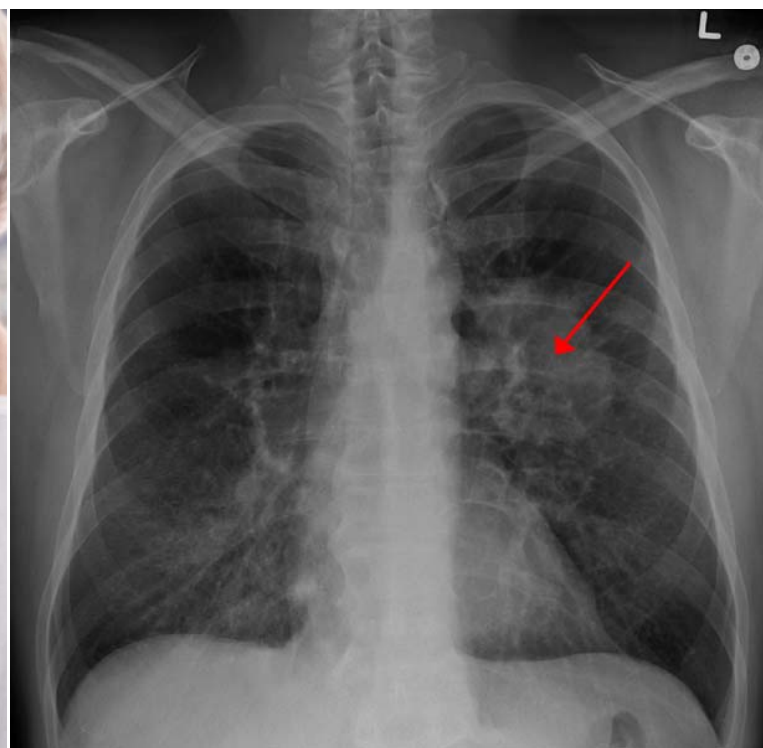


SYNTHESIS

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





Belgian Health Care Knowledge Centre

The Belgian Health Care Knowledge Centre (KCE) is an organization of public interest, created on the 24th of December 2002 under the supervision of the Minister of Public Health and Social Affairs. KCE is in charge of conducting studies that support the political decision making on health care and health insurance.

Executive Board

	Actual Members	Substitute Members
President	Pierre Gillet	
CEO - National Institute for Health and Disability Insurance (vice president)	Jo De Cock	Benoît Collin
President of the Federal Public Service Health, Food Chain Safety and Environment (vice president)	Dirk Cuypers	Christiaan Decoster
President of the Federal Public Service Social Security (vice president)	Frank Van Massenhove	Jan Bertels
General Administrator of the Federal Agency for Medicines and Health Products	Xavier De Cuyper	Greet Musch
Representatives of the Minister of Public Health	Bernard Lange	Brieuc Van Damme
	Bernard Vercruysse	Annick Poncé
Representatives of the Minister of Social Affairs	Lambert Stamatakis	Vinciane Quoidbach
	Ri De Ridder	Koen Vandewoude
Representatives of the Council of Ministers	Jean-Noël Godin	Philippe Henry de Generet
	Daniël Devos	Wilfried Den Tandt
Intermutualistic Agency	Michiel Callens	Frank De Smet
	Patrick Verertbruggen	Yolande Husden
	Xavier Brenez	Geert Messiaen
Professional Organisations - representatives of physicians	Marc Moens	Roland Lemye
	Jean-Pierre Baeyens	Rita Cuypers
Professional Organisations - representatives of nurses	Michel Foulon	Ludo Meyers
	Myriam Hubinon	Olivier Thonon
Hospital Federations	Johan Pauwels	Katrien Kesteloot
	Jean-Claude Praet	Pierre Smiets
Social Partners	Rita Thys	Leo Neels
	Paul Palsterman	Celien Van Moerkerke
House of Representatives	Lieve Wierinck	



Control

Government commissioner

Yves Roger

Management

Chief Executive Officer
Assistant Chief Executive Officer
Manager Program Management

Raf Mertens
Christian Léonard
Kristel De Gauquier

Contact

Belgian Health Care Knowledge Centre (KCE)
Doorbuilding (10th Floor)
Boulevard du Jardin Botanique, 55
B-1000 Brussels
Belgium

T +32 [0]2 287 33 88
F +32 [0]2 287 33 85
info@kce.fgov.be
<http://www.kce.fgov.be>

SYNTHESIS

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

ISABELLE WAUTERS, JO ROBAYS, LEEN VERLEYE, KIRSTEN HOLDT HENNINGSSEN, 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



COLOPHON

Title:	Non-Small Cell and Small Cell Lung Cancer: Diagnosis, Treatment and Follow-up - Summary
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 Ruyscher (Belgische Vereniging van Radiotherapie en Oncologie), Roland Hustinx (Société Belge de Médecine Nucléaire), Bart Ilse (UZ Brussel), Thierry Pieters (Société Belge de Pneumologie), Myriam Rimmelink (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)
Acknowledgements:	The authors wish to thank Françoise Mambourg, Sabine Stordeur and Carl Devos for the review of the translation.
Other reported interests:	<p>Fees or other compensation for writing a publication or participating in its development: Christophe Deroose</p> <p>A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Christophe Deroose, Jacques De Grève, Jan Van Meerbeeck (Unrestricted grant for datamanagement en fellowship from Ely Lilly Belgium), Johan Vansteenkiste (research funding: Astra-Zeneca Chair in Personalised Lung Cancer Care)</p> <p>Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Christophe Deroose, Thierry Pieters (Advisory Board Pfizer, Eli Lilly), Jacques De Grève, Jan Van Meerbeeck (Astra Zeneca, Galapagos, GSK, Sanofi-Aventis), Harry Groen (Roche, Eli Lilly, Pfizer), Johan Vansteenkiste (GSK Biologicals, Merck-Serono)</p> <p>Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Jacques De Grève, Christophe Deroose (symposia for medical companies), Harry Groen (travel subsidized by the Nederlandse Richtlijn ontwikkeling NSCLC), Patrick Pauwels (speakers fee and travel support), Thierry Pieters (sponsoring ASCO meeting), Vincent Remouchamps (speakers fee and education of sales)</p>



representatives of a medical company), Jan Van Meerbeeck (Pfizer, Boehringer Ingelheim, MSD), Isabelle Wauters (payments to speak), Birgit Weynand (travel support Eli Lilly)

Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Christophe Deroose, Harry Groen (Werkgroep Longoncologie NVALT)

Participation in scientific or experimental research as an initiator, principal investigator or researcher: Christophe Deroose, Thierry Pieters, Harry Groen

Other possible interests that could lead to a potential or actual conflict of interest: Christophe Deroose

Any other direct or indirect relationship with a producer, distributor or healthcare institution that could be interpreted as a conflict of interests: Jacques De Grève

Layout:

Ine Verhulst

Disclaimer:

- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

Publication date:

02 October 2013

Domain:

Good Clinical Practice (GCP)

MeSH:

Carcinoma, Non-Small-Cell Lung; Small Cell Lung Carcinoma; Practice Guideline [Publication Type]

NLM Classification:

WF 658

Language:

English

Format:

Adobe® PDF™ (A4)

Legal depot:

D/2013/10.273/55

Copyright:

KCE reports are published under a “by/nc/nd” Creative Commons Licence
<http://kce.fgov.be/content/about-copyrights-for-kce-reports>.



How to refer to this document?



Wauters I, Robays J, Verleye L, Holdt Henningsen K, Hulstaert F, Berghmans T, De Wever W, Lievens Y, Pauwels P, Stroobants S, Van Houtte P, Van Meerbeeck J, Van Schil P, Weynand B, De Grève J. Non-Small Cell and Small Cell Lung Cancer: Diagnosis, Treatment and Follow-up. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2013. KCE Reports 206Cs. D/2013/10.273/55.

This document is available on the website of the Belgian Health Care Knowledge Centre.



■ FOREWORD

KCE has during many years successfully collaborated with the College for Oncology, developing practice guidelines for the most important types of cancer. Lung cancer, a common cancer type, especially in men, was still missing on the list. Lung cancer is the most frequent cause of death by cancer in men, and the second most frequent in women.

For this guideline, it was decided to focus on *small-cell* en *non small-cell* lung cancer. Using novel diagnostic methods the non-small cell cancer can be subtyped. Each subtype has specific characteristics and sometimes a specific treatment, representing significant challenges in the guideline development process. The KCE overcame this due to the identification of recently published high quality guidelines from other countries and the help of an enthusiast team of experts who spent many hours at the KCE to develop this report.

Nearly sixty years ago Doll and Hill published a breakthrough paper in the BMJ, demonstrating the strong link between smoking and lung cancer. Since then we have the knowledge on how to prevent most of the lung cancers, and yet about a quarter of the population continues to smoke.

Despite the important progress seen in the treatment of lung cancer, the survival rates remain low. Prevention of smoking and encouragements to stop smoking therefore remain a priority for public health. This is also a priority from a social inequality point of view as addiction to smoking is distributed very unevenly over the social classes.

In addition to prevention, there is a high need for quality standards for diagnosis and treatment of patients with lung cancer. We hope these guidelines will contribute to this goal. Also on behalf of the patients, we thank the many clinicians, and especially the members of the guideline development group for investing their precious time and expertise in this project.

Christian LÉONARD
Assistant Chief Executive Officer

Raf MERTENS
Chief Executive Officer



■ TABLE OF CONTENTS

■	FOREWORD.....	1
■	TABLE OF CONTENTS	2
■	SUMMARY	4
1.	INTRODUCTION	4
2.	OBJECTIVES AND SCOPE.....	5
3.	METHODS	5
3.1.	THE SEARCH FOR CLINICAL PRACTICE GUIDELINES	5
3.2.	UPDATE SEARCH	5
3.3.	QUALITY APPRAISAL	5
3.4.	DATA EXTRACTION AND EVIDENCE SUMMARY	5
3.5.	GRADING OF EVIDENCE.....	6
3.6.	ELABORATION OF THE FINAL RECOMMENDATIONS	6
3.7.	VALIDATION OF THE GUIDELINE.....	6
4.	CLINICAL RECOMMENDATIONS	7
4.1.	DIAGNOSIS AND STAGING	7
4.1.1.	Staging of lung cancer.....	7
4.1.2.	Pathology and molecular testing	9
4.2.	TREATMENT OF NSCLC.....	10
4.2.1.	Treatment of early stage NSCLC (stage cI-II and selected stage cIIIA cT3N1)	10
4.2.2.	Treatment of stage cIII NSCLC	13
4.2.3.	Tumours involving the parietal pleura or the chest wall, and sulcus superior tumours.....	14
4.2.4.	Treatment of metastatic (stage cIV) and recurrent NSCLC	14
4.2.5.	Follow-up	15



4.3.	TREATMENT OF SCLC	16
4.3.1.	'Limited-stage disease' SCLC (broadly corresponding to T1-4, N0-3,M0)	16
4.3.2.	'Extensive stage disease' SCLC (broadly corresponding to T1-4, N0-3, M1a/b – including cerebral metastases).....	17
4.3.3.	Relapsed SCLC.....	17
5.	IMPLEMENTATION AND UPDATING OF THE GUIDELINE.....	18
5.1.	IMPLEMENTATION	18
5.2.	MONITORING THE QUALITY OF CARE.....	18
5.3.	GUIDELINE UPDATE.....	18
■	POLICY RECOMMENDATIONS.....	19
■	REFERENCES	21



■ SUMMARY

1. INTRODUCTION

As long as smoking is not effectively banned, lung cancer is expected to remain one of the most frequent cancers diagnosed. It is the second most frequent malignancy in males and the third most frequent in females.¹ In 2010, 5 616 men and 2 215 women were diagnosed with lung cancer in Belgium, corresponding to an age-standardised incidence rate of 82.5 per 100 000 person years in males and 30.6 per 100 000 person years in females.²

Lung cancer is the leading cause of cancer death in males and the second one in females. In both males and females, lung cancer presents most often in advanced stages. At diagnosis, the lung cancer stage in male patients is stage III in 27.7% and stage IV in 46% of all patients with a known disease stage. For females, the percentages for stage III and IV are 24.7% and 49.9% respectively.¹ More than half of the patients diagnosed with lung cancer die within the first year after diagnosis. Five-year relative survival is only 14.6% in males and 19.5% in females.

There are two main types of lung cancer, based on the cancer cell type. Small cell lung cancer (SCLC) accounts for about a quarter of all lung cancers. About three quarters of the lung cancers diagnosed are non-small cell lung cancers (NSCLC), with adenocarcinoma being the most common subtype of NSCLC. Further subtypes of NSCLC can be identified using molecular markers. Such molecular typing is rapidly becoming routine practice as more and more treatments targeting a specific molecular signature of the cancer become available.



2. OBJECTIVES AND SCOPE

This is the first clinical practice guideline for the management of lung cancer produced by KCE, in collaboration with the Belgian College of Oncology. The scope of this guideline was defined by the multidisciplinary guideline development group. This guideline covers diagnosis and staging, as well as treatment and follow-up of NSCLC and SCLC. Screening for lung cancer and the topic 'the single pulmonary nodule' were not covered.

Clinical practice guidelines are aimed at all providers of lung cancer care, including general practitioners and specialists in pathology, imaging, lung diseases, medical oncology, thoracic surgery and radiotherapy. Of course, guidelines always need to be interpreted in the context of the individual patient, taking into account the values and preferences of the patient. The recommendations are based as much as possible on clinical evidence. They do not always correspond to the criteria for the RIZIV – INAMI reimbursement of diagnostic and therapeutic interventions, as applicable today.

3. METHODS

We used the ADAPTE methodology (www.adapte.org) for the preparation of the guideline. This method starts from recent high-quality evidence-based guidelines, and adapts them in accordance with the more recently published evidence and the input of national experts and stakeholders representing the disciplines involved.

3.1. The search for clinical practice guidelines

Clinical practice guidelines on lung cancer published since 2009 were identified using OVID Medline, the National Guideline Clearinghouse (guideline.gov) and Guidelines International Network (www.g-i-n.net). Of the 23 guidelines identified, 18 were excluded on methodological grounds.

The 5 retained guidelines were scored by two independent researchers using the AGREE II instrument. Two of these five guidelines cover both lung cancer diagnosis, staging and treatment whereas the other three only cover treatment.

3.2. Update search

The update search for more recent peer-reviewed systematic reviews and primary studies included a search in OVID Medline, EMBASE, CENTRAL and the Cochrane Database of Systematic Reviews. Searches were run between April, 2012 and January, 2013.

3.3. Quality appraisal

The quality of the systematic reviews was assessed using the Dutch Cochrane checklist (www.cochrane.nl). 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.

3.4. Data extraction and evidence summary

For each clinical question, the evidence base and recommendations were extracted from the selected guidelines and summarized in text form. The update consisted of new findings reported in additional systematic reviews or primary studies.



3.5. Grading of evidence

For each recommendation on therapeutic interventions, the level of evidence and strength of recommendation was assigned using the 2013 GRADE system³ (Tables 1 and 2). The GRADE method was not used for diagnostic interventions.

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.	

Table 2 – Strength of recommendations according to the GRADE system.

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects (<i>the intervention is to be put into practice</i>), or the undesirable effects of an intervention clearly outweigh the desirable effects (<i>the intervention is not to be put into practice</i>).
Weak	The desirable effects of an intervention probably outweigh the undesirable effects (<i>the intervention probably is to be put into practice</i>), or the undesirable effects of an intervention probably outweigh the desirable effects (<i>the intervention probably is not to be put into practice</i>).

3.6. Elaboration of the final recommendations

The draft recommendations were formulated by KCE researchers and discussed with the guideline development group selected by the College of Oncology. A total of six meetings were held between July 2012 and April 2013 with the multidisciplinary group of external experts.

Next, the recommendations were reviewed by representatives of professional associations (stakeholders including patient organisations; see colophon) using a formal procedure.

Declarations of interest were recorded.

3.7. Validation of the guideline

Finally, three external validators assessed and validated this guideline by using the AGREE II checklist. The validation process was chaired by the Belgian Centre for Evidence-Based Medicine (CEBAM).



4. CLINICAL RECOMMENDATIONS

The details of the evidence used to formulate the recommendations and best practice below are available in the scientific report and its supplements. The tables follow the sequence of the chapters of the scientific report.

4.1. Diagnosis and Staging

4.1.1. Staging of lung cancer

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 via 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, (endobronchial ultrasound, EBUS guided) fiberoptic 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 (endoscopic ultrasound), 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.

4.1.2. 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.



4.2. Treatment of NSCLC

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

Criteria for operability

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 acetylsalicylic 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.

Assessment of lung function and exercise testing

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.



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.

(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

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

**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

4.2.2. 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.



4.2.3. 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

4.2.4. 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 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	high
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	weak	low



vinorelbine.		
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.

4.2.5. 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.



4.3. Treatment of SCLC

4.3.1. '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 safe 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 such '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 not 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



4.3.2. 'Extensive stage 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

4.3.3. 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 stage 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.



5. IMPLEMENTATION AND UPDATING OF THE GUIDELINE

5.1. Implementation

The implementation of this guideline will be facilitated by the College of Oncology. Possible strategies include the development of online implementation tools tailored to the caregivers (<http://www.collegeoncologie.be>). In addition, the scientific material of this guideline is intended to be disseminated by scientific and professional organisations. They can transform this material into attractive and user-friendly tools tailored to caregiver groups. They will also play a key role for the dissemination through diverse channels such as websites or sessions of continuous education.

5.2. Monitoring the quality of care

Supplementing the guidelines with an appropriate set of quality indicators would provide an opportunity to assess the quality of lung cancer care delivered in Belgium.

A quality indicator set covering the diagnostic and therapeutic options has been developed for other cancer types,⁴⁻⁹ but is still to be developed for lung cancer. This could be the topic of a separate KCE project.

Molecular tests used to guide targeted therapy deserve specific attention in terms of quality of the sample and of the test itself. Centralisation of tests may be required to guarantee robust and accurate test results, such that the targeted treatment reaches the right patient. Obligatory ISO accreditation for the test and participation of the laboratory to external quality assurance have been recommended in a previous KCE report on molecular diagnosis.¹⁰ Evaluations for reimbursement of targeted therapy at RIZIV-INAMI should include both the drug and the test.¹⁰

The current guideline recommends restricting lung cancer surgery to centres having the necessary patient volume and the right expertise such that high level expertise can be assured. In this respect, the Dutch society for surgery recommends a minimum of 20 lung cancer operations per year. This cut-off is endorsed by the Stichting Oncologische Samenwerking (Soncos) norms in the Netherlands. The Dutch society for thoracic surgery even recommends a minimum of 50 operations per year. For the same reason, a recent KCE report on innovative radiotherapy techniques recommends to centralise complex radiotherapy techniques for lung cancer treatment such as SBRT.¹¹

5.3. Guideline update

Within the next 5 years a pre-assessment of the literature should be conducted and the parts of this guideline that need an update will be identified. Awaiting an updated guideline, important new evidence can be found on the website of the College of Oncology (<http://www.collegeoncologie.be>).

■ POLICY RECOMMENDATIONS^a

To the Minister of Social Affairs and Public Health, the Federal Public Service for Health, the insurance committee, the Technisch Medische Raad - Conseil Technique Médical, the Commissie Tegemoetkoming Geneesmiddelen – Commission de Remboursement des Médicaments of the RIZIV – INAMI

- Lung cancer surgery should be restricted to centres with a high patient volume, such that a high level of expertise can be assured.
- Centralisation of stereotactic radiotherapy for lung cancer is indicated for reasons of assurance of expertise, quality assurance and cost reduction.
- For patients with early-stage lung cancer, experts in lung cancer surgery and stereotactic radiotherapy should participate to the multidisciplinary oncologic consultation.
- Reimbursement of erlotinib in the first or second line of care should be limited to patients with NSCLC with an activating EGFR mutation, or those patients who are not eligible for further chemotherapy and whose EGFR mutational status could not be determined despite maximal efforts.
- Only clinically validated molecular and cytogenetic tests guiding targeted therapy should be used. They should be performed only in laboratories that participate to external quality assurance rounds and that are ISO accredited for these tests. The evaluation and reimbursement of such tests should be evaluated together with the therapy at RIZIV – INAMI.

To the College of Oncology

- Tools and communication channels should be developed and used to support the implementation of the guideline. This may include presentations of the guideline at meetings where the involved disciplines are present.

An update of the guideline every five years is recommended. Pending an updated guideline, important new evidence should be listed on the website of the College of Oncology.

To the scientific and professional associations

- The implementation of this guideline should be stimulated by the creation of user-friendly tools tailored to the needs of specific caregivers. Various communication

^a The KCE has sole responsibility for the recommendations.



channels should be considered such as websites and continuing education seminars.

Research Agenda

- A set of quality indicators for the management of lung cancer in Belgium is to be elaborated



■ REFERENCES

1. Belgian Cancer Registry. Cancer survival in Belgium 2004-2008. In. Brussels; 2012.
2. Belgian Cancer Registry. Tabellen op jaarbasis. In; 2010.
3. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.
4. Vlayen J, Van De Water G, Camberlin C, Paulus D, Leys M, Ramaekers D, et al. Clinical Quality Indicators. Objective Elements - Communication (OEC). Brussels: Belgian Health Care Knowledge Centre (KCE); 2006 19/10/2006. KCE Reports 41 Available from: <https://kce.fgov.be/publication/report/clinical-quality-indicators>
5. Vlayen J, Verstreken M, Mertens C, Van Eycken E, Penninckx F. Quality insurance for rectal cancer - phase 2: development and testing of a set of quality indicators. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2008 03/07/2008. KCE Reports 81 Available from: <https://kce.fgov.be/publication/report/quality-insurance-for-rectal-cancer-phase-2-development-and-testing-of-a-set-of-q>
6. Vlayen J, Vrijens F, Beirens K, Stordeur S, Devriese S, Van Eycken E. Quality indicators in oncology: testis cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010. KCE Reports 149 Available from: <https://kce.fgov.be/publication/report/quality-indicators-in-oncology-testis-cancer>
7. Stordeur S, Vrijens F, Beirens K, Vlayen J, Devriese S, Van Eycken E. Quality indicators in oncology: breast cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2010. KCE Reports 150C (D/2010/10.273/101) Available from: https://kce.fgov.be/sites/default/files/page_documents/kce_150c_breast_cancer_1.pdf



8. Vlayen J, De Gendt C, Stordeur S, Schillemans V, Camberlin C, Vrijens F, et al. Quality indicators for the management of upper gastrointestinal cancer. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2013. KCE Reports 200 (D/2013/10.273/15) Available from: https://kce.fgov.be/sites/default/files/page_documents/KCE_200_Quality_indicators_for_the_management_of_upper_gastrointestinal_cancer.pdf
9. Vlayen J, Stordeur S, Vrijens F, Van Eycken E. Quality indicators in oncology: prerequisites for the set-up of a quality system. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowledge Centre (KCE); 2011. KCE Reports 152 Available from: <https://kce.fgov.be/publication/report/quality-indicators-in-oncology-prerequisites-for-the-set-up-of-a-quality-system>
10. Hulstaert FH, M. Van Den Bruel, A. Cleemput, I. Bonneux, L. Vernelen, K. Libeer, J.L. Ramaekers, D. HTA Moleculaire Diagnostiek in België. HTA report. . In: KCE reports. Brussels: Federaal Kenniscentrum voor de Gezondheidszorg (KCE); 2005.
11. Hulstaert F, Mertens A-S, Obyn C, Van Halewyck D, van der Straten B, Lievens Y. Innovative radiotherapy techniques : a multicentre time-driven activity-based costing study. Brussels: Belgian Health Care Knowledge Centre (KCE); 2013. KCE Reports 198 (D/2013/10.273/9) Available from: https://kce.fgov.be/sites/default/files/page_documents/KCE_198C_Innovativeradiotherapy.pdf

