracic surgery (weak recommendation, low level of evidence).	weak	low	5	5	100%		none
GCPP	The lymph node specimen should include at least six nodes, three removed from intrapulmonary and/or hilar stations and three removed from mediastinal stations, one of which must be the subcarinal station.			5	5	100%		none
GCPP	Surgery reports and pathology reports should contain minimal datasets as defined by (inter)national professional organisations, including the surgical and pathological TNM classification.			5	5	100%		none
	(Neo)adjuvant chemotherapy early stage NSCLC (stage cI-II, selected stage IIIA cT3N1 or unforeseen N2)							
REC	It is generally not recommended to offer neo-adjuvant chemotherapy to patients with NSCLC suitable for surgery outside a clinical trial. Exceptions should be discussed by a multidisciplinary team. (weak recommendation, low level of evidence)	weak	low	6	6	100%		none
REC	After R0 resection, offer postoperative chemotherapy to patients with good performance status (WHO 0 or 1) and pT1-3 pN1-2 M0 NSCLC (strong recommendation, moderate level of evidence)	strong	moderate	6	6	100%		none
REC	Consider postoperative chemotherapy in patients with good performance status (WHO 0 or 1) and pT2 pN0 M0 NSCLC with tumours greater than 4 cm in diameter or pT3 pN0 M0 NSCLC. Decisions should be discussed by a multidisciplinary team (weak recommendation, low level of evidence).	weak	low	6	6	100%		none
REC	After R0 resection, postoperative chemotherapy is not recommended for patients with tumours smaller than 4 cm and no lymph node involvement. (strong recommendation, low level of evidence)	strong	low	6	6	100%		none
REC	If adjuvant chemotherapy is considered, offer a cisplatin-based combination chemotherapy regimen validated by an RCT in the adjuvant setting (weak recommendation, low level of evidence)	strong	low	6	6	100%		none
	Postoperative radiotherapy in resected early stage NSCLC							
REC	The use of post-operative radiotherapy is not recommended in lung cancer patients with completely resected, pN0-1 disease (strong recommendation, moderate level of evidence).	strong	moderate	6	6	100%		none
REC	The use of post-operative radiotherapy can be considered in lung cancer patients with completely resected pN2 disease. Decisions should be discussed by a multidisciplinary team (weak recommendation, very low level of evidence)	weak	very low	6	6	100%		none
REC	The use of post-operative radiotherapy can be considered in patients with microscopically incompletely resected lung cancer. Decisions should be discussed by a multidisciplinary team (weak recommendation, very low level of evidence).	weak	very low	6	6	100%		none
REC	The use of post-operative (chemo)-radiation is recommended in patients with macroscopically incompletely resected lung cancer (strong recommendation, standard of care).	strong	standard care	6	6	100%		none
REC	Any early stage NSCLC patient not suitable for surgery should be offered radical radiotherapy (strong recommendation, standard of care).	strong	standard care	6	6	100%		none
REC	Treatment options for patients with peripheral T1-2 N0 tumours (outside a 2cm radius of main airways/proximal bronchial tree) should be discussed in a multidisciplinary team. If radiotherapy is considered, SBRT is recommended (weak recommendation, low level of evidence).	weak	low	4	6	67%	I disagree that this is a waek recommendation: it should be as strong as lobectomy for patients who are unfit for surgery: see full comment in the text. If the patient is fit for surgery, this option must be chosen.	modification

REC / GCPP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recommendation (weak, strong)	GRADE Level of evidence (Very low to High)	Scores 4, 5 (= agree)	Scores 1, 2, 4, 5	% agree	Comments (required if 1 or 2)	Changes made
	Treatment of stage cIII NSCLC							
REC	Chemoradiotherapy is recommended for patients with stage cIII NSCLC. (strong recommendation, moderate level of evidence).	strong	moderate	7	7	100%		none
REC	However, induction therapy followed by surgery can be considered in selected patients with stage IIIA-N2 disease considered resectable at the start of treatment (weak recommendation, level of evidence). Optimal treatment in patients with limited stage IIIA-N2 disease should be discussed by a multidisciplinary team taking into account resectability, response to induction treatment, availability and surgical expertise.	weak	low	7	7	100%	RCT not in favor	none
REC	When patients are considered for chemoradiation, it is recommended to offer concurrent chemotherapy in preference to sequential therapy if no contra-indications are present (strong recommendation, moderate level of evidence).	strong	moderate	7	7	100%		none
REC	Induction therapy followed by surgery is not recommended in patients with stage cIIIA-N2 disease considered unresectable at the start of treatment (strong recommendation, moderate level of evidence).	strong	moderate	7	7	100%		none
REC	Induction therapy followed by surgery is not recommended in patients with stage IIIA-N2 disease considered unresectable at the start of treatment (strong recommendation, moderate level of evidence).	strong	moderate	7	7	100%	redundant with previous item?	deleted
GCPP	If preoperative chemotherapy or chemoradiation is used, time needed for response assessment should be kept as short as possible to avoid prolonged overall treatment time and repopulation of the tumour in case no surgery is performed and chemo(radiation) treatment is completed.			4	6	67%	see text: the recommendation is too vague; if no surgery, the gap between RT series is detrimental; What is as short as possible?	modification
	Treatment of tumours involving the chest wall and sulcus superior tumours							
REC	Surgery should be considered for patients with NSCLC involving the parietal pleura or the chest wall if R0 resection is considered feasible (weak recommendation, very low level of evidence).	weak	very low	6	7	86%	strong recommendation	modification
REC	Neoadjuvant therapy followed by surgery or radical chemoradiation can be considered for patients with sulcus superior tumours if R0 resection is considered feasible. Treatment decisions should be discussed by a multidisciplinary team with an experienced thoracic surgeon. (weak recommendation, very low level of evidence).	weak	very low	6	7	86%	Clarify neoadjuvant (chemoradiation), see text	modification
	Treatment of metastatic (stage cIV) and recurrent NSCLC							
REC	The use of chemotherapy in patients with stage IV NSCLC with WHO/ECOG/Zubrod performance status of 0,1 and in some cases 2 is recommended (strong recommendation, high level of evidence).	strong	high	4	4	100%		none
REC	It is recommended to use receptor tyrosine kinase inhibitors (EGFR TKI) as first-line treatment of patients with advanced EGFR-mutation positive non-squamous NSCLC because of the better tolerance (strong recommendation, moderate level of evidence).	strong	moderate	3	4	75%	and better efficacy? not only because of better tolerance, also because of an easy way to administer and because of response	none
REC	Maximal efforts should be made to determine the EGFR mutation status in non-squamous NSCLC or never or very light smokers with squamous cell carcinoma. Treatment using EGFR TKI targeted therapies in patients with demonstrated wild type EGFR in non-squamous NSCLC cannot be recommended (in any line) because there is a lack of demonstrated efficacy.	strong	very low	3	5	60%	differs from older guidelines	modification
REC	If EGFR tyrosine kinase inhibitors are not given in first line in mutated patients they should be offered thereafter, either as switch maintenance or at progression as second line treatment (strong recommendation, moderate level of evidence).	strong	moderate	4	4	100%		none
REC	In patients with performance status of 0 or 1, evidence supports using a combination of two cytotoxic drugs for first-line therapy. Platinum combinations are preferred over non-platinum combinations because they are superior in response rate, and marginally superior in overall survival. Non-platinum therapy combinations are reasonable in patients who have contraindications to platinum therapy (strong recommendation, high level of evidence).	strong	high	4	4	100%		none
REC	The choice of either cisplatin or carboplatin is acceptable. Drugs that may be combined with platinum include the third generation cytotoxic drugs docetaxel, gemcitabine, irinotecan, paclitaxel, pemetrexed, and vinorelbine.(weak recommendation, low level of evidence).	weak	low	3	4	75%	CisPlatinum first choice, Carboplatine if kidney impairement	none
REC	The combination cisplatin gemcitabine is not recommended in non-squamous NSCLC for first-line chemotherapy (strong recommendation, low level of evidence).	strong	low	4	4	100%		none
REC	It is recommended to give second line chemotherapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line therapy (strong recommendation, moderate level of evidence).	strong	moderate	4	4	100%		none
REC	Crizotinib is recommended as second line therapy in ALK mutation positive patients (strong recommendation, low level of evidence).	strong	low	4	4	100%		none
REC	The use of pemetrexed (only in non-squamous NSCLC) or docetaxel is acceptable as second-line therapy for patients with advanced NSCLC with adequate performance status when the disease has progressed during or after first-line, platinum-based therapy. (weak recommendation, very low level of evidence).	weak	very low	4	4	100%		none
REC	Maintenance therapy after 4 cycles of chemotherapy with pemetrexed can be considered in patients who do not have disease progression (weak recommendation, very low level of evidence).	weak	very low	3	4	75%	the PARAMOUNT phase III study was published well before the first meeting with external expert of july 5th (Lancet Oncol 2012 March 13: 247-255) and showed significant advantage of continuous maintenance in good PF pts; thus, strong Rec	none

REC / GCPP	Recommendation(s) and Good Clinical Practice Point(s)	Strength of Recommendation (weak, strong)	GRADE Level of evidence (Very low to High)	Scores 4, 5 (= agree)	Scores 1, 2, 4, 5	% agree	Comments (required if 1 or 2)	Changes made
Follow-up (expert consensus)								
REC	Routine follow-up after surgical treatment or other treatments with curative intent of a patient with NSCLC consist of at least the following components: anamnesis, physical examination, a chest x-ray.			7	7	100%	anamnesis -> history	clarification
REC	It is recommend that follow-up by imaging where disease progression can be determined is useful only if there is an active second or third-line treatment available, for tracking and tracing late side-effects.			6	6	100%		none
REC	The following follow-up rate after surgical treatment is suggested: the first year after surgery: every 3 months (4 visits), in the second year after surgery: at least every 6 months (2 visits), hereafter: follow-up at least once per year (1 visit) for at least 5 years after completing treatment.			7	7	100%	It is not clear what "follow-up" means	clarification
REC	Low dose CT scan may detect second primary tumours, but there is no consistent evidence this leads to a survival benefit.			5	6	83%	It should be stated when this low dose CT should be performed. A low dose CT is not a good technique to detect mediastinal changes (tumor, lymphnodes)	deletion
FINAL RECOMMENDATIONS SCLC								
Staging								
	It is recommended to offer patients with limited-stage disease SCLC (broadly corresponding to T1-4, N0-3,M0) four to six cycles of platinum-based combination chemotherapy (strong recommendation, standard care).	strong	standard care	5	6	83%	agree but as formulated, no role for RT at quick reading...	none
	It is recommended to offer concurrent chemoradiotherapy (starting with cycle 1 or cycle 2) to patients with limited-stage disease SCLC (broadly corresponding to T1-4, N0-3, M0) and a WHO performance status of 0 or 1 if they present with disease that can be encompassed in a radical thoracic radiotherapy volume. Start the radiotherapy during the first or second cycle of chemotherapy (strong recommendation, high level of evidence).	strong	high	4	6	67%	ASCO 2012 Park K 7004; disagree because the definition of an encompassing field is outdated (see text)	none
	It is recommended to offer sequential radical thoracic radiotherapy to patients with limited-stage disease SCLC (broadly corresponding to T1-4, N0-3, M0) who are not candidate for concurrent chemoradiotherapy but who respond to chemotherapy.	strong	standard care	6	6	100%		none
	It is recommended to offer prophylactic cranial irradiation at a dose of 25 Gy in 10 fractions to patients with limited-stage disease SCLC and WHO performance status 2 or less, if their disease is in complete remission after first-line treatment (strong recommendation, moderate level of evidence).	strong	moderate	5	6	83%	See text: complete remission was based on old series using chest X-rays (with much less quality and hence less sensitivity than at present) and remission status is different after chemo-radiotheraoy than after chemotherapy alone.	none
	It is recommended to offer maintenance therapy only in the context of a clinical trial (strong recommendation, very low level of evidence).	strong	very low	5	6	83%		none
SCLC - extensive disease								
REC	It is recommended to offer platinum-based combination chemotherapy to patients with extensive-stage disease SCLC (broadly corresponding to T1-4, N0-3, M1a/b – including cerebral metastases) if they are fit enough (strong recommendation, standard care).	strong	standard care	5	6	83%	It is recommended to perform FDG PET in limited stage SCLC as there is real probability of upstaging	none
REC	It is recommended to offer maintenance therapy only in the context of a clinical trial (strong recommendation, very low level of evidence).	strong	very low	4	5	80%	same	none
REC	It is recommended to offer prophylactic cranial irradiation to patients with extensive-stage disease SCLC and WHO performance status 2 or less, if their disease has not progressed on first-line treatment.	strong	high	5	5	100%		modification
Relapsed SCLC								
REC	It is recommended to offer patients with relapsed SCLC, who are suitable for chemotherapy, second line treatment. A multidisciplinary team should decide on the second line treatment. Retreatment with first line chemotherapy can be considered in sensitive patients (strong recommendation, low level of evidence).	strong	low	4	4	100%		none
GCPP	Inform patients whose disease has not responded to first-line treatment that there is very limited evidence that second-line chemotherapy will be of benefit.			4	4	100%		none
GCPP	It is recommended to offer radiotherapy for palliation of local symptoms to patients with SCLC that has relapsed after first-line treatment.			4	4	100%	also in NSCLC	addition

Feedback from patient organisations

Suggestions for additional considerations with regard to patient information, psychosocial support and planning of care (including palliative care) were obtained from a patient organisation representating cancer patients (Vlaamse Liga tegen Kanker).

In particular, it was suggested to add the following statements.

-“The patient should be informed in detail and repeatedly about his disease, treatment options and related disorders”

-“The patient’s individual circumstances should be taken into account. Before deciding to operate, the interdisciplinary team must consider whether tumor-free resection margins can be achieved and what postoperative quality of life can be expected for the patient.”

Actions taken:

The section on general considerations of the report was extended as follows.

“Throughout the diagnostic and staging process, patients should repeatedly be informed in detail about his/her disease, and the effects and side-effects of the various treatment options. In view of the poor prognosis of the majority of patients, attention should be given to timely obtaining the patient's wishes with regard to the planning of care for advanced disease and for palliative care.”

An evaluation of the evidence concerning psychosocial support in cancer was considered out of scope of this report.

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