

The diagnosis and treatment of lung cancer (update)

Full Guideline

NICE's original guidance on diagnosis and treatment of lung cancer was published in February 2005; and subsequently updated in 2011. The guideline has undergone a further update (March 2019). The full, current recommendations can be found on the NICE website - see www.nice.org.uk/guidance/ng122

Evidence reviews and committee discussions from the 2019 update are contained in standalone documents - see www.nice.org.uk/guidance/ng122/evidence

This document preserves evidence reviews and committee discussions for areas of the guideline that have not been updated in 2019. It has been colour-coded as follows:

- Text without shading or a bar in the right hand margin indicates text from the original 2005 guideline that has not been amended by subsequent updates.
- Text with a bar in the right hand margin indicates text updated in 2011.
- Green shading indicates text from the 2011 update that has been reviewed and added to or updated by the 2019 update.
- Grey shading indicates text from 2005 or 2011 that has been amended but not replaced by the 2019 update.
- Black shading indicates text from 2005 or 2011 that has been replaced by the 2019 update.

Published by the National Collaborating Centre for Cancer (2nd Floor, Front Suite, Park House, Greyfriars Road, Cardiff, CF10 3AF) at Velindre NHS Trust, Cardiff, Wales.

First published 2011

© 2011 National Collaborating Centre for Cancer

No part of this publication may be reproduced, stored or transmitted in any form or by any means, without the prior written permission of the publisher or, in the case of reprographic reproduction, in accordance with the terms of licenses issued by the Copyright Licensing Agency in the UK. Enquiries concerning reproduction outside the terms stated here should be sent to the publisher at the UK address printed on this page.

The use of registered names, trademarks etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant laws and regulations and therefore for general use.

While every effort has been made to ensure the accuracy of the information contained within this publication, the publisher can give no guarantee for information about drug dosage and application thereof contained in this book. In every individual case the respective user must check current indications and accuracy by consulting other pharmaceutical literature and following the guidelines laid down by the manufacturers of specific products and the relevant authorities in the country in which they are practising.

The National Collaborating Centre for Cancer accepts no liability for loss or damage of any kind consequential upon use of this product.

Contents

Key priorities	v
Key research recommendations	vi
Methodology	vii
Algorithms	xvi
1 Epidemiology	1
1.1 Introduction	1
1.2 Incidence	2
1.3 Sex variation	2
1.4 Histological subtypes	3
1.5 Socio-economic status (SES)	4
1.6 Ethnic variation	5
1.7 Stage and performance status	6
1.8 Treatment received	8
1.9 Survival	12
1.10 Facilities available at NHS Trusts in England and Wales	15
1.11 Lung Cancer Specialist Nurse	16
2 Access to services and referral	25
2.1 The importance of early diagnosis	25
2.2 Referral and indications for chest radiography	26
3 Communication	28
4 Diagnosis and Staging	32
4.1 Introduction	32
4.2 Effectiveness of Diagnostic and Staging Investigations	33
4.3 Sequence of investigations	36
4.4 Organisational factors relevant to diagnosis and staging	45
5 Treatment with curative intent for NSCLC	51
5.1 Selection of patients with NSCLC for treatment with curative intent	51
5.2 Pulmonary optimisation	55
5.3 Options for treatment with curative intent for patients with NSCLC	58
5.4 Radiotherapy with curative intent	63
5.5 Combination Treatment for NSCLC	66
5.6 Prophylactic Cranial Irradiation in NSCLC	74
6 Chemotherapy for NSCLC	80
7 Treatment of small cell lung cancer (SCLC)	81
7.1 Staging of SCLC	81
7.2 Assessment of patients with SCLC	82
7.3 First line treatment of patients with limited stage disease SCLC (broadly staged as T1-4, N0-3, M0)	82
7.4 Surgical treatment for patients with SCLC	85
7.5 First line treatment for extensive stage disease small cell lung cancer (broadly staged as T1-4, N0-3, M1 a/b)	86
7.6 Second line treatment for patients with SCLC who relapse after primary treatment	92
8 Palliative interventions and Supportive and Palliative Care	98
8.1 Common symptoms of lung cancer	99
8.2 Palliative Radiotherapy	99

8.3	Management of endobronchial obstruction	100
8.4	Other treatments with palliative intent	102
8.5	Management of brain metastases	103
8.6	Spinal Cord Compression	105
8.7	Hypercalcaemia, Bone Pain and Pathological Fractures	105
8.8	Other symptoms: weight loss, loss of appetite, difficulty swallowing, fatigue and depression	106
9	Follow-up and patient perspectives	108
9.1	The Patient's Perspective	110
	Appendices:	
1	Needs assessment questionnaire sent to LHB's in Wales and lung cancer leads in England	113
2	Summary of the 7 th edition of the TNM staging system in comparison with the 6 th edition	116
3	Questions for histopathologists regarding update of nice lung cancer guideline	117
4	Economic model to compare different testing strategies to stage the mediastinum in patients with NSCLC	119
5	Abbreviations	145
6	Glossary	146
7	Guideline Scope	158
8	List of topics covered by each chapter	162
9	People and organisations involved in production of the guideline	163
10	The 2005 lung cancer guideline, including all original sections that have been updated by the 2011 document (see separate document)	
11	Full evidence review (see separate document)	

Key priorities

1. The public needs to be better informed of the symptoms and signs that are characteristic of lung cancer, through coordinated campaigning to raise awareness. **[2005]**
2. Ensure that a lung cancer clinical nurse specialist is available at all stages of care to support patients and carers. **[NEW 2011]**
3. Choose investigations that give the most information about diagnosis and staging with least risk to the patient. Think carefully before performing a test that gives only diagnostic pathology when information on staging is also needed to guide treatment. **[NEW 2011]**
4. [REDACTED]
5. [REDACTED]
6. [REDACTED]
7. Ensure all patients potentially suitable for multimodality treatment (surgery, radiotherapy and chemotherapy in any combination) are assessed by a thoracic oncologist and by a thoracic surgeon. **[NEW 2011]**
8. Arrange for patients with small-cell lung cancer (SCLC) to have an assessment by a thoracic oncologist within 1 week of deciding to recommend treatment. **[NEW 2011]**
9. Every cancer network should ensure that patients have rapid access to a team capable of providing interventional endobronchial treatments. **[NEW 2011]**
10. Offer all patients an initial specialist follow-up appointment within 6 weeks of completing treatment to discuss ongoing care. Offer regular appointments thereafter, rather than relying on patients requesting appointments when they experience symptoms. **[NEW 2011]**

¹ The GDG recognises that radiotherapy techniques have advanced considerably since the 2005 guideline and centres would reasonably wish to offer these techniques (including SBRT and 4-D planning) to patients. These treatments have the advantage of reducing the risk of damage to normal tissue (estimated by using measurements such as V20).

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

5. [Redacted text block]



Methodology

Introduction

This chapter sets out the methods used to generate the recommendations for clinical practice that are presented in the subsequent chapters of this updated guideline. The methods are in accordance with those set out by the National Institute for Health and Clinical Excellence (NICE) in *The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups* (available at www.nice.org.uk).

Updating a NICE clinical guideline

The 2005 guideline was developed by the National Collaborating Centre for Acute Care (NCC-AC) using the methodology recommended by NICE at that time. Guidelines developed by NICE are published with the expectation that they will be reviewed and updated as is considered necessary.

In March 2007 the National Collaborating Centre for Cancer (NCC-C) was asked by NICE to undertake a review about the need for, and extent of, an update to the original lung cancer guideline in accordance with the NICE guideline development process outlined in the 2007 edition of the guidelines manual (NICE, 2007). The criteria for deciding the update status of a clinical guideline is defined in the guidelines manual and requires a search for new evidence, using versions of the original search strategies, and to seek the views of healthcare professionals and patients to identify any change in practice or additional relevant published evidence. The detailed methodology used by the NCC-C and the Guideline Development Group (GDG) to update the lung cancer guideline is presented in this chapter.

This guideline contains both updates of topics contained in the 2005 guideline and new topics identified by the expert advisory group and stakeholders. As a result the recommendations in the guideline will be one of the following:

- Recommendations from the original 2005 guideline which have not been updated have been dated [2005].
- Recommendations from the 2005 guideline that have been updated but the recommendations have not been changed have been dated [2011].
- Recommendations from the 2005 guideline that have been updated and the recommendation revised are dated [NEW 2011]
- Recommendations on new topics are also dated [NEW 2011].

All supporting text from updated and new topics presented in this guideline have been highlighted by a strip down the right side of the page and labelled [updated 2011]. The background text which accompanies the original 2005 recommendations has been revised to reflect current practice, although the recommendations themselves have not been updated.

What is a clinical guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and on to more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the

practice of healthcare professionals, they do not replace their knowledge and skills. Clinical guidelines developed for NICE apply to the NHS in England, Wales and Northern Ireland.

National Collaborating Centres are independent of government and comprise partnerships between a variety of academic institutions, health profession bodies and patient groups. The NCC-C was asked in March 2007 to advise NICE whether the 2005 guideline required updating. The NCC-C was formally invited to update the topic of 'The diagnosis and treatment of lung cancer' in October 2007 as part of NICE's seventeenth wave work programme. However, the guideline development process began officially in February 2009 when sufficient capacity became available at the NCC-C.

Who is the guideline intended for?

This guideline does not include recommendations covering every detail of the diagnosis and treatment of lung cancer. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing Clinical Evidence Based Questions'.

This guideline is relevant to all healthcare professionals who come into contact with patients with lung cancer as well as to the patients themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

The remit of the guideline

The following remit for this guideline was received as part of NICE's seventeenth wave programme of work:

'To update the clinical guideline 24 (CG24) on the diagnosis and treatment of lung cancer.'

Involvement of Stakeholders

Key to the development of all NICE guidance is the involvement of relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2009). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the updated lung cancer guideline can be found in Appendix 9.2.

The process of guideline development – who develops the guideline?

Overview

The development of this updated guideline was based upon methods outlined in the 'guidelines manual' (NICE 2007). A team of health professionals, lay representatives and technical experts known as the GDG (see Appendix 9.1), with support from the NCC-C staff, undertook the development of this updated clinical guideline. The basic steps in the process of developing and updating a guideline are listed and discussed below:

- deciding on the need and extent of an update
- using the remit, define the scope which sets the parameters of the guideline
- forming the GDG
- developing clinical questions
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence

- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

Deciding whether to update the 2005 guideline

The NCC-C convened an expert advisory group of healthcare professionals and patient and carer members to assess whether the 2005 guideline required updating (see Appendix 9.5). Group members were asked to identify which of the recommendations in the clinical guideline required updating and to provide a brief explanation of the reasons for this. Members were also asked to submit a list of any new key clinical areas that should be considered. The expert advisory group also discussed any relevant new evidence identified in the NCC-C literature search. A full report of the proceedings of the expert advisory group was sent to NICE in July 2007 and was discussed by their Guidance Executive in September 2007. Based on this information NICE formally invited the NCC-C to undertake a full update of the 2005 lung cancer guideline in October 2007.

The Scope

The scope was prepared by the GDG Chair and Lead Clinician and staff at the NCC-C in accordance with processes established in the guidelines manual (NICE 2007). The recommendations of the expert advisory group were carefully considered and subsequently included in the scope where appropriate. The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C and the remit set by the DH
- inform professionals and the public about the expected content of the guideline
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the clinical questions and search strategy.

The scope was subject to a four week stakeholder consultation in accordance with processes established by NICE in the 'guidelines manual' (NICE 2007). The full scope is shown in Appendix 7. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from registered stakeholder organisations and the NICE Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed by the GRP, signed off by NICE and posted on the NICE website.

The Guideline Development Group (GDG)

The lung cancer GDG was recruited in line with the existing NICE protocol as set out in the 'guidelines manual' (NICE 2007). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were interviewed prior to being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Requests for applications were sent to the main stakeholder organisations, cancer networks and patient organisations/charities (see Appendix 9.2). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economic literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix 9.1).

The membership of the GDG that developed the 2005 guideline can be found in Appendix 9.1.

Guideline Development Group meetings

Eleven GDG meetings were held between 12 February 2009 and 24 June 2010. During each GDG meeting (either held over one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations prior to presenting it to the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer members

Individuals with direct experience of lung cancer gave an integral user focus to the GDG and the guideline development process. The GDG included three patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Developing clinical evidence-based questions

Background

Clinical guidelines should be aimed at improving clinical practice and should avoid ending up as 'evidence-based textbooks' or making recommendations on topics where there is already agreed clinical practice. Therefore the list of key clinical issues listed in the scope were developed in areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

From each of the key clinical issues identified in the scope the GDG formulated a clinical question. For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: the population (the population under study – P), the interventions (what is being done – I), the comparisons (other main treatment options – C) and the outcomes (the measures of how effective the interventions have been – O). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated. The final list of clinical questions can be found in Appendix 8.

Review of clinical literature

Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder (now NHS Evidence), National Guidelines Clearinghouse, Cochrane Database of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), DH Data, Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Searching for the evidence

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on 'Incorporating Health Economic Evidence').

For those clinical topics that were updated from the 2005 guideline, searches were set to only identify evidence published after December 2003 to ensure no relevant papers were missed. No date limits were applied to searches carried on new topics within the 2011 guideline.

Papers that were published or accepted for publication in peer-reviewed journals were considered as evidence. Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1985 onwards
- Psycinfo 1806 onwards
- Web of Science [specifically Science Citation Index Expanded]
- (SCI-EXPANDED) 1899 onwards and Social Sciences Citation Index (SSCI) 1956 onwards
- Biomed Central 1997 onwards.

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6–8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, 1st August 2010 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review accompanying this guideline.

Critical appraisal

From the literature search results database, a researcher scanned the titles and abstracts of every article for each question and full publications were ordered for any studies considered relevant or if there was insufficient information from the title and abstract to inform a decision. When the papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies which were then critically appraised. For each question, data on the type of population, intervention, comparator and outcomes (PICO) were extracted and recorded in evidence tables and an accompanying evidence summary prepared (including meta-analyses where appropriate) for the GDG (see evidence review). All evidence was considered carefully by the GDG for accuracy and completeness.

All procedures were fully compliant with NICE methodology as detailed in the guidelines manual (NICE 2007). In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

Needs assessment

As part of the guideline development process the NCC-C invited a specialist registrar, with the support of the GDG, to undertake a needs assessment (see Appendix 9.3). The needs assessment aims to describe the burden of disease and current service provision for patients with lung cancer in England and Wales, which informed the development of the guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented in the early stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

Incorporating health economic evidence

The aim of the economic input into the guideline was to inform the GDG of economic issues relating to lung cancer. It is important to investigate whether health services are cost effective (i.e. are they 'value for money') as well as clinically effective, in order to maximise health gain from available resources.

The health economist helped the GDG identify priority topics within the guideline that might benefit from economic analysis, reviewing the available economic evidence and, where necessary, conducting de novo economic analysis. Further details of the economic prioritisation are provided in the full evidence review.

In order to assess the cost-effectiveness of each priority topic, a broad review of the economic literature was conducted. The search strategy was designed to find any applied study estimating the cost or cost effectiveness of any topic relating to lung cancer. A health economist reviewed abstracts and relevant papers were ordered for appraisal. Where it was judged that an economic question could be answered by a review of existing literature alone this was presented alongside the review of the clinical evidence. Otherwise, relevant papers were used to inform the design of the independent modelling. Studies that were not likely to provide useful information for guideline decision-making were not critically appraised.

Published economic evidence was obtained from a variety of sources:

- Medline 1966 onwards
- Embase 1980 onwards
- NHS Economic Evaluations Database (NHS EED)
- EconLit 1969 onwards.

Economic modelling

In addition to the review of the relevant clinical evidence, the GDG were required to determine whether or not the cost-effectiveness of each of the individual clinical questions should be investigated. After the clinical questions were decided, the GDG agreed which topics were priorities for economic modelling. These 'economic priorities' were chosen on the basis of the following criteria, in accordance with the guidelines manual (NICE, 2007):

Overall relevance of the topic

- *The number of patients affected:* interventions affecting relatively large numbers of patients were given a higher economic priority than those affecting fewer patients
- *The health benefits to the patient:* interventions that were considered to have a potentially significant impact on both survival and quality of life were given a higher economic priority
- *The per patient cost:* interventions with potentially high financial (cost/savings) implications were given high priority compared to interventions expected to have lower financial implications

- *Likelihood of changing clinical practice*: priority was given to topics that were considered likely to represent a significant change to existing clinical practice.

Uncertainty

- *High level of existing uncertainty*: higher economic priority was given to clinical questions in which further economic analysis was considered likely to reduce current uncertainty over cost-effectiveness. Low priority was given to clinical questions when the current literature implied a clearly 'attractive' or 'unattractive' incremental cost-effectiveness ratio, which was regarded as generalisable to a UK healthcare setting
- *Likelihood of reducing uncertainty with further analyses (feasibility issues)*: when there was poor evidence for the clinical effectiveness of an intervention, then there was considered to be less justification for an economic analysis to be undertaken.

Once the economic priority clinical questions had been chosen, a feasibility assessment was carried out to determine the potential value of conducting independent modelling for each economic priority topic. This assessment was written up in the 'Economic Plan' (see full evidence review). After careful consideration by the GDG it was decided that a full economic analysis would only be carried out for one clinical question. The decision was based on the size and scale of the topic and the time and resource available to the health economist and the NCC-C.

For the clinical questions where an economic model was required, the information specialist performed supplemental literature searches to obtain additional data for modelling. Assumptions and designs of the models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

The clinical question in this guideline selected for modelling was chosen because at the time it was considered likely that the recommendations under consideration could substantially change clinical practice in the NHS and have important consequences for resource use. The details of the model are presented in the evidence review and Appendix 4.

During the modelling process the following general principles were adhered to:

- the GDG Chair, Clinical Lead and other members of the GDG that formed the topic subgroup were consulted during the construction and interpretation of the model
- the model assumptions were plausible and were reported fully and transparently
- the model was based on the best available evidence from relevant systematic reviews or national audit data
- the costs were calculated from a health services perspective
- the results were discussed and tested using sensitivity analysis
- the limitations of the model were acknowledged and discussed.

Linking to NICE technology appraisals

Since publication of the NICE Lung Cancer Guideline in 2005 a number of new systemic therapies have been granted a marketing authorisation by the EMEA for use in people with NSCLC. NICE has published several technology appraisals (TAs) which are relevant to the updated guideline including TAs for pemetrexed, gefitinib and erlotinib. A weblink to these TAs and their recommendations have been incorporated within relevant chapters of the updated guideline. NICE had planned to commission a separate guideline updating chemotherapy for NSCLC but this guideline will not now be developed. For NSCLC chemotherapy there are a number of technology appraisals with funding directives currently in place, several planned technology appraisals in the programme and several technology appraisals requiring updates. This restricted the scope of the proposed guideline and so it has been decided not to update the current guidance on chemotherapy for NSCLC.

The NHS has commissioned a review of first-line therapy for NSCLC through the NIHR HTA Programme that is due to be published in 2011.

Agreeing the recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and where appropriate economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying qualifying statement.

Qualifying statements

As clinical guidelines are currently formatted, there is limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, the NCC-C felt the need for an explicit, easily understood and consistent way of expressing the reasons for making each recommendation.

The way we have chosen to do this is by writing a 'qualifying statement' to accompany every recommendation and usually covering:

- the strength of evidence about benefits and harms for the intervention being considered
- the degree of consensus within the GDG
- the costs and cost-effectiveness of an intervention (if formally assessed by the health economics team).

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed. To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Consultation and validation of the guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (see Appendix 9.2) had one opportunity to comment on the draft guideline which was posted on the NICE website between 4 October 2010 and 29 November 2010 in line with NICE methodology (NICE 2009). The GRP also reviewed the guideline and checked that stakeholder comments had been addressed.

The pre-publication check process

Following stakeholder consultation and subsequent revision, the draft guideline was then subject to a pre-publication check (NICE 2009). The pre-publication check provides registered stakeholders with the opportunity to raise any concerns about factual errors and inaccuracies that may exist in the revised guideline after consultation.

During the pre-publication check the full guideline was posted on the NICE website for 15 working days, together with the guideline consultation table that listed comments received during consultation from stakeholders and responses from the NCC-C and GDG.

All stakeholders were invited to report factual errors using a standard proforma. NICE, the NCC and the GDG Chair and Lead Clinician considered the reported errors and responded only to those related to factual errors. A list of all corrected errors and the revised guideline were submitted to NICE, and the revised guideline was then signed off by Guidance Executive. The list of reported errors from the pre-publication check and the responses from the NCC-C were subsequently published on the NICE website.

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other versions of the guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc).

NICE also produces three other versions of the updated lung cancer guideline which are available from the NICE website:

- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations
- the Quick Reference Guide (QRG), which is a summary of the main recommendations in the NICE guideline. For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk
- 'Understanding NICE Guidance' ('UNG'), which describes the guideline using non-technical language. It is written chiefly for people suspected of, or diagnosed with, lung cancer but may also be useful for family members, advocates or those who care for patients with cancer of unknown primary. For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk

Updating the Guideline

Literature searches were repeated for all of the clinical questions at the end of the GDG development process, allowing any relevant papers published before 1 August 2010 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Three years after publication of the guideline, NICE will undertake a review to determine if the guideline needs to be updated and will commission a National Collaborating Centre to do this work.

Funding

The NCC-C was commissioned by NICE to develop this guideline. Health economic analysis for this guideline was provided by the London School of Hygiene and Tropical Medicine and funded by the NCC-C.

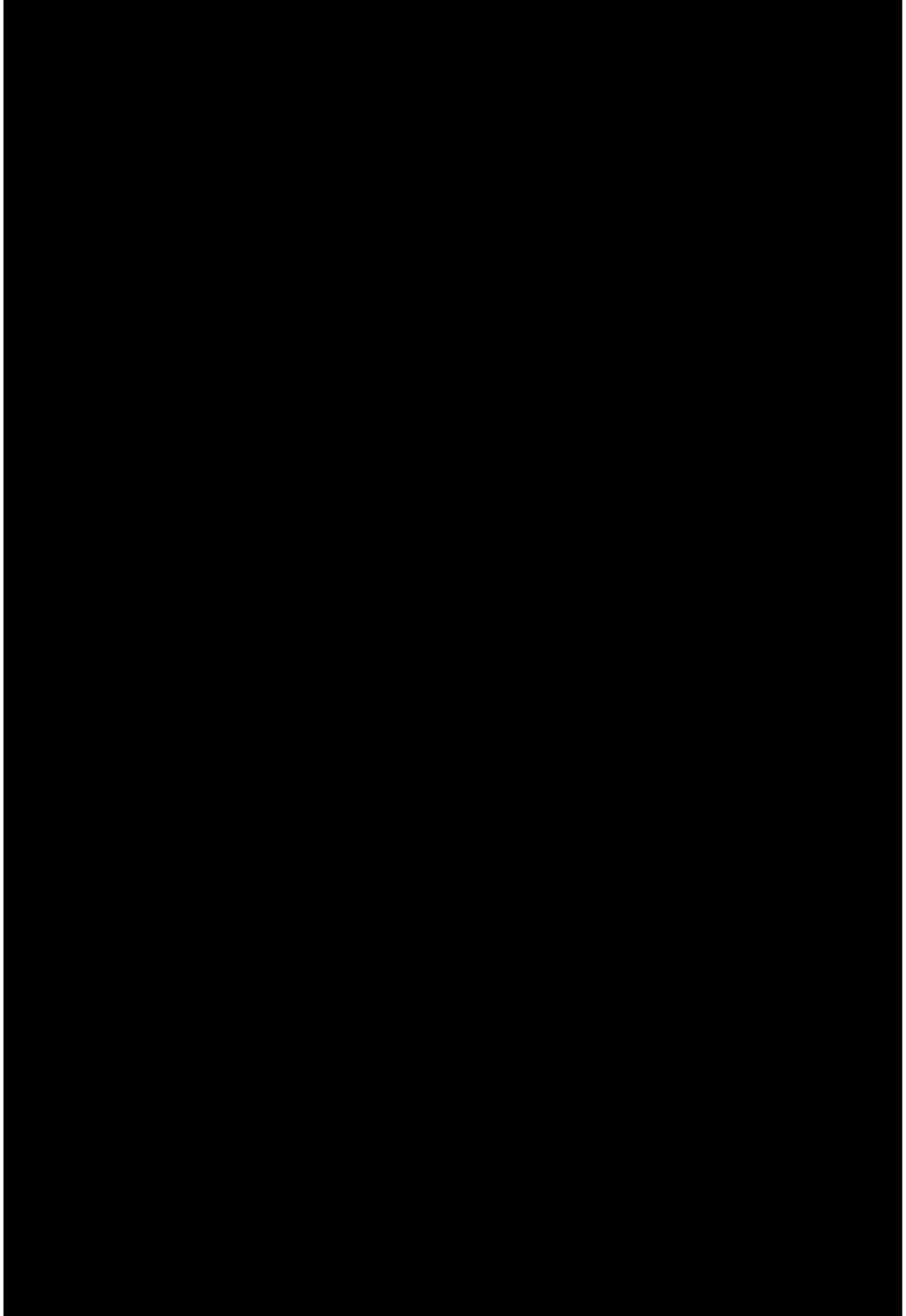
Disclaimer

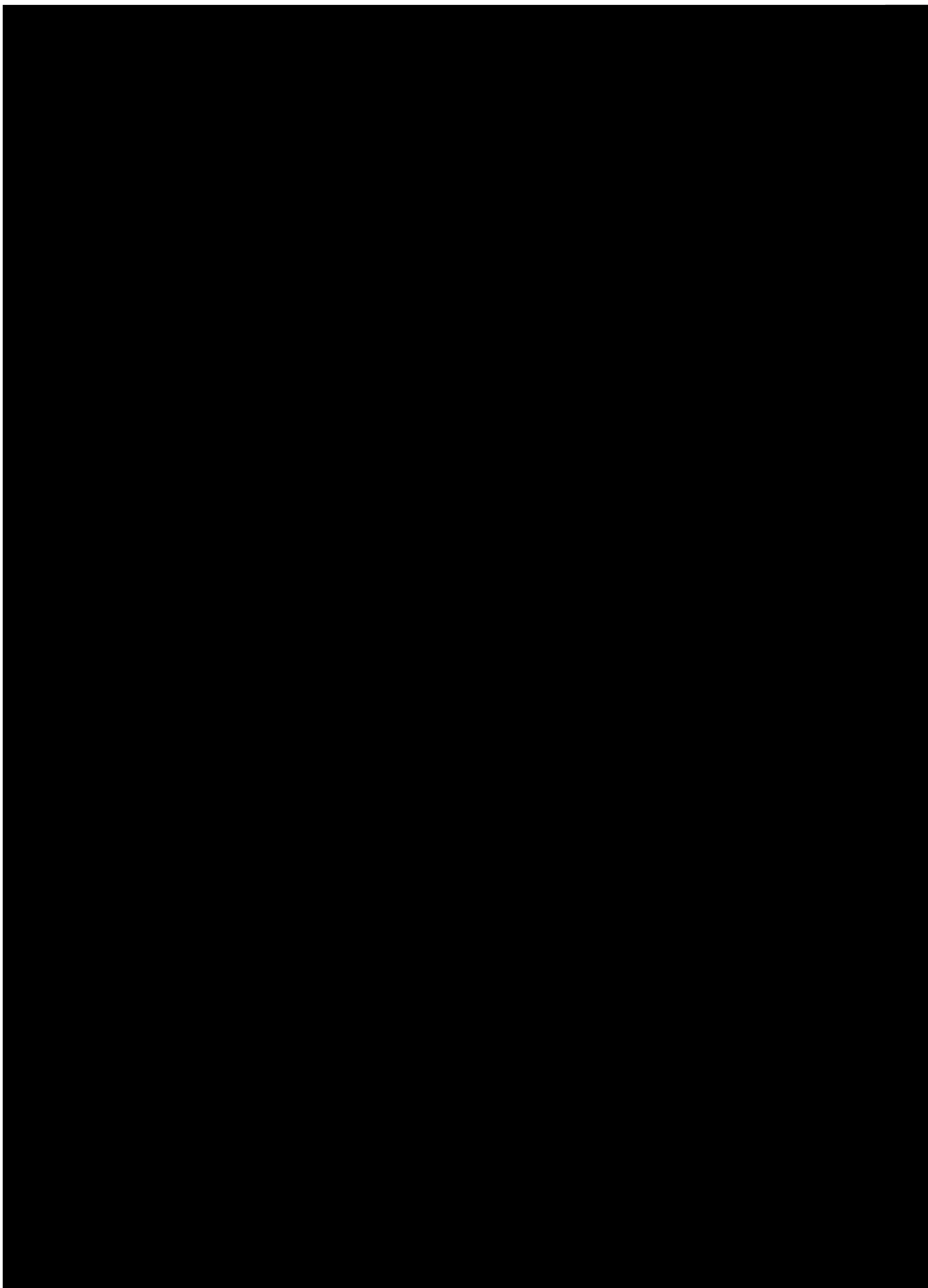
The GDG assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

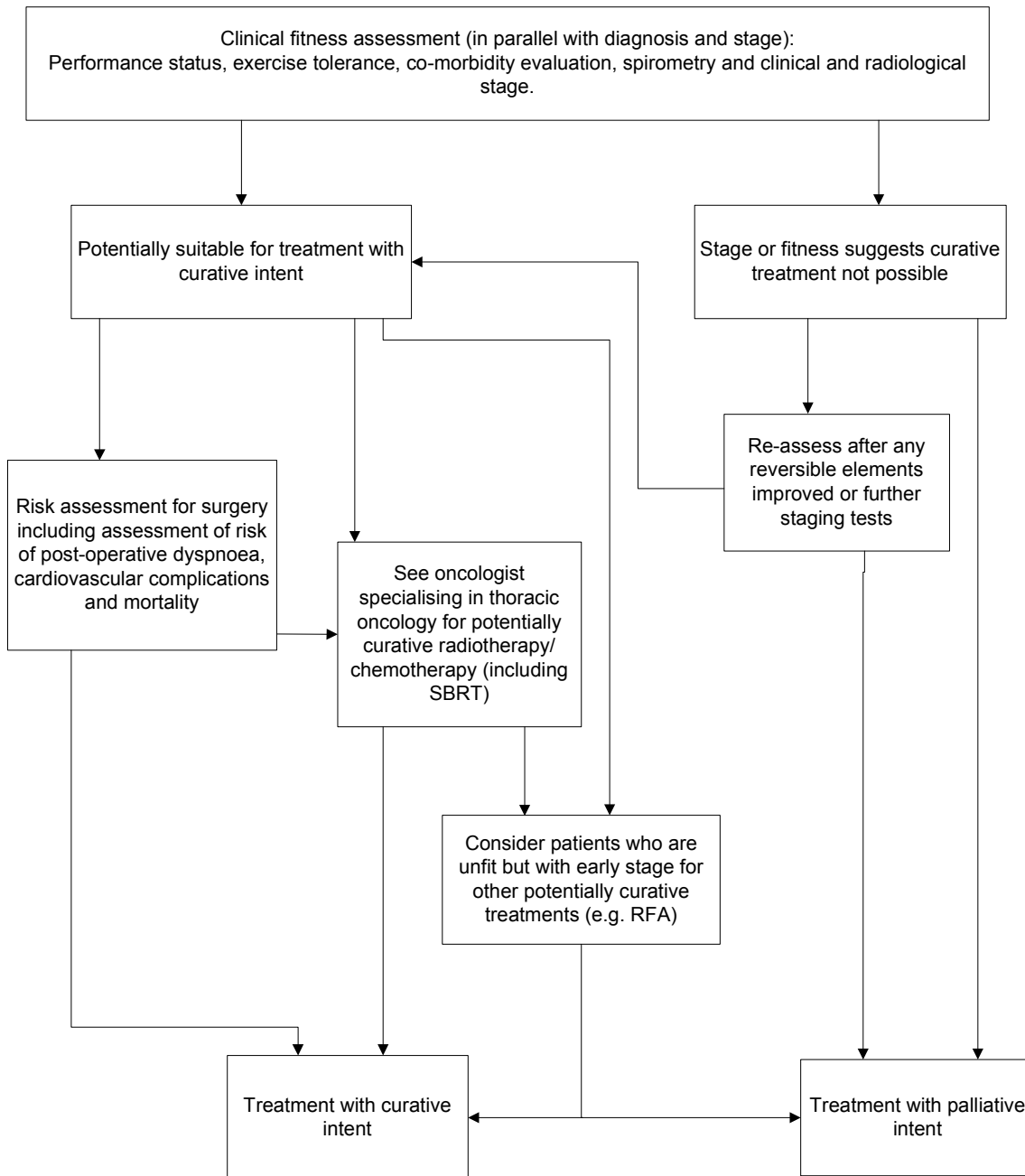
References

- National Institute for Health and Clinical Excellence (2007) The guidelines manual. London: National Institute for Health and Clinical Excellence.
- National Institute for Health and Clinical Excellence (2009) The guidelines manual. London: National Institute for Health and Clinical Excellence.





Fitness assessment clinical pathway



Updated 2011

1 Epidemiology

1.1 Introduction

The following chapter provides a summary of the full Needs Assessment that was carried out as part of the evidence review for this guideline. It includes information regarding the epidemiology of lung cancer regionally, nationally and internationally. This guideline update is not a comprehensive review of all aspects of lung cancer management but is limited to priority areas that were identified before and during the scoping exercise that were thought to be key topics that might help improve the overall standard and equity of care provided geographically. The purpose of this chapter therefore is to provide the context for the guideline, to describe the burden of disease and to assess whether variation exists in the treatment and outcome for individuals with lung cancer in England and Wales. We shall illustrate the need for improved diagnostic and staging procedures, and the link to selecting patients for their optimal therapy for improving survival and quality of life; whilst addressing the important issues of informed patient choice.

Since the 2005 NICE Guideline on Diagnosis and Treatment of lung cancer was published, (NICE CG24, 2005) the National Lung Cancer Audit (NLCA) has been established, and accrual has increased steadily over the past five years. It is estimated that the Audit gathered information on 85% of the incident cases of lung cancer in England and Wales in 2008 (NLCA, 2009). It is the largest contemporary, non-registry, clinical database of lung cancer patients in Europe, with over 100,000 patients in total. It is a non-mandatory dataset of clinical and socio-demographic features, and also records details of the treatment received. The dataset has been shown to be unbiased and representative of lung cancer patients in England (Rich et al., 2010). These data have been used within this NICE Lung Cancer Update along with contemporary data from Cancer Network Information System Cymru (CANISC) in Wales to describe the current demographics of individuals with lung cancer in England and Wales; the patterns of treatment they receive and their survival. Other information sources include the National Cancer Intelligence Network (NCIN), the National Cancer Registry, and the British Society of Cardiothoracic Surgery.

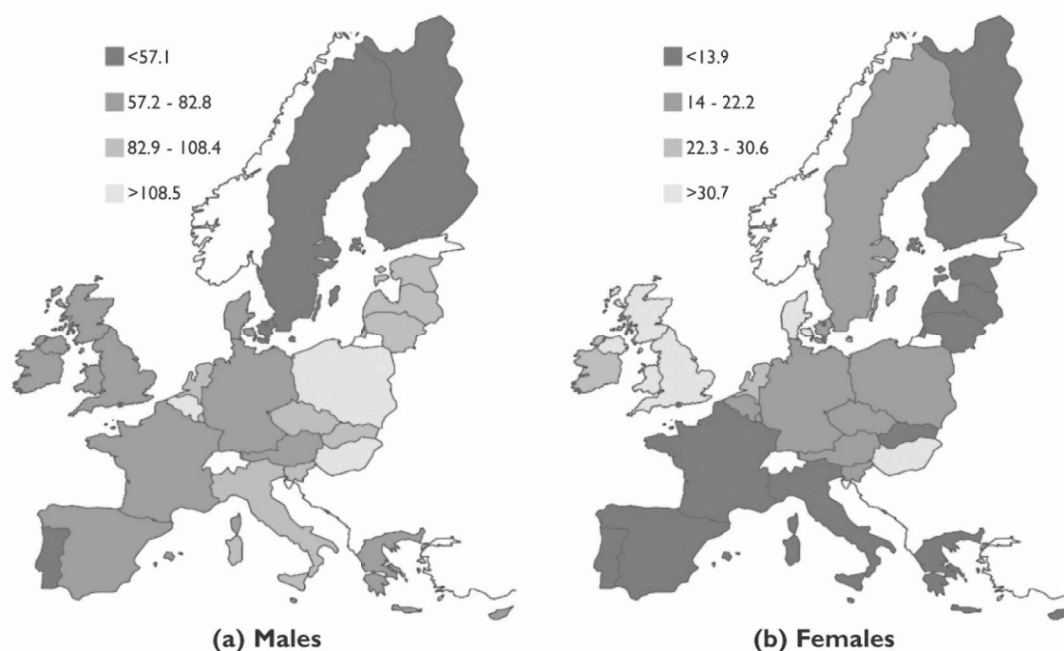
This NICE Lung Cancer Update has included a revision of several sections from the original guideline in 2005 (NICE CG24, 2005), and provided the opportunity to assess the progress that has been made over the last five years, and identify areas that have shown no improvement. In 2002 there were 29,000 deaths from lung cancer, and it was the second most common cause of cancer related death in women. In 2008, there were more than 35,000 deaths (Cancer Research UK, 2010), and it is now the leading cause of cancer related death in men and women. There has been an encouraging improvement in 1 year survival compared with the data quoted in the 2005 guideline; although regional variation in this outcome measure persist (DoH Cancer Reform Strategy, 2009). Regional variation was also described in 5 year survival, but contemporary data from the NLCA will not be available until 2011. The proportion of the overall patient cohort with small cell lung cancer was estimated as 20% in 2005. Current data from the NLCA shows the proportion having fallen to around 11% of all reported lung cancers (18% of all *histologically confirmed* lung cancer). Data from 1986-1994 (North Yorkshire Cancer Registry Information Services) demonstrated that 34% of patients had no histological confirmation of their lung cancer, and this figure has fallen very little over the last 15 years.

1.2 Incidence

The incidence of lung cancer in England and Wales is believed to be 47.4 per 100,000 population (Cancer Research UK). Data from ONS showed a total of 34,897 incident cases in England and Wales in 2008. It is the second commonest cancer in men, after prostate; and women, after breast cancer. The prognosis is very poor with a mortality rate of 40.1/100,000 population. The prevalence reflects this poor prognosis with an estimate of 65,000 individuals living with lung cancer in 2008 (Cancer Research UK, 2010). In the 2005 NICE Lung Cancer Guideline, deaths from lung cancer were believed to be the commonest cause of cancer related deaths in men, and the second most common cause in women. However, lung cancer has since become the commonest cause of cancer related death in both sexes.

Comparison within the European Union reveals that the incidence in men is similar to most of western Europe and lower than most of eastern Europe. The incidence in women is amongst the highest in the European Union (figure 1.1).

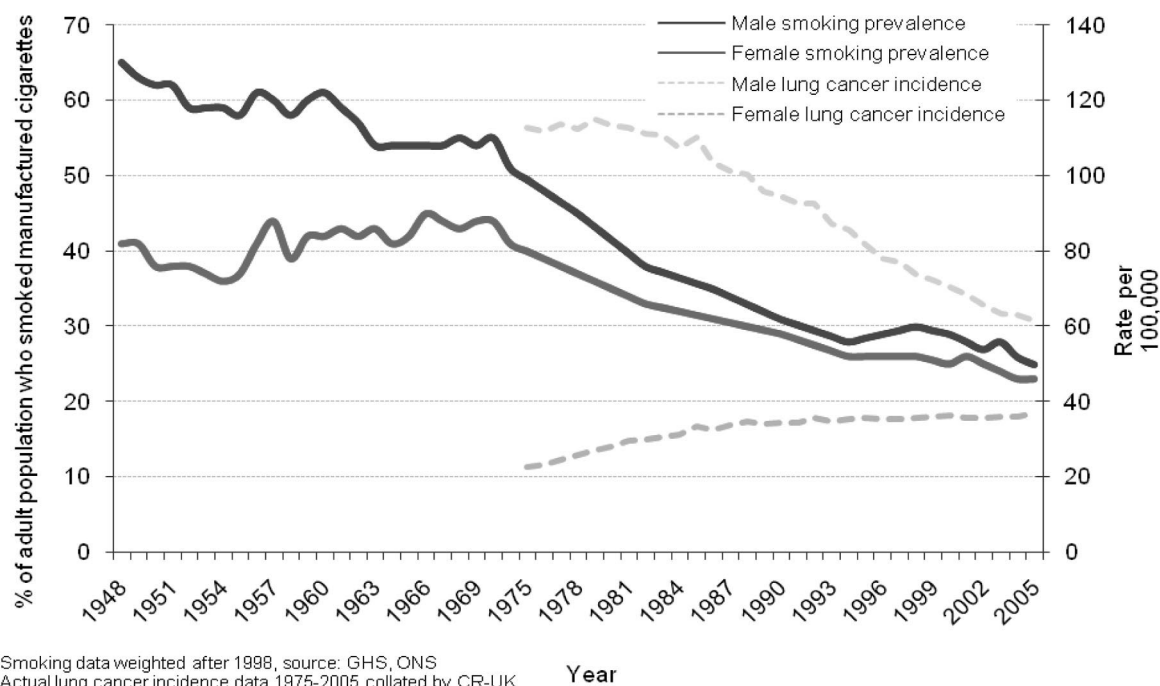
Figure 1.1. Age-standardised incidence rates (per 100,000 people) in the European Union (2000); Reproduced with the permission of Cancer Research UK.



1.3 Sex variation

The majority of individuals with lung cancer are male, and this is almost certainly a direct reflection of the proportion of smokers that are male. However, the proportion of men who smoke has fallen by 26% since the mid 1970's (Office of National Statistics, 2008.2010) and there has been a similar decline in the proportion of women who smoke over the same timeframe (figure 1.2). There is known to be a twenty year lag phase between smoking and the onset of lung cancer and so changes in the pattern of smoking between the sexes is a precursor of changes in the sex ratio amongst individuals with lung cancer (figure 1.2) (Cancer Research UK, 2010). The peak prevalence of smoking in *young* women was only reached in the 1990's, and so the incidence of lung cancer amongst older women has only recently stabilised (figure 1.2). The male:female ratio was >6:1 in 1973 compared with 1.5:1 in 2008 (1).

Figure 1.2: Rates of smoking and incidence of lung cancer in England and Wales 1975-2005. (Reproduced by kind permission of Cancer Research UK).



There is also evidence from the NLCA that females have better overall survival than males, with an adjusted hazard ratio of 0.89, $p < 0.001$ (95% confidence intervals, 0.88, 0.91) (Rich et al., 2010). This result indicates that women with lung cancer are 11% less likely to die than men, and this observation has been published in a number of other populations (Bouchardy et al., 1999; Thomas et al., 2005).

1.4 Histological subtypes

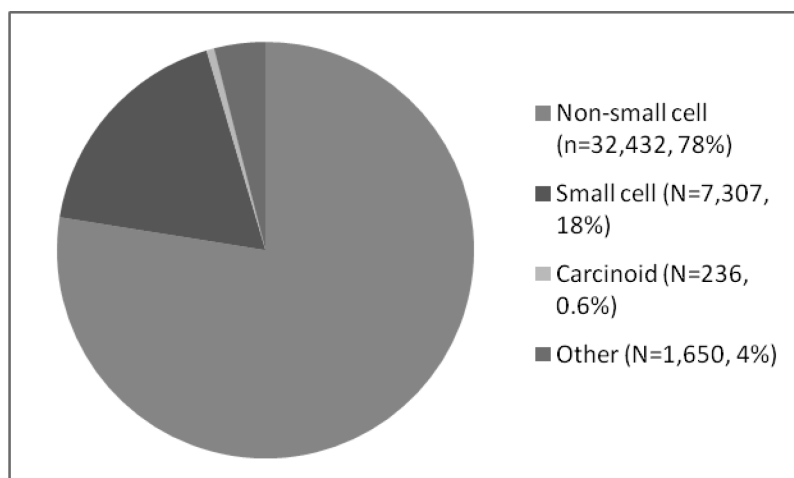
Obtaining a histological diagnosis for a lung tumour is usually necessary to ensure the most appropriate treatment regime is considered. If targeted treatment is an option, it is vital that samples and their analysis are adequate to allow identification of histological subtypes and specific mutations that directly determine suitability for specific treatment.

There is evidence from the National Lung Cancer Audit that a significant proportion of patients are diagnosed on the basis of clinical examination and radiological investigations alone, without histological evidence. The proportion of patients for whom this was the case is 23% in England and 32% in Wales (2006-08); which reflects some improvement on English data from 1986-94 of 34% (Aesculapius Medical Press, 2001). It is acknowledged that some patients do not require a histological diagnosis where they are either too unwell for active treatment or a decision to proceed to curative surgery has been made prior to histological confirmation, but for the majority histology should be confirmed. It is not possible to say what the histological confirmation rate should be but the GDG agreed with the DoH recommendation of around 80%. The NLCA shows that this is not the case across NHS Trusts in England with the median Histological Confirmation Rate being only 63% (interquartile range 47, 72%) (Rich et al., 2010).

The prevalence of the different histological types has changed with time, which is believed to be due to the temporal change in smoking prevalence, and also the use of filters and low tar cigarettes. Small cell lung cancer is believed to be most closely linked to smoking pack history, and the proportion of all lung cancers due to small cell has decreased from 20 to 10% (Stephens & Johnson, 2000). In 1950 the ratio of adenocarcinoma:squamous cell carcinoma was 1:1.8; but in 1994 was reported as 1:1.3 (11). This increase in adenocarcinoma was seen in both sexes and all ethnic groups.

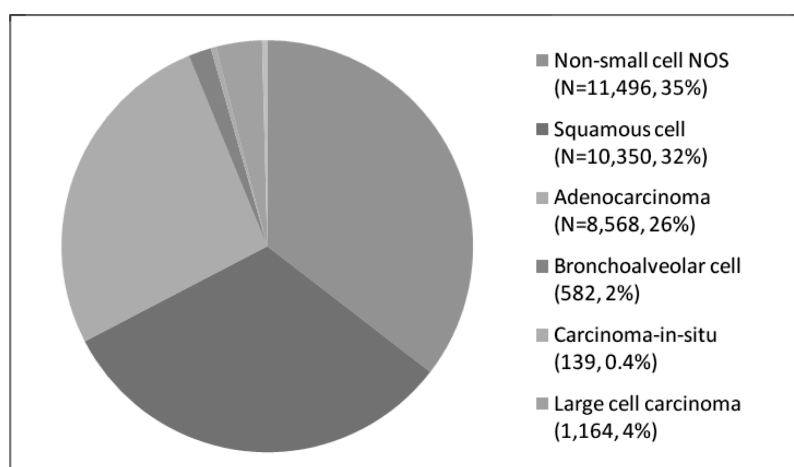
Data from the National Lung Cancer Audit demonstrate contemporary results for the variation in histological types, although these data are missing in 40% of the English and 32% of the Welsh cohorts.

Figure 1.3: Histological types in pathologically proven primary lung cancer. NLCA (England and Wales) 2006-08.



The NLCA holds data for the breakdown of subgroups of Non-small cell lung cancer, which highlights the increase in prevalence of adenocarcinoma, and also the large proportion of patients in whom an exact histological subtype is missing, Non-small cell “Not otherwise specified” (NOS).

Figure 1.4: Sub types of non-small cell lung cancer (N=32,432). NLCA (England and Wales) 2006-08.

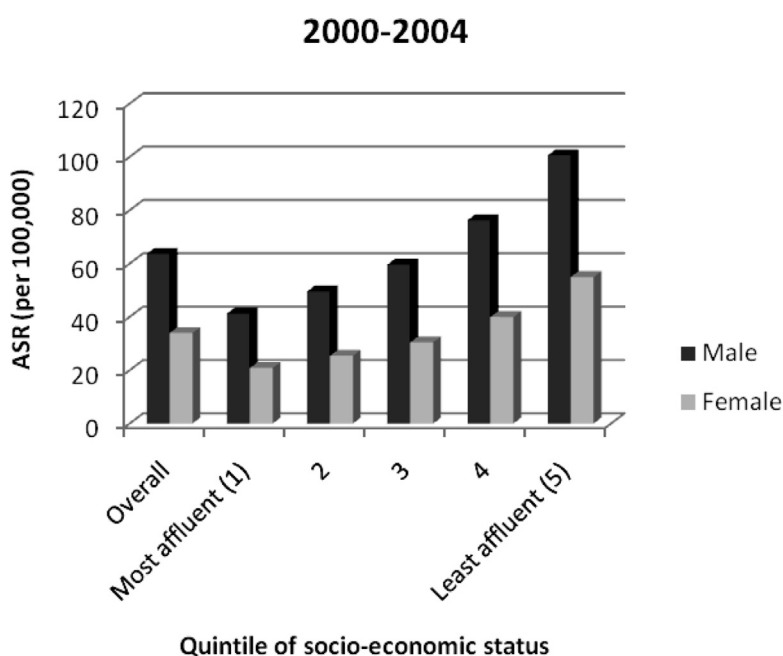


1.5 Socio-economic status (SES)

A number of papers have been published which indicate that there is an increased incidence of lung cancer in individuals from the lowest level of socio-economic strata, the least affluent group (Mackbenbach et al., 2004; Pugh et al., 1991; Pollock & Vickers, 1997). Historically this difference has been attributed to the increased rate of smoking in the least affluent group (Pugh et al., 1991), and there is evidence that histological subtypes vary with SES reflecting the variable influence of smoking on specific histological subtypes (Bennett et al., 2008). However, other factors will be involved including diet, nature of employment (manual vs professional), and educational attainment (Mackbenbach et al., 2004; Mao et al., 2001; Schwartz et al., 2003).

Differences also exist between individuals from different SES in terms of access to health services and health seeking behaviour (Raine et al., 2010). Crawford et al. (2009) found individuals from the most deprived group were less likely to receive a histological diagnosis. Shack et al. (2008) noted that the gradient in incidence of lung cancer across socio-economic groups in England was more marked in the North East, the North West and Yorkshire and Humber regions. Data from the NCIN illustrates a more than two fold variation in age standardised incidence rate in both men and women between the most and least affluent strata (figure 5).

Figure 1.5: Age standardised incidence rate (per 100,000 people) across quintiles of socio-economic status (Reproduced by kind permission of NCIN).



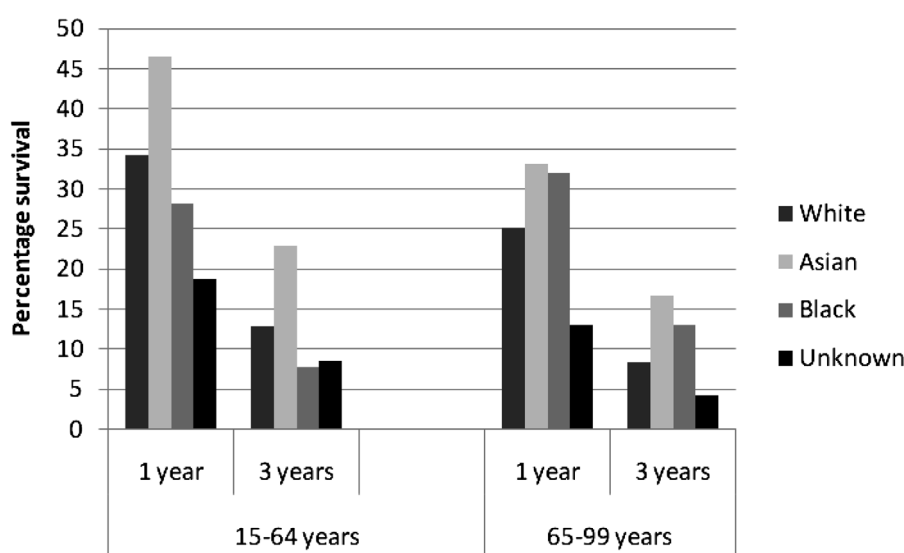
As well as the increase in incidence of lung cancer in the least affluent social group, there is evidence that these individuals present with more advanced disease (Schwartz et al., 2003; Kogevinas et al., 1991) and demonstrate a reduced uptake of resection for lung cancer (Raine et al., 2010; Crawford et al., 2009; Pollock et al., 1998). Data using Hospital Episode Statistics (HES) between 1992-95 stated a 40% reduction in the use of surgery between the least compared with the most affluent group of patients with lung cancer (unadjusted OR 0.58, 95% confidence interval 0.48, 0.70). However this figure may be misleading as it is not adjusted for age, sex, performance status, or stage. Contemporary data (2005-2008) from the NLCA demonstrated no variation in the use of surgery in proven NSCLC, based on socio-economic status, with an adjusted OR of 1.11 (95% confidence interval 0.96, 1.27) (Rich et al., 2010). Jack et al. (2006) reported a lower rate of chemotherapy use in patients within the South East region from the least affluent group (Jack et al., 2006), which has been reproduced using contemporary data from the NLCA (Rich et al., 2010). However, in neither study was social deprivation linked to poorer survival (Rich et al., 2010; Jack et al., 2006). Data from the NLCA demonstrated no variation in the use of radiotherapy for the overall cohort of patients with lung cancer, based on socio-economic status (Rich et al., 2010).

1.6 Ethnic variation

There is evidence of variation in the incidence of lung cancer amongst ethnic groups in England and Wales, which is related to demographic features, socio-economic deprivation and smoking prevalence. Black and minority ethnic groups (BME), have higher than average smoking rates, and are more likely to be from deprived areas with increased unemployment and lower levels of educational attainment (Harding et al., 2009; DoH, 2007). Evidence from

America demonstrated that African-Americans were more likely to present with advanced stage of lung cancer than Caucasians, which was related to socio-economic status rather than directly to ethnicity. In contrast race was an independent risk factor for advanced stage at presentation in breast and prostate cancer (Schwartz et al., 2003). In England and Wales, an increase in relative mortality was found in migrant individuals with lung cancer from Jamaica (Harding et al., 2009). Differences also exist in terms of accessing health services such as smoking cessation and screening between ethnic groups, with White-British individuals more likely to present via a two-week wait appointment than individuals from BME groups (DoH, 2007). There is also evidence that individuals from BME groups are underrepresented in cancer research (DoH, 2007).

Figure 1.6: Variation in age standardised relative male survival at 1 and 3 years by major ethnic groups in England and Wales. (Reproduced with kind permission of NCIN).



Asian individuals with lung cancer have a significantly higher percentage survival at 1 and 3 years compared with white patients, regardless of age. There was no significant difference in relative survival between BME groups at 1 or 3 years. Similar results were seen for women as for men.

Given potential cultural and language barriers for individuals from BME groups accessing lung cancer services within the NHS, it is very important that every effort is made to ensure that each component of the patient pathway is clear and user-friendly.

1.7 Stage and performance status

The stage of lung cancer at diagnosis is crucially important in terms of determining which patients have potentially curative disease, and which do not. Stage is also an important determinant of prognosis. The routine use of CT of the thorax and upper abdomen along with PET-CT has improved the accuracy of staging. Recently, the International Association for the Study of Lung Cancer group (IASLC) has produced a revised TNM staging system that has been adopted by the Union Internationale Contre le Cancer (UICC). Plans are already underway to collect more accurate staging data and relate this to prognosis to produce a yet more accurate staging system. Information regarding stage of disease at presentation is not collected by the Cancer Registries but is collected within the NLCA and CANISC, although these data are incomplete. Stage data were missing in 46% English and 30% Welsh patients overall, and in 27% and 17% of English and Welsh patients with proven NSCLC respectively.

Figure 1.7: Stage at presentation in those patients with stage recorded (N=40,492). NLCA (England and Wales) 2006-08.

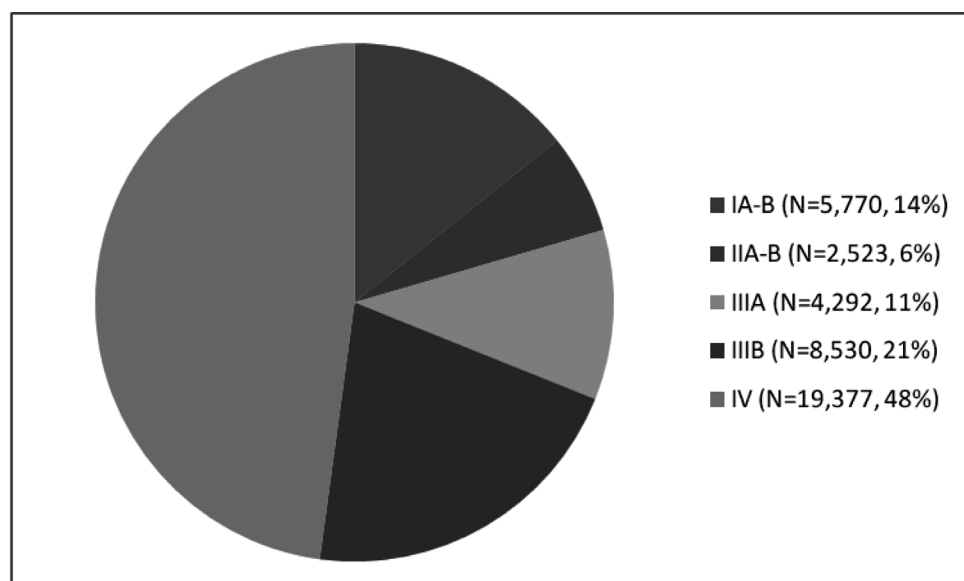


Table 1.2 demonstrates that across England and Wales a significant proportion of each age group presents with late stage metastatic disease. As a proportion of those patients with stage recorded, the youngest age groups have a similar burden of advanced disease to other groups, with the most elderly (>80 years) having significantly less. A significant proportion of people who are economically active and more likely to have dependent children will present with advanced disease. Late presentation in the younger age group will be multi-factorial but may reflect fear or ignorance on the part of young adults, and a lack of clinical suspicion in healthcare professionals.

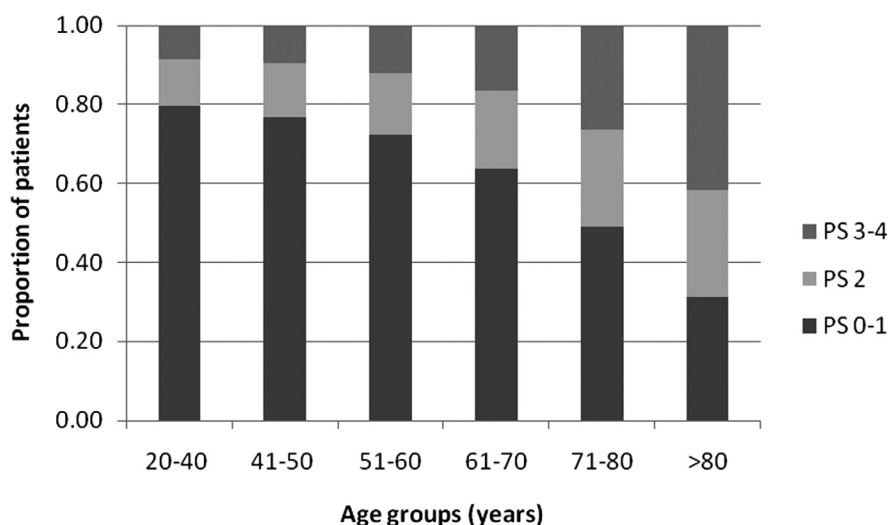
Table 1.1: Frequency of Stage IV disease based on age groups in England and Wales (2006-08). Data provided by NLCA and CANISC.

Age groups (yrs)	N	%*	%* if stage recorded
20-40	95	27	58
41-50	615	27	51
51-60	2807	29	52
61-70	5682	27	48
71-80	6711	26	47
>80 years	3397	24	45

%* percentage of each age group with Stage IV disease

Data are also collected by the NLCA and CANISC on performance status at diagnosis, although these data were missing in 38% of the English and 23% of the Welsh cohorts. Figure 1.8 demonstrates that as age increases so does the proportion of patients with performance status 3 or 4 at diagnosis. This will have implications on the treatment options available to elderly patients.

Figure 1.8: Variation in performance status at diagnosis based on patient age group (N=46,897). NLCA (England and Wales) 2006-08.



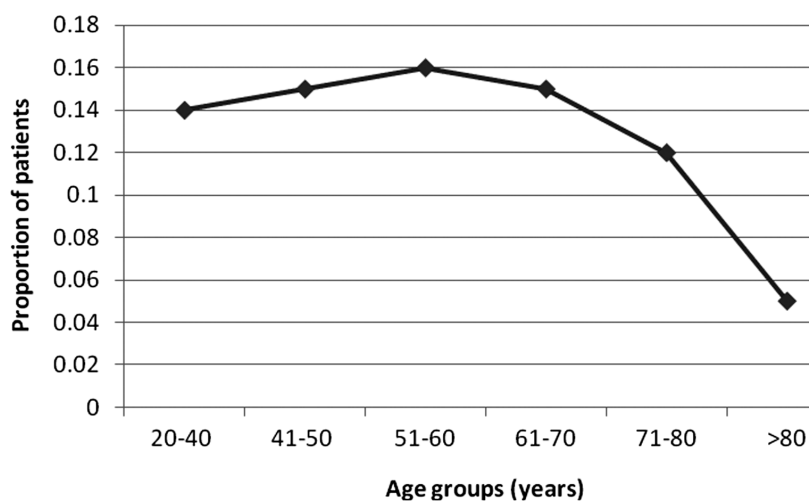
Information on co-morbidities is not reliable within the NLCA, and so work is on-going to link the LUCADA dataset to other datasets, such as Hospital Episode Statistics (HES), in order to evaluate the potential influence of patient co-morbidity and outcome measures for lung cancer.

1.8 Treatment received

Data from the NCLA (total for this analysis 67730 records) show that overall 13.5% of patients are recorded as receiving treatment with curative intent, 52.2% treatment with palliative intent and 17.7% supportive care only. In 16.3% no treatment was specified or data were missing

Surgery remains the mainstay of treatment with curative intent for NSCLC. Data from the NLCA for England reports an overall resection rate of 11%, which for the subgroup of patients with proven NSCLC rises to 14%. The data for Wales, indicates a resection rate of 6% overall, rising to 9% in proven NSCLC patients. Within this subgroup, the use of surgery varies according to age group of the patient as illustrated in figure 1.9.

Figure 1.9: Proportion of patients with proven NSCLC receiving surgery in England and Wales based on age (N=3,998). Data from NLCA and CANISC (2006-2008).



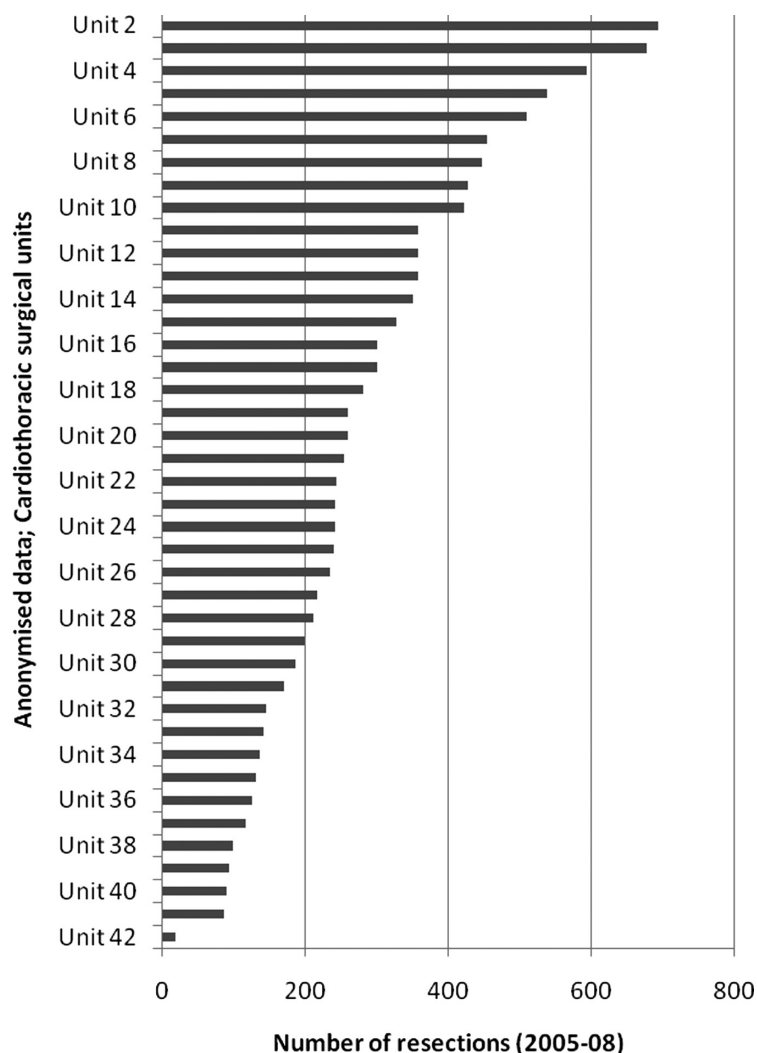
The resection rate in proven NSCLC patients appears to drop above the age of 70 years, and there is evidence that even adjusting for stage and performance status, those over 75 years are significantly less likely to be treated surgically, than those under 65 years (Rich et al., 2010; Peake et al., 2003; Jones et al., 2008). It is known that as age increases so does the level of

co-morbid illness (Khan et al., 2010), however it is important to ensure that patient's treatment is planned on the basis of their clinical state, including co-morbidities and performance status etc, not simply their chronological age.

Recent published evidence based on operation codes recorded in HES shows no increase in the rate of resection for lung cancer in England and Wales between 1999 and 2006 (Raine et al., 2010). In view of the fact surgical resection is the main component of treatment with curative intent, this is disappointing, and does illustrate apparent differences in practice between other parts of Europe and North America (17% and 21% resection rates respectively) (Cancer research UK survival data, 2010).

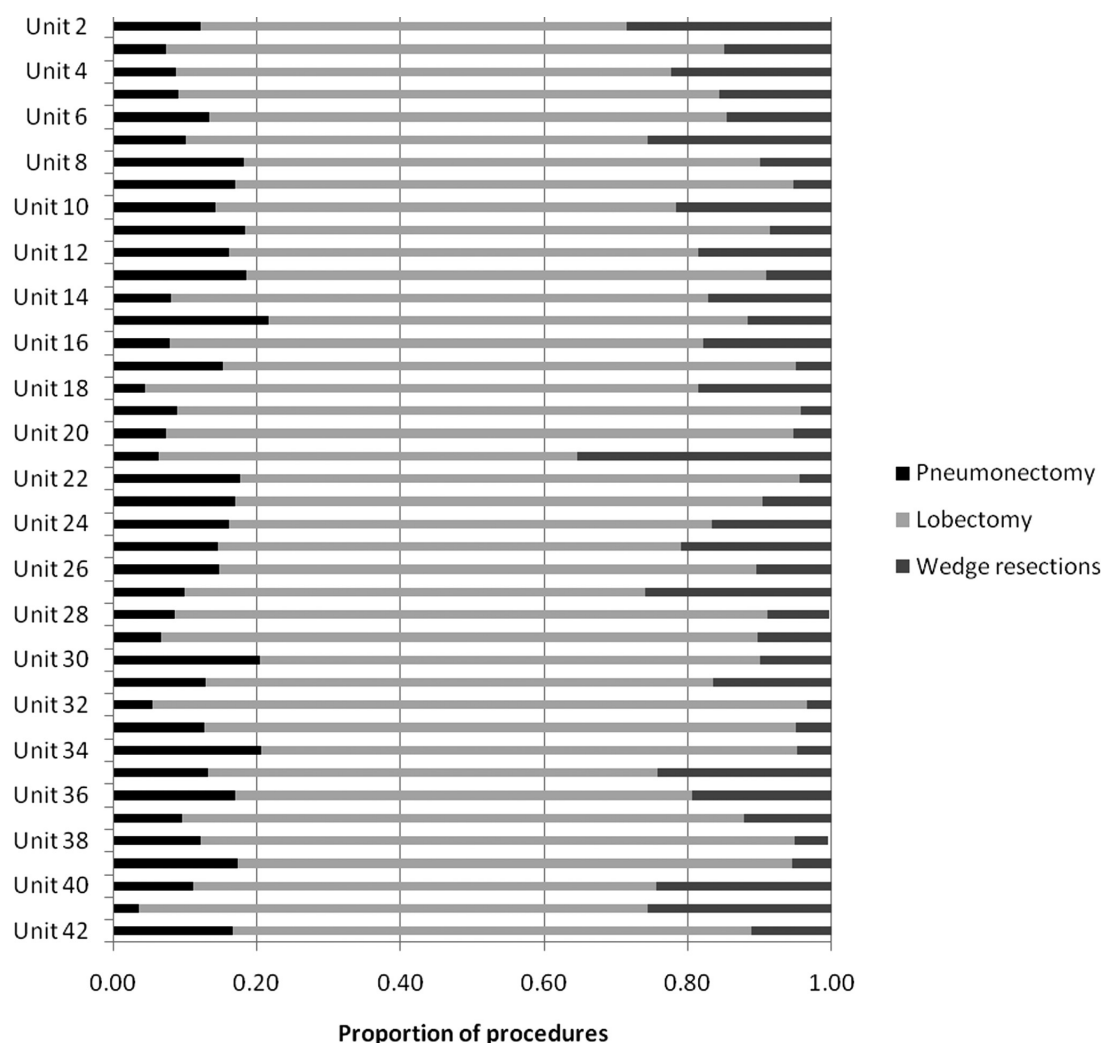
There are data on the number and type of resections being performed in surgical centres throughout Great Britain and Ireland, and these are shown below as figures 1.10 and 1.11. These data demonstrate that there is significant variability in the number of resections being performed in different surgical centres, although it is not known how much this reflects differences in patient population, or surgical practice.

Figure 1.10: Number of resections for primary lung cancer at surgical centres in Great Britain and Ireland (Reproduced by kind permission of Society of Cardiothoracic Surgery – Data 2005-2008).



There is no clear evidence as to what the 'optimal' number of resections per surgical centre should be. Anecdotally the theory is that fewer centres performing more resections would reduce the post-operative mortality and improve the long-term survival. There is evidence from America which describes a difference of >5% adjusted mortality rate between low volume and high volume institutions for pneumonectomies (Birkmeyer et al., 2002), whilst the effect on lobectomy adjusted mortality was <2%. However, research from Britain in 2003 found no such link between the number of lobectomies performed by an individual surgeon and in-hospital mortality (Treasure et al., 2003). Of note, 40% of the 102 surgeons performed <24 lobectomies per year, which is a reflection of the fact that the majority of lobectomies were performed by cardiothoracic, not pure thoracic, surgeons at the time of this study.

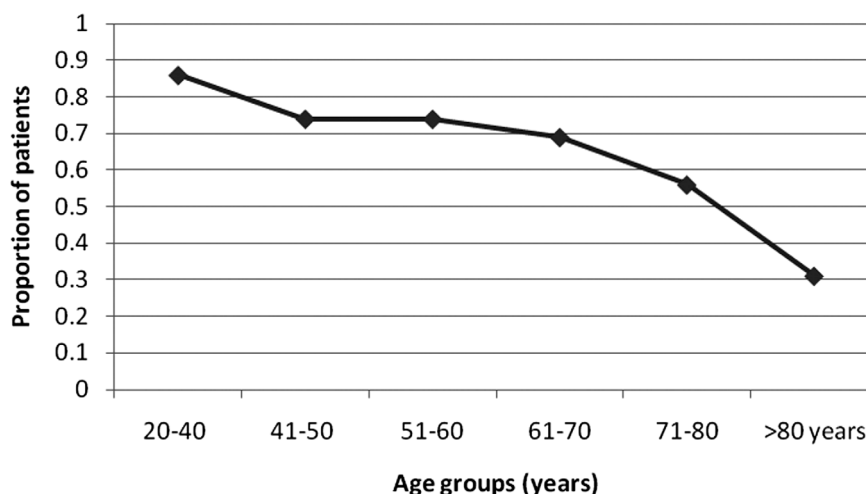
Figure 1.11: Types of resection for primary lung cancer at surgical centres in Great Britain and Ireland (Reproduced by kind permission of Society of Cardiothoracic Surgery – Data 2005-08).



There is also evidence that the type of procedure performed for lung cancer resection varies at different surgical centres (figure 1.11). The 2005 guideline states that the procedure of choice in stage I or II NSCLC should be lobectomy, rather than pneumonectomy, and figure 1.11 confirms the low proportion of operations that underwent pneumonectomy. Only three surgical centres had >20% of resections recorded as pneumonectomies.

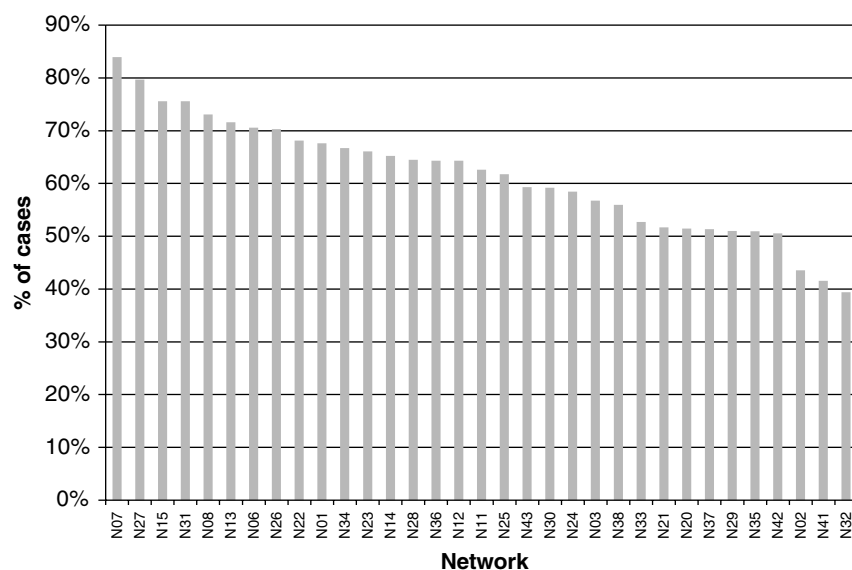
Chemotherapy is the mainstay of treatment for small cell lung cancer, ideally used with concurrent radiotherapy. Overall 64% of English and 48% of Welsh patients with proven small cell lung cancer received chemotherapy. However, evidence of chemo-radiation was only found in 12% of English and 28% of Welsh patients with small cell lung cancer. There is variation in the use of chemotherapy based on the age of a patient as illustrated in figure 1.12 below.

Figure 1.12: Proportion of patients with proven small cell lung cancer receiving chemotherapy in England and Wales based on age (N=4,530). Data from NLCA and CANISC (2006-2008).



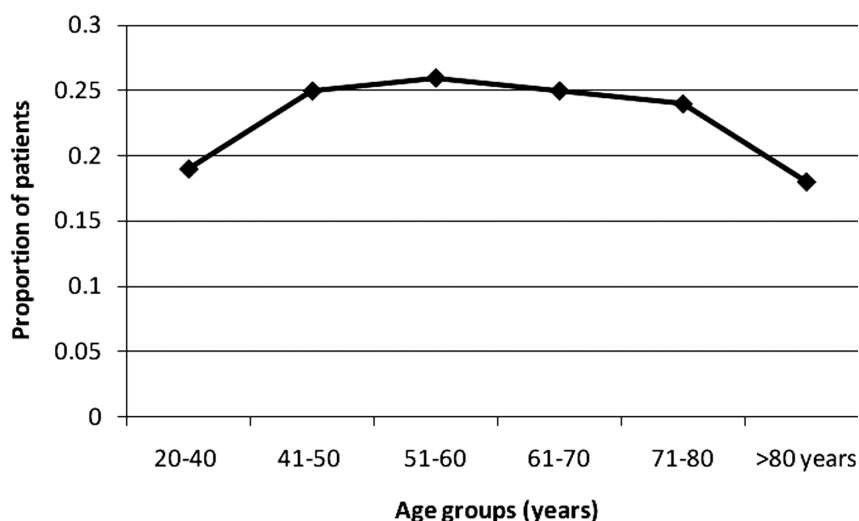
The NLCA 2009 Annual report published evidence that demonstrated variation in the proportion of patients with small cell lung cancer receiving chemotherapy across the Cancer Networks in England and Wales (NLCA, 2009) (figure 1.13).

Figure 1.13: Proportion of patients with small cell lung cancer receiving chemotherapy at level of Cancer Network (England and Wales). Data provided by NLCA.



Radiotherapy can be used in all histological subtypes and with both curative and palliative intent. It is not possible to differentiate accurately the treatment intent from data held within the NLCA, and so figure 1.14 illustrates the variation in use of radiotherapy with age for the whole cohort, regardless of histology.

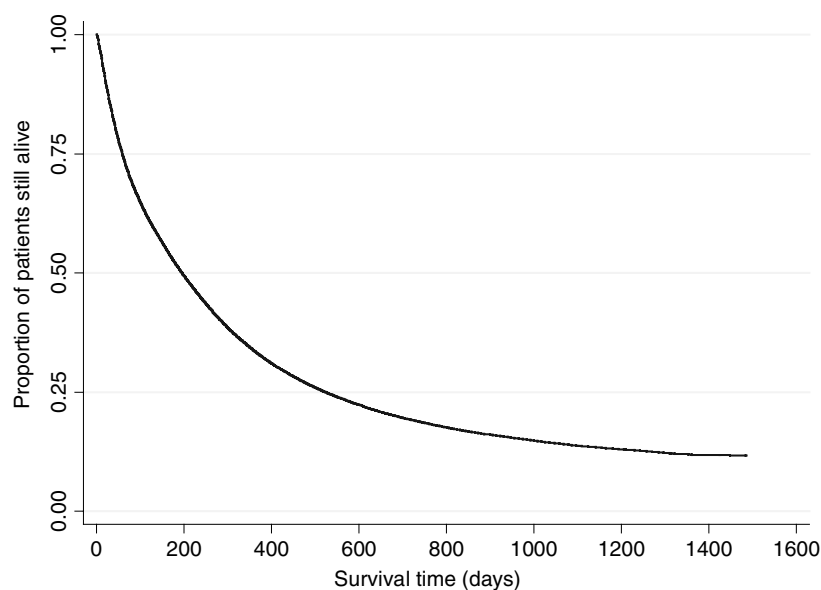
Figure 1.14: Proportion of overall cohort receiving radiotherapy in England and Wales based on age (N=73,730). Data from NLCA and CANISC (2006-2008).



1.9 Survival

The prognosis from lung cancer is poor, and it is the commonest cause of cancer related death in England and Wales, as well as worldwide. The median survival for individuals with lung cancer in England, is 203 days (interquartile range 62 to 545 days), and this is illustrated in figure 1.15 below.

Figure 1.15: Kaplan-Meier curve demonstrating overall survival of English patients with lung cancer (N=67,730). Data from NLCA (2006-08).

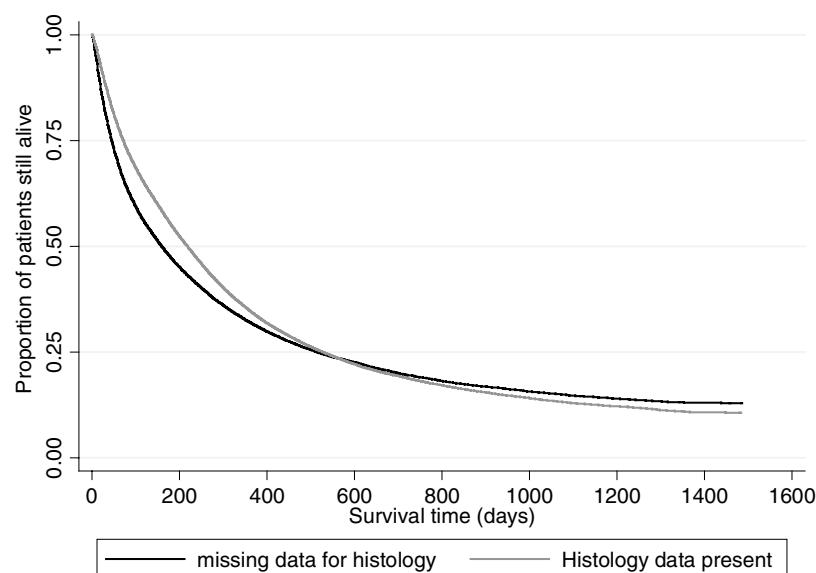


Evidence from the EUROCORE-4 report (Verdecchia et al., 2007) suggests there is significant variation in the 5 year survival rate across European countries, with a relative 5 year survival in England and Wales of 8.4% and 10.4% respectively. The mean 5 year survival rate for all countries within EUROCORE-4 was 10.9%, and for 13 registries within the American Surveillance Epidemiology and End Result (SEER) dataset was 15.7%. Survival rates were highest in Scandinavia, Belgium and Switzerland. It was noted, that for all areas, except central Europe, but including England and Wales, 5 year survival rates in lung cancer increased between 1991 and 2002. No adjustment can be made for stage of disease at presentation within EUROCORE-4, and this maybe an important limitation of the study.

There is evidence from a recent paper comparing national lung cancer survival between England, Sweden and Norway; that the excess mortality observed in England is primarily caused by excess deaths within the first three months after diagnosis (Holmberg et al., 2010). The comparisons of excess mortality between the countries for years 1-2, and 2-5 years post diagnosis showed very little variation. There was evidence that English patients were older than their Scandinavian counterparts. No histological data were used in this study, but previous research has not demonstrated any significant variation between European countries (Bennett et al., 2008). This study was based on registry data, and it was not possible to compare stage of disease, nor patient co-morbidity, and both these features will influence the proportion of patients receiving treatment with curative intent and their overall survival. Therefore the high rate of early death in individuals diagnosed with lung cancer in England could be the result of a number of features: advanced stage of disease at presentation, poor performance status and co-morbidity, access to healthcare being via a primary care physician rather than direct to secondary care, or different attitudes and rates of anti-cancer treatment.

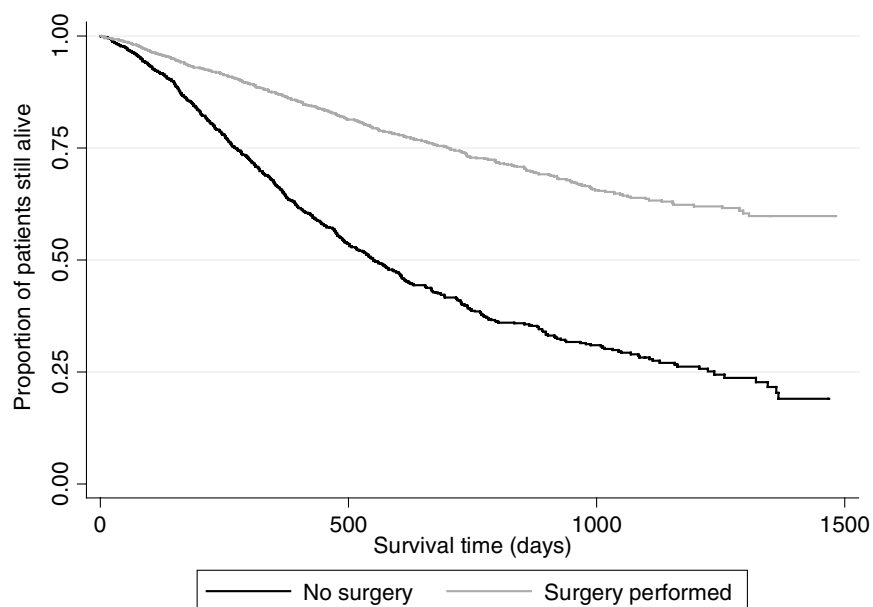
The lack of histological data for a large proportion of patients has already been mentioned, and may well be due in part to poor data entry to the NLCA. However, it may reflect ambivalence amongst clinicians to ensure a histological diagnosis is made in patients who are not candidates for active treatment. Therefore it is interesting to note that the survival curves for these two subgroups of patients, those with and those without a histological diagnosis; show early divergence with confluence latterly (figure 1.16). The median survival for those with a histological diagnosis is 217 days (interquartile range 71 to 527 days), compared to a median survival of 158 days (interquartile range 43 to 513 days) for those without histology recorded. Cox regression analysis reveals a small but significant benefit for those patients with, compared to those without, a histological diagnosis (unadjusted hazard ratio 0.93, 95% confidence interval 0.91, 0.94, $p < 0.001$). This is despite it being likely that obtaining a histological diagnosis lengthens the time to diagnosis and hence shortens survival time in the histology confirmed group. The most likely explanation for this observation is that fitter patients are more likely to be offered chemotherapy with a resultant survival benefit. Ensuring that all NHS Trusts offer the same proportion of their patients active treatment, might confer a meaningful improvement in median survival; via a modest reduction in early deaths.

Figure 1.16: Kaplan-Meier curve demonstrating the variation in survival based on whether data is entered on histology in NLCA (England only data, N=67,730).



It is possible to illustrate the effect of surgery on those patients with proven NSCLC who were performance status 0 or 1, and who had a stage recorded of IA-IIB. Although the numbers are relatively small, N=2,753, the Kaplan-Meier survival curve demonstrates a stark variation in their observed outcome (figure 1.17).

Figure 1.17: Kaplan-Meier curve demonstrating the observed outcome of a subgroup of patients with proven NSCLC, stage IA-IIIB, and performance status 0-1 (England only; N=2,753, of whom 1,698 had surgery, and 1,055 did not). Data from NLCA (2006-08).

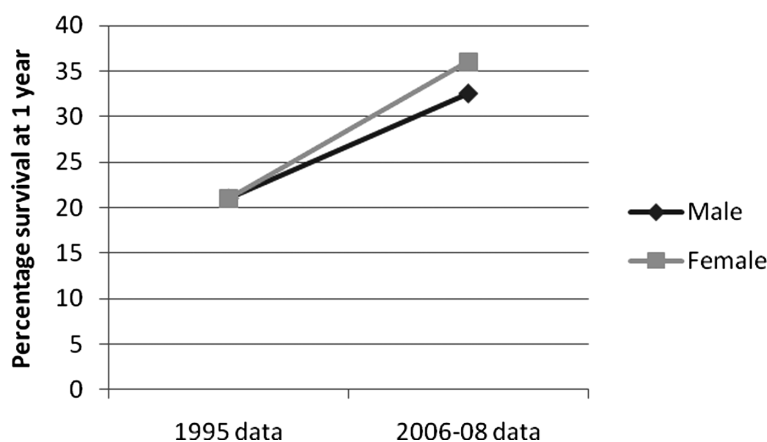


This highlights the need to proactively stage patients accurately and to assess their fitness for surgery, and if required optimise their co-morbidities prior to surgery, given the improved outcome observed in these patients after surgery.

One year survival

There has been a dramatic improvement in one year survival for individuals with lung cancer over the last 10 years. This may reflect improved cancer services within the National Health Service secondary to recommendations within the National Cancer Plan (34) and the Cancer Reform Strategy in England (35) and the Designed to Tackle Cancer in Wales Strategic Framework (36). Contemporary data reveals 32% of male patients and 35% female patients survive to one year in England, and 33% male and 37% female Welsh patients survive to one year (figure 1.18). These contemporary data suggest that one year survival in England and Wales is now approaching the figure of 37% quoted as 'good practice' in the EURO CARE-4 publication (Verdecchia et al., 2007). 'Good practice' is based on the highest one year survival rates of countries with 100% registration in EURO CARE-4.

Figure 1.18: One year survival data for England and Wales (2006-2008); Data from NLCA and CANISC.

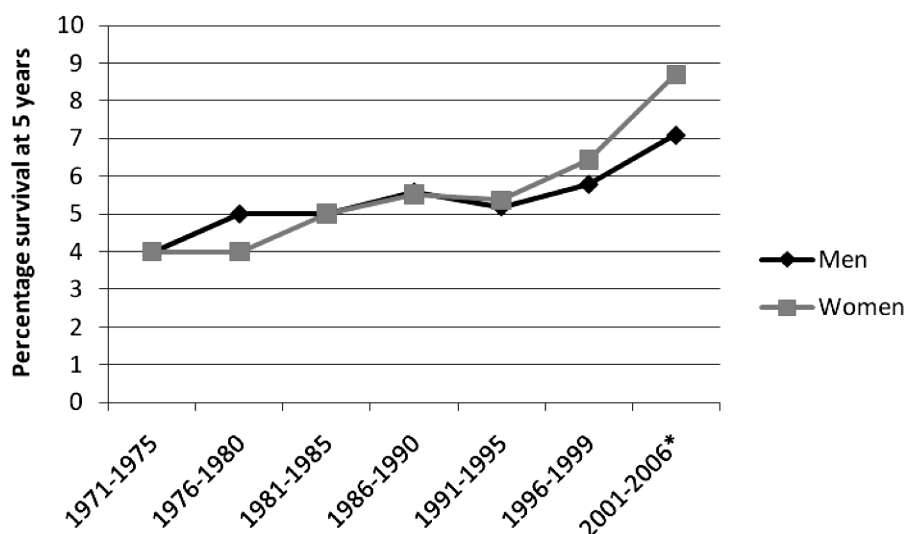


However, the improvement in overall percentage of patient's alive one year after diagnosis conceals the geographical variation that has been described between Primary Care Trusts (PCT) in England ranging from 15.4% to 43.7%. (DoH, 2009). This apparent discrepancy in survival will be influenced by patient features the infrastructure of the health service (specifically the availability of diagnostic and treatment facilities in individual PCTs) but importantly, may be influenced by the approach the local MDT takes to selection of patients for active treatment.

Five year survival

The percentage of patients surviving to 5 years, by definition cured, remains low, 7% for males and 9% for females. Although this has improved over the last 40 years, it remains lower than comparable European and North American countries (Verdecchia et al., 2007).

Figure 1.19: Five year survival data over time. Reproduced with kind permission of Cancer Research UK.



1.10 Facilities available at NHS Trusts in England and Wales

As part of the needs assessment exercise an online survey was distributed to all lung cancer MDT leads at NHS Trusts in England and all Local Health Boards in Wales (Appendix 1). The lung cancer leads were invited to complete the survey which primarily focussed on the composition of the multi-disciplinary team (MDT), and the diagnostic and therapeutic facilities

available within their Trust or their cancer Network. The response rate was 101 (66%) in England and 6 (43%) in Wales. The NHS in Wales underwent a major reorganisation in October 2009, with the formation of seven Local Health Boards from the previous configuration Local Health Boards and Trusts. Each new Local Health Board therefore encompasses several MDTs.

Cancer MDTs were recommended in the NHS Cancer Plan in England (DoH, 2000) and in the Cameron Report in Wales [WAG, 2005], and have been adopted across all cancer sites.

The aim was to provide a body of experience and breadth of knowledge such that patients under investigation for cancer could be rapidly assessed and the appropriate treatment started at the earliest opportunity. There are no fixed criteria on which medical disciplines should comprise the MDT, and the National Cancer Peer Review Programme in England (which is led by the National Cancer Action Team, NCAT) have recommended that all personnel deemed relevant to the decision making process should be involved either in person or via video/teleconferencing. The majority of lung cancer MDTs would include a chest physician, radiologist, pathologist, and specialist nurse; as well as oncologists, surgeons and members of the palliative care team if available. The Peer Review Programme provides important information on the number, structure, function and quality of all cancer MDTs across England. Between 2004 and 2008, peer reviews of cancer services were carried out in each cancer network, for each cancer site. The process has been modified over the last 6 years, and now occurs on an annual basis, involves a degree of self assessment, and there are 32 measures to which an Lung Cancer MDT is assessed for compliance. There are currently 161 lung cancer MDTs across 157 English NHS Trusts, and 14 MDTs in Wales.

In Wales the Welsh Assembly Government launched the National Cancer Standards in 2005, including lung cancer [WAG, 2005], with the objective that compliance should be achieved by March 2009. The National Cancer Standards have provided NHS Wales with a clear set of quality requirements that have been central to the Welsh Assembly Government's Cancer Policy since 2005 [WAG, 2005]. Compliance to these standards has been determined by using information provided by self assessment by NHS Trusts in Wales and the most recent data was published in 2009¹.

The survey distributed by the NICE GDG revealed that between 90-100% of MDTs in England and Wales had a respiratory physician, chest radiologist, pathologist, specialist nurse and clinical oncologist on the MDT. However, only 80% of MDTs had a medical oncologist, and 85% had a thoracic surgeon on the MDT.

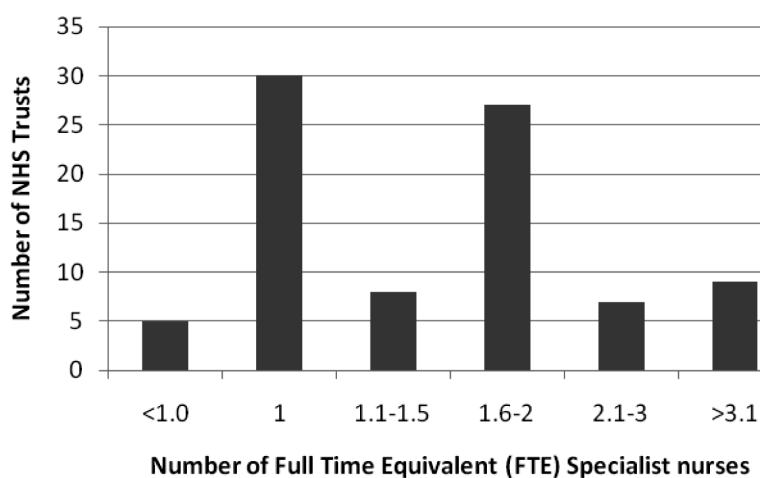
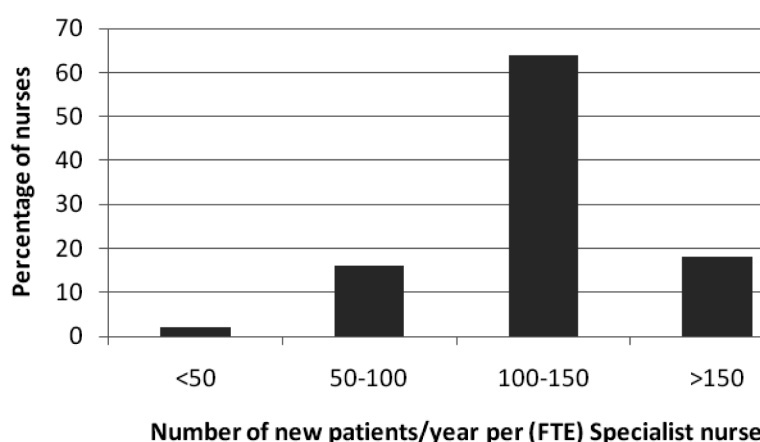
Of those English and Welsh MDTs responding to the survey, all now have an MDT coordinator, 95% have an electronic database, and 65% have a data administrator. These figures suggest that the lung cancer MDT is now an established component of every NHS Trust and the majority have adequate support staff.

The analyses described in the remainder of the Needs Assessment use only the on-line results from lung cancer leads at English NHS Trusts, because the number of Welsh responses would not allow appropriate statistical analysis nor could they be merged with the English responses.

1.11 Lung Cancer Specialist Nurse

The workload of the specialist nurse was also evaluated in the survey, and revealed significant variation in the number of new cases allocated to each full time equivalent (FTE) nurse, and the number of additional tasks they are expected to perform.

¹<http://www.wales.nhs.uk/sites3/page.cfm?orgid=322&pid=47547>

Figure 1.20: Number of (FTE) specialist nurses at NHS Trusts in England.**Figure 1.21:** The variation in workload of new patients per (FTE) specialist nurse (England only data).

The responsibilities of the specialist nurse can vary, and often involve inappropriate tasks that reduce the time they can spend with patients, their families and carers. The table below lists some of the tasks performed by specialist nurses in England.

Duties of the Specialist nurse	% of nurses
Telephone support	100
Nurse-led clinics	44
Support groups	52

Only 44% of specialist nurses have secretarial support, and 57% have formal cover arrangements for sick leave.

Access to diagnostic facilities

The results of this NICE lung cancer GDG survey reveal wide variation in the availability of diagnostic facilities at NHS Trusts in England (figure 1.22) and at the level of Cancer Networks (figure 1.23). Consequently some patients will be expected to travel considerable distances to undergo diagnostic procedures and for which there may be a moderate delay of more than 2 weeks (figures 1.24 and 1.25).

Figure 1.22: Endobronchial diagnostic facilities available at an NHS Trust (Survey data).

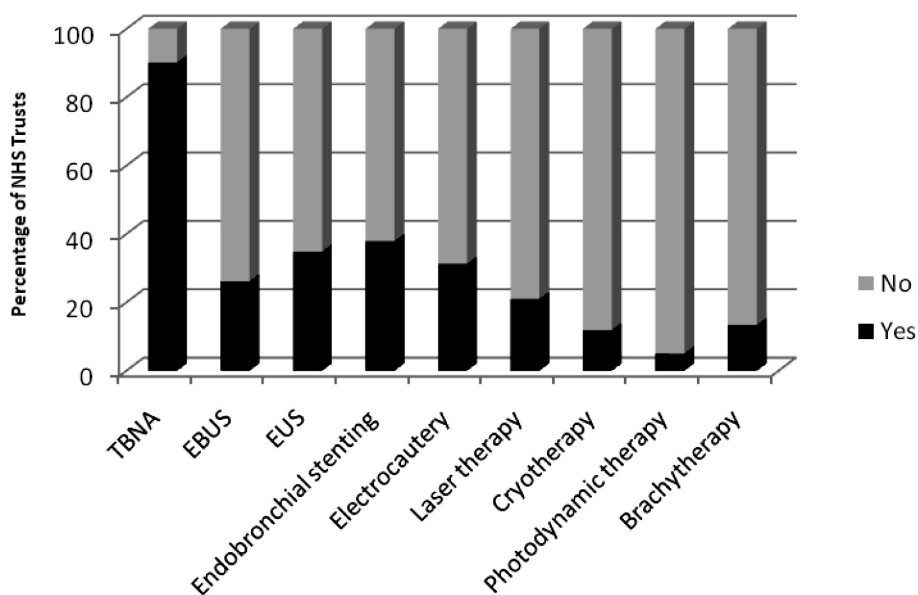


Figure 1.23: Endobronchial diagnostic and therapeutic facilities available within a Cancer Network (English only data).

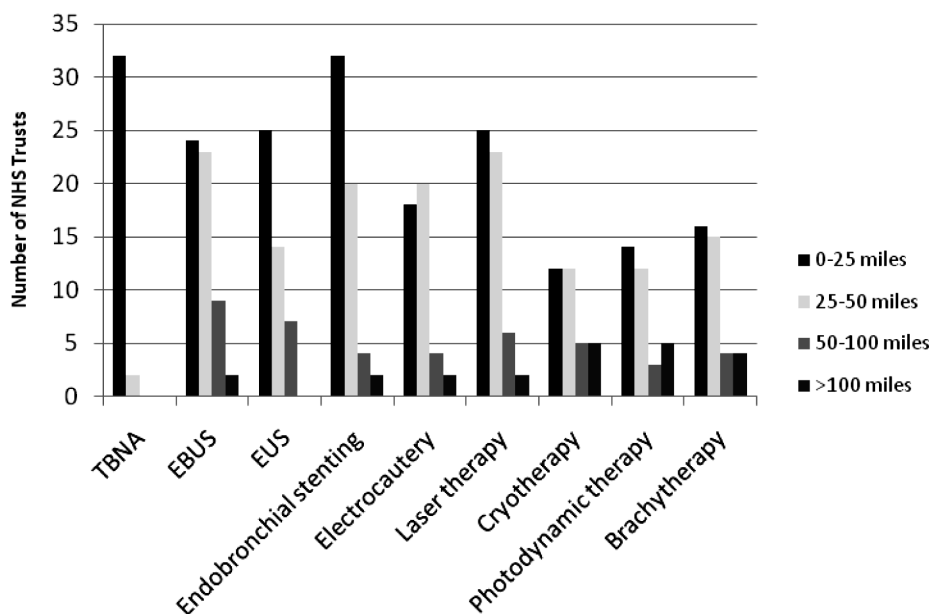


Figure 1.24: Distance required to access certain diagnostic and therapeutic services.

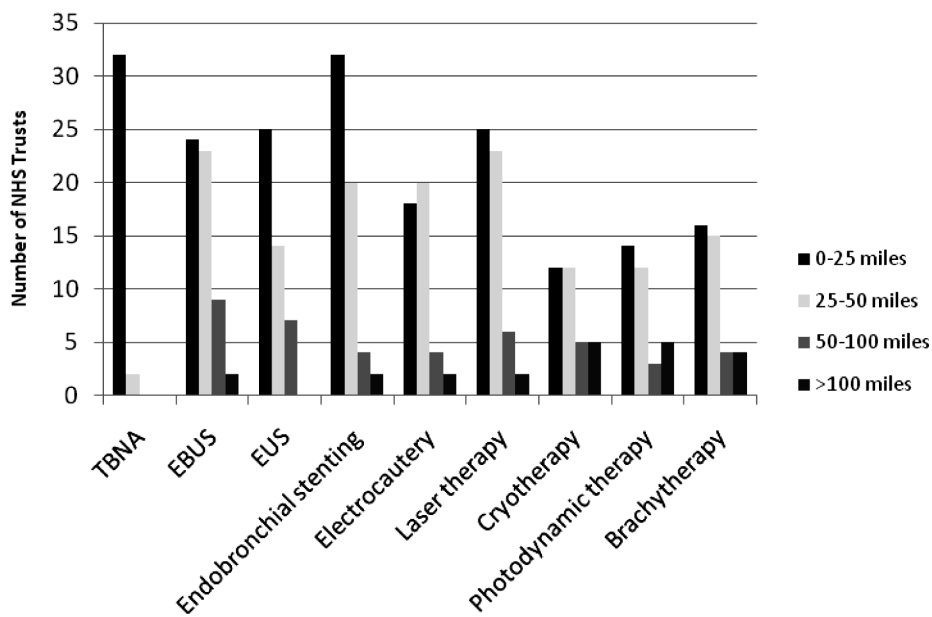
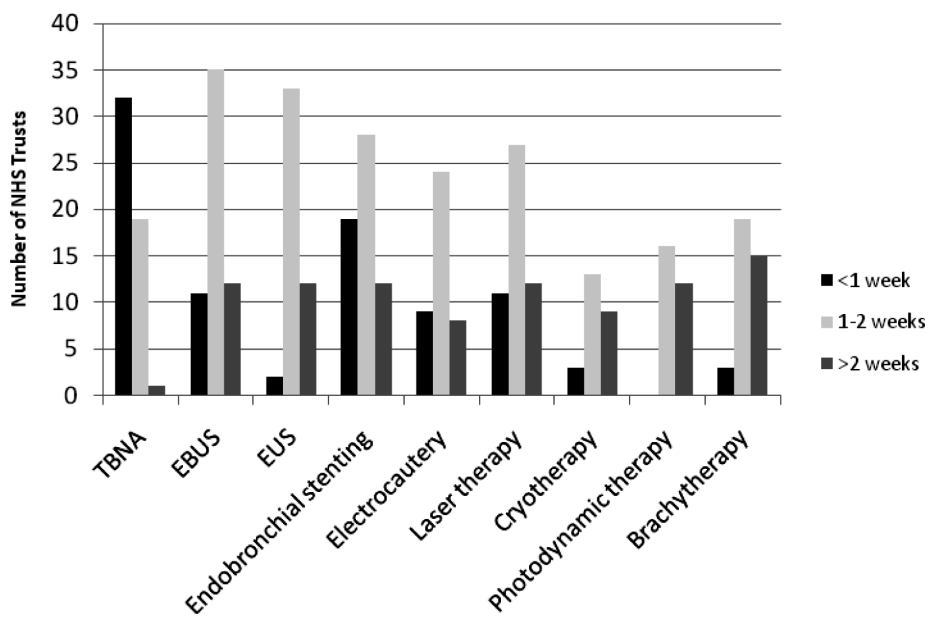


Figure 1.25: Interval between referral and access for certain diagnostic and therapeutic services.



Updated 2011

PET scanning

Over the past 15 years a number of publications have supported the use of FDG-PET scanning to assist the staging process of lung cancer. The 2005 NICE Guidelines for Diagnosis and Treatment of Lung Cancer 2005 (NICE CG24, 2005) recommended the use of this imaging modality, and the availability of PET-CT scanners has become almost universal. However, this availability may be at the level of the Cancer Network, rather than at individual NHS Trusts (see figures 1.26, 1.27 and 1.28).

Figure 1.26: Proportion of NHS Trusts and Cancer Networks with PET scanners (England only data).

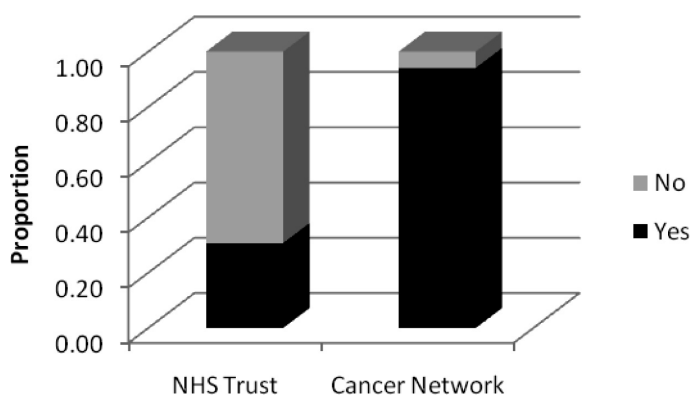


Figure 1.27: Distance travelled to access a PET scanner (England only data).

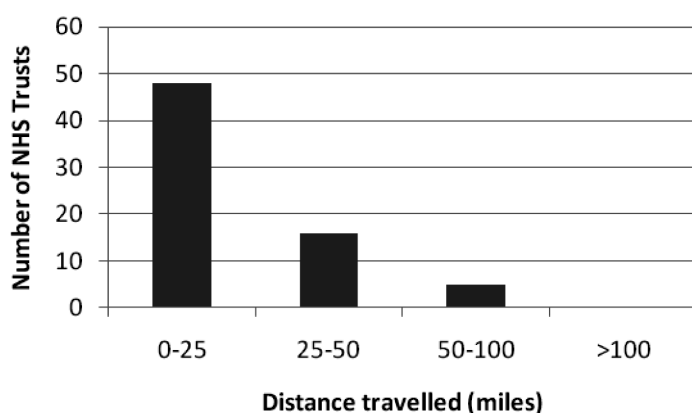
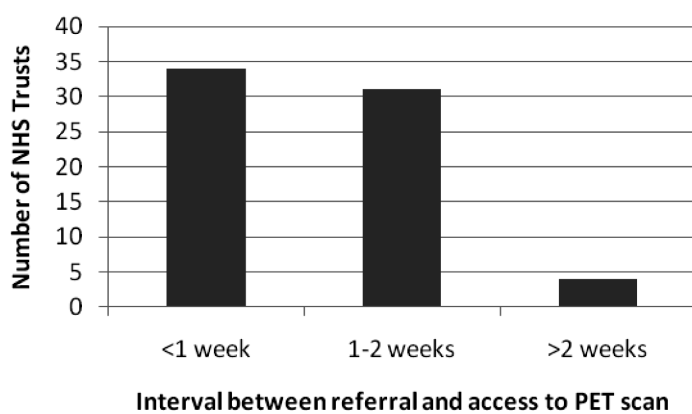


Figure 1.28: Interval between referral and access to PET scanning (England only data).



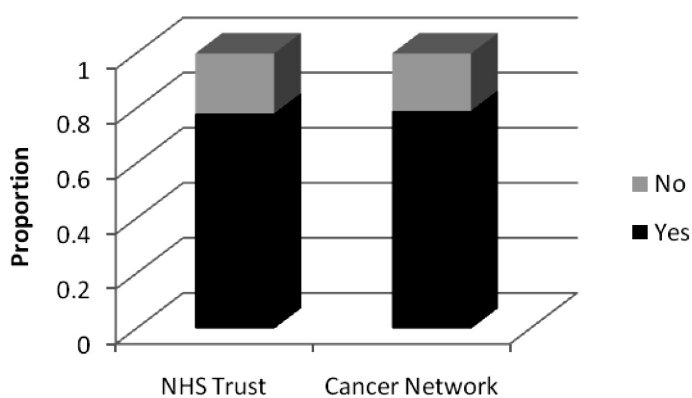
Pathological services

The importance of a uniformly high histological confirmation rate has already been emphasised, but it is also important that there is not an unnecessary delay in obtaining the histological report as this will delay the final diagnostic and therapeutic decision of the MDT. Results from the survey of lung cancer leads revealed 80% of diagnostic samples are returned within 5 days, i.e. within a working week, ensuring the result is available for the next MDT meeting.

Pulmonary rehabilitation services

There was good availability of pulmonary rehabilitation services across English lung cancer MDTs who completed the survey, with 78% of NHS Trusts having access to this service; and 79% of Cancer Networks (figure 1.29). 92% of NHS Trusts reported a patient would not have travel more than 25 miles to receive this service, although 86% stated that there would be a delay of more than 2 weeks to access this service.

Figure 1.29: Proportion of NHS Trusts and Cancer Networks with pulmonary rehabilitation services (England only data).



Access to treatment facilities

There is significant variation in the treatment facilities available at individual NHS Trusts. Amongst the 157 NHS Trusts in England there are only 31 Cardiothoracic surgical centres and 49 Radiotherapy centres. Figure 1.30 illustrates the variation in treatment facilities available at the level of an individual NHS Trust; although the majority of treatments are available within a Cancer Network (figure 1.31). There may well be a significant distance to travel and delay to receive the recommended treatment modality (figure 1.32 and 1.33 below).

Figure 1.30: Treatment facilities available at an NHS Trust (England only data).

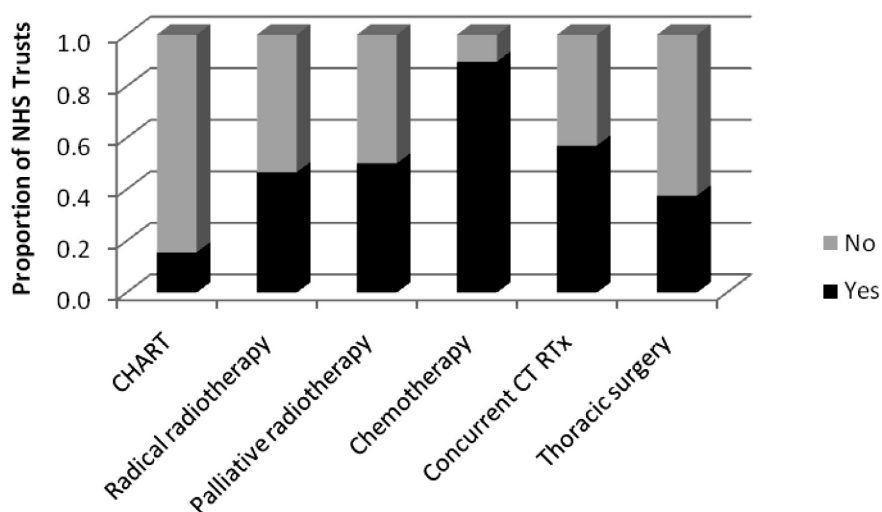


Figure 1.31: Treatment facilities available within a Cancer Network (England only data).

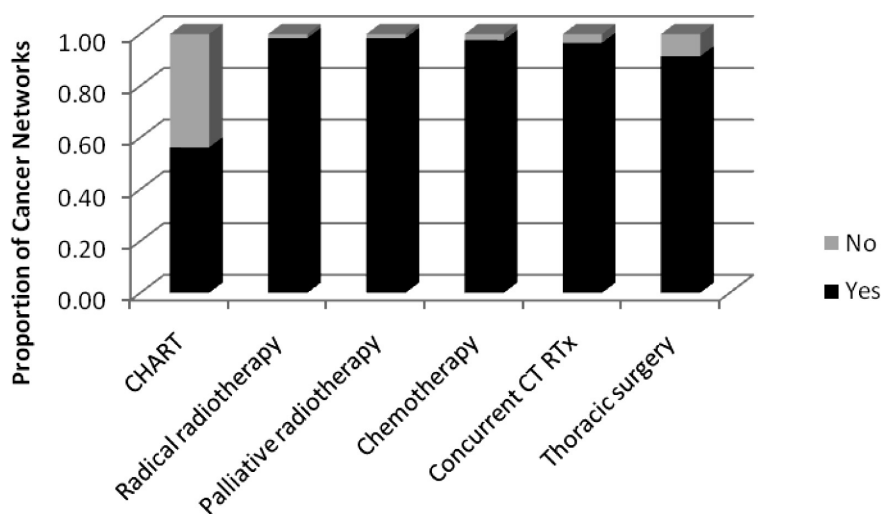


Figure 1.32: Distance required to access specific treatment modalities (England only data).

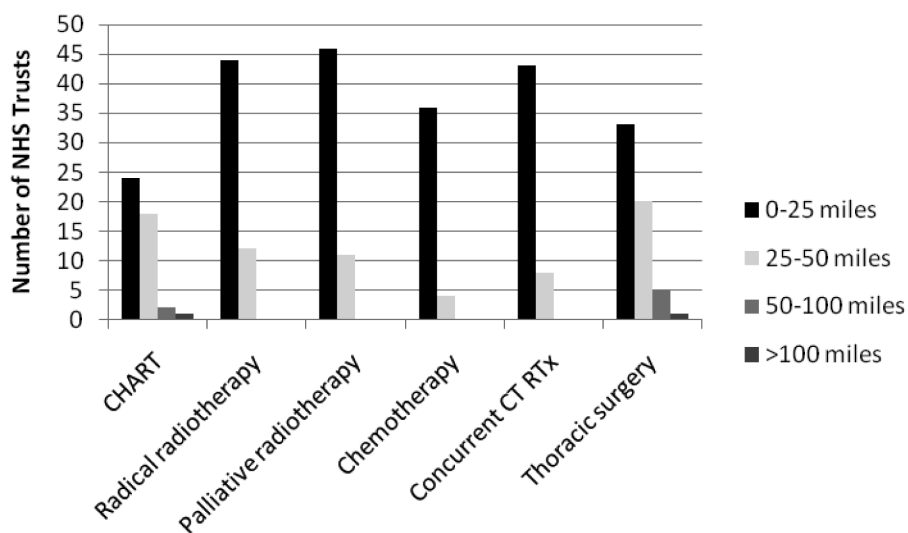
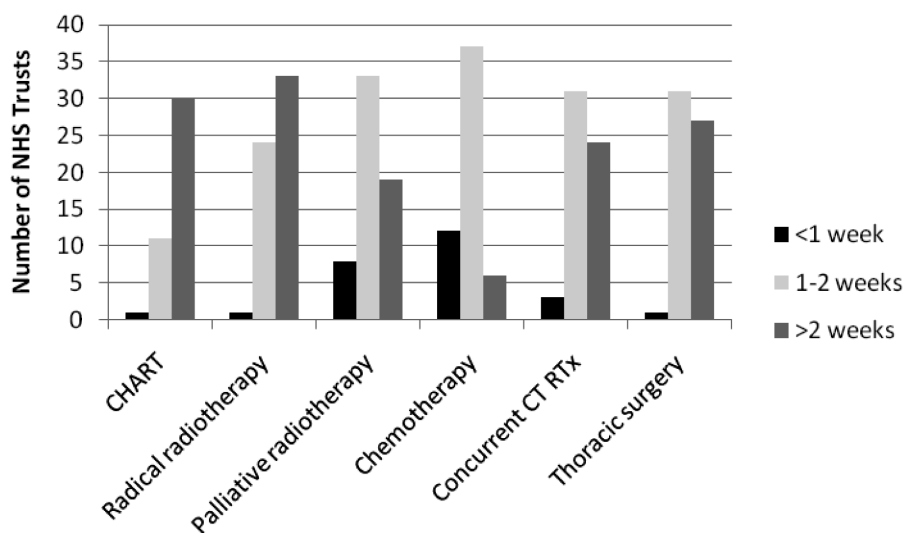


Figure 1.33: Interval between referral and access to specific treatment modalities (England only data).



There have been a number of publications which suggest that the longer a patient with cancer must travel to a treatment centre the less likely they are to undergo treatment (Crawford et al., 2009; Jones et al., 2008). Amongst patients with lung cancer in Northern England; the adjusted odds ratio for receiving surgery, chemotherapy and radiotherapy, was 0.76 (95% CI 0.68, 0.85), 0.70 (95% CI 0.63, 0.79), and 0.86 (95% CI 0.80, 0.91) respectively, for those living furthest, compared to those living closest, to the treatment centre (Jones et al., 2008).

Therefore, whilst specialised treatment centres may have increased expertise as the high throughput of patients will increase experience; this benefit must be balanced with the potential impact that fewer, centralised, specialised centres may result in reduced uptake of treatment by individuals in remote areas.

References

- Aesculapius Medical Press, editor. The effective management of lung cancer. 1 ed 2001.
- Bennett, V. A., Davies, E. A., Jack, R. H., Mak, V., Moller, H. Histological subtype of lung cancer in relation to socio-economic deprivation in South East England. *BMC cancer*. 2008;8:139.
- Beral, V. P. R. UK cancer survival statistics are misleading and make survival look worse than it is. *BMJ*. 2010;341.
- Birkmeyer, J. D., Siewers, A. E., Finlayson, E. V., Stukel, T. A., Lucas, F. L., Batista, I. et al. Hospital volume and surgical mortality in the United States. *N Engl J Med*. 2002 Apr 11;346(15):1128-37.
- Bouchardy, C., Fioretta G., De Perrot M., Obradovic, M., Spiliopoulos, A. Determinants of long term survival after surgery for cancer of the lung: A population-based study. *Cancer*. 1999 Dec 1;86(11):2229-37.
- Cancer Research UK survival data. 2010; Available from: <http://info.cancerresearchuk.org/cancerstats/types/lung/survival/index.htm#source14>
- Cancer Research UK. Cancer Stats. 2010; Available from: <http://info.cancerresearchuk.org/cancerstats/types/lung/index.htm?script=true#mortality>.
- Crawford, S. M., Sauerzapf, V., Haynes, R., Zhao, H., Forman, D., Jones, A. P. Social and geographical factors affecting access to treatment of lung cancer. *Br J Cancer*. 2009 Sep 15;101(6):897-901.
- Department of Health. Cancer Reform Strategy; Achieving local implementation - second annual report. 2009.
- Department of Health. Cancer Reform Strategy. 2007.
- Department of Health. Cancer Reform Strategy - Equality Impact Assessment. 2007.
- Department of Health. The NHS Cancer Plan. 2000.
- Harding, S., Rosato, M., Teyhan, A. Trends in cancer mortality among migrants in England and Wales, 1979-2003. *Eur J Cancer*. 2009 Aug;45(12):2168-79.
- Holmberg, L., Sandin, F., Bray, F., Richards, M., Spicer, J., Lambe, M. et al. National comparisons of lung cancer survival in England, Norway and Sweden 2001-2004: differences occur early in follow-up. *Thorax*. 2010 May;65(5):436-41.
- Jack, R. H., Gulliford, M. C., Ferguson, J., Moller, H. Explaining inequalities in access to treatment in lung cancer. *J Eval Clin Pract*. 2006 Oct;12(5):573-82.
- Jones, A. P., Haynes, R., Sauerzapf, V., Crawford, S. M., Zhao, H., Forman, D. Travel time to hospital and treatment for breast, colon, rectum, lung, ovary and prostate cancer. *Eur J Cancer*. 2008 May;44(7):992-9.

Khan, N. F., Perera, R., Harper, S., Rose, P. W. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Fam Pract.* 2010;11:1.

Kogevinas, M., Marmot, M. G., Fox, A. J., Goldblatt, P. O. Socioeconomic differences in cancer survival. *J Epidemiol Community Health.* 1991 Sep;45(3):216-9.

Mackenbach, J. P., Huisman, M., Andersen, O., Bopp, M., Borgan, J. K., Borrell, C. et al. Inequalities in lung cancer mortality by the educational level in 10 European populations. *Eur J Cancer.* 2004 Jan;40(1):126-35.

Mao, Y., Hu, J., Ugnat, A.M., Semenciw, R., Fincham, S. Socioeconomic status and lung cancer risk in Canada. *Int J Epidemiol.* 2001 Aug;30(4):809-17.

National Institute for Clinical Excellence. *The Diagnosis and Treatment of Lung Cancer.* 2005.

National Lung Cancer Audit. 2009.

Office of National Statistics. *General Lifestyle Survey 2008. Smoking and drinking among adults, 2008.2010.*

Peake, M. D., Thompson, S., Lowe, D., Pearson, M.G. Ageism in the management of lung cancer. *Age Ageing.* 2003 Mar;32(2):171-7.

Pollock, A. M., Vickers, N. Deprivation and emergency admissions for cancers of colorectum, lung, and breast in south east England: ecological study. *BMJ.* 1998 Jul 25;317(7153):245-52.

Pollock, A. M., Vickers, N. Breast, lung and colorectal cancer incidence and survival in South Thames Region, 1987-1992: the effect of social deprivation. *J Public Health Med.* 1997 Sep;19(3):288-94.

Pugh, H., Power, C., Goldblatt, P., Arber, S. Women's lung cancer mortality, socio-economic status and changing smoking patterns. *Soc Sci Med.* 1991;32(10):1105-10.

Raine, R., Wong, W., Scholes, S., Ashton, C., Obichere, A., Ambler, G. Social variations in access to hospital care for patients with colorectal, breast, and lung cancer between 1999 and 2006: retrospective analysis of hospital episode statistics. *Bmj.* 2010;340:b5479.

Rich, A. L., Tata, L. J., Stanley, R. A., Free, C. M., Peake, M. D., Baldwin, D. R. et al. Lung cancer in England: Information from the National Lung Cancer Audit (LUCADA). *Lung Cancer.* 2010 Aug 3.

Schwartz, K. L., Crossley-May, H., Vigneau, F. D., Brown, K., Banerjee, M. Race, socioeconomic status and stage at diagnosis for five common malignancies. *Cancer Causes Control.* 2003 Oct;14(8):761-6.

Shack, L., Jordan, C., Thomson, C. S., Mak, V., Moller, H. Variation in incidence of breast, lung and cervical cancer and malignant melanoma of skin by socioeconomic group in England. *BMC Cancer.* 2008;8:271.

Stephens, R. J., Johnson, D. H., Treatment and outcomes for elderly patients with small cell lung cancer. *Drugs Aging.* 2000 Sep;17(3):229-47.

Thomas, L., Doyle, L. A., Edelman, M. J. Lung cancer in women: emerging differences in epidemiology, biology, and therapy. *Chest.* 2005 Jul;128(1):370-81.

Treasure, T., Utley, M., Bailey, A. Assessment of whether in-hospital mortality for lobectomy is a useful standard for the quality of lung cancer surgery: retrospective study. *BMJ.* 2003 Jul 12;327(7406):73.

Verdecchia, A., Francisci, S., Brenner, H., Gatta, G., Micheli, A., Mangone, L. et al. Recent cancer survival in Europe: a 2000-02 period analysis of EURO-CARE-4 data. *Lancet Oncol.* 2007 Sep;8(9):784-96.

Welsh Assembly Government. *Designed to Tackle Cancer in Wales Strategic Framework.* 2005

Welsh Assembly Government. *National Standards for Lung Cancer Services.* 2005

The Welsh Office. *Cancer Services in Wales: A report by the Cancer Services Expert Group.* 1996.

Wynder, E. L., Muscat, J. E. The changing epidemiology of smoking and lung cancer histology. *Environ Health Perspect.* 1995 Nov;103 Suppl 8:143-8.

2 Access to services and referral

2.1 The importance of early diagnosis

Following consultation on the draft scope (see Chapter 1) there was general consensus amongst stakeholders not to update any of the topics on 'Access to services and referral' from the 2005 guideline. Therefore none of the the recommendations and associated clinical evidence in this Chapter has been updated.

The National Lung Cancer Audit shows that a large proportion of patients present with lung cancer at a late stage and with a performance status that makes treatment with curative intent difficult. This may in part be due to lack of symptoms in the early stages of lung cancer, but may also result from delays in patients reporting new symptoms. Better provision of information to the public on how to recognise symptoms, has been suggested as a way of getting people with suspected cancer to present to GPs sooner. Charities, the Department of Health and individuals (usually as part of research) have sponsored a variety of initiatives to raise awareness. Particularly noteworthy are the "Lung Cancer Awareness Month"¹, the Healthy Communities Collaborative Improvement Partnership pilots, and local initiatives such as the early intervention in lung cancer within Doncaster (EICiD) project. It is difficult to assess the effectiveness of these initiatives and although the GDG considered this an important area, it was not within the scope for the 2011 update.

Early diagnosis might also be achieved by screening. This has been shown in a number of studies employing imaging methods, most recently computed tomography (CT), though as yet no study has demonstrated an overall reduction in mortality as a result of screening. This topic was again considered important but not a priority for an evidence review, especially as there are many studies ongoing that will report after the publication of this guideline.

The 2007 Cancer Reform Strategy includes recommendations for early diagnosis and awareness, and established the National Awareness and Early Diagnosis Initiative (NAEDI). This is a public sector/third sector partnership between the Department of Health, National Cancer Action Team, and Cancer Research UK. The role of NAEDI is to co-ordinate and provide support to activities and research that promote the earlier diagnosis of cancer. Lung cancer is being prioritised within this initiative.

NAEDI activity is organised into the following work streams:

- Achieving early presentation by public and patients
- Optimising clinical practice and systems
- Improving GP access to diagnostics
- Research, evaluation and monitoring.

Late diagnosis in lung cancer is of key concern and it is anticipated that NAEDI will ensure improvement through evaluated interventions with the involvement of local communities and by strong GP leadership. For further details please see: <http://www.ncri.org.uk/default.asp?s=1&p=5&ss=11>

¹ The HCCIP ceased operating in January 2010

Recommendation

- The public needs to be better informed of the symptoms and signs that are characteristic of lung cancer, through coordinated campaigning to raise awareness. [2005]

2.2 Referral and indications for chest radiography

The 2005 guideline gave advice about key symptoms and signs of lung cancer and endorsed the NICE guidelines on urgent referral². The most important point was that the symptoms and signs of lung cancer can be difficult to distinguish from those of other diseases (some of which may coexist in lung cancer patients). The 2005 NICE guidance for referral or request for chest X-ray following three weeks of symptoms is endorsed. Many lung cancers are diagnosed via atypical pathways (e.g. emergency or A&E admissions, or via other specialities, or opportunistically).

Since the 2005 NICE guideline, the British Thoracic Society³ have issued a statement on criteria for referral, admission and discharge of respiratory diseases and this includes lung cancer.



² Referral Guidelines for suspected cancer, NICE 2005

³ British Thoracic Society Standards of Care Committee: BTS statement on criteria for specialist referral, admission, discharge and follow-up for adults with respiratory disease. *Thorax* 2008;63(Suppl 1):i1-i16. doi:10.1136/thx.2007.087627

2.2.1 Chest X-ray

This investigation is an essential tool in primary care or non-specialist secondary care to investigate suspicious symptoms. The evidence for the efficacy of chest X-ray was not reviewed as part of this update. The 2005 guideline commented that chest X-ray was a mandatory first-line investigation. However, the GDG noted that almost all patients referred to the specialist lung cancer team will have a CT thorax and therefore a chest X-ray might be omitted where this would not influence the decision to perform a CT.

[Redacted text block]

[Redacted text block]

3 Communication

Clinical topic: For patients with lung cancer and their carers, what is the effectiveness of communication methods to support decisions regarding treatment options?

People with lung cancer and their carers face an ever increasing amount of new and often complex information at a time when their ability to process and understand it can be impaired by the stress of their illness. The amount and nature of the information required by patients and given by health care professionals will change throughout the care pathway as information is gathered about the diagnosis, the stage of the disease, and the fitness for treatment.

Decision aids (DA) are assessed favourably by patients and their physicians and can assist patients in understanding the benefits and risks of treatment and to help them choose the treatment that is most appropriate for them without increasing patient anxiety.

The Department of Health recommends that any information provided is accurate, clear, full, prompt and presented at all stages of the pathway in a culturally sensitive way in verbal and other means accessible to the patient. The executive summary of the cancer reform strategy (2007) states: "We will improve information for patients through a range of product and pathway initiatives...." Later in the strategy it is stated that stakeholders consulted had "...strongly recommended that the issues of information, better face-to-face communication and support for decision making should be given the highest priority with regard to actions to improve patient experience." The Nursing Contribution to Cancer Care (2002), Integrating Lung Cancer Nursing: a Good Practice Guide (2004) and the Cancer Reform Strategy recommend that a clinical nurse specialist should be available to support patients and carers at all stages of the care pathway. The NHS Cancer Plan includes a commitment to advanced communication skills training and this is a Peer Review measure for all core members of the MDT. Tumour specific national information pathways are agreed. A partnership between, Cancer Research UK and Macmillan Cancer Support (now incorporating CancerBackup) is developing a system to provide sections of content to support the implementation of information prescriptions which will provide patients with high quality information, tailored to their individual needs.

The NICE *Guidance on Cancer Services: Improving Supportive and Palliative Care for Adults with Cancer*¹ (NICE 2004) gave a key recommendation: "Each multidisciplinary team or service should implement processes to ensure effective inter-professional communication within teams and between them and other service providers with whom the patient has contact. Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of 'key worker' for individual patients." This has been translated into the measures of the National Cancer Peer Review Programme so that there is a requirement that each patient should have a single named 'key worker' assigned to them and that it is the responsibility of the Clinical Nurse Specialist members of the MDT to ensure that the key worker is identified. The measures go on to give information on the responsibilities of this vital role which, with the patients consent and agreement, will aim to coordinate the patient's care and promote continuity, for example, by ensuring the patient knows who to access for information and advice. In practice, this role is invariably carried out by the Clinical Nurse Specialist and patient experience surveys have shown that patients may not understand or recognise the term 'Key Worker' and this Guideline will reflect this within its recommendation that a lung cancer nurse specialist is available at all stages of care to support patients and carers.

¹ <http://guidance.nice.org.uk/CSGSP>

Good communication is vital at all stages of the pathway. It is important to appreciate that the breaking of bad news occurs more than once and requires the same sensitive approach each time e.g. at diagnosis, during treatment, and at relapse. A specific area in which communication methods are vital in establishing patient's wishes is in end of life care. The Agency for Healthcare Research and Quality (2007) has recommended a pro-active approach to discussions concerning end of life care and UK guidelines are published that provide advice about how, when, and where to discuss this with patients http://www.endoflifecareforadults.nhs.uk/eolc/files/NHS_NEOlc_ADRT_082008.pdf.

In the 2005 NICE guideline, communication was recognised as an important topic. For the updated guideline the search for evidence was limited to communication methods assisting decisions about treatment. In deciding on treatment, patients and carers require information that they can understand so that they can make an informed decision. This is of particular benefit when the advantages of one option over another are marginal or when there are other complicating factors such as borderline fitness and hence more risk of harm.

Recommendations

- Find out what the patient knows about their condition without assuming a level of knowledge. Provide patients with the opportunity to discuss tests and treatment options in a private environment, with the support of carers, and time to make an informed choice. [NEW 2011]
- Ensure that a lung cancer clinical nurse specialist is available at all stages of care to support patients and carers. [NEW 2011]
- Offer accurate and easy-to-understand information to patients and their carers. Explain the tests and treatment options, including potential survival benefits, side effects and effect on symptoms. [NEW 2011]
- Consider tailor-made decision aids to help patients to:
 - understand the probable outcomes of treatment options
 - consider the personal value they place on benefits versus harms of treatment options
 - feel supported in decision-making
 - move through the steps towards making a decision
 - take part in decisions about their healthcare. [NEW 2011]
- Offer patients a record of all discussions that have taken place with them and a copy of any correspondence with other healthcare professionals. Ensure all communications are worded in such a way to assist understanding. [NEW 2011]
- Respect the patient's choice if they do not wish to confront future issues. [NEW 2011]
- Avoid giving patients unexpected bad news by letter. Only give unexpected bad news by phone in exceptional circumstances. [NEW 2011]
- Offer to discuss end-of-life care with the patient sensitively and when appropriate. Wherever possible, avoid leaving this discussion until the terminal stages of the illness. [NEW 2011]
- Document discussions with the patient about end-of-life care. In particular, document:
 - specific concerns of the patient
 - their understanding of their illness and its prognosis
 - important values or personal goals for care
 - their preferences for the types of care or treatment that may be beneficial in the future and their availability. [NEW 2011]

Recommendations (Cont.)

- Share information between healthcare professionals about:
 - any problems the patient has
 - the management plan
 - what the patient has been told
 - what the patient has understood (where possible)
 - the involvement of other agencies
 - any advance decision made by the patient. [NEW 2011]

Clinical evidence

The volume of evidence for this topic was extremely limited and of poor quality. The evidence reported includes two phase I studies (Brundage et al., 2001; Leighl et al., 2008) and three cross-sectional survey studies (Dubey et al., 2005; Gabrijel et al., 2008; Huskamp et al., 2009). Each of these studies had high levels of bias ranging from small sample sizes, selection bias of study participants, recall bias, and un-standardised information evaluated.

Brundage et al. (2001) conducted a phase I study to evaluate whether a decision aid (DA) could be implemented in a regional cancer centre and to examine what the criteria for an effective DA should be. Findings indicated that implementing the DA for patients with locally advanced NSCLC is feasible; that it is favorably assessed by patients and their physicians and that it can assist patients in understanding the benefits and risks of treatment and to choose the treatment that is most consistent with their values. Leighl et al. (2008) assessed the use and acceptability of a DA for patients with metastatic NSCLC for use during oncology consultations to facilitate patient decision-making regarding first-line chemotherapy treatment. The DA was shown to be feasible, acceptable to patients and to improve understanding of advanced NSCLC without increasing patient anxiety. Dubey et al. (2005) examined whether patients perceived that they were being informed of various chemotherapy side effects and options and showed that improved communication between physician and patient about the likelihood of side effects may reduce chemotherapy-related stress for patients. Gabrijel et al. (2008) investigated what information newly diagnosed patients with lung cancer recall and how satisfied they are with physicians' communication and reported that recall of information about the intent of treatment is poor, and satisfaction with communication of the intent of treatment is lacking among newly diagnosed patients with lung cancer. Huskamp et al. (2009) explored whether patients with stage IV lung cancer had discussed hospice with their healthcare provider and whether having discussed hospice influenced uptake of hospice care and found that patients who reported having discussed hospice with their healthcare provider were more likely to use hospice within a year of diagnosis compared to patients who reported not having discussed hospice with their healthcare provider.

Health economic evaluation

The GDG acknowledged that whilst there are potential economic implications for health benefits from well informed patient choice (at least one study shows that patients are more likely to choose treatment with curative intent if information is delivered effectively) these are likely to be small and will be difficult to attribute to the method of communication delivery. Therefore this topic was not considered a high priority for economic analysis (see Economic Plan in the full Evidence Review).

Qualifying Statement

These recommendations were based on limited and poor phase 1 studies and cross-sectional surveys. Despite the lack of high quality evidence in this area the evidence presented showed positive effects of some interventions and no negative or harmful effects. However, a lack of specific evidence limited the recommendations to several good practice points. The, GDG, as in 2005, felt that this subject was so important that recommendations for good practice and future research should be made.



Updated 2011

References

Brundage, M. D., Feldman-Stewart, D., Cosby, R., Gregg, R., Dixon, P., Youssef, Y., Davies, D. & Mackillop, W. J. (2001). Phase I study of a decision aid for patients with locally advanced non-small-cell lung cancer. *Journal of Clinical Oncology*, 19: 1326-1335.

Dubey, S., Brown, R. L., Esmond, S. L., Bowers, B. J., Healy, J. M., & Schiller, J. H. (2005). Patient preferences in choosing chemotherapy regimens for advanced non-small cell lung cancer. *The Journal of Supportive Oncology*, 3: 149-154.

Gabrijel, S., Grize, L., Helfenstein, E., Brutsche, M., Grossman, P. Tamm, M. & Kiss, A. (2008). Receiving the diagnosis of lung cancer: patient recall of information and satisfaction with physician communication. *Journal of Clinical Oncology*, 26: 297-302.

Huskamp, H. A., Keating, N. L. Malin, J. L., Zaslavsky, A. M., Weeks, J. C., Earle, C. C., Teno, J. M., Virnig, B. A., Kahn, K. L., He, Y. & Ayanian, J. Z. (2009). Discussions with physicians about hospice among patients with metastatic lung cancer. *Arch.Intern.Med.* 169 (10):954-962.

Leighl, N. B., Shepherd, F. A., Zawisza, D., Burkes, R. L., Feld, R., Waldron, J., Sun, A., Payne, D., Bezjak, A. & Tattersall, M. H. (2008). Enhancing treatment decision-making: pilot study of a treatment decision aid in stage IV non-small cell lung cancer. *British Journal of Cancer*, 98: 1769-1773.

O'Connor, A. M., Bennett, C. L., Stacey, D. Barry, M., Col, N. F., Eden, K. B., Entwistle, V. A., Fiset, V., Holmes-Rovner, M., Khangura, S., Llewellyn-Thomas, H. Rovner, D. (2003). Decision aids for people facing health treatment or screening decisions. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD001431. DOI: 10.1002/14651858.CD001431.

4 Diagnosis and staging

Please note that this area has been reviewed in 2019, please follow the link on the front page for the evidence review

Clinical topic: How effective are diagnostic and staging investigations in patients with suspected/confirmed lung cancer?

Clinical topic: What clinical factors and information from sequential tests determine the choice of next test for diagnosis and/or staging?

4.1 Introduction

Accurately determining the diagnosis and stage of lung cancer is important to enable patients to be offered the best possible treatment but the process is often complex. The complexity is augmented by the need to consider the fitness of the patient which itself may influence both diagnostic and treatment decisions and may require a change to the diagnostic and staging pathway.

It is axiomatic that minimising the number of individual steps in the diagnosis and staging pathway and completing them quickly will reduce delays. Investigations that provide both diagnostic and staging information will reduce the number of steps required. The risks of tests need to be considered, and be proportionate to the potential benefits.

Where appropriate, pathways need to be flexible enough to allow management of patients to proceed with minimal diagnostic and staging information (e.g. where a patient would clearly not benefit from anything more than active supportive care or where a patient is suitable for surgical resection without a prior pathological diagnosis).

The informed preferences of the patient are of over-riding importance throughout (see Chapter 3, Communication).

The challenge is to design a pathway that is both accurate and flexible enough to allow patients to choose the most appropriate treatment for them without delay.

For this chapter, there were two clinical topics: the first concerning the effectiveness of diagnostic and staging investigations and the second concerning the most effective sequence of investigations.

4.1.1 TNM staging System

The 7th Edition of the UICC TNM classification of lung cancer has been implemented in the UK since January 2010. Almost all of the evidence reviewed for this guideline update used the 6th edition of the TNM staging and so areas where this may have a bearing on recommendations have been clearly indicated. The 7th classification recommends that TNM staging be applied to small cell lung cancer. However, the TNM system does not easily map to the 'limited' and 'extensive' stage classification that has been used historically in many clinical trials (see Chapter 7 and Appendix 2).

4.1.2 Pathological Assessment

Newer drug therapies for non-small cell lung cancer work best if they are targeted on the basis of histological sub-type and/or predictive markers. Tissue samples of sufficient size and quality are therefore required to enable pathologists to classify non-small cell lung cancer into

squamous cell carcinoma or adenocarcinoma wherever possible. In addition, further tests, requiring additional tissue or cells, may also be needed to detect specific markers that predict whether targeted treatments are likely to be effective, for example epidermal growth factor receptor mutations. As more targeted therapies become available it is likely that further tests will need to be performed to detect the relevant predictive markers.

4.2 Effectiveness of Diagnostic and Staging Investigations

An updated review of all diagnostic tests was not undertaken where the place of the tests is not controversial. Therefore recommendations concerning these investigations (sputum cytology, CT scanning) have not been updated. It is worth noting however, that some pragmatic changes to practice have been made in some centres. For example, the extension of CT to include the lower neck may provide information about supraclavicular lymphadenopathy that may be easily biopsied to give pivotal diagnostic and staging information. The diagnosis and staging of pleural disease was also not reviewed as part of this update.

The place of diagnosis and staging investigations is determined by their accuracy in a given situation. In lung cancer, the initial clinical assessment and the information provided by the CT scan is able to classify patients into a limited number of groups that can suggest an appropriate preferred first test and sequence. The following subsequent investigations were considered further in this update.

Positron emission tomography (PET)

PET with computed tomography (PET-CT)

Magnetic resonance imaging (MRI)

Single photon emission computed tomography (SPECT)

Bronchoscopy ± biopsy

Transthoracic needle aspiration (TTNA)

Endoscopic ultrasound fine needle aspiration (EUS-FNA)

Endobronchial ultrasound trans-bronchial needle aspiration (EBUS-TBNA)

Non ultrasound-guided TBNA

Cutting needle biopsy

Mediastinoscopy

Video-assisted thoracic surgery (VATS)

4.2.1 PET-CT

PET-CT is now widely used to assess whether a primary lesion is likely to be malignant, to look for evidence of regional lymph node involvement and to detect distant metastases. However, PET-CT cannot provide a pathological diagnosis so there is often the dilemma about whether to obtain tissue, especially given the now well documented limitations of PET-CT.

In SCLC, occult metastases may be detected by PET-CT, however it is not clear in what way these findings should influence decisions about offering treatment with curative intent.

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

4.2.2 Other imaging modalities

MRI

MRI is generally superior to CT in its ability to resolve soft tissue anatomy, which was the basis of the 2005 recommendation to use MRI to clarify the extent of superior sulcus tumours, where necessary.

MRI is often used in other areas where clarification of anatomy is required, but this was not the subject of an evidence review.

The role of MRI as a primary staging procedure *compared with* CT was not examined in this update.

SPECT

SPECT imaging can be used in the same way as PET in diagnosis and staging of lung cancer but is not in widespread use.

Ultrasound

Ultrasound is a useful modality to guide needle aspiration or biopsy of cervical lymphadenopathy, peripheral tumours in contact with the pleura, distant metastases and sampling of pleural tissue or fluid.

4.2.3 Minimally invasive procedures

Fibreoptic bronchoscopy

Fibreoptic bronchoscopy is a safe and effective way to diagnose and stage many patients with lung cancer. As well as obtaining samples from endobronchial tumour it can be routinely combined with non-ultrasound guided transbronchial needle aspiration (non US-guided TBNA) to sample tumours beneath the mucosa and hilar and mediastinal lymphadenopathy detected by CT. There is debate about the place of non-US guided TBNA and especially where it fits with US guided TBNA.

Endobronchial Ultrasound (EBUS) and Endoscopic (oesophageal) Ultrasound (EUS)

EBUS and EUS offer real time ultrasound guided sampling. EBUS is able to access lymph node stations 2, 3P, 4, 7, 10 and 11. EUS is able to access lymph node stations 4L, 7, 8, 9, the left adrenal gland and the left lobe of the liver. Neither EBUS nor EUS are generally able to access the aorto-pulmonary window station 5 or para-aortic station 6. The role of EBUS and EUS is complex, especially where there are differing amounts of clinical information. How the results of a PET-CT influence effectiveness of these tests and how negative results provided by endosonographic tests should be followed is debated.

Autofluorescence and narrow band imaging bronchoscopy have been shown to increase the diagnostic sensitivity of standard white light bronchoscopy. The impact of this technique on diagnosis of early stage endobronchial tumours is the subject of ongoing randomised trials.

Transthoracic needle biopsy

Transthoracic needle biopsy is used to obtain diagnostic samples from lesions that are not accessible via the bronchial tree and where there is no obvious lymph node involvement. This is usually where there are one or more peripheral lesions. CT is used to guide biopsy where lesions are in difficult to reach locations or where they are completely surrounded by aerated lung. Ultrasound is used where the lesion abuts the chest wall and is visible on ultrasound.

4.2.4 Mediastinoscopy and surgical diagnostic and staging techniques

Mediastinoscopy

Mediastinoscopy is a more invasive technique than EBUS or EUS, but provides much larger samples. There is currently debate about whether mediastinoscopy is warranted in patients who are suitable for treatment with curative intent who have had a negative EBUS or EUS. This is partly because such patients, even if found to have microscopic involvement of lymph nodes, may still benefit considerably from treatment with curative intent.

Anterior Mediastinotomy

Anterior (parasternal) mediastinotomy has developed primarily as a means of staging carcinoma of the lung located in the left upper lobe. It has also been advocated to establish the diagnosis of primary masses in the anterosuperior mediastinum, especially in the setting of superior vena caval obstruction when needle biopsy may be contraindicated.

Video-assisted thoracoscopic surgery (VATS)

Video-assisted thoracoscopic assessment may allow biopsies direct from the tumour mass and can often establish whether there is tumour invasion into the central mediastinal structures. Lymph node stations 7, 8 and 9 can be sampled. It may also be employed to establish the diagnosis in single pulmonary nodules, especially where the lesion is in a peripheral location.

4.2.5 Adequacy of diagnostic samples for pathological sub-typing and determination of predictive markers

There is concern that some minimally invasive diagnostic and staging techniques may yield insufficient material to allow adequate assessment of tumour sub-type and predictive markers. Considerations include the increasing number of predictive markers as well as advances in detection methods. These requirements may mean that a change to the approach to diagnosis and staging is required.

Recommendations

- Sputum cytology is rarely indicated and should be reserved for the investigation of patients who have centrally placed nodules or masses and are unable to tolerate, or unwilling to undergo, bronchoscopy or other invasive tests. [2005]
- Patients with known or suspected lung cancer should be offered a contrast-enhanced chest CT scan to further the diagnosis and stage the disease. The scan should also include the liver and adrenals¹. [2005]
- In the assessment of mediastinal and chest wall invasion:
 - CT alone may not be reliable
 - other techniques such as ultrasound should be considered where there is doubt
 - surgical assessment may be necessary if there are no contraindications to resection. [2005]
- Ensure all patients potentially suitable for treatment with curative intent are offered PET-CT before treatment. [NEW 2011]
- Every cancer network should have a system of rapid access to PET-CT scanning for eligible patients. [2005]
- Magnetic resonance imaging (MRI) should not routinely be performed to assess the stage of the primary tumour (T-stage) in NSCLC. [2005]
- MRI should be performed, where necessary to assess the extent of disease, for patients with superior sulcus tumours. [2005]
- Offer EBUS-guided TBNA for biopsy of paratracheal and peri-bronchial intraparenchymal lung lesions. [NEW 2011]

¹This recommendation was outside the scope of the 2011 update but the GDG recognised that many centres include the lower neck when performing CT scans for the diagnosis of lung cancer. The GDG also recognised that contrast medium should only be given with caution to patients with known renal impairment.

Recommendations (Cont.)

- Every cancer network should have at least one centre with EBUS and/or EUS to ensure timely access. [NEW 2011]
- The local test performance of non-ultrasound guided TBNA, EBUS and EUS-guided FNA should be the subject of audit. [NEW 2011]
- Ensure adequate samples are taken without unacceptable risk to the patient to permit pathological diagnosis including tumour sub-typing and measurement of predictive markers. [NEW 2011]

Qualifying statement (efficacy of diagnostic and staging investigations)

Recommendations about efficacy of tests were based on a review of studies ranging from low to high quality including systematic reviews and prospective / retrospective case series. As stated, the evidence for CT and sputum cytology was not reviewed. A summary of the findings from the medium to high quality studies can be found in table 1. There have been several studies published on the performance of PET and some on the performance of PET-CT. However, the standard technology is now PET-CT so that the evidence provided about PET alone is not really applicable to current practice. Studies demonstrate considerable variation in sensitivities and specificities for some investigations, especially for imaging (PET-CT, SPECT, MRI and scintigraphy). Tests that involve tissue sampling generally show better performance, particularly specificity, and on the basis of this a recommendation was made about audit of local performance. The recommendation to use EBUS to sample paratracheal and peribronchial intra-parenchymal lesions was made on the basis of one diagnostic study and expert opinion.

Diagnostic samples, pathological sub-typing and predictive markers

There was no research evidence on which to inform this important topic so the GDG sought the opinion of three histopathologists who regularly process diagnostic samples and have considerable expertise in this area (please see acknowledgements). A questionnaire concerning the adequacy of samples, likely demands on the pathology service, ability of local services to provide the required expertise and developments in the field likely to be relevant was sent to each pathologist. The responses were used to develop a recommendation based on expert opinion. The questionnaire is re-produced in Appendix 3. Responses to the questionnaire can be found in the full evidence review which accompanies this guideline.

4.3 Sequence of investigations

The sequence of investigations varies according to a variety of linked factors including the clinical and radiological information, patient fitness, intended treatment and patient preference. Added to this is the cost-effectiveness of the approach and the need to achieve a management decision without delay. In this section the preferred approach is developed given specific clinical and radiological information, assuming the overall aim is to allow a rapid diagnosis and stage sufficient to allow the patient to make clinically appropriate choices. For the purpose of developing management algorithms, fitness was not assumed to influence the choice of tests, when in reality if a patient's fitness means that definitive diagnosis and staging is not required, a modified approach will be adopted. The following section deals with the approach given broad categories defined according to clinical and radiological findings after initial CT.

4.3.1 Peripheral and central primary tumours

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.

4.3.2 Mediastinal lymph node assessment

Sampling of mediastinal lymph nodes (and other mediastinal masses) may yield enough diagnostic and staging information to allow the appropriate treatment to be offered to patients. However, the extent of mediastinal lymphadenopathy may influence the approach. The most effective sequence of investigation is subject of current debate.

4.3.3 Distant metastases (stage M1b)

The majority of patients with SCLC and around 40% of patients with NSCLC have distant metastases at presentation. Identification of distant metastases by clinical examination or radiological investigations may identify the most appropriate site for a biopsy. Asymptomatic metastases are present in around 10% of patients with NSCLC and with improvements in imaging (e.g. PET-CT) these are increasingly identified in the staging process.

Imaging of brain metastases

The brain is one of the most common metastatic sites in lung cancer and the issues of when to investigate patients and with what imaging modality are debated. Brain imaging is increasingly used prior to treatment with curative intent to exclude metastases. This applies especially to the asymptomatic individual with more advanced disease.

Other distant metastases

The adrenal glands are another common site for metastases in lung cancer, detected by CT or PET-CT and can present diagnostic difficulties.

Distant metastases in small cell lung cancer

This topic was not reviewed as part of the 2011 update. In early stage small cell lung cancer it is not known if metastases detected by PET-CT influence whether potentially curative multi-modality treatment is offered.

4.3.4 Pleural Disease

Where CT shows pleural effusion or pleural thickening, a different management path is followed. The evidence for this was not reviewed as part of this update but the British Thoracic Society² has recently published guidance on the management of pleural disease.

²British Thoracic Society Pleural Disease Guideline 2010 Thorax, Vol 65, Suppl 2

Recommendations

- Choose investigations that give the most information about diagnosis and staging with the least risk to the patient. Think carefully before performing a test that gives only diagnostic pathology when information on staging is also needed to guide treatment. [NEW 2011]
- Chest CT should be performed before:
 - an intended fibreoptic bronchoscopy
 - any other biopsy procedure. [2005]

Peripheral primary tumour

- Offer CT- or ultrasound-guided transthoracic needle biopsy to patients with peripheral lung lesions when treatment can be planned on the basis of this test. [NEW 2011]
- Biopsy any enlarged mediastinal nodes (≥ 10 mm maximum short axis on CT) or other lesions in preference to the primary lesion if determination of stage affects treatment.³ [NEW 2011]

Central primary tumour

- Offer fibreoptic bronchoscopy to patients with central lesions on CT where nodal staging does not influence treatment. [REDACTED]

Mediastinal lymph node assessment

- Offer PET-CT as the preferred first test after CT showing a **low probability of mediastinal malignancy** (lymph nodes < 10 mm maximum short axis on CT) for patients who are potentially suitable for treatment with curative intent. [NEW 2011]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

Updated 2011

³Many patients with lung cancer will not be fit for treatment with curative intent. This needs to be taken into account when choosing diagnostic and staging investigations.

Recommendations (Cont.)

- [REDACTED]
- [REDACTED]

Stage M1b

- Confirm the presence of isolated distant metastases/synchronous tumours by biopsy or further imaging (for example, MRI or PET-CT) in patients being considered for treatment with curative intent. [NEW 2011]
- [REDACTED]
- Offer patients with features suggestive of intracranial pathology, CT of the head followed by MRI if normal, or MRI as an initial test. [NEW 2011]
- An X-ray should be performed in the first instance for patients with localised signs or symptoms of bone metastasis. If the results are negative or inconclusive, either a bone scan or an MRI scan should be offered. [2005]
- Avoid bone scintigraphy when PET-CT has not shown bone metastases. [NEW 2011]

4.3.5 Management Algorithms

The recommendations are summarised in diagrammatic form in management algorithms 1 and 2. The algorithms are flexible to allow for variation in local test accuracy, fitness and patient preference.

Research Recommendation

Consider research into the outcome of treatment of small cell lung cancer with low volume metastases detected by PET-CT. [NEW 2011]

Consider research into the use of MRI and PET-CT in routine brain imaging prior to treatment with curative intent. Include stratification by stage and other prior imaging modalities. [NEW 2011]

Qualifying Statement (Sequence of Investigations)

The evidence reviewed for the accuracy of diagnosis and staging investigations also served to inform about the best sequence of tests, but there was no evidence of sufficient quality that specifically compared different sequences. Expert opinion was used to make recommendations based on consideration of the clinical scenario, accuracy of the test and safety. The results of the health economic model were also used to make recommendations for mediastinal sampling.

Peripheral lesions

The recommendation to use transthoracic needle aspiration or biopsy was made on the basis of the accuracy of the test but as this comes at a cost of more frequent complications (pneumothorax requiring intervention 3-5%, death 0.1%), alternative approaches were considered. The recommendation to only use this test when treatment planning depended on the result was made partly from expert opinion but also from the evidence for the accuracy of other tests. There was insufficient evidence to make recommendations about newer techniques such as radial endobronchial ultrasound, electromagnetic navigation, fluoroscopy and ultra-

thin bronchoscopy. These are time-consuming, have lower sensitivities than transthoracic needle aspiration and are not widely used in the UK.

Central lesions

Recommendations were based on the evidence for accuracy of bronchoscopy and expert opinion.

[Redacted text block]

[Redacted text block]

[Redacted text block]

[Redacted text block]

Ultrasound of the neck ± biopsy

No studies that met inclusion criteria were found on US of the neck ± biopsy. Recommendations were therefore based on knowledge of limited case series and expert opinion.

Distant metastases

Recommendations about the place of CT and MRI in symptomatic and asymptomatic individuals with cerebral metastases were made from smaller comparative studies that showed that MRI is superior to CT but that CT will detect identify cerebral metastases in the majority of affected patients.

Recommendations about the use of PET-CT prior to treatment with curative intent were in part based on evidence that showed that adrenal lesions are readily detected by PET-CT (sensitivity of 94 to 100% and specificity of 80 to 100%). Recommendations concerning detection of bone metastases were based on the evidence review for bone scintigraphy including SPECT and PET-CT. Compared with PET-CT, the sensitivity of scintigraphy is less, though specificity may be better. The evidence for the use of MRI and plain x-ray was not reviewed as part of the 2011 update.

Clinical evidence (sections 4.2 and 4.3)

The evidence for the effectiveness of different diagnostic and staging tests for patients with suspected or confirmed NSCLC consisted of ninety-seven studies that ranged in quality from low to high and examined the following diagnostic and staging tests: Bronchoscopy (including endobronchial and endoscopic ultrasound and transbronchial biopsy), needle biopsy of the lung (including percutaneous biopsy), radionuclide imaging (PET-CT, NeoSpect, PET), ultrasound-guided biopsy of cervical lymph nodes, other biopsies of metastatic sites (other than lung), pleural biopsy, thoracoscopy (including medical and pleuroscopy), surgical techniques (including VATS, mediastinoscopy/mediastinotomy, frozen section), observation, and MRI/CT of the brain. The ranges of sensitivities and specificities reported by the studies of moderate to high quality for the different diagnostic and staging tests are summarised in table 4.1.

Table 4.1: Sensitivities and specificities of various diagnostic and staging tests for suspected/confirmed lung cancer reported by the moderate-high quality studies.

Table 4.1a: Diagnosis

Test (no of studies)	Sensitivity range (%)	Specificity range (%)
PET (5)	74-100	50-83
PET-CT (1)	96-98	68-87
MRI (1)	94	79
SPECT (3)	62-95	75-87.5
Scintigraphy (1)	94-98	52
Bronchoscopy ± biopsy (7)	60-100	44-100
Radial EBUS-TBNA (1)	8.9-91.9	62.4-100
Linear EBUS-TBNA (0)		
TTNA (10)	85.5-94.3	41.67-100
EUS-FNA (1)	85.5	100

Table 4.1b Staging

Test (no of studies)	Sensitivity range (%)	Specificity range (%)
PET		
T-staging (1)	64.5	
N-staging (14)	20.7-100	50-98
Overall M-staging (3)	46-100	59-98
Bone metastases (1)	90.9	97.1
Overall staging (2)	82.1-90.5	18.2-85.4
PET-CT		
T-staging (3)	77.3-96.1	
N-staging (10)	47-98.4	37.5-100
Overall M-staging (2)	65.5-84.1	94.5-97.7
Bone metastases (1)	96	85.6
MRI		
T-staging (2)	100	82.9
N-staging (3)	83.7-92.5	85.7-96.1
M-staging (2)	57.5-80	80-92
Brain metastases (1)	88	98.2
Bone metastases (1)	64-96	78.9-90
SPECT N-staging (2)	53.3-85.7	77.1-89.6
Scintigraphy: Bone metastases (2)	51.5-96	83.3-98.6
(Blind) TBNA (2)	39-78	99
Radial EBUS-TBNA (0)		
Linear EBUS-TBNA (7)	46-94	66.7-100
TTNA N-staging (1)	89	100
EUS-FNA N-staging (5)	50-84	97-99.5
Mediastinoscopy N-staging (2)	78	100
VATS N-staging (1)	75	100

Health economic evidence

In the 2005 NICE Lung cancer guideline (NICE 2005), the staging of non-small cell lung cancer was prioritised for independent economic modelling. Accurate diagnostic and staging information, particularly of mediastinal disease, helps the clinician decide which patients are suitable for treatment with curative intent; mediastinal lymph-node involvement reduces the chance of surgery being curative. Since 2005 a number of minimally invasive techniques have started to be used in some centres, and whilst PET-CT scanners are now routinely available, a question remains over where best to use them in the diagnostic and staging pathway.

An economic model was developed to assess the cost-effectiveness of PET-CT, TBNA, EBUS, mediastinoscopy and neck ultrasound in 26 clinically relevant sequences, from a UK NHS perspective see table 4.2. A detailed description of methods and results can be found in appendix 4. Separate analyses were run in three subgroups of patients with non-small cell lung cancer in which the prevalence of nodal and distant metastatic disease was low, intermediate or high. Not all staging strategies were considered by the GDG to be clinically relevant alternatives in each population subgroup; therefore the strategies considered in each analysis differ.

Table 4.2: Test sequences considered in each subgroup analysis

Strategies		LOW	INTER-MEDIATE	HIGH
X	PET-CT	√		
1	PET-CT Med	√	√	√
2	PET-CT TBNA	√	√	
3	PET-CT EBUS	√	√	
4	PET-CT TBNA EBUS	√	√	
5	PET-CT TBNA Med	√	√	
6	PET-CT EBUS Med	√	√	
7	PET-CT TBNA EBUS Med	√	√	
8	TBNA PET-CT		√	√
9	EBUS PET-CT		√	√
10	Med PET-CT		√	√
11	Neck US PET-CT Med		√	√
12	EBUS PET-CT Med		√	√
13	Neck US TBNA PET-CT		√	√
14	Neck US EBUS PET-CT		√	√
15	Neck US Med PET-CT		√	√
16	TBNA EBUS PET-CT		√	√
17	EBUS Med PET-CT		√	√
18	Neck US TBNA PET-CT Med		√	√
19	Neck US EBUS PET-CT Med		√	√
20	TBNA EBUS PET-CT Med		√	√
21	TBNA EBUS Med PET-CT		√	√
22	Neck US TBNA EBUS PET-CT		√	√
23	Neck US TBNA Med PET-CT		√	√
24	Neck US EBUS Med PET-CT		√	√
25	Neck US TBNA EBUS PET-CT Med		√	√
26	Neck US TBNA EBUS Med PET-CT		√	√

A decision tree approach was taken to model the staging alternatives with an embedded Markov process to model the longer term consequences resulting from treatment. For the purposes of the model, PET-CT only provides information on the presence of metastatic disease. If PET-CT is positive the patient is treated for distant metastasis. If PET-CT is negative the next test in the sequence is performed.

All other tests provide the clinician with information on the presence of nodal disease (defined as N2 or N3). If a test is positive the patient is treated for N2/3 M0 disease. Again, if a test is negative the next test in the sequence is performed.

The Markov model at the end of the decision tree branch is a simplified version of the natural progression of disease, accounting only for the possibility of death. Different stages of disease progression are not captured. Death can occur in the model as a result of a mediastinoscopy (in 0.5% of cases) or any other cause.

The decision about which treatment to offer patients on the basis of the staging test results was not evaluated in terms of cost-effectiveness (there are no embedded decision nodes in the decision tree). Instead the downstream consequences of the staging tests have been captured, as typified in current clinical practice or best practice as defined by relevant NICE guidance including recommendations within this guideline.

The model was populated with data from different sources considered to provide the best available evidence, as shown in table 4.3:

Table 4.3: Data sources used in to populate the model

Data required for model	Source
Prevalence	NATIONAL LUNG CANCER AUDIT + expert opinion
Test accuracy	Expert opinion (+ published literature)
Treatment options (proportions)	NATIONAL LUNG CANCER AUDIT
Survival estimates	NATIONAL LUNG CANCER AUDIT
Utility weights	published literature + expert opinion
Resource use	expert opinion
Unit costs	NHS Reference costs/Trust level data

Data from the National Lung Cancer Audit was chosen over randomised controlled trial data since they capture the real treatment options offered to patients, given the stage of their disease, thus increasing the external validity of the model results.

Data on test accuracy was not reported for our three sub groups, so were dictated by expert opinion from the GDG. Gaps in data on test accuracy (in the three patient subgroups), quality of life and the cost of EBUS were acknowledged and assumptions were made by the GDG. Despite the rich source of data for survival estimates from National Lung Cancer Audit, we had no information about patients' survival from treatment given as the result of misleading test results (i.e. false positives or false negatives) so assumptions were made about the resulting survival outcomes in these patients.

In accordance with the perspective of this analysis, the only costs considered were those relevant to the UK NHS. Costs were estimated in 2008-9 prices (since this is the price year from the most recent edition of NHS Reference costs, published June 2010). Five categories of costs considered in the model; the cost of diagnostic tests, the cost of treatment, the cost of treating adverse events, the cost of follow-up and the cost of supportive and palliative care which was applied to all patients regardless of which (if any) anti-cancer treatment they initially received.

Deterministic sensitivity analysis was conducted on relevant parameters in order to identify variables which contribute most to the uncertainty surrounding the results of the model. The results of the cost-effectiveness analyses show that different sequences of staging tests are likely to be cost-effective in different subgroups of patients, see table 4.4 below.

Table 4.4: Summary of results

SUBGROUP	LOW	INTERMEDIATE	HIGH
Result on CT	CT -ve (N0/1)	CT +ve (N2/3)	CT +ve (N2/3)
Definition of nodes	No enlarged nodes <10mm short axis on CT	Small volume nodes 1+ mediastinal lymph nodes of 10-20mm short axis	Bulky N2 disease Any node >20mm
Preferred strategy	Strategy 'X': PET-CT	Strategy 2: PET-CT, TBNA <i>but potential for some strategies to overlap and thus may change the incremental cost- effectiveness results</i>	Strategy 13: Neck US, TBNA, PET-CT
Incremental cost-effectiveness ratio	dominates all relevant comparators	£19,448 per QALY	dominates all relevant comparators

These results may seem on the surface to be counter-intuitive. Those sequences of tests which lead to more accurate staging information do not lead to overall better outcomes for patients.

However, test performance is only a surrogate endpoint – and the results of all three analyses are heavily dependent on assumptions made about downstream treatment decisions. Within the context of the model, strategies resulting in a higher number of false negatives allow a great proportion of patients with N2/3 disease to be offered surgery and other options for treatment with curative intent. Similarly if metastatic disease is missed, patients still achieve better outcomes with treatment for curative intent than with no anti-cancer treatment.

The sensitivity analysis performed showed the model was reasonably robust to small changes in the treatment options, the choice of radiotherapy schedules, the price of chemotherapy drugs, the price of diagnostic tests, the death rate from mediastinoscopy, changes in utility values as well as some assumptions about the choice of survival estimates for patients incorrectly staged. Other assumptions about utility values could not be tested without changing the model structure. Test accuracy data was not available for the three subgroups identified as relevant to the decision problem; as such we have relied on the expert opinion of the GDG.

Despite these acknowledged limitations, these three analyses provided the GDG with useful information in their deliberations when preparing recommendations on the best sequence in which to use tests to stage mediastinal disease in different subgroups of patients.

4.4 Organisational factors relevant to diagnosis and staging

Timing of treatment

In 1993, the Joint Council for Clinical Oncology (JCCO) issued targets for the time from first consultation to the start of radiotherapy or chemotherapy. Guidance on timing has also been issued by the Department of Health in the National Manual of Quality Measures for Cancer and the Welsh Assembly Government in the All Wales Minimum Standards for Lung Cancer. The 2005 guideline examined the evidence for the effect that delays in diagnosis or treatment might have on survival and quality of life and although the evidence was very limited, a number of recommendations were made. Since then the 62 and 31 day targets (for referral to treatment and diagnosis to treatment respectively) have been monitored nationally and some pressure has been placed on cancer centres and units to achieve them. The GDG considered that these targets had resulted in a marked improvement in the timeliness of care of lung cancer patients and every effort should be made to ensure compliance but without compromising the recommendations made in this guideline.

Rapid access clinics

The 2005 guideline reviewed the evidence in support of rapid access clinics in which patients are fast-tracked to respiratory physician-led clinics that either combine multiple investigations or are linked to early diagnostic and staging investigation appointments. The GDG noted that these clinics are now widespread and adopted the 2005 recommendation.

The Lung Cancer MDT

The central role of the MDT in ensuring that all patients are discussed by a full team of specialists is not disputed. A number of previous reports have affirmed this (the Calman- Hine report, Improving Outcomes in Lung Cancer (NHS Executive), NHS Cancer Plan, the Cancer Reform Strategy Clinical Oncology Information Network guidelines, British Thoracic Society recommendations on organising care for lung cancer patients and the American College of Chest Physicians). However, there remain concerns that some MDTs still do not have regular enough attendance by some specialists (especially thoracic surgeons) to ensure that all patients have a true multidisciplinary opinion. This is one reason put forward for the marked geographical differences in surgical resection and other treatment rate that have been shown by the National Lung Cancer Audit. The 2005 guideline included recommendations based on the expert opinion and formal consensus in the above reports.

Recommendations

- Patients who have lung cancer suitable for radical treatment, or chemotherapy, or need radiotherapy or ablative treatment for relief of symptoms, should be treated without undue delay, according to the Welsh Assembly Government and Department of Health recommendations (within 31 days of the decision to treat and within 62 days of their urgent referral). [2005]

Multidisciplinary teams

- All patients with a likely diagnosis of lung cancer should be referred to a member of a lung cancer MDT (usually a chest physician). [2005]
- The care of all patients with a working diagnosis of lung cancer should be discussed at a lung cancer MDT meeting. [2005]

Rapid access lung clinics

- Rapid access clinics⁴ should be provided where possible for the investigation of patients with suspected lung cancer, because they are associated with faster diagnosis and less patient anxiety. [2005]

Cancer clinical nurse specialists

- All cancer units/centres should have one or more trained lung cancer clinical nurse specialists to see patients before and after diagnosis, to provide continuing support, and to facilitate communication between the secondary care team (including the MDT), the patient's GP, the community team and the patient. Their role includes helping patients to access advice and support whenever they need it. [2005]

References

- Akata, S. Kajiwara, N. Park, J. Yoshimura, M. Kakizaki, D. Abe, K. et al. (2008). Evaluation of chest wall invasion by lung cancer using respiratory dynamic MRI. *Journal of Medical Imaging & Radiation Oncology*, 52, 36-39.
- Alkhalwaldeh, K. Bural, G. Kumar, R. & Alavi, A. (2008). Impact of dual-time-point (18)F-FDG PET imaging and partial volume correction in the assessment of solitary pulmonary nodules. *European Journal of Nuclear Medicine & Molecular Imaging*, 35, 246-252.
- Alongi, F. Ragusa, P. Montemaggi, P. & Bona, C. M. (2006). Combining independent studies of diagnostic fluorodeoxyglucose positron-emission tomography and computed tomography in mediastinal lymph node staging for non-small cell lung cancer. *Tumori*, 92, 327-333.
- Annema, J. T. (2010). Implementation of endoscopic ultrasound for lung cancer staging. *Gastrointestinal Endoscopy*, 71, 64-70.
- Annema, J. T. Meerbeck, J.P.v. Rintoul, R.C. Dooms, C. et al. (2010). Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: A randomized trial. *Journal of the American Medical Association*, 304, 2245-2252.
- Anraku, M. Miyata, R. Compeau, C. & Shargall, Y. (2010). Video-assisted mediastinoscopy compared with conventional mediastinoscopy: are we doing better? *Annals of Thoracic Surgery*, 89, 1577-1581.
- Axelsson, R. Herlin, G. Baath, M. Aspelin, P. & Kolbeck, K. G. (2008). Role of scintigraphy with technetium-99m depreotide in the diagnosis and management of patients with suspected lung cancer. *Acta Radiologica*, 49, 295-302.
- Bandoh, S. Fujita, J. Tojo, Y. Yokomise, H. Satoh, K. Kobayashi, S. et al. (2003). Diagnostic accuracy and safety of flexible bronchoscopy with multiplanar reconstruction images and ultrafast Papanicolaou stain: evaluating solitary pulmonary nodules. *Chest*, 124, 1985-1992.
- Bango, A. (2003). Bronchoscopic needle aspiration and biopsy of paratracheal tumors and hilar and mediastinal lymph nodes: Security yield and cost-effectiveness. *Journal of Bronchology*, 10, 183-188.

⁴These were previously known as early diagnosis clinics.

- Bilaceroglu S. C. (2007). Computed tomography-guided transthoracic needle aspiration in diagnosing and staging hilar and mediastinal masses of lung cancer after negative bronchoscopy. *Journal of Bronchology*, 14, 149-155.
- Birim, O. Kappetein, A. P. Stijnen, T. & Bogers, A. J. (2005). Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer (DARE structured abstract). *Annals of Thoracic Surgery*, 79, 375-382.
- Borrego, D. I, Lopez, G. C. Vazquez, A. R. Ginel, C. A. & Barrot, C. E. (2007). [Evaluation of efficacy and clinical impact of FDG-PET on patients with potentially resectable non-small cell lung cancer]. [Spanish]. *Revista Espanola de Medicina Nuclear*, 26, 335-344.
- Brink, I. Schumacher, T. Mix, M. Ruhland, S. Stoelben, E. Digel, W. et al. (2004). Impact of [18F]FDG-PET on the primary staging of small-cell lung cancer. *European Journal of Nuclear Medicine & Molecular Imaging*, 31, 1614-1620.
- Bryant, A. S. (2006). The Maximum Standardized Uptake Values on Integrated FDG-PET/CT Is Useful in Differentiating Benign From Malignant Pulmonary Nodules. *Annals of Thoracic Surgery*, 82, 1016-1020.
- Cerfolio, R. J. Ojha, B. Bryant, A. S. Bass, C. S. Bartalucci, A. A. & Mountz, J. M. (2003). The role of FDG-PET scan in staging patients with nonsmall cell carcinoma. *Annals of Thoracic Surgery*, 76, 861-866.
- Cerfolio, R. J. Bryant, A. S. Ojha, B. & Eloubeidi, M. (2005). Improving the inaccuracies of clinical staging of patients with NSCLC: a prospective trial. *Annals of Thoracic Surgery*, 80, 1207-1213.
- Chao, T. Y. Chien, M. T. Lie, C. H. Chung, Y. H. Wang, J. L. & Lin, M. C. (2009). Endobronchial ultrasonography-guided transbronchial needle aspiration increases the diagnostic yield of peripheral pulmonary lesions: a randomized trial. *Chest*, 136, 229-236.
- Cheran, S. K. Herndon, J. E. & Patz, E. F. Jr. (2004). Comparison of whole-body FDG-PET to bone scan for detection of bone metastases in patients with a new diagnosis of lung cancer. *Lung Cancer*, 44, 317-325.
- Cronin, P. Dwamena, B. A. Kelly, A. M. & Carlos, R. C. (2008). Solitary pulmonary nodules: meta-analytic comparison of cross-sectional imaging modalities for diagnosis of malignancy.[see comment]. *Radiology*, 246, 772-782.
- D'Alessandro, V. Parracino, T. Stranieri, A. Greco, A. De, C. A. Sperandeo, M. et al. (2007). Computed-tomographic-guided biopsy of thoracic nodules: a revision of 583 lesions. *Clinica Terapeutica*, 158, 509-513.
- Demura, Y. Tsuchida, T. Ishizaki, T. Mizuno, S. Totani, Y. Ameshima, S. et al. (2003). 18F-FDG accumulation with PET for differentiation between benign and malignant lesions in the thorax. *Journal of Nuclear Medicine*, 44, 540-548.
- Detterbeck, F. C. Jantz, M. A. Wallace, M. Vansteenkiste, J. Silvestri, G. A. & American College of Chest Physicians. (2007). Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*, 132, 202S-220S.
- Diacon, A. H. Schuurmans, M. M. Theron, J. Schubert, P. T. Wright, C. A. & Bolliger, C. T. (2004). Safety and yield of ultrasound-assisted transthoracic biopsy performed by pulmonologists.[see comment]. *Respiration*, 71, 519-522.
- Diacon, A. H. (2007). Ultrasound-assisted transthoracic biopsy: Fine-needle aspiration or cutting-needle biopsy? *European Respiratory Journal*, 29, 357-362.
- Eberhardt, R. Anantham, D. Herth, F. Feller-Kopman, D. & Ernst, A. (2007). Electromagnetic navigation diagnostic bronchoscopy in peripheral lung lesions.[see comment]. *Chest*, 131, 1800-1805.
- Eberhardt, R. (2010). Comparison of suction catheter versus forceps biopsy for sampling of solitary pulmonary nodules guided by electromagnetic navigational bronchoscopy. *Respiration*, 79, 54-60.
- Ebihara, A. Nomori, H. Watanabe, K. Ohtsuka, T. Naruke, T. Uno, K. et al. (2006). Characteristics of advantages of positron emission tomography over computed tomography for N-staging in lung cancer patients. *Japanese Journal of Clinical Oncology*, 36, 694-698.
- Ernst, A. Eberhardt, R. Krasnik, M. & Herth, F. J. (2009). Efficacy of endobronchial ultrasound-guided transbronchial needle aspiration of hilar lymph nodes for diagnosing and staging cancer. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*, 4, 947-950.
- Fernandez-Villar, A. Botana, M. Leiro, V. Gonzalez, A. Represas, C. & Ruano-Ravina, A. (2010). Validity and reliability of transbronchial needle aspiration for diagnosing mediastinal adenopathies. *BMC Pulmonary Medicine*, 10, 24.
- Fielding, D. (2009). Endobronchial ultrasound convex-probe transbronchial needle aspiration as the first diagnostic test in patients with pulmonary masses and associated hilar or mediastinal nodes. *Internal Medicine Journal*, 39, 435-440.
- Fletcher, J. W. Kymes, S. M. Gould, M. Alazraki, N. Coleman, R. E. Lowe, V. J. et al. (2008). A comparison of the diagnostic accuracy of 18F-FDG PET and CT in the characterization of solitary pulmonary nodules.[erratum appears in *J Nucl Med*. 2008 Mar;49(3):353]. *Journal of Nuclear Medicine*, 49, 179-185.
- Fujita, S. Nagamachi, S. Wakamatsu, H. Nishii, R. Futami, S. Tamura, S. et al. (2008). Usefulness of triple-phase thallium-201 SPECT in non-small-cell lung cancer (NSCLC): association with proliferative activity. *Annals of Nuclear Medicine*, 22, 833-839.
- Fuso, L. Pagliari, G. Boniello, V. Trove', A. Varone, F. Longobardi, A. et al. (2005). Autofluorescence bronchoscopy to identify pre-cancerous bronchial lesions. *Monaldi Archives for Chest Disease*, 63, 124-128.
- Garcia-Olive, I. Valverde Forcada, E. X. Andreo, G. F. Sanz-Santos, J. Castilla, E. Llatjos, M. et al. (2009). [Linear endobronchial ultrasound as the initial diagnostic tool in patients with indications of mediastinal disease]. [Spanish]. *Archivos de Bronconeumologia*, 45, 266-270.
- Geraghty, P. R. Kee, S. T. McFarlane, G. Razavi, M. K. Sze, D. Y. & Dake, M. D. (2003). CT-guided transthoracic needle aspiration biopsy of pulmonary nodules: needle size and pneumothorax rate.[see comment]. *Radiology*, 229, 475-481.
- Gong, Y. (2006). Transthoracic fine-needle aspiration vs concurrent core needle biopsy in diagnosis of intrathoracic lesions: A retrospective comparison of diagnostic accuracy. *American Journal of Clinical Pathology*, 125, 438-444.
- Gould, M. K. Kuschner, W. G. Rydzak, C. E. Maclean, C. C. Demas, A. N. Shigemitsu, H. et al. (2003). Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis.[see comment]. [Review] [109 refs] DARE Structured Abstract available. *Annals of Internal Medicine*, 139, 879-892.

- Gu, P. Zhao, Y. Z. Jiang, L. Y. Zhang, W. Xin, Y. & Han, B. H. (2009). Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. [Review] [41 refs]. *European Journal of Cancer*, 45, 1389-1396.
- Herder, G. J. Kramer, H. Hoekstra, O. S. Smit, E. F. Pruim, J. van, T. H. et al. (2006). Traditional versus up-front [18F] fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: a Dutch cooperative randomized study. DARE Structured Abstract available. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 24, 1800-1806.
- Herth, F. J. F. (2003). Endobronchial Ultrasound Improves Classification of Suspicious Lesions Detected by Autofluorescence Bronchoscopy. *Journal of Bronchology*, 10, 249-252.
- Hetzel, M. (2003). F-18 NaF PET for Detection of Bone Metastases in Lung Cancer: Accuracy, Cost-Effectiveness, and Impact on Patient Management. *Journal of Bone and Mineral Research*, 18, 2206-2214.
- Holty, J. E. Kuschner, W. G. & Gould, M. K. (2005). Accuracy of transbronchial needle aspiration for mediastinal staging of non-small cell lung cancer: a meta-analysis.[see comment]. [Review] [44 refs] DARE Structured Abstract available. *Thorax*, 60, 949-955.
- Hwangbo, B. Kim, S. K. Lee, H. S. Lee, H. S. Kim, M. S. Lee, J. M. et al. (2009). Application of endobronchial ultrasound-guided transbronchial needle aspiration following integrated PET/CT in mediastinal staging of potentially operable non-small cell lung cancer. *Chest*, 135, 1280-1287.
- Kahn, D. Menda, Y. Kernstine, K. Bushnell, D. McLaughlin, K. Miller, S. et al. (2004). The utility of 99mTc depreotide compared with F-18 fluorodeoxyglucose positron emission tomography and surgical staging in patients with suspected non-small cell lung cancer. *Chest*, 125, 494-501.
- Kim, B. T. Lee, K. S. Shim, S. S. Choi, J. Y. Kwon, O. J. Kim, H. et al. (2006). Stage T1 non-small cell lung cancer: preoperative mediastinal nodal staging with integrated FDG PET/CT--a prospective study. *Radiology*, 241, 501-509.
- Kuo, C. H. Lin, S. M. Chen, H. C. Chou, C. L. Yu, C. T. & Kuo, H. P. (2007). Diagnosis of peripheral lung cancer with three echoic features via endobronchial ultrasound. *Chest*, 132, 922-929.
- Laspas, F. Roussakis, A. Efthimiadou, R. Papaioannou, D. Papadopoulos, S. & Andreou, J. (2008). Percutaneous CT-guided fine-needle aspiration of pulmonary lesions: Results and complications in 409 patients. *Journal of Medical Imaging & Radiation Oncology*, 52, 458-462.
- Lee, B. E. von, H. D. Lown, T. Lau, D. Calhoun, R. & Follette, D. (2007). Advances in positron emission tomography technology have increased the need for surgical staging in non-small cell lung cancer. *Journal of Thoracic & Cardiovascular Surgery*, 133, 746-752.
- Lee, W. W. Chung, J. H. Jang, S. J. Eo, J. S. Park, S. Y. Sung, S. W. et al. (2006). Consideration of serum glucose levels during malignant mediastinal lymph node detection in non-small-cell lung cancer by FDG-PET.[see comment]. *Journal of Surgical Oncology*, 94, 607-613.
- Lee, Y. S. (2008). Computed tomography-guided transthoracic needle aspiration biopsy of intrapulmonary lesions: Utility of a liquid-based cytopreparatory technique. *Acta Cytologica*, 52, 665-670.
- Lee, H. Y. Lee, K. S. Kim, B. T. Cho, Y. S. Lee, E. J. Yi, C. A. et al. (2009). Diagnostic efficacy of PET/CT plus brain MR imaging for detection of extrathoracic metastases in patients with lung adenocarcinoma. *Journal of Korean Medical Science*, 24, 1132-1138.
- Lee, J. W. (2009). 18F-FDG PET/CT in mediastinal lymph node staging of non-small-cell lung cancer in a tuberculosis-endemic country: Consideration of lymph node calcification and distribution pattern to improve specificity. *European Journal of Nuclear Medicine and Molecular Imaging*, 36, 1794-1802.
- Maziak, D. E. Darling, G. E. Incelet, R. I. Gulenchyn, K. Y. Driedger, A. A. Ung, Y. C. et al. (2009). Positron emission tomography in staging early lung cancer: a randomized trial. *Annals of Internal Medicine*, 151, 221-228.
- Medford, A. R. (2009). A performance and theoretical cost analysis of endobronchial ultrasound-guided transbronchial needle aspiration in a UK tertiary respiratory centre. *QJM : monthly journal of the Association of Physicians*, 102, 859-864.
- Melek, H. Gunluoglu, M. Z. Demir, A. Akin, H. Olcmen, A. & Dincer, S. I. (2008). Role of positron emission tomography in mediastinal lymphatic staging of non-small cell lung cancer. *European Journal of Cardio-Thoracic Surgery*, 33, 294-299.
- Micames, C. G. McCrory, D. C. Pavey, D. A. Jowell, P. S. & Gress, F. G. (2007). Endoscopic ultrasound-guided fine-needle aspiration for non-small cell lung cancer staging: A systematic review and metaanalysis. [Review] [38 refs]. *Chest*, 131, 539-548.
- Montaudon, M. Latrabe, V. Pariente, A. Corneloup, O. Begueret, H. & Laurent, F. (2004). Factors influencing accuracy of CT-guided percutaneous biopsies of pulmonary lesions. *European Radiology*, 14, 1234-1240.
- Morikawa, M. Demura, Y. Ishizaki, T. Ameshima, S. Miyamori, I. Sasaki, M. et al. (2009). The effectiveness of 18F-FDG PET/CT combined with STIR MRI for diagnosing nodal involvement in the thorax. *Journal of Nuclear Medicine*, 50, 81-87.
- Nomori, H. Watanabe, K. Ohtsuka, T. Naruke, T. Suemasu, K. & Uno, K. (2004). The size of metastatic foci and lymph nodes yielding false-negative and false-positive lymph node staging with positron emission tomography in patients with lung cancer. *Journal of Thoracic & Cardiovascular Surgery*, 127, 1087-1092.
- Ohno, Y. Hatabu, H. Takenaka, D. Higashino, T. Watanabe, H. Ohbayashi, C. et al. (2003). CT-guided transthoracic needle aspiration biopsy of small (< or = 20 mm) solitary pulmonary nodules. *AJR, American Journal of Roentgenology*. 180, 1665-1669.
- Ohno, Y. (2004). Metastases in mediastinal and hilar lymph nodes in patients with non-small cell lung cancer: Quantitative and qualitative assessment with STIR turbo spin-echo MR imaging. *Radiology*, 231, 872-879.
- Ohno, Y. Koyama, H. Nogami, M. Takenaka, D. Yoshikawa, T. Yoshimura, M. et al. (2007). Whole-body MR imaging vs. FDG-PET: comparison of accuracy of M-stage diagnosis for lung cancer patients. *Journal of Magnetic Resonance Imaging*, 26, 498-509.
- Ohno, Y. Koyama, H. Nogami, M. Takenaka, D. Yoshikawa, T. Yoshimura, M. et al. (2007). STIR turbo SE MR imaging vs. coregistered FDG-PET/CT: quantitative and qualitative assessment of N-stage in non-small-cell lung cancer patients. *Journal of Magnetic Resonance Imaging*, 26, 1071-1080.

- Ohno, Y. Koyama, H. Onishi, Y. Takenaka, D. Nogami, M. Yoshikawa, T. et al. (2008). Non-small cell lung cancer: whole-body MR examination for M-stage assessment--utility for whole-body diffusion-weighted imaging compared with integrated FDG PET/CT. *Radiology*, 248, 643-654.
- Oki, M. Saka, H. Kitagawa, C. Tanaka, S. Shimokata, T. Mori, K. et al. (2008). Novel thin bronchoscope with a 1.7-mm working channel for peripheral pulmonary lesions. *European Respiratory Journal*, 32, 465-471.
- Oki, M. (2009). Endobronchial ultrasound-guided transbronchial biopsy using novel thin bronchoscope for diagnosis of peripheral pulmonary lesions. *Journal of Thoracic Oncology*, 4, 1274-1277.
- Pauls, S. Buck, A. K. Hohl, K. Halter, G. Hetzel, M. Blumstein, N. M. et al. (2007). Improved non-invasive T-Staging in non-small cell lung cancer by integrated 18F-FDG PET/CT. *Nuclear-Medizin*, 46, 9-14.
- Pauls, S. Buck, A. K. Halter, G. Mottaghy, F. M. Mucbe, R. Bluemel, C. et al. (2008). Performance of integrated FDG-PET/CT for differentiating benign and malignant lung lesions--results from a large prospective clinical trial.[erratum appears in *Mol Imaging Biol*. 2008 May-Jun;10(3):176]. *Molecular Imaging & Biology*, 10, 121-128.
- Plathow, C. Aschoff, P. Lichy, M. P. Eschmann, S. Hehr, T. Brink, I. et al. (2008). Positron emission tomography/computed tomography and whole-body magnetic resonance imaging in staging of advanced nonsmall cell lung cancer--initial results. *Investigative Radiology*, 43, 290-297.
- Pinto Filho, D. R. Avino, A. J. Brandao, S. L. & Spiandorello, W. P. (2009). Joint use of cervical mediastinoscopy and video-assisted thoracoscopy for the evaluation of mediastinal lymph nodes in patients with non-small cell lung cancer. *Jornal Brasileiro De Pneumologia: Publicacao Oficial Da Sociedade Brasileira De Pneumologia E Tisiologia*, 35, 1068-1074..
- Pozo-Rodriguez, F. Martin de Nicolas, J. L. Sanchez-Nistal, M. A. Maldonado, A. Garcia de, B. S. Calero-Garcia, R. et al. (2005). Accuracy of helical computed tomography and [18F] fluorodeoxyglucose positron emission tomography for identifying lymph node mediastinal metastases in potentially resectable non-small-cell lung cancer.[see comment]. *Journal of Clinical Oncology*, 23, 8348-8356.
- Priola, A. M. (2007). Accuracy of CT-guided transthoracic needle biopsy of lung lesions: Factors affecting diagnostic yield. *Radiologia Medica*, 112, 1142-1159.
- Quaia, E. Tona, G. Gelain, F. Lubin, E. Pizzolato, R. Boscolo, E. et al. (2008). Integrated fluorine-18 fluorodeoxyglucose (18F-FDG) PET/CT compared to standard contrast-enhanced CT for characterization and staging of pulmonary tumors eligible for surgical resection. *Acta Radiologica*, 49, 995-1004.
- Reed, C. E. Harpole, D. H. Posther, K. E. Woolson, S. L. Downey, R. J. Meyers, B. F. et al. (2003). Results of the American College of Surgeons Oncology Group Z0050 trial: the utility of positron emission tomography in staging potentially operable non-small cell lung cancer.[erratum appears in *J Thorac Cardiovasc Surg*. 2007 Apr;133(4):864]. *Journal of Thoracic & Cardiovascular Surgery*, 126, 1943-1951.
- Rodriguez, F. A. Gomez, R. M. Llamas Elvira, J. M. Sanchez-Palencia, R. A. Bellon, G. M. Ramos, F. C. et al. (2007). Diagnosis efficacy of structural (CT) and functional (FDG-PET) imaging methods in the thoracic and extrathoracic staging of non-small cell lung cancer. *Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societies & of the National Cancer Institute of Mexico*, 9, 32-39.
- Satoh, S. Ohdama, S. Matsubara, O. Okochi, Y. Tanaka, R. & Kimura, Y. (2005). CT-guided automated cutting needle biopsy by a combined method for accurate specific diagnosis of focal lung lesions. *Radiation Medicine*, 23, 30-36.
- Sawhney, M. S. Kratzke, R. A. Lederle, F. A. Holmstrom, A. M. Nelson, D. B. & Kelly, R. F. (2006). Endoscopic ultrasound and positron emission tomography for lung cancer staging 552. *Clinical Gastroenterology & Hepatology*, 4, 846-851.
- Sawhney, M. S. Kratzke, R. A. Lederle, F. A. Holmstrom, A. M. Nelson, D. B. & Kelly, R. F. (2006). EUS-guided FNA for the diagnosis of advanced lung cancer. *Gastrointestinal Endoscopy*, 63, 959-965.
- Schillaci, O. Spanu, A. Scopinaro, F. Monteleone, F. Solinas, M. E. Volpino, P. et al. (2003). Mediastinal lymph node involvement in non-small cell lung cancer: evaluation with 99mTc-tetrofosmin SPECT and comparison with CT. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine*, 44, 1219-1224.
- Shah, P. L. (2006). The role of transbronchial fine needle aspiration in an integrated care pathway for the assessment of patients with suspected lung cancer. *Journal of Thoracic Oncology*, 1, 324-327.
- Shim, S. S. Lee, K. S. Kim, B. T. Chung, M. J. Lee, E. J. Han, J. et al. (2005). Non-small cell lung cancer: prospective comparison of integrated FDG PET/CT and CT alone for preoperative staging. *Radiology*, 236, 1011-1019.
- Song, J. W. Oh, Y. M. Shim, T. S. Kim, W. S. Ryu, J. S. & Choi, C. M. (2009). Efficacy comparison between (18)F-FDG PET/CT and bone scintigraphy in detecting bony metastases of non-small-cell lung cancer. *Lung Cancer*, 65, 333-338.
- Stratakos, G. Porfyridis, I. Papas, V. Kandaraki, C. Zisis, C. Mariatou, V. et al. (2008). Exclusive diagnostic contribution of the histology specimens obtained by 19-gauge transbronchial aspiration needle in suspected malignant intrathoracic lymphadenopathy. *Chest*, 133, 131-136.
- Suzuki, K. Yamamoto, M. Hasegawa, Y. Ando, M. Shima, K. Sako, C. et al. (2004). Magnetic resonance imaging and computed tomography in the diagnoses of brain metastases of lung cancer. *Lung Cancer*, 46, 357-360.
- Szlubowski, A. (2009). Endobronchial ultrasound-guided needle aspiration in the non-small cell lung cancer staging. *European Journal of Cardio-Thoracic Surgery*, 35, 332-336.
- Szlubowski, A. (2010). A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non-small-cell lung cancer staging - a prospective trial. *European Journal of Cardio-Thoracic Surgery*, 37, 1175-1179
- Takenaka, D. (2009). Detection of bone metastases in non-small cell lung cancer patients: Comparison of whole-body diffusion-weighted imaging (DWI), whole-body MR imaging without and with DWI, whole-body FDGPET/CT, and bone scintigraphy. *Journal of Magnetic Resonance Imaging*, 30, 298-308.

- Tombesi, P. Nielsen, I. Tassinari, D. Trevisani, L. Abbasciano, V. & Sartori, S. (2009). Transthoracic ultrasonography-guided core needle biopsy of pleural-based lung lesions: prospective randomized comparison between a Tru-cut-type needle and a modified Menghini-type needle. *Ultraschall in der Medizin (Stuttgart, Germany : 1980)*, 30, 390-395.
- Turkmen, C. Sonmezoglu, K. Toker, A. Yilmazbayhan, D. Dilege, S. Halac, M. et al. (2007). The additional value of FDG PET imaging for distinguishing N0 or N1 from N2 stage in preoperative staging of non-small cell lung cancer in region where the prevalence of inflammatory lung disease is high. *Clinical Nuclear Medicine*, 32, 607-612.
- Uesaka, D. Demura, Y. Ishizaki, T. Ameshima, S. Miyamori, I. Sasaki, M. et al. (2008). Evaluation of dual-time-point 18F-FDG PET for staging in patients with lung cancer.[see comment]. *Journal of Nuclear Medicine*, 49, 1606-1612.
- Uskul, B. T. Turker, H. Gokce, M. Kant, A. Arslan, S. & Turan, F. E. (2009). CT-guided transthoracic fine needle aspiration of pulmonary lesions: accuracy and complications in 134 cases. *Tuberkuloz ve Toraks*, 57, 177-185.
- Verhagen, A. F. Bootsma, G. P. Tjan-Heijnen, V. C. van der Wilt, G. J. Cox, A. L. Brouwer, M. H. et al. (2004). FDG-PET in staging lung cancer: how does it change the algorithm? *Lung Cancer*, 44, 175-181.
- Viney, R. C. Boyer, M. J. King, M. T. Kenny, P. M. Pollicino, C. A. McLean, J. M. et al. (2004). Randomized controlled trial of the role of positron emission tomography in the management of stage I and II non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 22, 2357-2362.
- Yang, W. Fu, Z. Yu, J. Yuan, S. Zhang, B. Li, D. et al. (2008). Value of PET/CT versus enhanced CT for locoregional lymph nodes in non-small cell lung cancer. *Lung Cancer*, 61, 35-43.
- Yasuda, I. (2009). Mediastinal lymph node staging in potentially resectable non-small cell lung cancer: A prospective comparison of CT and EUS/EUS-FNA. *Respiration*, 78, 423-431.
- Yu, Y. H. Hsu, W. H. Hsu, N. Y. Lin, T. Y. Hsia, T. C. Sun, S. S. et al. (2004). The use of dual phase 201Tl SPECT for differentiating pulmonary malignancies from benign lesions. *Japanese Journal of Clinical Oncology*, 34, 445-451.
- Zaric, B. Becker, H. D. Perin, B. Stojanovic, G. Jovelic, A. Eri, Z. et al. (2010). Autofluorescence imaging videobronchoscopy improves assessment of tumor margins and affects therapeutic strategy in central lung cancer. *Japanese Journal of Clinical Oncology*, 40, 139-145.

5 Treatment with curative intent for NSCLC

5.1 Selection of patients with NSCLC for treatment with curative intent

Clinical topic: Key measures of fitness that predict whether or not patients with lung cancer can be treated with curative intent.

Surgery is the most common treatment given with curative intent. Others include radiotherapy, combined chemoradiotherapy and adjuvant chemotherapy. There is a wide variation in the rate of treatment with curative intent between Cancer Networks in England and Wales; one likely reason for this is variation in selection criteria applied by clinical teams.

There are many factors for the patient and healthcare professionals to consider when deciding if treatment with curative intent is appropriate. The best outcome for the patient should be the over-riding aim. The most important factors are the likelihood of treatment achieving a cure and the fitness of the patient. The former is essentially about either the ability to clear the cancer surgically, with or without other modalities, or the ability to treat all the cancer with radiotherapy with curative intent. The latter has two components – the extent of risk to the patient in terms of mortality and the degree of morbidity (principally post operative dyspnoea and quality of life). Fitness and ability to cure are also linked; a patient whose fitness is borderline may not be able to tolerate a more extensive resection needed to achieve cure. Ultimately decisions about treatment are made by the patient following an informed discussion. Issues can be complex, especially in borderline situations.

During development of the scope of this guideline update, the assessment of fitness was identified as a priority area within the selection process that required clarification. This has been shown to be prescient by the fact that two comprehensive guidelines^{1,2} on selection of patients for treatment with curative intent, published during the progression of this guideline, differ on this key topic. The approach taken by the Guideline Development Group (GDG) was to review these guidelines as part of the evidence review with particular attention to areas of controversy.

This section also applies to patients with SCLC although it is acknowledged that fewer of these patients will have treatment with curative intent. Please see chapter 7.

¹ Lim E, Baldwin D, Beckles M et al. (2010) British Thoracic Society and the Society for Cardiothoracic Surgery in Great Britain and Ireland. Guidelines on the Radical Management of Patients with Lung Cancer. *Thorax*, 65, supplement III.

² Brunelli, A., Charloux, A., Bolliger, C.T., Rocco, G., Sculier, J.P., Varela, G., Licker, M., Ferguson, M.K., Faivre-Finn, C., Huber, R.M., Clini, E.M., Win, T., De Ruyscher, D., & Goldman, L. (2009). ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *European Respiratory Journal*, 34, 17-41.

Recommendations

Risk assessment for operative mortality

- When evaluating surgery as an option for patients with NSCLC, consider using a global risk score such as Thoracoscore to estimate the risk of death. Ensure the patient is aware of the risk before giving consent for surgery. [NEW 2011]

Risk assessment for cardiovascular morbidity

- Avoid surgery within 30 days of myocardial infarction. [NEW 2011]
- Seek a cardiology review in patients with an active cardiac condition, or three or more risk factors, or poor cardiac functional capacity. [NEW 2011]
- Offer surgery without further investigations to patients with two or fewer risk factors and good cardiac functional capacity. [NEW 2011]
- Optimise any primary cardiac treatment and begin secondary prophylaxis for coronary disease as soon as possible. [NEW 2011]
- Continue anti-ischaemic treatment in the perioperative period, including aspirin, statins and beta-blockers. [NEW 2011]
- If a patient has a coronary stent, discuss perioperative anti-platelet treatment with a cardiologist. [NEW 2011]
- Consider revascularisation (percutaneous intervention or coronary artery bypass grafting) before surgery for patients with chronic stable angina and conventional indications for revascularisation. [NEW 2011]

Assessment of lung function

- Perform spirometry in all patients being considered for treatment with curative intent. Measure T_LCO if breathlessness is disproportionate or there is other lung pathology (for example, lung fibrosis). [NEW 2011]
- Offer patients surgery if they have an FEV_1 within normal limits and good exercise tolerance. [NEW 2011]
- Offer patients with predicted postoperative FEV_1 or T_LCO below the recommended limit of 30% the option of undergoing surgery if they accept the risks of dyspnoea and associated complications. [NEW 2011]
- When considering surgery perform a segment count to predict postoperative lung function. [NEW 2011]

Exercise testing

- Consider using shuttle walk testing (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. [NEW 2011]
- Consider cardiopulmonary exercise testing to measure VO_2 max 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. [NEW 2011]
- A clinical oncologist specialising in thoracic oncology should determine suitability for radiotherapy with curative intent, taking into account performance status and co-morbidities. [NEW 2011]

Clinical evidence

The evidence for preoperative prediction of postoperative morbidity and mortality by exercise tests, lung function tests and global or cardiac risk scores in patients with resectable lung cancer consisted of 54 studies. This collection of studies is marked by a number of limitations generally. The vast majority of these studies were retrospective observational studies and the patient samples of a large proportion of the included studies consisted of a mixture of patients undergoing pulmonary surgery for a variety of reasons that included lung cancer, but also other malignant as well as benign conditions. In addition to these concerns, the body of evidence that deals with risk models is marked by an absence of validation of the models in independent samples of patients with resectable lung cancer. The interpretation of the often conflicting results is further complicated by the fact that the studies vary in the number and type of predictor variables that are analysed, the types of outcomes (single or composite) that are investigated and the type of cardio-pulmonary exercise tests employed. The limitations pertaining to study design, mixed populations and the absence of risk model validation in independent samples of lung cancer patients must be borne in mind when interpreting the results outlined in this evidence review as they collectively serve to compromise and question the validity of the results as well as the applicability of the results to patients with resectable lung cancer. The sections on the preoperative assessment of fitness for radical treatment included in the NICE Guideline on the Diagnosis and Treatment of Lung Cancer (2005) complete this evidence summary.

FEV1 and TLCO

The results of the studies vary with a number of studies finding that

- FEV1 is predictive of postoperative complications and/or mortality (e.g., Bernard et al., 2000; Benzo et al., 2007; Berry et al., 2010; Brunelli et al., 2004a, 2004b, 2006b [mortality], 2007; 2008a-d, 2009 [morbidity]; Cerfolio et al., 2009; Cywinski et al., 2009; Ferguson et al., 2008a [depending on population and outcome], 2008b [depending on population and outcome]; Keegan et al., 2007; Leo et al., 2006; Licker et al., 2006; Loewen et al., 2007 [complicated v uncomplicated course]; Myrdal et al., 2001 [life-threatening complications incl. mortality]; Sekine et al. 2007 [depending on outcome]; Shiono et al., 2007 [pneumonia])
- DLCO is predictive of postoperative complications and/or mortality (e.g., Amar et al., 2010; Berry et al., 2010; Brunelli et al., 2006, 2008b; Cerfolio et al., 2009; Ferguson et al., 1995, 2008a [depending on population and outcome], 2008b [depending on population and outcome], 2009; Loewen et al., 2007; Yano et al., 1997)
- FEV1 is not predictive of postoperative outcome (e.g., Amar et al., 2010; Berrisford et al., 2005; Bonde et al., 2002; Brunelli et al., 2002 [although FEV1 was predictive in patients with FEV1 \geq 70%], 2006a, 2009 [mortality]; Falcoz et al., 2007; Ferguson et al., 1995, 2008a [depending on population and outcome], 2008b [depending on population and outcome], 2009; Loewen et al., 2007 [satisfactory v poor outcome]; Myrdal et al., 2001 [mortality]; Ploeg et al., 2003; Pastorino et al., 2008; Powell et al., 2009; Sekine et al., 2007 [depending on outcome]; Shiono et al., 2007 [empyema]; Wright et al., 2008; Yano et al., 1997) and
- DLCO is not predictive of postoperative outcome (e.g., Berrisford et al., 2005; Brunelli et al., 2007a; Ferguson et al., 2008a, [depending on population and outcome], 2008b [depending on population and outcome]; Keegan et al., 2007; Licker et al., 2006; Pastorino et al., 2008).

Exercise testing

A small number of studies have examined the potential for measures derived from exercise testing to predict postoperative complications and mortality and have found that some of these measures appear to be related to some (e.g., Benzo et al., 2007 [peak watt]; Brunelli et al., 2008c, 2008d; Loewen et al., 2007 [complicated v uncomplicated course]) but seemingly not all (e.g., Loewen et al., 2007) postoperative outcomes.

Risk models

A similar point as was made with regards to the predictive ability of exercise testing can be made when it comes to the ability of different global risk models to predict postoperative outcome. A number of models are able to predict some (e.g., Brunelli et al., 1999 [POSSUM predicting post-operative complications incl. death]; Brunelli et al., 2005 [POSSUM predicting cardio-pulmonary complication]; Falcoz et al., 2007 [Thoracoscore predicting mortality]; Chamogeorgakis et al., 2007 [modified Thoracoscore predicting mortality]; Ferguson et al., 2003 [EVAD, POSSUM and CRPI models each predicting some outcomes]; Yamashita et al., 2004 [CRS of E-PASS predicting morbidity]; Yamashita et al., 2006 [CRS of E-PASS predicting morbidity]), but seemingly not other (Brunelli et al., 2005 [POSSUM not predicting mortality]; Ferguson et al., 2003 [EVAD, PUSSUM and CRPI models each not predicting some of the outcomes]) postoperative outcomes.

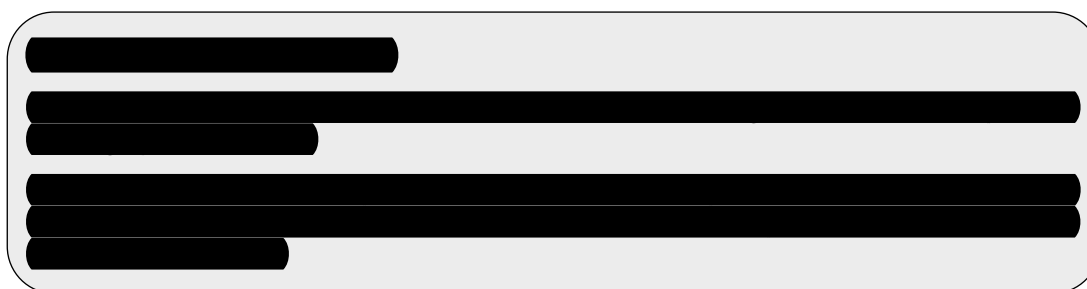
Health economic evaluation

The GDG noted that the issue of advanced methodology for fitness assessment does have cost implication but was not considered a high priority. This question does not involve a comparison of interventions in terms of their associated costs and health outcomes, and is therefore not amenable to economic evaluation.

Qualifying statement

Recommendations about risk assessment for post operative morbidity and mortality were made after review of the evidence for a variety of risk scores. This evidence consisted largely of retrospective analyses and some prospective. The populations studied often included patients with benign disease and non-lung cancer thoracic surgery. In interpreting this evidence, the GDG considered, as well as the quality of the studies, the validity of outcome measures employed in terms of their relevance to clinical practice. Risk models were often similar in structure, those with the best performance are referred to in the recommendations.

Studies looking at lung function testing and predicted post operative FEV1 showed variable results but overall, a correlation with post operative outcomes (not all studies). The GDG recognised the value of normal lung function as a strong predictor of a good outcome and reflected this in the recommendations. Review of the evidence did not show a reliable lower limit of lung function and so the GDG made a consensus statement concerning this. Studies of exercise testing were found to be variable in quality and difficult to compare. Few addressed the important issue of a lower limit before operative risks became unacceptable (although this in itself implies patient choice). Thus recommendations were confined to the use of CPET to clarify whether borderline patients are likely to have a good outcome and for other less complex exercise tests to be considered, with only one having an adequately evidence-based cut-off.



5.2 Pulmonary optimisation

Clinical topic: Does pre-operative smoking cessation/pre-operative pulmonary rehabilitation improve outcomes following lung cancer surgery?

Smoking cessation

The majority of patients presenting for lung cancer surgery have a history of smoking. Current smokers or those who have recently stopped do less well, overall, than never or ex-smokers. However, before any recommendations can be made about delaying treatment in smokers, there would need to be good evidence that the delay resulted in improved outcomes. It is unlikely that such a study would be conducted as all the emphasis is on rapid access to treatment and patients are reluctant to accept delays. Thus it is appropriate to examine the effect of immediate smoking cessation in the timeframe of the usual work-up of patients with lung cancer, but not to delay treatment for longer periods than that. Even if it were possible to delay treatment for longer, the difficulty which patients face in trying to stop smoking while waiting for treatment of a life threatening disease makes a delay unhelpful in terms of the patients actually achieving cessation of their smoking habit.

There are a number of confounding factors that influence the effect of smoking and smoking cessation on the risk of post-operative complications. Current smokers are likely to be younger than those who stopped many years previously and therefore have a higher performance status and better pulmonary reserve despite their history of recent smoking. Studies must also control for the amount of smoking and the presence of co-morbid conditions caused by smoking.

It is sensible to prescribe nicotine replacement therapy to allow patients to cope with the physical effects of smoking cessation, especially in the early post-operative period.

Pulmonary rehabilitation

Pulmonary rehabilitation prior to lung cancer surgery is an attractive technique for reducing post-operative respiratory complications. Unfortunately as patients who are selected for rehabilitation are those with the lowest pulmonary reserve, the same confounding variables that are present when assessing the risks of post operative complications will need to be controlled for, when trying to identify any beneficial effect for rehabilitation. In addition, the time taken to complete the rehabilitation course will lead to unacceptable delay as mentioned above.

Recommendations

- Inform patients that smoking increases the risk of pulmonary complications after lung cancer surgery. [NEW 2011]
- Advise patients to stop smoking as soon as the diagnosis of lung cancer is suspected and tell them why this is important. [NEW 2011]
- Offer nicotine replacement therapy and other therapies to help patients to stop smoking in line with 'Smoking cessation services' (NICE public health guidance 10) and 'Varenicline for smoking cessation' (NICE technology appraisal guidance 123). [NEW 2011]
- Do not postpone surgery for lung cancer to allow patients to stop smoking. [NEW 2011]

Clinical evidence

The search for systematic reviews and primary studies examining the effectiveness of pre-operative smoking cessation or the effectiveness of pre-operative pulmonary rehabilitation in patients with lung cancer considered for surgery revealed five studies (Barrera et al., 2005; Groth et al., 2009; Mason et al., 2009; Nia et al., 2005; Vaporciyan et al., 2002) examining the effect of pre-operative smoking cessation on surgical outcomes in patients with lung

cancer and one study (Sekine et al., 2005) examining the effect of pulmonary rehabilitation on surgical morbidity and lung function in lung cancer patients with COPD. An additional study on pre-operative smoking cessation (Nakagawa et al., 2001) was identified from one of the studies found in the search. None of these studies were RCTs, rather they tended to be retrospective case-series of low quality.

Pre-operative smoking cessation

Barrera et al. (2005) prospectively examined in 300 thoracic surgical patients with primary (N = 221) or secondary (N = 79) lung tumours whether post-operative pulmonary complication rates differed between non-smokers, ex-smokers and current smokers, and found that the overall rate of post-operative pulmonary complications was significantly higher in smokers than in the non-smokers, but did not differ between the different categories of smokers. The four groups did not differ in terms of rates of other reported outcomes although current smokers stayed significantly longer in hospital than non-smokers. Multivariate analyses on the data from the three groups of smokers found that pulmonary complications and pneumonia were both associated with > 60 pack-years smoking. However, the four patient groups were not comparable at baseline, and this study constitutes low-quality evidence.

Groth et al. (2009) conducted a retrospective study of low quality and found no differences in post-operative complications, length of stay or post-operative pulmonary function between distant smokers (N = 81), recent smokers (N = 16) and current smokers (N = 23). However, at baseline the rate of 'other malignancy' was significantly higher (and similar) in the distant smokers and smokers compared to the recent smokers, the distant smokers were also significantly older than the other two groups, and the recent smokers had a significantly higher preoperative Karnofsky score than the smokers. In addition, the distant smokers had lower pre-operative forced vital capacity (FVC; L) than the recent smokers (the smokers did not differ from either group), and the recent smokers had higher pre-operative FVC (%) than the smokers (the distant smokers did not differ from either group).

Mason et al. (2009) retrospectively assigned patients who had undergone lung cancer resection to one of the following groups on the basis of their smoking status: (1) Active smoker or smoking cessation within 2 weeks of surgery (N = 1595), (2) Smoking cessation > 2 weeks to 1 month before surgery (N = 404), (3) Smoking cessation 1-12 months before surgery (N = 940), (4) Smoking cessation > 12 months before surgery (N = 4026), and (5) Never smoked or smoked < 100 cigarettes in their lifetime (N = 1025). In this study of low-moderate quality. Mason et al. found that the odds of dying in hospital for groups (1) and (2) relative to group (5) were significantly higher whereas the odds of dying in hospital were not significantly higher for groups (3) and (4) relative to group (5). Similarly, the odds of experiencing pulmonary complications were also significantly higher in group (1) relative to group (5) whereas the odds for groups (2) – (4) were not significantly different from those of group (5) on this outcome measure.

Nakagawa et al. (2001) retrospectively examined the association between timing of smoking cessation and post-operative pulmonary complications in 288 consecutive patients who had undergone a pulmonary surgical procedure. Nakagawa et al. (2001) found that the incidence of post-operative pulmonary complications was significantly higher in current smokers and recent smokers compared to non-smokers, but that the incidence of post-operative pulmonary complications did not differ significantly between the current and the recent smokers and between these two groups and ex-smokers. However, when the effect of smoking status on post-operative pulmonary complications was adjusted for gender, age, pulmonary function test and duration of surgery, the differences in incidence of post-operative pulmonary complications between the current and recent smokers and the non-smokers disappeared and the odds of developing post-operative pulmonary complications were not statistically significantly increased in any of the three smoker groups relative to the non-smokers. The evidence provided by Nakagawa et al. (2001) is of low quality.

In another low-quality retrospective study with 311 patients who had undergone curative resection for primary NSCLC Nia et al. (2005) found that compared to current smoking, non-smoking, distant smoking cessation and recent smoking cessation were all statistically significantly associated with longer survival. Nia et al. (2005) also found that recurrence was statistically significantly associated with current smoking relative to distant smoking, but not relative to non-smoking or recent smoking.

In a low-quality retrospective study with 223 patients (198 of whom had primary lung cancer) who had undergone pneumonectomy Vaporciyan et al. (2002) found that still smoking within 1 month prior to the operation was associated with increased odds of developing of major pulmonary events (defined as pneumonia or acute respiratory distress syndrome) after surgery compared to pre-operative smoking cessation ≥ 1 month of the operation (odds ratio = 2.7).

Pre-operative pulmonary rehabilitation

In a low-quality prospective study with historical controls, Sekine et al. (2005) gave 22 prospectively recruited patients pre-operative pulmonary rehabilitation from the time of admission until operation (ca. 2 weeks) which consisted of incentive spirometry, abdominal breathing and breathing exercises with pursed lips, huffing and coughing after nebulising for 15 min with a bronchodilator 5 times a day, pulmonary exercise for 30 min at the rehabilitation room and walking > 500 steps every day for 2 weeks preoperatively. In addition to the pre-operative pulmonary rehabilitation, the same pulmonary rehabilitation schedule was restarted post-operatively as soon as the patients started "walking around the bed". Immediately after the operation, the patients also received squeezing for 10 minutes after nebulising with a bronchodilator by physiotherapists, expert nurses or thoracic doctors every 4-6 hours in the daytime for ≥ 4 days. All the current smokers were instructed to stop smoking at the first visit to hospital and their smoking cessation was confirmed. All the prospectively recruited patients received pulmonary rehabilitation and this patient group was compared to 60 retrospectively enrolled patients (historical control group) who had received incentive spirometry for enhancing lung expansion 2 weeks before surgery and, when the patients felt difficulty in coughing out sputum, chest physiotherapy by expert nurses. At baseline, FEV₁ (L), predicted FEV₁ (%), and FEV₁/FVC (%) were all significantly lower in the prospectively enrolled pulmonary rehabilitation patients compared to the historical controls. Post-operatively, the groups did not differ in the proportion of patients who experienced pneumonia, interstitial pneumonia, bronchial stump dehiscence, empyema, prolonged O₂ supplements ≥ 7 days, mechanical ventilation ≥ 3 days, tracheostomy, and 30-day mortality. However, the postoperative hospital stay was longer in the historical controls than in the pulmonary rehabilitation patients. Post-operatively, the groups did not differ in mean PaO₂ (mmHg), PaCO₂ (mmHg), FVC, predicted FVC, FEV₁ and predicted FEV₁. However, post-operative FEV₁/FVC (%) was still significantly lower in the pulmonary rehabilitation patients compared to the historical controls. The changing ratios of FVC, FEV₁ and FEV₁/FVC (representing % change = (postoperative value – preoperative value)/preoperative value X 100) were calculated and FEV₁ was found to be significantly less diminished in the rehabilitation group than in the historical control group whereas the FVC and FEV₁/FVC did not differ statistically significantly between the groups. The ratio of actual postoperative FEV₁ to predicted postoperative FEV₁ was significantly higher in the pulmonary rehabilitation group relative to the historical control group.

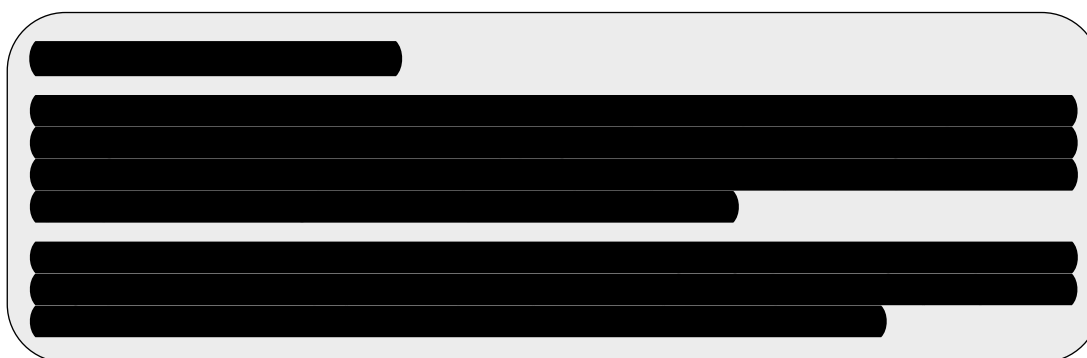
Health economic evaluation

This topic was agreed as a medium priority for health economic analysis because whilst the topic addresses the use of a broad range of therapeutic interventions that can be used before, during and after surgery to reduce morbidity, these interventions were not thought to be costly in themselves.

Qualifying statement

These recommendations are based on six low quality observational studies which tried to ascertain the risk of pulmonary complications after surgery for cancer in patients who were active smokers, ex-smokers of various durations and never-smokers. All the studies showed that the biggest difference in this risk was between never-smokers and smokers of any description; there was little improvement in this risk being gained for people who have recently stopped smoking. Patients who continue to smoke after surgery had a shortened lifespan, compared to ex-smokers. The recommendations have therefore been constructed from this evidence, specifically that it is reasonable to inform patients of the long term risks of smoking, to discuss specifically any special operative risks associated with smoking, but not to delay potentially curative surgery to allow patients to stop smoking.

Only one low-quality, prospective study with historical controls was found on pre-operative pulmonary rehabilitation, therefore the GDG decided to make a recommendation for further research on this area.



5.3 Options for treatment with curative intent for patients with NSCLC

Clinical topic: What is the most effective treatment for patients with resectable non-small cell lung cancer?

Surgery remains the preferred treatment option in NSCLC provided that the cancer can be resected and this can be done with acceptable mortality and morbidity. The evidence for the effectiveness of surgical resection against other treatments for NSCLC was reviewed recently in a Cochrane Review³. What trials there are compare one form of surgery (e.g. limited resection), against a more radical form, usually open lobectomy. Newer treatments such as radio frequency ablation (RFA) and stereotactic body radiotherapy (SBRT), that might be applied to resectable disease have not been compared with surgery, and it seems unlikely that they will, except in selected groups of patients where there are good reasons to suppose that a newer treatment might improve local control or reduce toxicity. These patients are those where the surgical option is less certain because of either borderline fitness or borderline resectability or both. In these circumstances a clear understanding of the options for treatment is needed and the willingness to explain this to patients. The question of assessment of fitness for surgery has been addressed earlier but this cannot be taken in isolation as fitness and treatment offered are linked. Surgery for later stage disease may require a more extensive resection that may result in a higher mortality and morbidity, whilst at the same time achieving a lower cure rate than for earlier stage disease. In these circumstances the benefit of surgery over other treatments with curative intent may be less marked. Another factor is the surgical technique used which can influence whether an operation can be done with greater safety yet still achieve complete resection. Finally the influence of multi-modality treatment on surgical outcome may influence the decision to offer surgery. The British and European Guidelines^{4,5} on selection of patients for

³ Manser et al., 2010

⁴ British Thoracic Society and the Society for Cardiothoracic Surgery in Great Britain and Ireland (2010). Guidelines on the Radical Management of Patients with Lung Cancer. Thorax, 65, supplement III.

treatment with curative intent review the surgical techniques as well as specific stages of disease.

5.3.1 Surgical techniques

The most common procedure performed in the UK is lobectomy (69%). Video assisted thoracic surgery (VATS) accounts for only 2% of these lobectomies. Lobectomy has a lower mortality than pneumonectomy (2.4% vs 6.2%). Segment counting is employed to predict post operative lung function and therefore the risk of post operative dyspnoea. This can determine whether or not surgery is offered. Perfusion scans are also used, particularly where pneumonectomy is contemplated. Sub-lobar and broncho-angioplastic resections allow fewer segments to be resected and therefore can extend the boundaries of surgery.

Sub-lobar resections

Sub-lobar resections comprise wedge resections and segmental resections. Wedge resection involves resection of the tumour with a surrounding margin of normal lung tissue, and does not follow anatomical boundaries, whereas segmental resection involves the division of vessels and bronchi to a distinct anatomical segment(s). Segmental resection removes draining lymphatics and veins and intuitively might be expected to result in lower recurrence rates, although there is no evidence for this. Segmental resection may not always be technically feasible, and is best suited to the left upper lobe (lingula, apicoposterior and anterior segments) and the apical segment of both lower lobes.

Broncho-angioplastic resections

Bronchoplastic resections involve removing a portion of either the main bronchus or bronchus intermedius with a complete ring of airway followed by the re-anastomosis of proximal and distal airway. Angioplastic resections involve removing part of the main pulmonary artery followed by end-to-end anastomosis or reconstruction.

Lung volume reduction surgery (LVRS)

In patients who have a lung cancer within an area of severe emphysema, case series have shown that surgical resection is possible with improvement in quality of life. However, there are no randomised trials and outcome measures are not as rigorous as for the trials of lung volume reduction in emphysema. Patient selection for this approach needs to be individualised, bearing in mind the separate, but overlapping indications for LVRS and cancer surgery.

Intraoperative nodal sampling

There is considerable variation in the practice of lymph node sampling from lobe specific sampling to systematic nodal dissection.

5.3.2 Locally advanced disease

T3 tumours are considered resectable and therefore surgery is generally offered first for patients who are otherwise fit. The 7th edition of the TNM staging system now includes in the T3 category, tumours with a diameter of >7cm and tumours that have a nodule in the same lobe. T4 tumours are generally not resectable but may be suitable for radiotherapy with curative intent. Surgery is sometimes performed for T4 tumours but only in highly selected cases and outcomes are only reported in limited case series.

Surgery for N2 disease has been the subject of a number of clinical trials, usually with surgery as part of multimodality therapy. N2 disease includes a spectrum of nodal involvement from single nodes through single zones and multiple zones. N2 disease is also described as “bulky” or “non-bulky” with no clear definitions. Intuitively a tumour that has only spread to a local

⁵ Brunelli, A., Charloux, A., Bolliger, C.T., Rocco, G., Sculier, J.P., Varela, G., Licker, M., Ferguson, M.K., Faivre-Finn, C., Huber, R.M., Clini, E.M., Win, T., De Ruyscher, D., & Goldman, L. (2009). ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *European Respiratory Journal*, 34, 17-41.

group of N2 nodes in close proximity to one another might be helped by surgical resection. Unfortunately these studies looking at treatment with curative intent in N2 disease have not adequately classified N2 disease into subgroups and therefore the question of whether to offer surgery with curative intent remains controversial.

Recommendations

- [REDACTED]
- Offer more extensive surgery (bronchoangioplastic surgery, bilobectomy, pneumonectomy) only when needed to obtain clear margins. [NEW 2011]
- Perform hilar and mediastinal lymph node sampling or en bloc resection for all patients undergoing surgery with curative intent. [NEW 2011]
- 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. [2005]

Clinical evidence

The evidence for the effectiveness of treatments in patients with resectable non-small cell lung cancer (NSCLC) consisted of a Cochrane systematic review (Manser et al., 2010), an RCT (Nosotti et al., 2010) and two retrospective studies (Crabtree et al., 2010; Grills et al., 2010). The Cochrane review covered the literature up until October 2009 on the majority of interventions in the PICO for this topic (i.e., RCTs comparing surgical resection (including lobectomy, sleeve resection, pneumonectomy, segmentectomy or wedge resection (with or without mediastinal node dissection)) alone or in combination with other therapy to no treatment, sham surgery, radiotherapy (RT) or chemotherapy alone or in combination in patients with pathologically confirmed stage I-IIIa NSCLC and RCTs comparing different types of surgical resection in patients with pathologically confirmed stage I-IIIa NSCLC). Our search therefore only covered the literature from October 2009 for these interventions, and identified one additional study (Nosotti et al., 2010). The Cochrane review and the NICE Guideline on the Diagnosis and Treatment of Lung Cancer (2005) did not cover radiofrequency ablation and stereotactic radiotherapy. Consequently, separate full searches (with no date limits) were undertaken for these interventions. Two low quality retrospective studies comparing stereotactic body radiation therapy (SBRT) to surgery were identified (Crabtree et al., 2010; Grills et al., 2010), but the search found no studies comparing radiofrequency ablation to surgery.

Surgical treatment of NSCLC

In a Cochrane review Manser et al. (2010) aimed 1) to determine whether surgical resection of cancer improves disease-specific and all-cause mortality compared with no treatment, radiotherapy or chemotherapy in patients with early stage NSCLC and 2) to compare the effectiveness of different surgical approaches in improving disease-specific or all-cause mortality in patients with early stage lung cancer. This review included 13 RCTs with a total of 2290 patients. These RCTs, none of which were of high quality, examined a total of 8 different

comparisons with 1-3 studies covering each of these 8 comparisons. The results of both the study that compared surgery alone to radiotherapy alone for local and loco-regional stage I-III NSCLC (Morrison et al., 1963) and the two studies that compared chemotherapy plus surgery to radiotherapy alone in stage IIIA NSCLC (Shepherd et al., 1998; Stephens et al., 2005) were inconclusive due to small sample sizes. Warram et al. (1975) compared surgery to no surgery in patients with initially inoperable loco-regional cancer treated with radiotherapy and found that although no statistically significant differences were evident in 5-year survival and disease free survival, respiratory complications (respiratory infection, radiation pneumonitis, respiratory insufficiency) did occur statistically significantly more in the surgery patients compared to the patients who did not receive surgery. Three RCTs compared chemotherapy followed by surgery to chemotherapy followed by radiotherapy in stage IIIA NSCLC (Johnstone et al., 2002; Stathopoulos et al., 1996; van Meerbeeck et al., 2007). These studies were, however, not combined in a meta-analysis due to clinical and statistical heterogeneity. The study conducted by Johnstone et al. (2002) was terminated early due to phase II trials demonstrating the feasibility of preoperative concurrent chemoradiation in patients population and the results are therefore inconclusive. Stathopoulos et al. (1996) found that significantly more patients who had received surgery were alive at 5 years than patients who had received radiotherapy and not surgery. Van Meerbeeck et al. (2007) found no statistically significant difference in 5-year overall or progression-free survival between the treatments. Although Albain et al. (2003) did not find any statistically significant differences in overall survival between patients who had received concurrent chemotherapy and full course radiotherapy and patients who had received induction chemotherapy and radiotherapy followed by surgery, progression-free survival was, however, longer in the induction chemoradiation + surgery group compared to the full course chemoradiation group. The incidence of grade 3 or 4 oesophagitis was significantly higher in the full course chemoradiation group compared to the chemoradiation + surgery group. Other toxicities were not found to differ significantly between the two groups. The one study that compared limited resection (wedge excision or segmentectomy) to lobectomy for stage IA peripheral NSCLC (Ginsberg et al., 1995) found no statistically significant differences between the treatment groups in 5-year survival or the rate of deaths with cancer. However, the rate of recurrence per person/year was statistically significantly higher in the limited resection group than in the lobectomy group. The non-local recurrence rates did not differ significantly between the two groups. Sugi et al. (2000) compared video-assisted thoracoscopic surgery (VATS) lobectomy with conventional lobectomy for stage I NSCLC and found that 3- and 5-year survival rates were similar between the patient groups. It should, however, be noted that 13% of the open group and 8% of the VATS group had more advanced disease than stage I intra-operatively and two patients in the VATS group had small cell cancer but none of these were excluded from the analysis.

A meta-analysis of the three studies that compared complete mediastinal lymph node dissection (CMLND) to mediastinal lymph node systematic sampling (SS) in patients with resectable NSCLC (Izbicki et al., 1998; Sugi et al., 1998; Wu et al., 2002) showed a significant reduction in the risk of death in the group undergoing CMLND (HR = .63), a significant reduction in any cancer recurrence (local or distant) in the CMLND group (RR = .79), which appeared to be mainly due to a reduction in the number of distant recurrences (RR = .78), and no difference between the groups in 30-day operative mortality. Izbicki et al. (1998) reported no difference in disease-free survival between the groups with a median follow up of 47.5 months. Pooled analyses of postoperative complications reported by Izbicki et al. (1998) and Sugi et al. (1998) showed that air leak lasting more than five days was significantly more common in CMLND patients (RR = 2.94). All other reported postoperative complications were not found to differ significantly between the sampling and dissection groups.

Nosotti et al. (2010) compared muscle sparing thoracotomy (MST; N = 50) to posterolateral thoracotomy (PLT; N = 50) in patients scheduled for lobectomy for stage I or II NSCLC and found that the none of the reported outcomes differed between the groups with the exception

of the length of postoperative stay, which were shorter in the MST than in the PLT group and analgesic consumption during the hospital stay and the following two weeks which was higher in the PLT than in the MST patients.

Stereotactic radiation therapy (SBRT)

Crabtree et al. (2010) found that among their group of patients with clinical stage I NSCLC significantly more patients who had received surgical treatment were alive at 3 years than patients who had received SBRT. The treatment groups did not differ in terms of 3-year cancer-specific survival or local control. When the analyses were limited to patients with clinical stage IA 3-year disease-free survival did not differ significantly between the SBRT (N = 57) and surgery (N = 288) patients, but the surgery patients achieved significantly higher rates of local control at 3 years compared to the SBRT patients. Analysis of the patients with clinical stage IB found no differences in 3-year disease-free survival or local control between the SBRT (N = 19) and surgery (N = 174) patients. In a separate series of analyses the authors attempted to address the baseline differences between the treatment groups in terms of age, clinical T stage, comorbidities and % predicted FEV₁ and DLCO by matching surgery patients to the SBRT patients. Subsequent matched-patient analyses revealed no differences between the groups in terms of overall survival, disease-specific survival, or local control. No treatment-related deaths occurred as a consequence of SBRT although some other complications were associated with the treatment. In the surgery group, the operative mortality rate was 15 / 462 patients and 179 / 462 patients experienced complications associated with the surgical treatment.

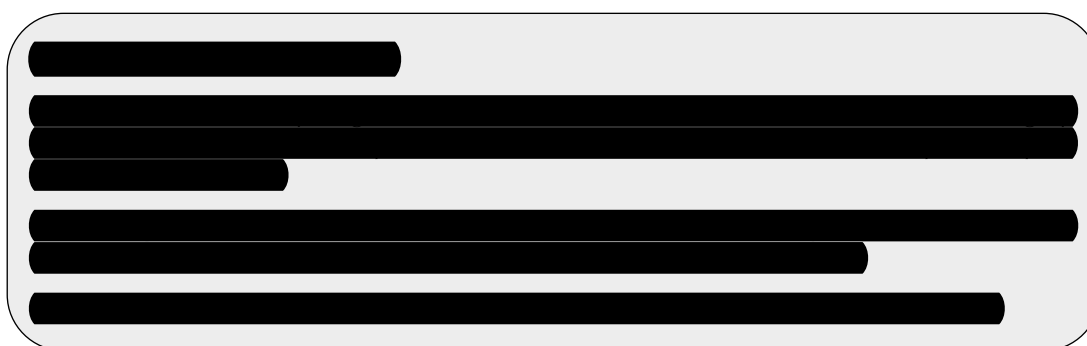
Grills et al. (2010) reported that rates of freedom from any failure, causes-specific survival, distant metastasis and local, regional, and loco-regional recurrence did not differ significantly between patients with stage I NSCLC who had received treatment with either SBRT or wedge resection, but the overall survival rate was significantly higher in the surgery patients than in those patients who had received SBRT. A second set of analyses excluding patients with pT4, synchronous primary or no biopsy revealed similar results with the exception of for the loco-regional occurrence rate which was now significantly higher in the patients who had received surgery. Multivariate analyses showed that in the patients who had received SBRT squamous histology and the presence of synchronous primary tumour were significant predictors of distant metastasis and in the patients who had received wedge resection visceral pleural invasion and stage IB were significant predictors of distant metastasis. In addition, in all patients, age > 71 years was a significant predictor of overall survival. No treatment-related deaths were observed as a consequence of either treatment, but a number of adverse events were associated with both treatments.

Health economic evaluation

The GDG noted that there were two potential economic questions for this topic. Firstly what is the most cost-effective surgical treatment for patients considered fit for surgery? Secondly whether surgery is cost-effective in borderline patients compared to radiotherapy with curative intent? An economic analysis should attempt to quantify the trade-off between a more effective selection of patients for surgery (resulting in improved outcomes for a minority of patients) against delays in treatment for all patients and higher mortality rates due to surgery on riskier patients. However the GDG were aware that it was unlikely that good quality randomised clinical evidence, needed to inform such an economic analysis, would be found. This topic was therefore not prioritised for economic analysis because of feasibility issues.

Qualifying statement

These recommendations are largely based on a Cochrane systematic review which found a lack of good trial data supporting surgical resection against other forms of treatment. The natural history of survival with untreated stage I lung cancer is low (Raz et al. 2007). Early stage (I&II) lung cancer, if resected, is associated with long term survival, as evidenced from the recent data from the IASLC 7th staging project, but surgery is accepted as the treatment of choice by consensus rather than from high quality trials. Higher stage (IIIA-specifically N2) has a better evidence base from two randomised trials which demonstrated no particular advantage for surgery over chemoradiotherapy. However, survival in the surgical arms remained acceptable and is an alternative to that treatment. It is too early to say whether SBRT is a good alternative to surgery, and may form the basis of a randomised trial.



5.4 Radiotherapy with curative intent

Radiotherapy with curative intent commonly means external beam radiotherapy, conventionally delivered as 1 fraction per day (usually 1.8 - 2Gy per fraction), 5 days per week, over 5 - 7 weeks. Several other fractionation schedules have been developed either, on an empirical basis or more recently to take advantage of different radiobiological properties of tumour and normal tissues and these are illustrated in table 5.1 below.

Table 5.1: Fractionation schedules used in radiotherapy practice

	Fractions	* size Gy	* / day	week
Conventional	****o****o****o**** oo****o****o**	2	1	6 - 7
Split course	****o****o*****o*****o*****o*****o*****o*****	> 2	1	> 5
Hypofractionated	****o****o****o****	> 2	1	< 5
Hyperfractionated	****o****o****o****o****o****o****o**** ****o****o****o****o****o****o****o****	1 – 1.3	2	6
CHART	***** ***** *****	1.5	3	2
HART	****o****o*** ****o****o*** ****o****o***	1.6	3	2.5

* Radiotherapy Fraction o No treatment day

The ability to give high doses of radiation to lung tumours needs accurate delineation of the cancer and knowledge of its position throughout the planning and treatment process. The quality of treatment planning and delivery has an important effect on the outcome of patients treated for NSCLC.

Studies from the 1980's report results of treatment that used two dimensional (2-D) planning with set up checked by conventional simulation. These techniques were generally based on field size with poor definition of anatomical and tumour boundaries and can only give limited information about the true radiation dose being delivered to the cancer and surrounding normal tissues. In the 1990s, developments in imaging and computing led to 3-D conformal radiation therapy, which was aimed at tailoring the high dose volume to the target volume while delivering a low dose to the normal tissues. The technical advances that are required to deliver the 3-D conformal treatment have continued since the turn of the century with the development of intensity-modulated radiotherapy, (IMRT), 4-D planning (accounting for tumour movement over the breathing cycle) and the delivery of SBRT for early stage NSCLC. The use of these techniques has increased the accuracy of treatment delivery and allows a reduction in the planning margins added around the tumour that allow for day to day variations in treatment set up. This reduction of margin has the potential to minimise normal tissue damage, particularly pneumonitis and enable a higher dose to be delivered to the tumour. Conversely any reduction in margins needs a robust Quality Assurance System to confirm that the treatment is delivered as planned and safety is maintained.

Radiotherapy is suitable for treating a wide variety of NSCLC patients. Potentially curative radiotherapy may be the treatment of choice for patients with early stage lung cancer and co-morbidity who present a high surgical risk or where the patient makes an informed choice not to have surgery. Radiotherapy can also be given with potential curative intent in patients with locally advanced NSCLC usually in combination with chemotherapy and occasionally surgery.

Late treatment effects (e.g. pulmonary fibrosis, radiation myelitis) develop in the months that follow irradiation are irreversible and have the potential to cause profound problems for the patient. It is the risk of these late effects that currently limits the dose delivered in lung cancer treatments and total dose is the main determinant. However, the risk of late effects is raised by increasing treatment volume and fraction size. The severity of the radiation reactions will be dependent on fitness of the patient, presence of co-morbidities and the heterogeneous dose distribution across the organ or normal tissue at risk.

5.4.1 Assessment of patients for radiotherapy with curative intent

The suitability of patients for radiotherapy with curative intent depends on a number of factors including stage and performance status. Clinical oncologists recognise the need for caution in those patients with a low FEV¹.

In practice, in planning conformal radiotherapy, 3-D planning systems create dose-volume histograms (DVHs) to give a graphical representation of the dose across planned target volume (PTV) as well as normal tissues including lung, oesophagus, heart and spinal cord. The DVH can be used to evaluate different treatment plans and aid selection of the most appropriate on the basis of the coverage of the PTV and sparing of normal tissues. In addition DVH parameters have shown predictive ability for radiation pneumonitis which is the major dose limiting toxicity.

It is good practice to encourage patients to stop smoking during radiotherapy with curative intent.

Recommendations

- [REDACTED]
- All patients should undergo pulmonary function tests (including lung volumes and transfer factor) before having radical radiotherapy for NSCLC. [2005]
- [REDACTED]
- [REDACTED]
- Patients receiving radiotherapy with curative intent should be part of a national quality assurance programme⁷. [NEW 2011]

Updated 2011

[REDACTED]

5.4.2 Treatment of Stage IIIA and IIIB NSCLC with radiotherapy with curative intent

Untreated, patients with stage IIIA and IIIB NSCLC have a poor prognosis. In this section we examined the effectiveness of radiotherapy with curative intent alone in these patients, the suitability of different patient groups for this treatment and the associated morbidity.

Some of the evidence on which the recommendations are based included a small number of stage I and II patients. Although the data for these patients cannot be separated, the numbers are small and the effect on the results is unlikely to be significant.

⁶ The GDG recognises that radiotherapy techniques have advanced considerably since the 2005 guideline and centres would reasonably wish to offer these techniques (including SBRT and 4-D planning) to patients. These treatments have the advantage of reducing the risk of damage to normal tissue (estimated by using measurements such as V20).

⁷ The GDG recognises that radiotherapy techniques have advanced considerably since the 2005 guideline and centres would reasonably wish to offer these techniques (including SBRT and 4-D planning) to patients. These treatments have the advantage of reducing the risk of damage to normal tissue (estimated by using measurements such as V20).

Recommendations

- Patients with stages IIIA or IIIB NSCLC who are eligible for radical radiotherapy and who cannot tolerate or do not wish to have chemoradiotherapy should be offered the CHART regimen. [2005]
- If CHART is not available, conventionally fractionated radiotherapy to a dose of 64–66 Gy in 32–33 fractions over 6½ weeks or 55 Gy in 20 fractions over 4 weeks should be offered. [2005]

5.5 Combination Treatment for NSCLC

Clinical topic: Combination treatment for patients with non-small cell lung cancer.

Although NSCLC patients may benefit from treatment with surgery or radiotherapy alone, the cure rate remains disappointingly low. Data reviewed for the 2005 Lung Cancer guideline suggest that improved survival may be gained from combinations of treatment modalities. The 2005 guidelines defined a number of the terms used in this section. (see table 5.2) It is important to distinguish *neo-adjuvant* treatment (usually chemotherapy) and *combined* chemo-radiotherapy from *primary* chemotherapy. In both of the former settings (neo-adjuvant and combined) the aim of adding chemotherapy is to improve the cure rate obtained with surgery or radiotherapy alone. The aim of primary chemotherapy is to down-stage tumours that at presentation cannot be treated with curative intent but with a reduction in tumour volume might be suitable for potentially treatment with curative intent.

Table 5.2: Definitions of chemotherapy and radiotherapy.

Term used to describe chemotherapy or radiotherapy	Description
Induction chemotherapy	A general term that includes neo-adjuvant chemotherapy and primary chemotherapy.
Adjuvant chemotherapy or radiotherapy	Treatment given after potential curative surgery or radiotherapy, in an attempt to improve the cure rate.
Neo-adjuvant chemotherapy	Chemotherapy given before planned surgery or radiotherapy in patients with potentially curable disease at presentation.
Combined chemo-radiotherapy	Treatment given to patients eligible for potential curative radiotherapy at presentation and the treatments are either given sequentially or concurrently.
Primary chemotherapy	Chemotherapy given to patients who at the time of presentation are not considered suitable for curative surgery or radiotherapy because the tumour is too large or appears unresectable. Chemotherapy is given with the aim to down-stage the tumour to enable them to then proceed to treatment with curative intent. The response rates and survival are much lower in this setting.

There is variation in the definitions and interpretation of the terms *resectable* and *unresectable* in regard to pre and postoperative treatment. It may refer to a primary tumour in the chest being technically unresectable at the time of surgery or biologically unresectable because nodes or metastases in other organs must be left behind, meaning that removal of the tumour does not affect the course of the patient's disease. Furthermore, it is often unclear whether categorization of patients as resectable or unresectable refers to the patient's status at the time of presentation or after primary chemotherapy. Thus, the terms *resectable* and *unresectable* should be used with respect to a surgeon's ability to remove all the tumour tissue in its entirety.

One of the difficulties in reviewing studies of combination therapy is various methods are used for patient selection with substantial heterogeneity in clinical status. While some studies used

radiological (clinical) staging with CT and increasingly PET scanning, others have used surgical (pathological) staging with mediastinoscopy.

In this section, we investigate the evidence for combined treatment of NSCLC patients with two or more of these modalities. Various combinations and orders of treatment have been included.

5.5.1 Combined Chemo-radiotherapy

NSCLC accounts for more than 85% of cases of lung cancer and approximately 40% of patients with NSCLC will present with locally advanced unresectable disease. Until the 1990s high dose conventionally fractionated radiotherapy was standard treatment for patients with good performance status whose disease could be encompassed in a radical radiotherapy volume. However, the curative potential of this radiotherapy treatment is low, and most patients will die with both uncontrolled local and disseminated disease. Consequently, chemotherapy is used as a systemic treatment to control micro-metastases. In addition many chemotherapy agents have a radiation sensitizing effect and offer potential benefits in loco-regional control.

Chemo-radiotherapy is now an established approach to treatment with curative intent of patients with NSCLC where surgery is not suitable. How best these two modalities are combined remains unclear, and the combination of accelerated fractionated radiotherapy schedules with chemotherapy is a potentially productive research area.

5.5.2 Surgery with or without other treatment modalities

Despite complete pathological clearance of tumour by surgical resection, the IASLC staging project showed that 5 year survival is still around 70% for stage IA, 40% for stage II and less for stage III. Thus even in the selected group of patients that are suitable for surgical treatment with curative intent, there is a high risk of local and distant recurrence. Adjuvant treatments with either chemotherapy or radiotherapy have been used to try and improve the outcome following surgery. Subsequently a number of large randomised studies were designed to explore these issues, and in particular better define the patient subgroups most likely to derive any benefit and to determine the most effective chemotherapy combinations. In addition studies were also designed to test the theoretical advantages of offering the chemotherapy before surgery. The clinical rationale for neo-adjuvant is three-fold:

- regression of the primary cancer making subsequent surgery easier, more limited, and more effective
- potential micro-metastases are dealt with at the start of treatment
- inhibition of the putative stimulus to residual cancer by growth factors released by surgery.

Recommendations

- [REDACTED]
- Consider chemoradiotherapy for patients with stage II or III NSCLC who are not suitable for surgery. Balance potential benefit in survival with the risk of additional toxicities. [NEW 2011]
- Ensure all patients potentially suitable for multimodality treatment (surgery, radiotherapy and chemotherapy in any combination) are assessed by a thoracic oncologist and by a thoracic surgeon. [NEW 2011]
- Offer postoperative chemotherapy to patients with good performance status (WHO 0 or 1) and T1-3 N1-2 M0 NSCLC. [NEW 2011]

Recommendations (Cont.)

- 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. [NEW 2011]
- Offer a cisplatin-based combination chemotherapy regimen for adjuvant chemotherapy. [NEW 2011]
- For patients with NSCLC who are suitable for surgery, do not offer neo-adjuvant chemotherapy outside a clinical trial. [NEW 2011]
- Ensure eligible patients have the benefit of detailed discussion of the risks and benefits of adjuvant chemotherapy. [NEW 2011]

Clinical evidence

CHART/HART versus radiotherapy (RT) with curative intent alone / sequential chemotherapy / concurrent chemoradiation ± induction chemotherapy:

One study of low quality was identified that examined the effectiveness of induction chemotherapy + hyperfractionated accelerated radiotherapy (HART) relative to the effectiveness of induction chemotherapy + standard once-daily RT in patients with stage IIIA and IIIB NSCLC (Belani et al., 2005). Overall survival, progression-free survival, response and incidence of grade 3 and above toxicities did not differ between the treatment groups.

Concurrent chemoradiation versus RT with curative intent alone

The search identified an updated Cochrane review with meta-analyses that compared the effectiveness of concurrent chemoradiation treatment to that of radical RT alone (O'Rourke et al., 2010 [the original Cochrane review (Rowell & O'Rourke, 2004) was included in the 2005 guideline]). The systematic review included a total of 2728 patients from 19 studies and found that compared to RT alone concurrent chemoradiation was associated with longer survival, longer progression-free survival and longer loco-regional progression-free survival as well as with higher rates of acute oesophagitis, neutropenia and anaemia. Rates of treatment-related deaths, acute pneumonitis, pulmonary fibrosis, and late oesophagitis were not found to differ between the treatment groups. However, a number of these analyses were marked by between-study heterogeneity and the results must therefore be interpreted with caution. Subgroup analyses also found that compared to RT alone, concurrent chemoradiation was associated with longer survival when considering only the trials using platinum-based chemotherapy, taxane-based chemotherapy, weekly chemotherapy, 2-4 weekly chemotherapy, once-daily RT, high-dose RT and trials with follow up ≥ 22 months or of uncertain duration, respectively. Further subgroup analyses that considered only trials that used daily chemotherapy, low dose cisplatin/carboplatin, high dose cisplatin/carboplatin, follow up < 22 months, twice daily RT or high dose RT, respectively, did not find that survival differed between the concurrent chemoradiation and RT alone groups. However, these subgroup analyses are also in many cases marked by heterogeneity between the studies, which compromises the integrity of the findings and the evidence provided by this systematic review can therefore only be considered to be of moderate quality.

Concurrent chemoradiation versus sequential chemoradiation

One RCT (Belderbos et al., 2005) and one Cochrane review with meta-analysis (O'Rourke et al., 2010 [the original Cochrane review (Rowell & O'Rourke, 2004) was included in the 2005 guideline]) examined the effectiveness of concurrent versus sequential chemoradiation. The RCT which provided evidence of low quality and included 158 patients found no differences in survival, progression-free survival or response between the concurrent and sequential chemoradiation groups. O'Rourke et al. (2010) who included 1024 patients from 6 studies in a meta-analysis found longer survival in the patients who had received concurrent chemoradiation compared to sequential chemoradiation but no differences in

progression-free survival between the treatment groups. O'Rourke et al. (2010) did not find any differences in treatment-related deaths, anaemia, acute pneumonitis or neutropenia between the chemoradiation regimens, but concurrent chemoradiation appeared to be associated with higher rates of acute oesophagitis. Subgroup analyses also found that compared to sequential chemoradiation, concurrent chemoradiation was associated with longer survival when considering only the trials with long follow up. Further subgroup analyses that considered only trials that had follow up < 22 months or used high dose RT did not find that survival differed between the concurrent and sequential chemoradiation groups. It should however be noted that heterogeneity was evident between the studies in some of the above analyses, which compromises the conclusions.

Surgery alone versus neoadjuvant chemotherapy + surgery

The search identified three RCTs (Felip et al., 2010; Gilligan et al., 2007; Mattson et al., 2003) and two meta-analyses (Burdett et al., 2007; Song et al., 2010) that compared the effectiveness of surgery to the effectiveness of neoadjuvant chemotherapy followed by surgery (Burdett et al., 2007; Felip et al., 2010; Gilligan et al., 2007; Song et al., 2010) or surgery/curative RT (Mattson et al., 2003). Burdett et al. included 988 patients from 7 studies in the meta-analysis of survival which revealed a survival advantage in the patients who received neoadjuvant chemotherapy + surgery compared to the patients who received surgery alone (hazard ratio = .82). However, this result failed to reach statistical significance when the data from Gilligan et al. (2007) was added to the meta-analysis. Mattson et al. (2003) and Felip et al. (2010) did also not find any statistically significant difference in survival between the neoadjuvant chemotherapy + surgery groups and the surgery alone groups. However, in a meta-analysis that included all the data analysed by Burdett et al. (2007), the data from Gilligan et al. (2007) as well as the data from an additional 5 studies (total Ns = 1637 and 1587 in the neoadjuvant and surgery alone groups, respectively) Song et al. (2010) found that patients who had received neoadjuvant chemotherapy experienced longer overall survival than the patients given surgery alone. This survival advantage appeared to hold when only stage III patients were included in the analysis, but this result is compromised by between-study heterogeneity. Burdett et al. (2007) included 457 patients from 3 studies in the meta-analysis of disease-free progression and found that neoadjuvant chemotherapy was associated with longer disease-free survival (hazard ratio = .78), however, there was heterogeneity between the studies in this analysis, which compromises the result, and neither Felip et al. (2010), Gilligan et al. (2007) nor Mattson et al. (2003) found any differences in disease-free survival between the treatment groups. Gilligan et al. (2007) also reported that quality of life did not differ between the treatment groups apart from role functioning at 6 months which was decreased in the neoadjuvant group.

Surgery alone versus surgery + adjuvant chemotherapy

Five systematic reviews with meta-analyses (Auperin et al., 2010; Berghmans et al., 2005; Bria et al., 2009; Hamada et al., 2005; Hotta et al., 2004), one meta-analysis of the five largest trials on cisplatin-based adjuvant chemotherapy (Douillard et al., 2010) and four RCTs (Felip et al., 2010; Ichinose et al., 2003; Ou et al., 2010; Wang et al., 2007) examined the effectiveness of surgery alone compared to surgery followed by adjuvant chemotherapy. The systematic reviews were all of moderate quality and there was substantial overlap between the studies included within these meta-analyses. Auperin et al. (2010) included individual-patient data from 8447 patients and found that surgery in combination with adjuvant chemotherapy was associated with longer survival (hazard ratio = .86) 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. (2007) included 7644 patients from 19 studies and found that adjuvant chemotherapy was associated with longer survival (hazard ratio = .84) and this survival advantage held

when only including in the meta-analysis trials using platinum-based chemotherapy, trials using tegafur + uracil chemotherapy, trials without post-operative RT or trials with post-operative RT. Bria et al. (2009) included 13 studies with a total of 7334 patients and similarly found that adjuvant chemotherapy conferred a survival advantage, although this result is compromised by between-study heterogeneity. Additional meta-analyses including only the trials with at least 100 patients and only the trials with stage I patients with no between-study heterogeneity suggested that adjuvant chemotherapy is associated with some survival advantage. Bria et al. (2009) also found longer disease-free survival to be associated with adjuvant chemotherapy, but also in this case was the finding compromised by between-study heterogeneity. Limiting the meta-analysis to the trials with at least 100 patients however still suggested that adjuvant chemotherapy is associated with longer disease-free survival. Furthermore, one of the included studies reported that some aspects of quality of life was inferior in the adjuvant chemotherapy patients at 3 months, whereas at 9 months the quality of life profiles of the treatment groups differed with both advantages and disadvantages being conferred by adjuvant chemotherapy. Douillard et al. (2010) conducted a meta-analysis of the individual-patient data from the five largest trials (see next section) and reported that patients who received adjuvant chemotherapy consisting of cisplatin + vinorelbine had longer survival than both patients who did not receive chemotherapy, but also than patients who received other combinations of adjuvant chemotherapy. These other combinations of chemotherapy were not shown to significantly affect survival. Similar analyses of disease-free survival showed that cisplatin + vinorelbine treatment was associated with longer disease-free survival than no adjuvant chemotherapy treatment and than other combinations of adjuvant chemotherapy treatment. These other combinations of chemotherapy were, however, were still shown to be associated with some disease-free survival benefit. The results also indicated that adjuvant chemotherapy was associated with more non-cancer related deaths in the first 6 months of follow up regardless of the chemotherapy combination. Over the whole period of follow up, the patients who received cisplatin + vinorelbine did not differ from their respective control patients in the rate of non-cancer related deaths, the cisplatin + vinorelbine patients did however experience fewer cancer-related deaths. The patients who received other combinations of chemotherapy experienced a significantly higher rate of non-cancer related deaths compared to their respective controls over the whole period of follow up. Hamada et al. (2005) included 2082 patients from 6 studies that all examined the effect of tegafur + uracil adjuvant chemotherapy and found, in agreement with Berghmans et al. (2005) that adjuvant chemotherapy consisting of tegafur + uracil was associated with longer survival. Hotta et al. (2004) included 5716 patients from 11 studies and similarly found longer survival in patients who have received adjuvant chemotherapy and that this relationship held when only considering the CDDP trials and when only considering the tegafur + uracil trials. However, 16 toxicity-related deaths occurred in their full study population.

In an RCT of moderate quality Felip et al. (2010) did not find any differences in disease-free or overall survival between patients who had received treatment with surgery alone (N = 210) or with surgery and adjuvant paclitaxel and carboplatin (N = 210). In a high quality RCT by Ichinose et al. (2003) completely resected patients received either adjuvant bestatin or placebo. The patients who received bestatin experienced both longer overall survival and increased rates of 5-year cancer-free survival as well as more anorexia, but otherwise equal toxicity to the placebo group. Ou et al. (2010) found that adjuvant vinorelbine/paclitaxel + carboplatin chemotherapy (N = 79) was associated with both longer overall and longer disease-free survival (HRs = 1.466 and 1.56, respectively) compared to surgery alone (N = 71). In addition, in this low quality RCT, Ou et al. (2010) also reported that distant (excluding brain), but not locoregional or brain (first site) recurrence rates were lower in the adjuvant group compared to the control group. Wang et al. (2007) in a low quality RCT found that the 1- and 2-year survival rates were higher in the patients who had received surgery and adjuvant vinorelbine + carboplatin (N = 79) compared to the patients who had received surgery alone (N = 71). Median and 3-year survival and deaths from brain metastases did, however, not differ between the treatment groups.

Surgery alone versus surgery + adjuvant chemotherapy: Large (N > 300) trials already included in the meta-analyses in section C a.2:

The GDG requested the individual appraisal of the five large (N > 300) trials (Arriagada et al., 2010 [updated analysis of data from Arriagada et al., 2004]; Butts et al., 2010 [updated analysis of data from Winton et al., 2005], Douillard et al., 2006; Scagliotti et al., 2003; Waller et al., 2004) examining the effectiveness of surgery followed by adjuvant chemotherapy relative to surgery alone although the data from these trials were all included in the meta-analyses by Auperin et al. (2010), Bria et al. (2009) and Douillard et al. (2010) with data from two of the trials (Arriagada et al., 2010; Scagliotti et al., 2003) also included in the meta-analyses by Berghmans et al. (2005) and Hotta et al. (2004). In an RCT of moderate methodological quality Arriagada et al. (2010) found that the effect of chemotherapy interacted with time, that is, within the first 5 years of follow up cisplatin-based adjuvant chemotherapy (N = 935) was associated with longer survival (hazard ratio = .86) and longer disease-free survival compared to surgery alone (N = 932), whereas after 5 years of follow up, chemotherapy was associated with shorter survival but not with any difference in disease-free survival. The rates of local and distant recurrence and non-brain metastasis were lower in the patients who had received chemotherapy compared to the surgery alone patients, but the rates of death from non-lung cancer, second malignancies and brain metastasis did not differ between the treatment groups. The results of Arriagada et al. (2010) are broadly consistent with those reported by Douillard et al. (2006) who also found that adjuvant chemotherapy (consisting of cisplatin + vinorelbine; N = 407) was associated with longer survival and longer disease-free survival in addition to lower rates of local relapse and bone metastasis relative to surgery alone (N = 433). Rates of distant relapse and brain metastasis did not differ between the groups in the RCT by Douillard et al. (2006), which was of low quality. Butts et al. (2010) also found, in a moderate-quality RCT, that patients who received surgery followed by adjuvant chemotherapy (consisting of cisplatin + vinorelbine; N = 242) survived longer, experienced longer disease-specific survival and had a lower risk of dying from lung cancer than patients who received surgery alone (N = 240). The risk of dying from other causes did not differ between the two patient groups. In contrast to these results, a moderate-quality RCT by Scagliotti et al. (2003) found no difference in survival or progression-free survival between patients who received surgery followed by adjuvant chemotherapy (consisting of cisplatin + mitomycin C + vindesine; N = 548) and patients receiving surgery only (N = 540). Waller et al. (2004) also found no effect of surgery + adjuvant cisplatin-based chemotherapy (N = 192) on survival and progression-free survival relative to surgery alone (N = 189) in an RCT of low methodological quality.

Induction/consolidation/maintenance/add-on treatment as part of combination treatments

Three studies examined the effectiveness of concurrent chemoradiation ± induction chemotherapy (Vokes et al., 2007), ± consolidation chemotherapy (Hanna et al., 2008), + consolidation chemotherapy ± maintenance chemotherapy (Kelly et al., 2008), respectively, and one study compared the effectiveness of induction chemotherapy + concurrent chemoradiation + radical loco-regional treatment to the effectiveness of induction chemotherapy + surgery + RT (Thomas et al., 2008) while a fifth study examined the effect of adding AE-941 to chemoradiation (Lu et al., 2010). In an RCT of moderate quality Vokes et al. (2007) found no effect of induction chemotherapy on survival, disease-free survival or toxicity other than higher rates of grade 4 maximum toxicity and grade 3-4 ANC in the patients who received induction treatment. Apart from higher rates of grade 3-5 infections and pneumonitis in the patients who received consolidation chemotherapy, Hanna et al. (2008) did not find any effect of consolidation chemotherapy on survival, progression-free survival or treatment-related deaths in an RCT of low-moderate quality. Kelly et al. (2007) in a low-moderate quality RCT found that although progression-free survival did not differ between the treatment groups, maintenance gefitinib was associated with significantly shorter survival than placebo. Although Thomas et al. (2008) found some differences in the toxicity profiles between the treatment groups, the groups did not differ in terms of survival, progression-free survival, surgery complications and overall receipt of complete

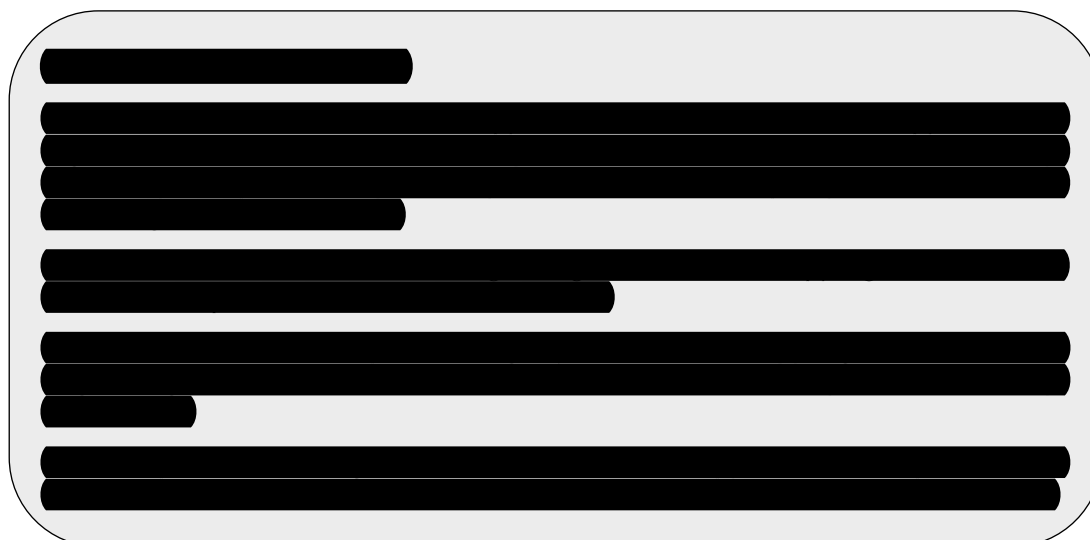
resection. There was however some suggestion that of those patients who had tumour resection surgery, the rate of complete resection was higher in the group who received concurrent chemoradiation. In a low-quality RCT, Lu et al. (2010) found no differences in median survival, median time to progression, response rate or individual grade 3-5 toxic events between patients who received chemoradiation and concurrent AE-941 (N = 188) and patients who received chemoradiation with concurrent placebo (N = 191). The AE-941 patients did however experience a lower total incidence of grade 3-5 toxic events than the placebo patients.

Health Economic Evaluation

The GDG felt that this topic could be a high priority for economic analysis because approximately one third of NSCLC patients could be eligible for treatment with curative intent. The interventions were numerous and could be given in various sequences, with the aim of combination treatment being to improve the cure rate associated with surgery or radiotherapy alone. The GDG noted that combination treatments were thought to be more expensive, but the difference in cost of different combination therapies was also likely to be significant. The RCT base for this question was large but these trials rarely compared more than two interventions. The GDG considered whether it would be possible to undertake a mixed treatment comparison to synthesize the available evidence. However they felt that there was likely to be heterogeneity in clinical status and prognosis of patients in these RCTs, which meant a mixed treatment comparison was not possible. Further economic analysis was therefore not undertaken.

Qualifying statement

These recommendations are based on evidence from RCTs, a systematic review, a case series and expert opinion. Although all the studies were randomised trials or, in six cases, systematic reviews with meta-analyses, the majority of the included studies and analyses were marked by methodological short-comings and, in the case of the systematic reviews, between-study heterogeneity and/or substantial overlap between included studies.



5.5.3 Pancoast tumours

Clinical topic: Combination treatment for patients with non-small cell lung cancer.

The precise definition of a Pancoast tumour is controversial and although there is no universally accepted definition, the American College of Chest Physicians (ACCP) recently stated that:

“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 and middle scalene muscles on the first rib.”

Pancoast syndrome results from invasion of the C8, T1-2 nerve roots and the sympathetic chain and is a constellation of symptoms and signs that include shoulder and arm pain along the distribution of the C8 and T1-2 nerve roots, Horner’s syndrome, and weakness and atrophy of the hand. According to the ACCP definition above, the presence of Pancoast syndrome is not a prerequisite for a tumour to be designated a Pancoast tumour.

The biology of NSCLC Pancoast tumours is no different to that of NSCLC in general and the unique features of Pancoast tumours result from the relationship to the anatomy of the lung apex. The 2005 management of lung cancer guidelines recommended that Pancoast tumours should be managed as for other NSCLC cases of similar stage. However, Pancoast tumours, by definition, involve the chest wall, and their anatomical location means they can invade a variety of structures so that surgical resection may be technically very difficult or impossible. This has led, historically, to a different treatment paradigm to NSCLC located elsewhere in the chest, despite Pancoast tumours being staged in the same way as all NSCLC. Pancoast tumours are at least T3 and become T4 if there is invasion of vertebral bodies or mediastinal structures. Lymphadenopathy in Pancoast tumours may be treated differently since ipsilateral supraclavicular lymphadenopathy, although stage N3, may be removed by en bloc resection. In contrast ipsilateral mediastinal nodes (N2) cannot.

Recommendation

- Treat Pancoast tumours in the same way as other types of NSCLC. Offer multimodality therapy according to resectability, stage of the tumour and performance status of the patient. [NEW 2011]

Clinical evidence

Pancoast tumours: Radiotherapy alone versus neoadjuvant chemoradiation + surgery / neoadjuvant RT + surgery

No studies were identified that met the inclusion criteria.

Health Economic Evaluation

See health economic evaluation section above.

Qualifying statement

This recommendation is based on expert opinion as there are no high quality clinical trials specifically evaluating the treatment of Pancoast tumours. Clinical consensus within the GDG emphasized that the biological behaviour of the tumour would be same as primary cancers occurring at other sites within the lung and the subcategory of Pancoast Tumour is anatomical, based on the close proximity of a number important and sensitive normal structures. A number of case series exist that suggest, when the disease is localised a multi-modality approach that includes surgery can be considered with good 2 and 5 year survival. However this must be balanced against the knowledge that pursuing a surgical approach will incur a mortality of 1-3% and a morbidity of approximately 30% (extrapolating from the surgical data for the resection of NSCLC from other sites within the lung).

5.6 Prophylactic Cranial Irradiation in NSCLC

Clinical topic: How effective is treatment in the management of brain metastases in lung cancer patients?

The risk of patients with NSCLC developing central nervous system involvement at some point in their disease is about 40%. This rate is likely to rise as the more widespread use of multi-modality treatments leads to better control of the primary tumour and the brain is the most frequently observed site of distant relapse. Therefore, the potential role of prophylactic cranial radiotherapy in reducing the risk of cerebral metastasis needs to be clarified and studies are required to see if this translates into an overall survival benefit.

Clinical evidence

PCI in non small cell lung cancer (NSCLC)

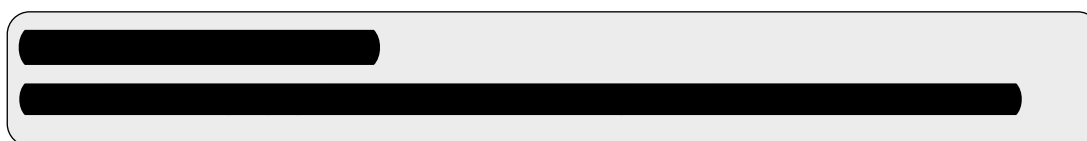
Lester et al. (2005) conducted a Cochrane review without meta-analysis that included 4 RCTs that compared PCI to observation in patients with NSCLC treated with radical intent. Three of the four trials found that PCI was associated with a significantly lower incidence of brain metastasis with one of the trials finding that the time to brain metastasis was significantly longer in the PCI group and another trial finding that the prevalence of brain metastasis at 1 and 2 years did not differ significantly between the PCI and observation groups. Three of the four trials found that PCI was not associated with any difference in survival whereas one of the trials found that PCI was associated with significantly shorter survival than no PCI. Pöttgen et al. (2007) conducted an RCT with a total of 106 patients with resectable stage IIIA NSCLC that terminated early due to slow accrual. The patients in arm A received primary curative resection followed by postoperative thoracic radiation therapy and patients in arm B received induction chemotherapy followed by concurrent chemoradiotherapy and then PCI. After completion of chemo- and radiotherapy the patients in arm B were referred to thoracic surgery aiming at resection with curative intent. Five-year overall and event-free survival as well as extracerebral relapses and intercurrent deaths during the first 3 years after treatment did not differ significantly between the treatment groups. Pöttgen et al. did however find that the incidence of brain metastasis as the first site of failure was significantly higher in the patients who had not received PCI and that the probability of overall brain-relapse at 5-years was significantly lower in those patients who had received PCI.

Health economic evaluation

The GDG considered this topic a low priority for health economic analysis.

Qualifying statement

This recommendation is based on evidence from a high quality meta-analysis, systematic reviews of RCTs and RCTs with a low risk of bias.



References

- Albain, K. Swann, R. S. Rusch, V.W. Turrisi, A. T. Shepherd, F. A. Smith, C. Che, Y. Livingston, R. B. Feins, R. H. Gandara, D. R. Fry, W.A. Darling, G. Johnson, D.H. Green, M. Miller, R.C. Ley, J. Sause, W.T. Cox, J.D. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009;374(Suppl 2):379-86.
- Amar, D. Munoz, D. Shi, W. Zhang, H. Thaler, H.T. A clinical prediction rule for pulmonary complications after thoracic surgery for primary lung cancer. *Anesthesia & Analgesia* 2010 May;110(5):1343-8.
- Arriagada, R. Bergman, B., Dunant, A. Le, C. T., Pignon, J. P., Vansteenkiste, J. & International Adjuvant Lung Cancer Trial Collaborative Group (2004) Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *The New England journal of medicine*, 350: 351-360.
- Arriagada, R. Dunant, A. Pignon, J.P. Bergman, B. Chabowski, M. Grunenwald, D. Kozlowski, M. Le, Pechoux C. Pirker, R. Pinel, M. I.; Tarayre, M.; Le, Chevalier T. (2010). Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. *Journal of Clinical Oncology*, 28, 35-42. Updated analysis of Arriagada et al. (2004) *Included in meta-analyses by Berghmans et al., Hotta et al., and Bria et al.*
- Auperin, A. Le Chevalier, T. Le Pechoux, C. Pignon, J. P. Tribodet, H. Burdett, S. Stewart, L.A. Tierney, J. F. Stephens, R. J. Arriagada, R. Higgins, J.P. Johnson, D.H. van Meerbeeck, J. Parmar, M.K.B. Souhami, R.L. Bergman, B. Dautzenberg, B. Douillard, J.Y. Dunant, A. Endo, C. Girling, D.J. Imaizumi, M. Kato, H. Keller, S.M. Kimura, H. Knuuttila, A. Kodama, K. Komaki, R. Kris, M.G. Lad, T. Mineo, T. Park, J.H. Piantadosi, S. Pyrhonen, S. Rosell, R. Scagliotti, G.V. Seymour, L.W. Shepherd, F.A. Spiro, S.G. Strauss, G.M. Sylvester, R. Tada, H. Tanaka, F. Torri, V. Wada, H. Waller, D. Xu, G.C. (2010). Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. *Lancet*, 375, 1267-77.
- Barrera, R. Shi, W. J., Amar, D. Thaler, H. T., Gabovich, N., Bains, M. S. et al. (2005). Smoking and timing of cessation - Impact on pulmonary complications after thoracotomy. *Chest*, 127, 1977-1983.
- Belani, C. P., Wang, W. Johnson, D. H., Wagner, H., Schiller, J. Veeder, M. et al. (2005). Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small-cell lung cancer. *Journal of clinical oncology*, 23, 3760-3767.
- Belderbos, J. Uitterhoeve, L. van, Z. N. Belderbos, H. Rodrigus, P. van, d. V et al. (2007). Randomised trial of sequential versus concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973). *European journal of cancer (Oxford, England : 1990)*, 43, 114-121.
- Benzo, R. Kelley, G.A. Recchi, L. Hofman, A. Sciruba, F. Complications of lung resection and exercise capacity: a meta-analysis (Provisional abstract). *Respir Med* 2007;101:1790-7.
- Berghmans, T. Paesmans, M. Meert, A. P. Mascaux, C. Lothaire, P. Lafitte, J. J. et al. (2005). Survival improvement in resectable non-small cell lung cancer with (neo)adjuvant chemotherapy: results of a meta-analysis of the literature. *Lung Cancer*, 49, 13-23.
- Bernard, A. Ferrand, L. Hagry, O. Benoit, L. Cheynel, N. Favre, J.P. Identification of prognostic factors determining risk groups for lung resection. *Ann Thorac Surg* 2000 Oct;70(4):1161-7.
- Berrisford, R. Brunelli, A. Rocco, G. Treasure T, Utley M, Audit and guidelines committee of the European Society of Thoracic Surgeons, et al. The European Thoracic Surgery Database project: modelling the risk of in-hospital death following lung resection. *Eur J Cardiothorac Surg* 2005 Aug;28(2):306-11.
- Berry, M. F. Villamizar-Ortiz, N. R. Tong, B.C. Burfeind, W. R. Jr. Harpole, D. H. D'Amico, T. A, et al. Pulmonary function tests do not predict pulmonary complications after thoracoscopic lobectomy. *Ann Thorac Surg* 2010 Apr;89(4):1044-51.
- Bezjak, A. Lee, C. W. Ding, K. Brundage, M. Winton, T. Graham, B. et al. (2008). Quality-of-life outcomes for adjuvant chemotherapy in early-stage non-small-cell lung cancer: results from a randomized trial, JBR.10. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 26, 5052-5059. (Included in appraisal of Bria et al.)
- Bonde, P. Lung surgery: Identifying the subgroup at risk for sputum retention. *Eur J Cardiothorac Surg* 2002;22(1):18-22.
- Bousamra, I.M. Early and late morbidity in patients undergoing pulmonary resection with low diffusion capacity. *Ann Thorac Surg* 1996;62(4):968-75.
- Bria, E. Gralla, R. J. Raftopoulos, H. Cuppone, F. Milella, M. Sperduti, I. et al. (2009). Magnitude of benefit of adjuvant chemotherapy for non-small cell lung cancer: meta-analysis of randomized clinical trials. *Lung Cancer*, 63, 50-57.
- Brunelli, A. Fianchini, A. Gesuita, R. Carle, F. POSSUM scoring system as an instrument of audit in lung resection surgery. Physiological and operative severity score for the enumeration of mortality and morbidity. *Ann Thorac Surg* 1999 Feb;67(2):329-31.
- Brunelli, A. Al, R. M. Monteverde, M. Sabbatini, A. Xiume, F. Fianchini, A. Predictors of early morbidity after major lung resection in patients with and without airflow limitation. *Ann Thorac Surg* 2002 Oct;74(4):999-1003.
- Brunelli, A. Monteverde, M. Borri, A. Salati, M. Marasco, R.D, Fianchini, A. Predictors of prolonged air leak after pulmonary lobectomy. *Ann Thorac Surg* 2004a;77(4):1205-10.
- Brunelli, A. Fianchini, A. Al, R. M. Salati, M. A model for the internal evaluation of the quality of care after lung resection in the elderly. *Eur J Cardiothorac Surg* 2004b May;25(5):884-9.
- Brunelli, A. Sabbatini, A. Xiume, F. Borri, A. Salati, M. Marasco, R. D, et al. Inability to perform maximal stair climbing test before lung resection: a propensity score analysis on early outcome. *Eur J Cardiothorac Surg* 2005 Mar;27(3):367-72.
- Brunelli, A. Refai, M. A. Salati, M. Sabbatini, A. Morgan-Hughes, N.J. Rocco, G. Carbon monoxide lung diffusion capacity improves risk stratification in patients without airflow limitation: evidence for systematic measurement before lung resection. *Eur J Cardiothorac Surg* 2006a Apr;29(4):567-70.

- Brunelli, A. Institutional report - Pulmonary: Risk-adjusted morbidity, mortality and failure-to-rescue models for internal provider profiling after major lung resection. *Interactive Cardiovascular and Thoracic Surgery* 2006b;5(2):92-6.
- Brunelli, A. Internal validation of risk models in lung resection surgery: Bootstrap versus training-and-test sampling. *J Thorac Cardiovasc Surg* 2006c;131(6):1243-7.
- Brunelli, A. Risk-adjusted morbidity and mortality models to compare the performance of two units after major lung resections. *J Thorac Cardiovasc Surg* 2007a;133(1):88-96.
- Brunelli, A, Varela, G, Rocco, G, Socci, L, Novoa, N, Gatani, T. et al. A model to predict the immediate postoperative FEV1 following major lung resections. *Eur J Cardiothorac Surg* 2007b Nov;32(5):783-6.
- Brunelli, A, Varela, G, Van, S.P, Salati, M, Novoa, N, Hendriks, J.M. et al. Multicentric analysis of performance after major lung resections by using the European Society Objective Score (ESOS). *Eur J Cardiothorac Surg* 2008a Feb;33(2):284-8.
- Brunelli, A, Ferguson, M.K, Rocco, G, Pieretti, P, Vigneswaran, W.T, Morgan-Hughes, N.J. et al. A scoring system predicting the risk for intensive care unit admission for complications after major lung resection: a multicenter analysis. *Ann Thorac Surg* 2008b Jul;86(1): 213-8.
- Brunelli, A, Refai, M, Xiume, F, Salati, M, Sciarra, V, Socci, L. et al. Performance at symptom-limited stair-climbing test is associated with increased cardiopulmonary complications, mortality, and costs after major lung resection. *Ann Thorac Surg* 2008c Jul;86(1):240-7.
- Brunelli, A, Refai, M, Xiume, F, Salati, M, Marasco, R, Sciarra, V. et al. Oxygen desaturation during maximal stair-climbing test and postoperative complications after major lung resections. *Eur J Cardiothorac Surg* 2008d Jan;33(1):77-82
- Brunelli, A, Berrisford, R.G, Rocco, G, Varela, G. European Society of Thoracic Surgeons Database Committee. The European Thoracic Database project: composite performance score to measure quality of care after major lung resection. *Eur J Cardiothorac Surg* 2009 May;35(5):769-74.
- Burdett, S, Stewart, L. & Rydzewska, L. (2007). Chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *Cochrane Database of Systematic Reviews: Reviews*. In *Cochrane Database of Systematic Reviews 2007 Issue 3* (Chichester (UK): John Wiley & Sons, Ltd.
- Butts, C, A, Ding, K, Seymour, L, Twumasi-Ankrah, P, Graham, B, Gandara, D, Johnson, D, H, Kesler, K, A, Green, M, Vincent, M, Cormier, Y, Goss, G, Findlay, B, Johnston, M, Tsao, M.S, Shepherd, F.A. (2010). Randomized Phase III Trial of Vinorelbine Plus Cisplatin Compared With Observation in Completely Resected Stage IB and II Non-Small-Cell Lung Cancer: Updated Survival Analysis of JBR-10. *Journal of Clinical Oncology*, 28, 29-34. (Updated analysis of Winton et al., 2005)
- Cerfolio, R.J, Bryant, A.S. Different diffusing capacity of the lung for carbon monoxide as predictors of respiratory morbidity. *Ann Thorac Surg* 2009 Aug;88(2):405-10.
- Chamogeorgakis, T, P, Connery, C, P, Bhora, F, Nabong, A, Toumpoulis, I, K. Thoracoscore predicts midterm mortality in patients undergoing thoracic surgery. *Journal of Thoracic & Cardiovascular Surgery* 2007 Oct;134(4):883-7.
- Crabtree, T, D, Denlinger, C, E, Meyers, B, F, El, Naqa, I, Zoole, J, Krupnick, A, S, Kreisel, D, Patterson, G, A, Bradley, J, D. (2010). Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg*.
- Cywinski, J, B. Predictors of Prolonged Postoperative Endotracheal Intubation in Patients Undergoing Thoracotomy for Lung Resection. *J Cardiothorac Vasc Anesth* 2009;23(6):766-9.
- Damhuis, R, Coonar, A, Plaisier, P, Dankers, M, Bekkers, J, Linklater, K. et al. A case-mix model for monitoring of postoperative mortality after surgery for lung cancer. *Lung Cancer* 2006 Jan;51(1):123-9.
- Douillard, J, Y, Rosell, R, De Lena, M, Carpagnano, F, Ramlau, R, Gonzales-Larriba, J, L, Grodzki, T, Pereira, J, R, Le Groumellec, A, Lorusso, V, Clary, C, Torres, A, J, Dahabreh, J, Souquet, P, J, Astudillo, J, Fournel, P, rta-Cortes, A, Jassem, J, Koubkova, L, His, P, Riggi, M, & Hurloup, P. (2006) Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncology*, 7: 719-727. *Included in meta-analysis by Bria et al.*
- Douillard, J, Y, Tribodet, H, Aubert, D, Shepherd, F.A, Rosell, R, Ding, K, Y, Veillard, A.S, Seymour, L, Le Chevalier, T, Spiro, S, Stephens, R, Pignon, J.P. (2010). Adjuvant Cisplatin and Vinorelbine for Completely Resected Non-small Cell Lung Cancer Subgroup Analysis of the Lung Adjuvant Cisplatin Evaluation. *Journal of Thoracic Oncology*, 5, 220-228.
- Falcoz, P.E, Conti, M, Brouchet, L, Chocron, S, Puyraveau, M, Mercier, M. et al. The Thoracic Surgery Scoring System (Thoracoscore): risk model for in-hospital death in 15,183 patients requiring thoracic surgery. *Journal of Thoracic & Cardiovascular Surgery* 2007 Feb;133(2):325-32.
- Felip, E, Rosell, R, Maestre, J, A, Rodriguez-Paniagua, J.M, Moran, T, Astudillo, J, Alonso, G, Borro, J.M, Gonzalez-Larriba, J, L, Torres, A, Camps, C, Guijarro, R, Isla, D, Aguiló, R, Alberola, V, Padilla, J, Sanchez-Palencia, A, Sanchez, J, J, Hermsilla, E, Massuti, B. (2010). Preoperative Chemotherapy Plus Surgery Versus Surgery Plus Adjuvant Chemotherapy Versus Surgery Alone in Early-Stage Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, 28, 3138-3145.
- Ferguson, M, K, Reeder, L, B, Mick, R. Optimizing selection of patients for major lung resection. *Journal of Thoracic & Cardiovascular Surgery* 1995 Feb;109(2):275-81.
- Ferguson, M, K, Durkin, A.E. A comparison of three scoring systems for predicting complications after major lung resection. *Eur J Cardiothorac Surg* 2003 Jan;23(1):35-42.
- Ferguson, M.K, Vigneswaran, W, T. Diffusing capacity predicts morbidity after lung resection in patients without obstructive lung disease. *Ann Thorac Surg* 2008a Apr;85(4):1158-64.
- Ferguson, M, K, Siddique, J, Karrison, T. Modeling major lung resection outcomes using classification trees and multiple imputation techniques. *Eur J Cardiothorac Surg* 2008b Nov;34(5):1085-9.
- Ferguson, M, K, Gaissert, H, A, Grab, J, D, Sheng, S. Pulmonary complications after lung resection in the absence of chronic obstructive pulmonary disease: the predictive role of diffusing capacity. *Journal of Thoracic & Cardiovascular Surgery* 2009 Dec;138(6):1297-302.

- Gilligan, D. Nicolson, M. Smith, I. Groen, H. Dalesio, O. Goldstraw, P. et al. (2007). Preoperative chemotherapy in patients with resectable non-small cell lung cancer: results of the MRC LU22/NVALT 2/EORTC 08012 multicentre randomised trial and update of systematic review. *Lancet*, 369, 1929-1937.
- Ginsberg, R.J. Rubinstein, L.V. for the Lung Cancer Study Group. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. *Annals of Thoracic Surgery* 1995;60:615-23.
- Groen, H.J. van der Leest, A. H. Fokkama, E. Timmer, P.R. Nossent, G. D. Smit, W. J. Nabers, J. Hoekstra, H. J. Hermans, J. Otter, R. van Putten, J. W. et al. (2004). Continuously infused carboplatin used as radiosensitizer in locally unresectable non-small-cell lung cancer: A multicenter phase III study. *Annals of Oncology*, 15, 427-32. (Included in appraisal of Rowell et al.)
- Groth, S. S. Whitson, B. A. Kuskowski, M. A. Holmstrom, A. M. Rubins, J. B. & Kelly, R. F. (2009). Impact of preoperative smoking status on postoperative complication rates and pulmonary function test results 1-year following pulmonary resection for non-small cell lung cancer. *Lung Cancer*, 64, 352-357.
- Grills, I.S. Mangona, V.S. Welsh, R. Chmielewski, G. McInerney, E. Martin, S. Wloch, J. Ye, H. Kestin, L.L. (2010). Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *Journal of Clinical Oncology*, 28, 928-35
- Hamada, C. Tanaka, F. Ohta, M., Fujimura, S. Kodama, K. Imaizumi, M. et al. (2005). Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small-cell lung cancer. *Journal of Clinical Oncology*, 23, 4999-5006.
- Hanna, N. Neubauer, M. Yiannoutsos, C. McGarry, R. Arseneau, J. Ansari, R. et al. (2008). Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *Journal of clinical oncology*, 26, 5755-5760.
- Harpole, D.H. Decamp, M.M. Daley, J. Hur, K. Oprian, C.A. Henderson, W.G. et al. Prognostic models of thirty-day mortality and morbidity after major pulmonary resection. *J Thorac Cardiovasc Surg* 1999;117(5):969-79.
- Haruki T. 'Lung age' predicts post-operative complications and survival in lung cancer patients. *Respirology* 2010;15(3):495-500.
- Hotta, K. Matsuo, K. Ueoka, H. Kiura, K. Tabata, M. & Tanimoto, M. (2004). Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomized controlled trials.[see comment]. *Journal of Clinical Oncology*, 22, 3860-3867.
- Ichinose, Y. Genka, K. Koike, T. Kato, H. Watanabe, Y. Mori, T. et al. (2003). Randomized double-blind placebo-controlled trial of bestatin in patients with resected stage I squamous-cell lung carcinoma. *Journal of the National Cancer Institute*, 95, 605-610.
- Izbicki, J.R. Passlick, B. Pantel, K. Pichlmeier, U. Hosch, S.B. Karg, O. et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: Results of a prospective randomized controlled trial. *Annals of Surgery* 1998;227(1):138-44.
- Johnstone, D.W. Byhardt, R.W. Ettinger, D. Scott, C.B. Phase III study comparing chemotherapy and radiotherapy with preoperative chemotherapy and surgical resection in patients with non-small cell lung cancer spread to mediastinal lymph nodes (N2); final report of RTOG 89-01. *International Journal of Radiation Oncology, Biology, Physics* 2002;54(2):365-9.
- Kates, M. Perez, X. Gribetz, J. Swanson, S.J. McGinn, T. Wisnivesky, J.P. Validation of a model to predict perioperative mortality from lung cancer resection in the elderly. *American Journal of Respiratory & Critical Care Medicine* 2009 Mar 1;179(5):390-5.
- Keegan, M.T. Harrison, B.A. Brown, D.R. Whalen, F.X. Cassivi, S.D. Afessa, B. The acute physiology and chronic health evaluation III outcome prediction in patients admitted to the intensive care unit after pneumonectomy. *Journal of Cardiothoracic & Vascular Anesthesia* 2007 Dec;21(6):832-7.
- Kelly, K. Chansky, K. Gaspar, L. E. Albain, K. S. Jett, J. Ung, Y. C. et al. (2008). Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *Journal of clinical oncology*, 26, 2450-2456.
- Kohman, L.J. Meyerm, J.A. Ikins, P.M. Oates, R.P. Random versus predictable risks of mortality after thoracotomy for lung cancer. *Journal of Thoracic & Cardiovascular Surgery* 1986 Apr;91(4):551-4.
- Leo, F. Venissac, N. Pop, D. Anziani, M. Leon, M.E. Mouroux, J. Anticipating pulmonary complications after thoracotomy: the FLAM Score. *Journal Of Cardiothoracic Surgery* 2006;1:34.
- Lester, Jason, F. Coles, Bernadette, and MacBeth, Fergus. Prophylactic cranial irradiation for preventing brain metastases in patients undergoing treatment with curative intent for non-small cell lung cancer. *Cochrane Database of Systematic Reviews: Reviews*. Cochrane Database of Systematic Reviews 2005 Issue 2. [2]. 2005. Chichester (UK), John Wiley & Sons, Ltd.
- Licker, M. J. Operative Mortality and Respiratory Complications After Lung Resection for Cancer: Impact of Chronic Obstructive Pulmonary Disease and Time Trends. *Ann Thorac Surg* 2006;81(5):1830-7.
- Loddenkemper, R. Criteria of functional operability in patients with bronchial carcinoma: Preoperative assessment of risk and prediction of postoperative function. *Thorac Cardiovasc Surg* 1983;31(6):334-7.
- Loewen, G. M. Watson, D. Kohman, L. Herndon, J. E. Shennib, H. Kernstine, K. et al. Preoperative exercise Vo2 measurement for lung resection candidates: results of Cancer and Leukemia Group B Protocol 9238. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer* 2007 Jul;2(7):619-25.
- Lu, C. Lee, J. J. Komaki, R. Herbst, R. S. Feng, L. Evans, W.K. Choy, H. Desjardins, P. Esparaz, B.T. Truong, M. T. Saxman, S. Kelaghan, J. Bleyer, A. Fisch, M.J. (2010). Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial. *Journal of the National Cancer Institute*, 102, 859-865
- Manser, R. Wright, G. Hart, D. Byrnes, G. Campbell, D. Wainer, Z. Tort, S. (2010). Surgery for early stage non-small cell lung cancer. *Cochrane Database of Systematic Reviews: Reviews* 1.
- Mason, D. P. Subramanian, S. Nowicki, E. R. Grab, J. D. Murthy, S. C. Rice, T. W. et al. (2009). Impact of smoking cessation before resection of lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database study. *Annals of Thoracic Surgery*, 88, 362-370.

- Mattson, K. V. Abratt, R. P. ten, V. G. & Krofta, K. (2003). Docetaxel as neoadjuvant therapy for radically treatable stage III non-small-cell lung cancer: a multinational randomised phase III study. *Annals of Oncology*, 14, 116-122.
- Morrison, R. Deeley, T. J. Cleland, W. P. The treatment of carcinoma of the bronchus: A clinical trial to compare surgery and supervoltage radiotherapy. *Lancet* 1963;1:683-4.
- Mishra, P. K. Cardiac comorbidity is not a risk factor for mortality and morbidity following surgery for primary non-small cell lung cancer. *Eur J Cardiothorac Surg* 2009;35(3):439-43.
- Myrdal, G. Gustafsson, G. Lambe, M. Horte, L.G. Stahle, E. Outcome after lung cancer surgery. Factors predicting early mortality and major morbidity. *Eur J Cardiothorac Surg* 2001;20(4):694-9.
- Nakagawa, M. Tanaka, H. Tsukuma, H. & Kishi, Y. (2001). Relationship between the duration of the preoperative smoke-free period and the incidence of postoperative pulmonary complications after pulmonary surgery. *Chest*, 120, 705-710. *Please note: This paper was not identified by the search, but from the reference list of one of the studies identified by the search*
- Nia, P. S. Weyler, J. Colpaert, C. Vermeulen, P. Van Marck, E. & Van Schil, P. (2005). Prognostic value of smoking status in operated non-small cell lung cancer. *Lung Cancer*, 47, 351-359.
- Nosotti, M. Baisi, A.; Mendogni, P. Palleschi, A. Tosi, D. Rosso, L. (2010). Muscle sparing versus posterolateral thoracotomy for pulmonary lobectomy: randomised controlled trial. *Interact. Cardiovasc. Thorac. Surg.*
- O'Rourke, N. Roqué, J. Figuls, M. Farré Bernadó, N. Macbeth, F. (2010). Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database of Systematic Reviews: Reviews* 6.
- Ou, W. Sun, H.B. Ye, X.O. Zhang, B.B. Yang, H. Fang, Q. Li, P. Wang, S.Y. (2010). Adjuvant Carboplatin-based Chemotherapy in Resected Stage IIIA-N2 Non-small Cell Lung Cancer. *Journal of Thoracic Oncology*, 5, 1033-1041
- Pastorino, U. Borasio, P. Francese, M. Miceli, R. Calabro, E. Solli, P. et al. Lung cancer stage is an independent risk factor for surgical mortality. *Tumori* 2008 May;94(3):362-9.
- Ploeg, A. J. Kappetein, A. P van Tongeren, R. B. Pahlplatz, P. V. Kastelein, G. W. Breslau, P. J. Factors associated with perioperative complications and long-term results after pulmonary resection for primary carcinoma of the lung. *Eur J Cardiothorac Surg* 2003 Jan;23(1):26-9.
- Pöttgen, C. Eberhardt, W. Grannass, A. Korfee, S. Stüben, G. Teschler, H. Stamatis, G. Wagner, H. Passlick, B. Petersen, V. Budach, V. Wilhelm, H. Wanke, I. Hirche, H. Wilke, H. J. and Stuschke, M. Prophylactic cranial irradiation in operable stage IIIA non small-cell lung cancer treated with neoadjuvant chemoradiotherapy: results from a German multicenter randomized trial. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 25[31], 4987-4992. 2007.
- Powell, E. S, Pearce, A. C. Cook, D. Davies, P. Bishay, E. Bowler, G.M. et al. UK pneumonectomy outcome study (UKPOS): a prospective observational study of pneumonectomy outcome. *Journal Of Cardiothoracic Surgery* 2009;4:41.
- Raz, D.R. Zell, J.A. Ignatius, O. Gandara, D.R. Anton-Culver, H. Jablons, D.M Natural history of Stage I lung cancer *Chest* 2007 132 (1) 193-199
- Rowell, N. P. & O'Rourke, N. (2004). Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database of Systematic Reviews: Reviews*. In *Cochrane Database of Systematic Reviews 2004 Issue 4* (Chichester (UK): John Wiley & Sons, Ltd.
- Scagliotti, G. V. Fossati, R. Torri, V. Crinò, L. Giaccone, G. Silvano, G. Martelli, M. Clerici, M. Cignetti, F. Tonato, M. & Adjuvant Lung Project Italy/European Organisation for Research Treatment of Cancer-Lung Cancer Cooperative Group Investigators (2003) Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell Lung cancer. *Journal of the National Cancer Institute.*, 95: 1453-1461. *Included in meta-analyses by Berghmans et al., Hotta et al., and Bria et al.*
- Sekine, Y, Yamada, Y. Chiyo, M. Iwata, T. Nakajima, T. Yasufuku, K. et al. Association of chronic obstructive pulmonary disease and tumor recurrence in patients with stage IA lung cancer after complete resection. *Ann Thorac Surg* 2007 Sep;84(3):946-50.
- Sekine, Y. Chiyo, M. Iwata, T. Yasufuku, K. Furukawa, S. Amada, Y. et al. (2005). Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. *Japanese Journal of Thoracic & Cardiovascular Surgery*, 53, 237-243.
- Shepherd, F. A. Johnston, M.R. Payne, D. Burkes, R. Deslauriers, J. Cormier, Y. et al. Randomized study of chemotherapy and surgery versus radiotherapy for stage IIIA non-small cell lung cancer: a National Cancer Institute of Canada Clinical Trials Group Study. *British Journal of Cancer* 1998;78(5):683-5.
- Shiono, S. Yoshida, J. Nishimura, M. Hagiwara, M. Hishida, T. Nitadori J, et al. Risk factors of postoperative respiratory infections in lung cancer surgery. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer* 2007 Jan;2(1):34-8.
- Song, W.A. Zhou, N.K. Wang, W. Chu, X.Y. Liang, C.Y. Tian, X.D. Guo, J.T. Liu, X. Liu, Y. Dai, W.M. (2010). Survival Benefit of Neoadjuvant Chemotherapy in Non-small Cell Lung Cancer An Updated Meta-Analysis of 13 Randomized Control Trials. *Journal of Thoracic Oncology*, 5, 510-516.
- Stathopoulos, G. P. Papakostas, P. Malamos, N. A. Samelis, G.F. Moschopoulos N. Chemo-radiotherapy versus chemo-surgery in stage IIIA non-small cell lung cancer. *Oncology Reports* 1996;3:673-6.
- Stephens, R. J. Girling, D.J. Hopwood, P. Thatcher N on behalf of the Medical Research Council Lung Cancer Working Party. A randomised controlled trial of pre-operative chemotherapy followed, if feasible, by resection versus radiotherapy in patients with inoperable stage T3, N1, M0 or T1-3, N2, M0 non-small cell lung cancer. *Lung Cancer* 2005;49:395-400.
- Strand, T. E. Rostad, H. Damhuis, R. A. Norstein, J. Risk factors for 30-day mortality after resection of lung cancer and prediction of their magnitude. *Thorax* 2007 Nov;62(11):991-7.
- Sugi, K. Nawata, K. Fujita, N. Ueda, K. Tanaka, T. Matsuoka, T. et al. Systematic lymph node dissection for clinically diagnosed peripheral non-small cell lung cancer less than 2 cm in diameter. *World Journal of Surgery* 1998;22:290-5.
- Sugi, K. Kaneda, Y. Esato, K. Video-assisted thoracoscopic lobectomy achieves a satisfactory long-term prognosis in patients with clinical stage IA lung cancer. *World Journal of Surgery* 2000;24:27-31.

- Thomas, M. RüBe, C. Hoffknecht, P. Macha, H. N. Freitag, L. Linder, A. et al. (2008). Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *The lancet oncology*, 9, 636-648.
- van Meerbeeck, J.P. Kramer, G.W.P.M. Van Schil, P.E.Y. Legrand, C. Smit, E.F. Schramel, F et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 Non-small cell lung cancer. *J Natl Cancer Inst* 2007;99:442-50.
- Vaporciyan, A. A. Merriman, K. W. Ece, F. Roth, J. A. Smythe, W. R. Swisher, S. G. et al. (2002). Incidence of major pulmonary morbidity after pneumonectomy: Association with timing of smoking cessation. *Annals of Thoracic Surgery*, 73, 420-425.
- Vokes, E. E. Herndon, J. E. Kelley, M. J. Cicchetti, M. G. Ramnath, N. Neill, H. et al. (2007). Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *Journal of clinical oncology*, 25, 1698-1704.
- von Knorring, J. Lepantalo, M. Lindgren, L. Lindfors, O. Cardiac arrhythmias and myocardial ischemia after thoracotomy for lung cancer. *Ann Thorac Surg* 1992 Apr;53(4):642-7.
- Waller, D. Peake, M. D. Stephens, R. J. Gower, N. H. Milroy, R. Parmar, M. K. Rudd, R. M. & Spiro, S. G. (2004) Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *European journal of cardio thoracic surgery : official journal of the European Association for Cardio thoracic Surgery*, 26: 173-182. *Included in meta-analysis by Bria et al.*
- Wang, S.-Y. Ou, W. Lin, Y.-B. Liang, Y. Ye, X. Zhang, B.-B. et al. (2007). A prospective randomized study of adjuvant chemotherapy in completely resected stage III-N2 non small cell lung cancer. *Chinese Journal of Cancer Research.*, 19, 189-194.
- Warram, J. on behalf of collaborating investigators. Preoperative irradiation of cancer of the lung: final report of a therapeutic trial (a collaborative study). *Cancer* 1975;36(3):914-25.
- Winton, T. Livingston, R. Johnson, D. Rigas, J. Johnston, M. Butts, C. Cormier, Y. Goss, G. Incelet, R. Vallieres, E., Fry, W., Bethune, D. Ayoub, J. Ding, K. Seymour, L. Graham, B. Tsao, M. S. Gandara, D. Kesler, K. Demmy, T. Shepherd, F. National Cancer Institute of Canada Clinical Trials Group & National Cancer Institute of the United States Intergroup JBR. (2005) Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *The New England journal of medicine*, 352: 2589-2597.
- Wright, C.D. Gaissert, H.A. Grab, J.D. O'Brien, S.M. Peterson, E.D. Allen, M.S. Predictors of prolonged length of stay after lobectomy for lung cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk-adjustment model. *Ann Thorac Surg* 2008 Jun;85(6):1857-65.
- Wu, Y.L. Huang, Z.F. Wang, S.Y. Yang, X.N. Ou, W. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer* 2002;36:1-6.
- Yamashita, S. Haga, Y. Nemoto, E. Nagai, S. Ohta, M. E-PASS (The Estimation of Physiologic Ability and Surgical Stress) scoring system helps the prediction of postoperative morbidity and mortality in thoracic surgery. *Eur Surg Res* 2004 Jul;36(4):249-55.
- Yamashita, S. Haga, Y. Nemoto, E. Imanishi, N. Ohta, M. Kawahara, K. Comparison of surgical outcome using the prediction scoring system of E-PASS for thoracic surgery. *Japanese Journal of Thoracic & Cardiovascular Surgery* 2006 Sep;54(9):391-5.
- Yano, T. The current status of postoperative complications and risk factors after a pulmonary resection for primary lung cancer A multivariate analysis. *Eur J Cardiothorac Surg* 1997;11(3):445-9.
- Zatloukal, P. Petruzelka, L. Zemanova, M. Havel, L. Janku, F. Judas, L. Kubik, A. Krepela, E. Fiala, P. Pecen, L. (2004). Concurrent versus sequential radiochemotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer. a randomized study. *Lung Cancer*, 46, 87-98. *Included in appraisal of Rowell et al.*

6 Chemotherapy for NSCLC

Since publication of the NICE Lung Cancer Guideline in 2005 a number of new systemic therapies have been granted a marketing authorisation by the EMEA for use in people with NSCLC. NICE has published technology appraisals for pemetrexed, gefitinib and erlotinib. NICE had planned to commission a separate guideline updating chemotherapy for NSCLC but this guideline will not now be developed. For NSCLC chemotherapy there are a number of technology appraisals with funding directives currently in place, several planned technology appraisals in the programme and several technology appraisals requiring updates. This restricted the scope of the proposed guideline and so it has been decided not to update the current guidance on chemotherapy for NSCLC.

The NHS has commissioned a review of first-line therapy for NSCLC through the NIHR HTA Programme that is due to be published in 2011.



For Technology Appraisals in development please visit the NICE website.
<http://www.nice.org.uk/guidance/ta/indevelopment/index.jsp>

7 Treatment of small cell lung cancer (SCLC)

Please note that this area has been reviewed in 2019, please follow the link on the front page for the evidence review

In England and Wales approximately 10% of patients diagnosed with lung cancer each year are found to have small cell lung cancer (SCLC). This represents around 3000 new cases per year. SCLC is considered to be an aggressive form of lung cancer that grows rapidly and has often spread (metastasised) beyond the lung at the time of diagnosis. SCLC frequently responds to treatment with chemotherapy but in the majority of patients, whilst length of life can be extended, the cancer is not curable. Decisions about appropriate treatments for SCLC are determined by the extent of the disease at presentation and the fitness of the patient. National Lung Cancer Audit data has identified that, despite high response rates to chemotherapy and/or radiotherapy over 30% of patients in England and Wales receive neither treatment (National Lung Cancer Audit¹).

7.1 Staging of SCLC

In clinical practice and most research trials, the Veterans' Administration Lung Study Group (VALSG) definitions for staging small cell lung cancer have been used. This pragmatic treatment based classification divides SCLC into limited stage disease (LD SCLC) and extensive stage disease (ED SCLC). LD SCLC is characterised by tumours confined to one hemi-thorax; local extension and ipsilateral supraclavicular lymph nodes can be present if they can be encompassed in a potentially curative radiotherapy volume. No extra- thoracic metastases should be present. All other disease is classified as ED SCLC.

More recently, the International Association for the Study of Lung Cancer (IASLC) has proposed the adoption of the seventh edition of the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre Le Cancer (UICC) tumour, node, metastasis (TNM) staging system for the clinical staging of SCLC. Validation of TNM for SCLC has been conducted using the IASLC data-base including survival analyses for over 12 000 patients with SCLC (Shepherd et al., 2007; Goldstraw et al., 2006; Rami-Porta et al., 2007). More accurate staging of nodal stations is predicted to facilitate planning of radiotherapy and provide improved estimates for prognosis, according to the extent of the disease.

Whilst the use of the TNM staging system has been proposed for future staging of patients with small cell lung cancer, the clinical trial evidence reviewed in this section has mostly been reported according to the VALSG staging system with inclusion of patients with either LD or ED SCLC. As such the VALSG staging will be referred to in this section with LD SCLC broadly including patients who are staged T1-4, N0-3, M0 and ED SCLC including patients who are T1-4, N0-3, M1a/b in the updated TNM staging classification. Patients with malignant pleural effusions are included in the ED SCLC group, although in the IASLC staging database these conferred an intermediate prognosis between LD and ED.

For clarity this section will refer to limited and extensive stage disease although clinicians are encouraged to stage patients with SCLC according to the revised seventh editions of the UICC TNM staging system for lung cancer.

¹ National Lung Cancer Audit. 2009.

7.2 Assessment of patients with SCLC

The prognosis for patients with SCLC who do not receive treatment is poor with estimates for average survival ranging between two and four months. Whilst there are no high quality clinical trials evaluating the impact of prompt referral and assessment by a specialist thoracic oncologist, clinical consensus within the Guideline Development Group (GDG) emphasised the importance of this. This was based on the understanding that SCLC is an aggressive cancer that commonly spreads outside the lung and can lead to a rapid change in an individual's fitness for treatment.

Recommendation

- Arrange for patients with small-cell lung cancer (SCLC) to have an assessment by a thoracic oncologist within 1 week of deciding to recommend treatment. [NEW 2011]

Health economic evaluation

This topic was considered a low priority for health economic analysis because the incidence of SCLC is decreasing and the population in question is now small (approximately 10% of lung cancer patients). In addition the GDG felt that it would not be possible to accurately evaluate the economic impact of assessment within one week compared to a later assessment.

Qualifying statement

Data from National Lung Cancer Audit suggests that, despite SCLC being a chemotherapy sensitive cancer, at least one third of patients do not receive any chemotherapy. Whilst there is no direct clinical trial evidence supporting the time from diagnosis to assessment for treatment as influencing whether patients are offered chemotherapy the GDG agreed that SCLC frequently progresses rapidly and that patients' fitness for treatment can change over a short period of time. The expert opinion was that, in order to facilitate patients being appropriately assessed for chemotherapy, this recommendation should include a specific time frame that emphasises to clinical teams the need to avoid delays and for patients to be rapidly referred for review by specialist oncologists.

7.3 First line treatment of patients with limited stage disease SCLC (broadly staged as T1-4, N0-3, M0)

Clinical topic: What is the most effective first line treatment for patients with limited stage disease small cell lung cancer?

Approximately 35% of patients with SCLC will, at the time of diagnosis, be considered to have LD SCLC (National Lung Cancer Audit²). Without treatment the average life expectancy for this group of patients is less than four months. SCLC is usually a chemotherapy and radiotherapy sensitive tumour. Combining chemotherapy and thoracic radiotherapy is now the standard first line treatment for LD SCLC with randomised controlled trials reporting a median survival of between 14 and 18 months. A small proportion of patients (<20%) will survive for at least 5 years.

For most patients with LD SCLC initial review by a thoracic oncologist will include an assessment of fitness for treatment with chemotherapy and thoracic radiotherapy. Identification of prognostic factors may help to inform discussions with patients about likely response to, and toxicity from, treatment as well as provide information to help estimate survival.

² National Lung Cancer Audit. 2009.

Recommendations

- Offer patients with limited-stage disease SCLC (broadly corresponding to T1-4, N0-3, M0) four to six cycles of cisplatin-based combination chemotherapy. Consider substituting carboplatin in patients with impaired renal function, poor performance status (WHO 2 or more) or significant comorbidity. [NEW 2011]

- [REDACTED]

- [REDACTED]

Clinical evidence

Chemotherapy

Nine studies examined the effectiveness of different regimens of chemotherapy on the treatment of LD SCLC (Altinbas et al., 2004; Amarasena et al., 2008; Artal-Cortés et al., 2004; Baka et al., 2008; Grote et al., 2005; Jiang et al., 2009; Reck et al., 2003, 2006 [same data as Reck et al., 2003]; Thatcher et al., 2005) and the quality of the evidence ranged from low to high.

Platinum versus non-platinum containing agents

A Cochrane Review (Amarasena et al. 2008) included a meta-analysis of eight studies which showed no statistically significant difference in tumour response or overall survival (with high heterogeneity of data) between platinum-based or non-platinum-based chemotherapy. Baka et al. (2008) found that patients who received doxorubicin+cyclophosphamide+etoposide as first-line treatment gained no benefit in survival compared with patients who received cisplatin+etoposide.

High dose/intensive chemotherapy schedules

Artal-Cortés et al. (2004) found no differences in survival, time-to-progression, responses, febrile neutropenia, haemoglobin or platelet counts in patients given high-dose epirubicin+cisplatin compared to those given cisplatin+etoposide. However, patients receiving cisplatin+etoposide experienced lower rates of grade 3/4 neutropenia. Jiang et al. (2009) conducted a systematic review of five low-moderate quality studies and showed no differences in objective response rate, overall survival or leucocyte nadir between intensive first line chemotherapy with haematopoietic progenitors (IHP) and standard chemotherapy. IHP was however found to be associated with significantly higher rates of haemoglobin nadir and platelet nadir.

Different chemotherapy regimens

Thatcher et al. (2005) determined that ifosfamide + carboplatin + etoposide + mesna + vincristine conferred a survival advantage to patients with LD SCLC compared to standard chemotherapy (usually cisplatin + etoposide or doxorubicin + cyclophosphamide + etoposide). The regimens did not differ in terms of treatment response, toxicity or quality of life. Reck et al. (2003, 2006 [same data]) found that although treatment response was similar, survival was improved for patients who had received paclitaxel+etoposide+carboplatin compared to those who received carboplatin+etoposide+vincristine. Grote et al. (2005) found no difference in tumour response by adding either epoetin alfa or a placebo to cisplatin+etoposide. Altinbas et al. (2004) showed that the addition of low molecular weight

heparin to chemotherapy with cyclophosphamide+epirubicin+vincristine improved overall survival, progression-free survival and tumour response rate.

Chemoradiation

Seven randomised trials examined the effectiveness of different regimens of combination chemo- and radiotherapy on the treatment of LD-SCLC (Blackstock et al., 2005; Schild et al., 2004, 2005 [same data as Schild et al., 2004]; Han et al., 2008; McClay et al., 2005; Bogart et al., 2008 [same data as McClay et al., 2005]; Sculier et al., 2008) and the quality of the evidence ranged from low to moderate.

Blackstock et al. (2005) gave their patients a chemotherapy regimen consisting of cisplatin + etoposide in cycles 1, 2 and 5 and of cyclophosphamide + vincristine + doxorubicin in cycles 3, 4 and 6. This chemotherapy regimen was combined with either split-course radiotherapy (RT) consisting of a total of 50 Gy in 20 fractions (20 Gy in 8 fractions on days 8-17 in cycles 1 and 2 and 10 Gy in 4 fractions on days 8 and 11 in cycle 3) or continuous RT consisting of a total of 50 Gy in 25 fractions (5 days/week in cycles 1 and 2). The split-course RT and continuous RT groups did not differ in terms of survival, response, toxicity or ipsi-lateral pulmonary failure. Schild et al. (2004) examined the effect of twice-daily RT (48 Gy in 32 fractions) compared to once daily RT (50.4 Gy in 28 fractions) in two groups of patients who were also receiving cisplatin and etoposide chemotherapy. The once-daily RT and twice-daily RT groups did not differ in terms of survival, progression-free survival, failure rates or haematologic toxicity, but the twice daily RT group experienced more grade 3+ and grade 5 non-haematologic toxicity than the once-daily RT group. Han et al. (2008) investigated if amifostine and epoetin-alfa administration were associated with any differences in outcomes in patients who received a chemo-radiation regimen consisting of cisplatin and irinotecan induction therapy followed by a treatment regimen consisting of hyper-fractionated RT (twice-daily RT to a total of 45 Gy) and etoposide+cisplatin. Han et al. found that survival, progression-free survival and response did not differ between the amifostine and epoetin-alfa groups. The amifostine group experienced more febrile neutropenia, grade 2/3 nausea and grade 2/3 anaemia than the epoetin-alfa group and the net decrease in haemoglobin was also larger in the amifostine group than in the epoetin-alfa group during chemoradiation treatment. McClay et al. (2005) examined the effect of high-dose tamoxifen on survival, progression-free survival, response and toxicity in patients who received chemo-radiation treatment consisting of cisplatin + etoposide and 50 Gy RT in 25 fractions, and found that all the outcomes were comparable to a control group who had received the same chemoradiation regimen of cisplatin + etoposide and 50 Gy RT in 25 fractions but without the tamoxifen. Sculier et al. (2008) added daily cisplatin (6 mg/m² on days 1-5, 8-12 and 15-19) as a radio-sensitiser to the first cycle of induction chemoradiation which consisted of cisplatin (90 mg/m² on day 1) + etoposide (days 1-3) and 39.9 Gy of RT in 15 fractions (started on day 1), but found that compared to a control group who received the same standard treatment but without the daily radio-sensitiser cisplatin dose, daily cisplatin administration was not associated with any differences in survival, progression-free survival, response, nephro- and respiratory toxicity or oesophagitis. The patients who received daily cisplatin did, however, experience higher rates of thrombocytopenia.

Maintenance therapy

In addition to the evidence examining the effectiveness of first-line chemoradiation treatment, two studies have investigated whether oral vandetanib or vaccinations with Bec2/BCG influences survival in patients with LD SCLC who have had a major response to first-line treatment consisting of chemoradiation for the majority of the patients and of chemotherapy only for the remainder (Arnold et al., 2007, and Giaccone et al., 2005, respectively). These studies found that vandetanib and Bec2/BCG vaccinations, respectively, did not influence overall or progression-free survival. There was also no effect of Bec2/BCG vaccinations on quality of life, apart from in week 6 when the Bec2/BCG group appeared to experience more shoulder and arm pain than the control group (Giaccone et al., 2005; Bottomley et al., 2008 [same data as Giaccone et al., 2005]). A third study (Lee et al., 2009) did not find any difference in survival in patients with LD SCLC who had taken either

thalidomide or placebo capsules concurrently with and subsequent to first-line chemotherapy for 2 years.

Prognostic factors for survival in patients with LD-SCLC

Five studies (Artal-Cortés et al., 2004; Bogart et al., 2008; Giaccone et al., 2005; Sculier et al., 2008; Schild et al., 2005) conducted some analyses on prognostic factors for survival, the majority of which were multivariate analyses. The most consistent finding was that a good performance status was predictive of longer survival (Artal-Cortés et al., 2004; Bogart et al., 2008; Sculier et al., 2008).

A number of prognostic factors were reported by different individual studies (i.e., age, weight loss prior to diagnosis, duration of symptoms, gender, lactate dehydrogenase grade, platelet level, concomitant chest radiotherapy, prophylactic cranial irradiation and tumour status) and when considered in concert with the low -moderate quality of the evidence assessing prognostic factors in general no conclusions can therefore be made with regards to these variables.

Health economic evaluation

This topic was considered a low priority for health economic analysis because the incidence of SCLC is decreasing and the population in question is now small (approximately 10% of lung cancer patients). The GDG also noted that the chemotherapy regimens in question use older agents which are not as costly.

Qualifying statement

These recommendations are based on low to high quality randomised trials and systematic reviews. RCT evidence supports up to 6 cycles of chemotherapy with a cisplatin based schedule. The GDG did not consider the evidence strong enough to make a specific recommendation about the optimum schedule of radiotherapy, which remains the subject of ongoing clinical trials (for example the CONVERT trial³). Similarly, the GDG did not find evidence that maintenance treatment for patients with LD SCLC offered a survival advantage.

7.4 Surgical treatment for patients with SCLC

Clinical topic: How effective is surgical treatment for patients with small cell lung cancer?

SCLC is usually a systemic disease at presentation and surgery is generally not regarded as an appropriate first line treatment even when confined to one hemi-thorax. However, the use of surgery in SCLC has been reported in two distinct settings. Firstly SCLC may be diagnosed where a single pulmonary nodule has been resected and the diagnosis is made at frozen section during surgery, or at final pathological examination. Secondly, there may be an apparently early stage SCLC that has been diagnosed pre-operatively.

The limited studies that have been conducted did not employ modern imaging methods that increase the accuracy of pre-operative staging. The disappointing results cannot therefore be extrapolated into modern day practice. Surgery is likely to be applicable to a very small number of patients and must be considered with the associated morbidity and potential mortality.

In the UK about 1000 patients present annually with LD SCLC and of that number, perhaps between 50 and 100 patients could be potential candidates to undergo surgery.

Overall the benefit of surgery for SCLC is unknown and the influence of modern staging techniques and more effective non-surgical treatments on the comparative benefit of surgery needs to be defined. Fitness assessment as for NSCLC is equally pertinent, please see chapter 5. Most patients who undergo surgery for SCLC would also be considered for chemotherapy and/or radiotherapy.

³ <http://www.christie.nhs.uk/research/themes/convert/default.aspx#patients>

Recommendation

- Consider surgery in patients with early-stage SCLC (T1-2a, N0, M0). [NEW 2011]

Clinical evidence

The evidence for the effectiveness of surgical treatment of SCLC consisted of two retrospective comparative studies (Badzio et al., 2004; Scriber et al., 2010). Badzio et al. (2004) compared surgery + adjuvant chemotherapy ± PCI in 67 patients with a post-operative diagnosis of SCLC to chemotherapy ± RT in 67 matched SCLC patients and found that surgical treatment was associated with longer survival, longer time to progression/relapse and lower rates of local relapse compared to non-surgical treatment. The rates of distant relapse did not differ between the treatment groups. Multivariate analysis identified surgical treatment, female gender and no involvement of regional lymph nodes, but not tumour stage, weight loss, performance status, age or tumour size as significant predictors of survival. Scriber et al. (2010) compared surgery ± postoperative RT (N = 863) to non-surgical treatment (N = 13316) and found that surgery was associated with longer survival whether the analyses included all patients or were confined to patients with localised disease, with regional disease, with N0, with N1, or with N2.

Health Economic Evaluation

This topic was considered a low priority for health economic analysis because surgery is only considered in a very small group of patients with SCLC.

Qualifying statement

These recommendations are based on case series studies and phase 2 studies. A number of case series exist that suggest, in very limited disease, that surgery can be considered with a surprisingly good 5 year survival. However, a limitation of these case series is that many patients had their diagnosis of SCLC made after surgical resection. This makes extrapolation into decision making for a patient with known SCLC more difficult. This is compounded by a lack of randomised trials and the small numbers involved. Pursuing a surgical approach will incur a mortality (1-3% with an expectation that the number of pneumonectomies will be low, as many of the tumours will be small in size) and a morbidity of approximately 30%, extrapolating from the non small cell surgical data. A 5 year survival of up to 40% could be expected. A stronger case can be made for continuing the resection in those cases where the diagnosis is discovered intraoperatively. A counter argument can be made that this special subgroup of patients with early stage SCLC could do well with standard chemoradiotherapy and 5 year survival in this select group could approach the surgical case series figures mentioned.

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

Clinical topic: What is the most effective regimen of chemotherapy for patients with extensive stage disease small cell lung cancer?

Approximately two thirds of patients diagnosed with SCLC have extensive stage disease at the time of presentation (National Lung Cancer Audit⁴). Most will have symptoms from their cancer and many will have other pre-existing illnesses. Some patients will be too unwell for chemotherapy and will only be suitable for palliative radiotherapy or supportive care. Many patients will develop rapid progression of symptoms and urgent assessment by thoracic oncologists, as part of a multi-disciplinary team is essential. The median survival for patients without treatment is two months. However, initial response rates to chemotherapy are high

⁴ National Lung Cancer Audit. 2009.

with the median overall survival for patients treated with chemotherapy extended to between 9 and 12 months.

Fitness assessment (including performance status) and validated prognostic scoring systems are often used to predict the relative benefits and risks of treatment to support patients' choices.

Patients with ED SCLC considered fit for chemotherapy are normally treated with a combination chemotherapy schedule including cisplatin or carboplatin, usually with etoposide. Depending upon response and toxicity, most patients receive between 4 and 6 cycles. For patients whose disease responds to chemotherapy, prophylactic cranial irradiation (PCI) and for some patients, thoracic radiotherapy, is offered.

Despite high initial response rates to chemotherapy, most patients will ultimately develop progressive disease. There remains a need for focused research to improve outcomes.

Recommendations

- 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. [NEW 2011]
- 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. [NEW 2011]

- [REDACTED]

Maintenance treatment for SCLC

Recommendation

- Offer maintenance treatment to patients with SCLC only in the context of a clinical trial. [NEW 2011]

Clinical evidence

Platinum versus non-platinum containing agents

Five studies compared the effectiveness of platinum and non-platinum based regimens of chemotherapy for the treatment of ED SCLC (Amarasena et al., 2008; Baka et al., 2008; De Jong et al., 2007; Greco et al., 2005 [included in Amarasena et al., 2008]; Quoix et al., 2005 [included in Amarasena et al., 2008]) and the quality of the evidence ranged from low to high. Amarasena et al. (2008) conducted a Cochrane Review which included 16 studies and found that 6- but not 12- or 24-month survival differed between the regimens with the platinum-based regimens conferring longer 6-months survival compared to the non-platinum-based regimens. Amarasena et al. (2008) also reported that although overall response did not differ between the regimens, the platinum-based chemotherapy was associated with a higher incidence of complete responses compared to non-platinum-based chemotherapy. Baka et al. (2008) found that the survival of patients who received platinum-

based first-line treatment did not differ from patients who received non-platinum-based first-line treatment. De Jong et al. (2007) also found that survival did not differ between patients receiving platinum- or non-platinum-based chemotherapy and neither did response, progression-free survival, and duration of response. However, the non-platinum-based regimen was associated with more grade 4 leucocytopenia, treatment-related deaths and hospitalisations. Both the RCTs conducted by Baka et al. (2008) and De Jong et al. (2007) were of moderate methodological quality. We calculated four meta-analyses by adding the data from Baka et al. (2008) and De Jong et al. (2007) to the meta-analyses calculated by Amarasena et al. (2008) for 12-month survival, 24-month survival (outcome not reported by De Jong et al.), overall and complete response rates (outcome not reported by Baka et al.). These analyses did not alter the direction of results reported by Amarasena et al. (2007), that is, 12- and 24-month survival and overall response rate did not differ between the platinum-based and non-platinum based regimens whereas the platinum-based regimens were associated with a higher rate of complete responses relative to the non-platinum-based regimens.

Cisplatin versus carboplatin

Okamoto et al. (2007) conducted an RCT of low methodological quality and found that survival, progression-free survival, response, palliation and toxicity apart from thrombocytopenia did not differ between the patients who received cisplatin + etoposide and those who received carboplatin + etoposide. The carboplatin + etoposide regimen was, however, associated with an elevated rate of grade 3-4 thrombocytopenia compared to the cisplatin + etoposide regimen. Socinski et al. (2006) conducted a phase II trial with random allocation of their patients to receive either cisplatin + pemetrexed or carboplatin + pemetrexed. However, the results of this prospective randomised phase II trial were only analysed descriptively and will therefore not be reported any further here.

Maintenance chemotherapy in patients responding to induction chemotherapy

In a randomised phase II trial of low-moderate quality Arnold et al. (2007) found no differences in survival or progression-free survival between vandetanib maintenance treatment and placebo. Han et al. (2008) compared irinotecan maintenance treatment to observation only in a randomised phase II trial. However, the results were only analysed descriptively and will therefore not be reported any further in this section. In an RCT of moderate quality Lee et al. (2009b) found shorter survival in patients with ED SCLC who had taken thalidomide concurrently with and subsequent to first-line chemotherapy for 2 years compared to patients who had received placebo capsules instead of thalidomide. A phase II randomised trial of low quality conducted by Pandya et al. (2007) found longer survival in the patients who received a high dose of temsirolimus compared to patients receiving a low dose of temsirolimus. Progression-free survival was not found to differ between the groups and it is unclear whether the toxicity profiles of the different doses differed. Pujol et al. (2008) conducted an RCT of moderate to high methodological quality and found that survival, progression-free survival and response did not differ between patients who received maintenance therapy consisting of thalidomide or placebo.

Chemotherapy with the addition of growth factors/blood support

In an RCT of moderate-high quality Grote et al. (2005) randomised patients to receive cisplatin + etoposide with epoetin alfa or placebo and found no differences in response rates after 3 or 6 cycles between the two groups. Niell et al. (2005) reported in an RCT providing evidence of moderate quality that survival and progression-free survival did not differ between patients receiving a regimen of cisplatin + paclitaxel + etoposide with human granulocyte colony-stimulating factor (G-CSF) and patients receiving a regimen consisting of cisplatin + etoposide. It is unclear whether the response rate and toxicity profiles differed between these two regimens. In an RCT of moderate-high quality Pirker et al. (2008) compared patients receiving a platinum-containing first-line chemotherapy regimen with darbepoetin alfa or with placebo and found that survival, progression-free survival and change in functional assessment score did not differ between the treatment groups, but the

placebo group experienced a larger change in haemoglobin concentration from baseline and received more blood transfusions than the darbepoetin alfa group. However, the darbepoetin group experienced a higher rate of cardiovascular/ thromboembolic adverse events than the placebo group. It is unclear whether the groups differed in terms of other toxicity-related adverse events. Heigener et al. (2009) compared a three-weekly regimen consisting of carboplatin + etoposide (190 mg/m²) with lenograstim to a four-weekly regimen consisting of carboplatin and etoposide (140 g/m²) and found no difference between these regimens in terms of survival, progression-free survival, response and grade 3-4 infections, anaemia and fatigue. However, the three-weekly regimen was associated with higher rates of grade 3-4 thrombocytopenia and lower rates of grade 3-4 neutropenia than the four-weekly regimen. The evidence provided by the RCT by Heigener et al. (2009) is of low quality. In a randomised phase II trial Sekine et al. (2008) randomised patients to receive irinotecan + cisplatin with or without etoposide and prophylactic filgrastim/lenograstim and found no differences in survival, response rate, grade 3-4 febrile neutropenia, anaemia, diarrhea, fatigue, hyponatraemia, vomiting, elevation of AST or CRN and need of platelet concentrates between the groups. However, progression-free survival was longer and the incidences of grade 3-4 neutropenia, leucocytopenia, thrombocytopenia, and red blood cell transfusions were increased in the regimen with etoposide and prophylactic filgrastim/lenograstim compared to the cisplatin + irinotecan alone regimen. Altinbas et al. (2004) conducted an RCT providing low-moderate quality evidence where patients were randomised to receive a chemotherapy regimen consisting of cyclophosphamide + epirubicin + vincristine with or without low molecular weight heparin. Although the response rate did not differ between the groups, the patients who received heparin had longer survival and longer progression-free survival than those patients who did not receive heparin. There were no treatment-related deaths in this study.

Dose intensity and schedule

Ardizzoni et al. (2005) in a sample that consisted of patients with both limited and extensive disease SCLC but were all aged 70 or above (and therefore may be considered poorer prognosis patients regardless of disease state) compared full with attenuated dose cisplatin + etoposide treatment. In this randomised phase II trial of low methodological quality, Ardizzoni et al. (2005) found that the response was higher in the full than in the attenuated dose group (deduced on the basis of the reported 95% confidence intervals), but as the results were analysed descriptively, no further details will be provided here. Artal-Cortés et al. (2004) conducted an RCT of low-moderate methodological quality comparing patients who received high-dose epirubicin + cisplatin to patients who received cisplatin + etoposide and found no differences between the groups in survival, time-to-progression, response, febrile neutropenia, haemoglobin and platelets. However, the patients who received high-dose epirubicin + cisplatin did experience lower rates of grade 3-4 neutropenia compared to patients who received cisplatin + etoposide. Jiang et al. (2009) conducted a systematic review with meta-analyses of low-moderate quality examining the efficacy and safety of intensified chemotherapy with haematopoietic progenitors (IHP) treatment relative to those of control chemotherapy without the use of haematopoietic treatment in SCLC patients, a sizeable minority of whom had extensive stage disease. This systematic review included 626 patients from 5 randomised studies of which four studies examined first-line chemotherapy treatment and found no differences in objective response rate, overall survival or leucocyte nadir between the treatment groups. IHP was however found to be associated with significantly higher rates of haemoglobin nadir and platelet nadir than standard chemotherapy. In a randomised phase II trial providing low quality evidence Sekine et al (2003) compared a regimen consisting of weekly cisplatin + alternating bi-weekly irinotecan (on weeks 1, 3, 5, 7, and 9) and bi-weekly etoposide (on weeks 2, 4, 6 and 8 + G-CSF) with 4-weekly cisplatin + irinotecan + etoposide + G-CSF. Although the results were analysed descriptively and will therefore not be reported in detail here, it was clear that response did not differ between the regimens.

Different chemotherapy regimens

Jiang et al. (2010) conducted a high-quality systematic review of trials comparing efficacy and toxicities associated with irinotecan + platinum treatment to those associated with etoposide + platinum treatment. In the meta-analysis by Jiang et al. (2010) response, overall survival and progression-free survival were not found to differ significantly between the two treatment regimens whether or not the trials employing carboplatin were excluded from the analyses. The irinotecan-containing regimen was however found to be associated with lower rates of anaemia and thrombocytopenia and higher rates of vomiting and diarrhoea than the etoposide-containing regimen. The two regimens did not differ significantly in the number of deaths that were attributed to the treatment. Hermes et al. (2008; data also included in meta-analysis by Jiang et al., 2010) and Schmittel et al. (2006; data also included in meta-analysis by Jiang et al., 2010) both compared irinotecan + carboplatin treatment to etoposide + carboplatin treatment. Hermes et al. (2008) found longer survival, increased rates of complete response, better emotional functioning, higher rates of palliation of sleep problems and dyspnea, but also higher rates of grade 3-4 diarrhea in the irinotecan + carboplatin group compared to the etoposide + carboplatin group. Rates of other recorded toxicities, quality of life measures and palliation did not differ between the treatment groups in this RCT of low-moderate methodological quality. Schmittel et al. (2006) found longer progression-free survival and lower rates of grade 3-4 neutropenia, thrombocytopenia and leucopenia in the irinotecan + carboplatin group relative to the etoposide + carboplatin group in their randomised phase II trial. Response, response duration and other recorded toxicities did not differ between the groups. The evidence provided by the Schmittel et al. (2006) trial is of low methodological quality. In two RCTs providing evidence of moderate quality survival, progression-free survival and response were not found to differ between patients who received treatment with either irinotecan + cisplatin or etoposide + cisplatin (Hanna et al., 2006 [data also included in meta-analysis by Jiang et al., 2010]; Lara et al., 2009 [data also included in meta-analysis by Jiang et al., 2010]). Hanna et al. (2006) did, however, find that the rates of grade 3-4 neutropenia were decreased in the irinotecan + cisplatin group compared to the etoposide + cisplatin group. Lee et al. (2009a) compared a chemotherapy regimen consisting of cisplatin + etoposide with a regimen consisting of gemcitabine + carboplatin and found that although the regimens did not differ in terms of survival, response or time-to-progression, they were associated with different toxicity and quality of life profiles. The incidence of grade 3-4 thrombocytopenia, anaemia and leucopenia were increased in the gemcitabine + carboplatin group as were the extent of improved cognitive functioning. On the other hand, the incidence of chemotherapy-related hospitalisations, grade 2-3 nausea and alopecia, and being upset by hair loss were increased in the cisplatin + etoposide groups relative to the gemcitabine + carboplatin group. The treatment regimens did not differ in terms of incidences of grade 3-4 neutropenia and infection or rash and other recorded toxicities. The trial by Lee et al. (2009a) is of low methodological quality. Reck et al. (2003, 2006 [same data]) conducted an RCT of moderate methodological quality and found that neither survival nor response differed between their groups of patients receiving either a regimen of paclitaxel + etoposide + carboplatin or a regimen consisting of carboplatin + etoposide + vincristine. In a low-moderate quality randomised phase II trial, De Marinis et al. (2005) treated patients with a regimen consisting of cisplatin + gemcitabine with or without etoposide (24/70 patients in each treatment group had poor prognosis limited disease). Although the results were only analysed descriptively, it is clear that response and response duration did not differ between the treatment regimens. Rudin et al. (2008) in a randomised phase II trial of low methodological quality gave their patients carboplatin + etoposide with or without oblimersen and found that although failure-free survival, response and grade 4+ toxicity did not differ between the groups, the patients who did not receive oblimersen survived longer than those who received oblimersen. In an RCT of low-moderate quality Socinski et al. (2009) found that patients treated with a combination of etoposide and carboplatin had longer overall and progression-free survival as well as higher rates of objective response, neutropenia, leukopenia, febrile neutropenia and alopecia and higher rates of use of G-CSF or GM-CSF and antibiotics than patients treated with pemetrexed and carboplatin. The patients treated with pemetrexed + carboplatin had higher rates of anaemia

and nausea than the etoposide + cisplatin group. The rates of thrombocytopenia, fatigue, diarrhoea, vomiting and hyponatremia did not differ significantly between the treatment groups and neither did the use of erythropoietic agents nor the number of patients who received one or more transfusions or who needed one or more hospitalisations for drug-related adverse events.

Prognostic factors for survival in patients with ED-SCLC

Five studies (Artal-Cortés et al., 2004; Niell et al., 2005; Okamoto et al., 2007; Pujol et al., 2007; Rudin et al., 2008) examined different variables for their prognostic value for survival. The most consistent findings were that gender (Niell et al., 2005; Okamoto et al., 2007; Pujol et al., 2007; Rudin et al., 2008) and performance status (Artal-Cortés et al., 2004; Okamoto et al., 2007; Pujol et al., 2007; Rudin et al., 2008) were not predictive of survival. Two studies examined the prognostic value of race and found that race was not associated with survival (Niell et al., 2005; Rudin et al., 2008). Three out of the four studies that examined age as a prognostic factor found that age was not significantly associated with survival (Artal-Cortés et al., 2004; Okamoto et al., 2007; Rudin et al., 2008) whereas the fourth study found that an age below 70 years was associated with longer survival than aged ≥ 70 years (Niell et al., 2005). Two studies considered lactate dehydrogenase (LDH) level as a prognostic factor for survival and one of these studies (Okamoto et al., 2007) found that a low level of LDH was associated with improved survival compared to a high level (HR = 1.69). The other study (Artal-Cortés et al., 2004) did not find that LDH level was significantly prognostic for survival. Finally, a number of prognostic factors were reported by different individual studies (i.e., alkaline phosphatase level, leucocyte count, liver metastases, ethnicity, weight loss, pleural effusion, brain metastases, and number of metastatic sites) and when considered in concert with the low -moderate quality of the evidence assessing prognostic factors in general no conclusions can therefore be made with regards to these variables.

See also clinical evidence in 'Management of brain metastases' (Section 8.5).

Health economic evaluation

This topic was considered a low priority for health economic analysis because the incidence of SCLC is decreasing and the population in question is now small (approximately 10% of lung cancer patients). The GDG also noted that the chemotherapy regimens in question use older agents which are not as costly.

Qualifying statement

The recommendation for the choice of chemotherapy treatment and duration of treatment is derived from a systematic review incorporating RCT's published both prior to and since 2003. The majority of RCT's have treated patients with up to 6 cycles of chemotherapy and the GDG did not find evidence to support longer courses of treatment. Similarly, maintenance treatment has been studied in several RCT's and no evidence was found to support this. The recommendation concerning chemotherapy for cerebral metastases is based on evidence from case control and cohort studies, supplemented by extrapolated evidence from RCTs of the use of chemotherapy for disease at other sites.

7.5.1 Prophylactic Cranial Irradiation (PCI) in SCLC

Clinical topic: How effective is treatment in the management of brain metastases in lung cancer patients?

Brain metastases are common in SCLC. At the time of diagnosis, up to 18% of SCLC patients have symptomatic or asymptomatic brain metastases, whilst during the course of the disease the incidence of brain metastases increases considerably, with a risk at 2 years of up to 80%.

Recommendation

- 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 has not progressed on first-line treatment. [NEW 2011]
- [REDACTED]

Clinical evidence

One well-conducted RCT found that PCI in patients with ED 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). Cao et al. (2005) in an RCT of low-moderate quality found that although the incidence of brain metastases were reduced in their sample of patients with LD SCLC who received PCI relative to controls, there was no difference between the groups in terms of survival. Le Péchoux et al. (2009) compared standard-dose PCI to high-dose PCI in patients with LD SCLC in an RCT of moderate-high quality and found that the incidence of brain metastasis and extracranial metastasis as well as 2-year overall and disease-free survival did not differ significantly between the treatment groups. However, the 2-year incidence of relapse was lower and the incidence of brain metastasis as an isolated site of first failure was higher in the standard-dose PCI treatment group than in the high-dose treatment group. The groups did not appear to differ in treatment-related adverse/toxic events.

Health economic evaluation

The GDG considered this topic a low priority for health economic analysis.

Qualifying statement

These recommendations are based on evidence from a high quality meta-analysis, systematic reviews of RCTs and RCTs with a low risk of bias. The recommendation about limited stage disease is based on a RCT using the specified dose. The recommendation for extensive disease was based on a RCT comparing PCI versus no PCI with different fractionation doses used in the treatment arm.

Updated 2011

7.6 Second line treatment for patients with SCLC who relapse after primary treatment

Clinical topic: Which group of patients with small cell lung cancer are suitable for second line treatment?

The clinical benefits from second line chemotherapy for patients with SCLC who relapse after primary treatment are uncertain and is administered with palliative intent. In general, patients with a good performance status and those who have responded to first-line chemotherapy are more likely to be considered suitable for second line treatment. The introduction of prophylactic cranial irradiation (PCI) for ED SCLC has led to a greater number of patients being considered fit for second line chemotherapy.

Response rates are lower than those of first line therapy, although for suitable patients median overall survival can be extended by several months with combination chemotherapy. Depending upon the duration of response to the first line schedule, the choice of second line chemotherapy is usually to re-treat patients with a platinum containing schedule or to consider an anthracycline based combination chemotherapy schedule such as CAV (cyclophosphamide, doxorubicin and vincristine) or ACE (doxorubicin, cyclophosphamide and etoposide). To date no high quality

randomised clinical trials have been reported that compare the effectiveness of re-treatment with platinum-containing regimens and etoposide against anthracycline based schedules.

Topotecan, available as both oral and intra-venous preparations, is the only licensed single agent chemotherapy drug available as second line treatment for relapsed SCLC and has been assessed by NICE Technology Appraisal 184⁵.

Recommendations

- Offer patients with SCLC that has relapsed after first-line treatment assessment by a thoracic oncologist. [NEW 2011]
- 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. [NEW 2011]
- 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. [NEW 2011]
- Offer radiotherapy for palliation of local symptoms to patients with SCLC that has relapsed after first-line treatment. [NEW 2011]

Topotecan

Refer to 'Topotecan for the treatment of small-cell lung cancer' (NICE technology appraisal guidance 184 [2009]), available at www.nice.org.uk/guidance/TA184.

Clinical evidence

Chemotherapy

One study examined the efficacy and safety of pemetrexed in patients with relapsed SCLC (Socinski et al., 2008). A total of 121 patients were divided into four groups on the basis of their response to first-line treatment (i.e., sensitive/refractory) and on the basis of the dose of pemetrexed they received (500 or 900 mg/m²). However the results of this prospective randomised phase II trial were only analysed descriptively and will therefore not be reported further here.

Prognostic factors for survival in patients with relapsed SCLC

Three studies (Froeschl et al., 2008; Kim et al., 2008; Sundstrøm et al., 2005) examined different variables for potential prognostic value. Froeschl et al. (2008) analysed all the patients in their case series who had been considered for second-line treatment regardless of whether they actually received the treatment (which 107/169 patients did not). Kim et al. (2008) and Sundstrøm et al. (2005) only included patients who had received second-line chemotherapy in their analyses. All three studies found that a good performance status at recurrence was associated with longer survival and that gender was not associated with survival (Froeschl et al., 2008; Kim et al., 2008; Sundstrøm et al., 2005). Response rate to first-line treatment and haemoglobin and platelet levels/counts do also not appear to be associated with survival (Froeschl et al., 2008; Sundstrøm et al., 2005). Kim et al. (2008) found that sensitivity (vs refractory) to first-line treatment was prognostic for survival, but both Froeschl et al. (2008) and Sundstrøm et al. (2005) reported that sensitivity to first-line treatment was not prognostic for survival. Two of the studies reported that neither disease extent (limited or extensive) at recurrence nor age were associated with survival (Kim et al., 2008; Sundstrøm et al., 2005), whereas Froeschl et al (2008) did find an association between age and survival.

⁵ <http://guidance.nice.org.uk/TA184>

A number of different prognostic factors were reported by only one study and when considered in concert with the low quality of the evidence assessing prognostic factors in general no conclusions can therefore be made with regards to these variables.

Health economic evaluation

Second-line chemotherapy for patients with SCLC affects a relatively small number of patients. In addition the incremental health benefits between different regimens are small compared to other topics within this guideline, despite likely differences in toxicity and cost. The GDG therefore considered this topic a low priority for health economic analysis.

Qualifying statement

The GDG considered that the evidence for second-line treatment effectiveness in patients with SCLC is limited with very few studies published since 2003. The GDG reviewed RCT evidence to evaluate which patients should be considered for second line treatment at relapse with most studies only including patients who were WHO performance status 0 – 2. Some studies have stratified patients according to their response to first line treatment and it was accepted that, whilst evidence is limited for those patients who have not responded to first line chemotherapy, this should not be an absolute exclusion for offering second line treatment. The role of radiotherapy to palliate symptoms was not formally reviewed as part of the evidence. However, expert opinion was that radiotherapy should be considered for patients with relapsed SCLC for palliation of local symptoms attributed to the cancer.

References

- Altinbas, M. Coskun, H. S. Er, O. Ozkan, M. Eser, B. Unal, A. Cetin, M. & Soyuer, S. (2004) A randomized clinical trial of combination chemotherapy with and without low-molecular-weight heparin in small cell lung cancer. *Journal of thrombosis and haemostasis : JTH.*, 2: 1266-1271.
- Artal-Cortés, A. Gomez-Codina, J. Gonzalez-Larriba, J. L. Barneto, I. Carrato, A. Isla, D. Camps, C. Garcia-Giron, C. Font, A. Meana, A. Lomas, M. Vadell, C. Arrivi, A. Alonso, C. Maestu, I. Campbell, J. & Rosell, R. (2004) Prospective randomized phase III trial of etoposide/cisplatin versus high-dose epirubicin/cisplatin in small-cell lung cancer. *Clinical Lung Cancer*, 6: 175-183.
- Amarasena, I. U. Walters Julia, A. E. Wood-Baker, R. & Fong, K. (2008). Platinum versus non-platinum chemotherapy regimens for small cell lung cancer. Cochrane Database of Systematic Reviews: Reviews. *Cochrane Database of Systematic Reviews 2008 Issue 4* Chichester (UK): John Wiley & Sons, Ltd.
- Ardizzoni, A. Favaretto, A. Boni, L. Baldini, E. Castiglioni, F. Antonelli, P. Pari, F. Tibaldi, C. Altieri, A.M. Barbera, S. Cacciani, G. Raimondi, M. Tixi, L. Stefani, M. Monfardini, S. Antilli, A. Rosso, R. Paccagnella, A. (2005). Platinum-etoposide chemotherapy in elderly patients with small-cell lung cancer: results of a randomized multicenter phase II study assessing attenuated-dose or full-dose with lenograstim prophylaxis--a Forza Operativa Nazionale Italiana Carcinoma Polmonare and Gruppo Studio Tumori Polmonari Veneto (FONICAP-GSTPV) study. *Journal of Clinical Oncology*, 23, 569-575.
- Arnold, A. M. Seymour, L. Smylie, M. Ding, K. Ung, Y. Findlay, B. Lee, C. W. Djurfeldt, M. Whitehead, M. Ellis, P. Goss, G. Chan, A. Meharchand, J. Alam, Y. Gregg, R. Butts, C. Langmuir, P. Shepherd, F. & National Cancer Institute of Canada Clinical Trials Group Study BR. (2007) Phase II study of vandetanib or placebo in small-cell lung cancer patients after complete or partial response to induction chemotherapy with or without radiation therapy: National Cancer Institute of Canada Clinical Trials Group Study BR.20. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 25: 4278-4284.
- Artal-Cortés, A. Gomez-Codina, J. Gonzalez-Larriba, J. L. Barneto, I. Carrato, A. Isla, D. Camps, C. Garcia-Giron, C. Font, A. Meana, A. Lomas, M. Vadell, C. Arrivi, A. Alonso, C. Maestu, I. Campbell, J. & Rosell, R. (2004) Prospective randomized phase III trial of etoposide/cisplatin versus high-dose epirubicin/cisplatin in small-cell lung cancer. *Clinical Lung Cancer*, 6: 175-183.
- Badzio, A. Kurowski, K. Karnicka-Mlodkowska, H. & Jassem, J. (2004) A retrospective comparative study of surgery followed by chemotherapy vs. non-surgical management in limited-disease small cell lung cancer. *European Journal of Cardio-Thoracic Surgery*, 26: 183-188.
- Baka, S. Califano, R. Ferraldeschi, R. Ascroft, L. Thatcher, N. Taylor, P. Faivre-Finn, C. Blackhall, F. & Lorigan, P. (2008) Phase III randomised trial of doxorubicin-based chemotherapy compared with platinum-based chemotherapy in small-cell lung cancer. *British Journal of Cancer*, 99: 442-447.
- Blackstock, A. W. Bogart, J. A. Matthews, C. Lovato, J. F. Mccoy, T. Livengood, K. Ho, C. White, D. Atkins, J. N. & Miller, A. A. (2005) Split-course versus continuous thoracic radiation therapy for limited-stage small-cell lung cancer: final report of a randomized phase III trial. *Clinical Lung Cancer*, 6: 287-292.
- Bogart, J. A. Watson, D. Mcclay, E. F. Evans, L. Herndon, J. E. Laurie, F. Seagren, S. L. Fitzgerald, T. J. Vokes, E. & Green, M. R. (2008) Interruptions of once-daily thoracic radiotherapy do not correlate with outcomes in limited stage small cell lung cancer: analysis of CALGB phase III trial 9235. *Lung cancer (Amsterdam, Netherlands)*, 62: 92-98.
- Bottomley, A. Debruyne, C. Felip, E. Millward, M. Thiberville, L. D'Addario, G. Rome, L. Zatloukal, P. Coens, C. & Giaccone, G. (2008) Symptom and quality of life results of an international randomised phase III study of adjuvant vaccination with Bec2/BCG in responding patients with limited disease small-cell lung cancer. *European journal of cancer (Oxford, England : 1990)*, 44: 2178-2184

- Cao, K. J. Huang, H. Y. Tu, M. C. & Pan, G. Y. (2005). Long-term results of prophylactic cranial irradiation for limited-stage small-cell lung cancer in complete remission. *Chinese Medical Journal*, 118, 1258-1262.
- De Jong, W. K. Groen, H. J. Koolen, M. G. Biesma, B. Willems, L. N. Kwa, H. B. van, B. A. van, T. H. & Smit, E. F. (2007) Phase III study of cyclophosphamide, doxorubicin, and etoposide compared with carboplatin and paclitaxel in patients with extensive disease small-cell lung cancer. *European journal of cancer (Oxford, England : 1990)*, 43: 2345-2350.
- De, Marinis, F. Nelli, F. Lombardo, M. Ferraú, F. Barbera, S. Bertetto, O. Barni, S. Michetti, G. Labianca, R. & Gridelli, C. (2005) A multicenter, randomized, Phase II study of cisplatin, etoposide, and gemcitabine or cisplatin plus gemcitabine as first-line treatment in patients with poor-prognosis small cell lung carcinoma. *Cancer*, 103: 772-779.
- Dong, R. Chen, X. Wu, T. & Liu, G. J. (2007). Elemene for the treatment of lung cancer. Cochrane Database of Systematic Reviews: Reviews. *Cochrane Database of Systematic Reviews 2007 Issue 4* Chichester (UK): John Wiley & Sons, Ltd.
- Eckardt, J. R. von, P. J. Papai, Z. Tomova, A. Tzekova, V. Crofts, T. E. Brannon, S. Wissel, P. & Ross, G. (2006) Open-label, multicenter, randomized, phase III study comparing oral topotecan/cisplatin versus etoposide/cisplatin as treatment for chemotherapy-naïve patients with extensive-disease small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 24: 2044-2051.
- Froeschl, S. Nicholas, G. Gallant, V. & Laurie, S. A. (2008) Outcomes of second-line chemotherapy in patients with relapsed extensive small cell lung cancer.[see comment]. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*, 3: 163-169.
- Giaccone, G. Debruyne, C. Felip, E. Chapman, P. B. Grant, S. C. Millward, M. Thiberville, L. D'Addario, G. Coens, C. Rome, L. S. Zatloukal, P. Masso, O. & Legrand, C. (2005) Phase III study of adjuvant vaccination with Bec2/bacille Calmette-Guerin in responding patients with limited-disease small-cell lung cancer (European Organisation for Research and Treatment of Cancer 08971-08971B; Silva Study). *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 23: 6854-6864.
- Greco, F. A. Thompson, D. S. Morrissey, L. H. Erland, J. B. Burris, H. A. Spigel, D. R. Joseph, G. Corso, S. W. Spemulli, E. & Hainsworth, J. D. (2005) Paclitaxel/carboplatin/etoposide versus paclitaxel/topotecan for extensive-stage small cell lung cancer: a Minnie Pearl Cancer Research Network randomized, prospective phase II trial. *The oncologist*, 10: 728-733. (Reported in Amarasena et al., 2008)
- Grote, T. Yeilding, A. L. Castillo, R. Butler, D. Fishkin, E. Henry, D. H. Deleo, M. Fink, K. & Sullivan, D. J. (2005) Efficacy and safety analysis of epoetin alfa in patients with small-cell lung cancer: a randomized, double-blind, placebo-controlled trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 23: 9377-9386.
- Han, J. Y. Kim, H. T. Lim, K. Y. Yoon, S. J. Lee, D. H. & Lee, J. S. (2008) Randomized phase II study of maintenance irinotecan therapy versus observation following induction chemotherapy with irinotecan and cisplatin in extensive disease small cell lung cancer. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*, 3: 1039-1045.
- Han, H. S. Han, J. Y. Yu, S. Y. Pyo, H. R. Kim, H. Y. Cho, K. H. Lee, D. H. Kim, H. T. & Lee, J. S. (2008) Randomized phase 2 study of subcutaneous amifostine versus epoetin-alpha given 3 times weekly during concurrent chemotherapy and hyperfractionated radiotherapy for limited-disease small cell lung cancer. *Cancer*, 113: 1623-1631.
- Hanna, N. Bunn, P. A. Langer, C. Einhorn, L. Guthrie, T. Beck, T. Ansari, R. Ellis, P. Byrne, M. Morrison, M. Hariharan, S. Wang, B. & Sandler, A. (2006) Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 24: 2038-2043.
- Heigener, D. F. Manegold, C. Jäger, E. Saal, J. G. Zuna, I. & Gatzemeier, U. (2009) Multicenter randomized open-label phase III study comparing efficacy, safety, and tolerability of conventional carboplatin plus etoposide versus dose-intensified carboplatin plus etoposide plus lenograstim in small-cell lung cancer in "extensive disease" stage. *American Journal of Clinical Oncology*, 32: 61-64.
- Hermes, A. Bergman, B. Bremnes, R. Ek, L. Fluge, S. Sederholm, C. Sundström, S. Thaning, L. Vilsvik, J. Aasebø, U. & Sörenson, S. (2008) Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: a randomized phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 26: 4261-4267.
- Ignatiadis, M. Mavroudis, D. Veslemes, M. Boukovinas, J. Syrigos, K. Agelidou, M. Agelidou, A. Gerogianni, A. Pavlakou, G. Tselepatiotis, E. Nikolakopoulos, J. & Georgoulis, V. (2005) Sequential versus alternating administration of cisplatin/etoposide and topotecan as first-line treatment in extensive-stage small-cell lung cancer: preliminary results of a Phase III Trial of the Hellenic Oncology Research Group. *Clinical Lung Cancer*, 7: 183-189.
- Jiang, L. Yang, K. H. Mi, D. H. Liu, Y. L. Tian, J. H. Ma, B. Tan, J. Y. & Bai, Z. G. (2007) Safety of irinotecan/cisplatin versus etoposide/cisplatin for patients with extensive-stage small-cell lung cancer: a metaanalysis. *Clinical Lung Cancer*, 8: 497-501.
- Jiang, J.; Shi, H. Z.; Deng, J. M.; Liang, Q. L.; Qin, S. M.; Wu, C. (2009). Efficacy of intensified chemotherapy with hematopoietic progenitors in small-cell lung cancer: A meta-analysis of the published literature. *Lung Cancer*, 65, 214-18.
- Jiang, J. W.; Liang, X. H.; Zhou, X. L.; Huang, L. Z.; Huang, R. F.; Chu, Z. H.; Zhan, Q. O. (2010). A Meta-Analysis of Randomized Controlled Trials Comparing Irinotecan/Platinum with Etoposide/Platinum in Patients with Previously Untreated Extensive-Stage Small Cell Lung Cancer. *Journal of Thoracic Oncology*, 5, 867-873.
- Kim, Y. H. Goto, K. Yoh, K. Niho, S. Ohmatsu, H. Kubota, K. Saijo, N. & Nishiwaki, Y. (2008) Performance status and sensitivity to first-line chemotherapy are significant prognostic factors in patients with recurrent small cell lung cancer receiving second-line chemotherapy. *Cancer*, 113: 2518-2523.
- Lara, P. N.; Natale, R.; Crowley, J.; Lenz, H.J.; Redman, M. W.; Carleton, J. E.; Jett, J.; Langer, C. J.; Kuebler, J. P.; Dakhil, S. R.; Chansky, K.; Gandara, D. R. (2009). Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. *Journal of Clinical Oncology*, 27, 2530-2535.
- Le, Pécoux C. Dunant, A. Senan, S. Wolfson, A. Quoix, E. Faivre-Finn, C. Ciuleanu, T. Arriagada, R. Jones, R. Wanders, R. Lerouge, D. Laplanche, A. and Prophylactic Cranial Irradiation (PCI) Collaborative Group. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic

radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *The Lancet Oncology* 10(5), 467-474. 2009.

Lee, S. M. James, L. E. Qian, W. Spiro, S. Eisen, T. Gower, N. H. Ferry, D. R. Gilligan, D. Harper, P. G. Prendiville, J. Hocking, M. & Rudd, R. M. (2009a) Comparison of gemcitabine and carboplatin versus cisplatin and etoposide for patients with poor-prognosis small cell lung cancer. *Thorax*, 64: 75-80.

Lee, S. M.; Woll, P. J.; Rudd, R.; Ferry, D.; O'Brien, M.; Middleton, G.; Spiro, S.; James, L.; Ali, K.; Jitlal, M.; Hackshaw, A. (2009b). Anti-angiogenic therapy using thalidomide combined with chemotherapy in small cell lung cancer: a randomized, double-blind, placebo-controlled trial. *Journal of the National Cancer Institute*, 101, 1049-57.

McClay, E. F. Bogart, J. Herndon, J. E. Watson, D. Evans, L. Seagren, S. L. Green, M. R. & Cancer and Leukemia Group (2005) A phase III trial evaluating the combination of cisplatin, etoposide, and radiation therapy with or without tamoxifen in patients with limited-stage small cell lung cancer: Cancer and Leukemia Group B Study (9235). *American Journal of Clinical Oncology*, 28: 81-90.

Niell, H. B. Herndon, J. E. Miller, A. A. Watson, D. M. Sandler, A. B. Kelly, K. Marks, R. S. Perry, M. C. Ansari, R. H. Otterson, G. Ellerton, J. Vokes, E. E. Green, M. R. & Cancer and Leukemia Group (2005) Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 23: 3752-3759.

Okamoto, H. Watanabe, K. Kunikane, H. Yokoyama, A. Kudoh, S. Asakawa, T. Shibata, T. Kunitoh, H. Tamura, T. & Saijo, N. (2007) Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. *British Journal of Cancer*, 97: 162-169.

Pandya, K. J. Dahlberg, S. Hidalgo, M. Cohen, R. B. Lee, M. W. Schiller, J. H. Johnson, D. H. & Eastern Cooperative Oncology Group (2007) A randomized, phase II trial of two dose levels of temsirolimus (CCI-779) in patients with extensive-stage small-cell lung cancer who have responding or stable disease after induction chemotherapy: a trial of the Eastern Cooperative Oncology Group (E1500). *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*, 2: 1036-1041.

Pirker, R. Ramlau, R. A. Schuetz, W. Zatloukal, P. Ferreira, I. Lillie, T. & Vansteenkiste, J. F. (2008) Safety and efficacy of darbeopetin alpha in previously untreated extensive-stage small-cell lung cancer treated with platinum plus etoposide. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 26: 2342-2349.

Pujol, J. L. Breton, J. L. Gervais, R. Tanguy, M. L. Quoix, E. David, P. Janicot, H. Westeel, V. Gerneroff, S. Genève, J. & Maraninchi, D. (2007) Phase III double-blind, placebo-controlled study of thalidomide in extensive-disease small-cell lung cancer after response to chemotherapy: an intergroup study FNCLCC cleo04 IFCT 00-01. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 25: 3945-3951.

Quoix, E. Breton, J. L. Gervais, R. Wilson, J. Schramel, F. Cardenal, F. Ross, G. Preston, A. Lymboura, M. & Mattson, K. (2005) A randomised phase II study of the efficacy and safety of intravenous topotecan in combination with either cisplatin or etoposide in patients with untreated extensive disease small-cell lung cancer. *Lung cancer (Amsterdam, Netherlands)*, 49: 253-261. (Reported in Amarasena et al. 2008)

Reck, M. von, P. J. Macha, H. N. Kaukel, E. Deppermann, K. M. Bonnet, R. Ulm, K. Hessler, S. & Gatzemeier, U. (2003) Randomized phase III trial of paclitaxel, etoposide, and carboplatin versus carboplatin, etoposide, and vincristine in patients with small-cell lung cancer. *Journal of the National Cancer Institute*. 95: 1118-1127.

Reck, M. von, P. J. Macha, H. N. Kaukel, E. Deppermann, K. M. Bonnet, R. Ulm, K. Hessler, S. & Gatzemeier, U. (2006) Efficient palliation in patients with small-cell lung cancer by a combination of paclitaxel, etoposide and carboplatin: quality of life and 6-years'-follow-up results from a randomised phase III trial. *Lung cancer (Amsterdam, Netherlands)*, 53: 67-75.

Rudin, C. M. Salgia, R. Wang, X. Hodgson, L. D. Masters, G. A. Green, M. & Vokes, E. E. (2008) Randomized phase II Study of carboplatin and etoposide with or without the bcl-2 antisense oligonucleotide oblimersen for extensive-stage small-cell lung cancer: CALGB 30103. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 26: 870-876.

Schaefer, P. L. Marks, R. S. Mahoney, M. R. Sloan, J. A. Bauman, M. D. Tazelaar, H. D. Kugler, J. W. Mailliard, J. A. Ebbert, L. P. & Wiesenfeld, M. (2003) Randomized phase II study of daily versus continuous-infusion schedules of topotecan in the treatment of extensive-stage small cell lung cancers. *American Journal of Clinical Oncology*, 26: 236-240.

Schild, S. E. Bonner, J. A. Shanahan, T. G. Brooks, B. J. Marks, R. S. Geyer, S. M. Hillman, S. L. Farr, G. H. Tazelaar, H. D. Krook, J. E. Geoffroy, F. J. Salim, M. Arusell, R. M. Mailliard, J. A. Schaefer, P. L. & Jett, J. R. (2004) Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. *International journal of radiation oncology, biology, physics*. 59: 943-951.

Schild, S. E. Stella, P. J. Brooks, B. J. Mandrekar, S. Bonner, J. A. McGinnis, W. L. Mailliard, J. A. Krook, J. E. Deming, R. L. Adjei, A. A. Jatoi, A. & Jett, J. R. (2005) Results of combined-modality therapy for limited-stage small cell lung carcinoma in the elderly. *Cancer*, 103: 2349-2354.

Schmittel, A. Fischer von, W. L. Sebastian, M. Martus, P. Schulze, K. Hortig, P. Reeb, M. Thiel, E. & Keilholz, U. (2006) A randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin treatment in patients with extended disease small-cell lung cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 17: 663-667.

Schreiber, D.; Rineer, J.; Weedon, J.; Vongtama, D.; Wortham, A.; Kim, A.; Han, P.; Choi, K.; Rotman, M. (2010). Survival Outcomes With the Use of Surgery in Limited-Stage Small Cell Lung Cancer Should Its Role Be Re-Evaluated? *Cancer*, 116, 1350-1357

Sculier, J. P. Lafitte, J. J. Efreimidis, A. Florin, M. C. Lecomte, J. Berchier, M. C. Richez, M. Berghmans, T. Scherpereel, A. Meert, A. P. Koumakis, G. Leclercq, N. Paesmans, M. Van, H. P. & European Lung Cancer Working Party (ELCWP) (2008) A phase III randomised study of concomitant induction radiochemotherapy testing two modalities of radiosensitisation by cisplatin (standard versus daily) for limited small-cell lung cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 19: 1691-1697.

- Seifart, U. Jensen, K. Ukena, J. Mueller, C. Schröder, M. Fuhr, H. G. Keppler, U. Neubauer, A. Staab, H. J. & Wolf, M. (2005) Randomized phase II study comparing topotecan/cisplatin administration for 5 days versus 3 days in the treatment of extensive stage small cell lung cancer (SCLC). *Lung cancer (Amsterdam, Netherlands)*, 48: 415-422.
- Seifart, U. Fink, T. Schade-Brittinger, C. Hans, K. Mueller, C. Koschel, G. Schroeder, H. Lorenz, R. Dethling, J. & Wolf, M. (2007) Randomised phase II study comparing topotecan/carboplatin administration for 5 versus 3 days in the treatment of extensive-stage small-cell lung cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.*, 18: 104-109.
- Sekine, I. Nishiwaki, Y. Noda, K. Kudoh, S. Fukuoka, M. Mori, K. Negoro, S. Yokoyama, A. Matsui, K. Ohsaki, Y. Nakano, T. Saijo, N. & Japan Clinical Oncology Group (JCOG) Lung Cancer Study Group (2003) Randomized phase II study of cisplatin, irinotecan and etoposide combinations administered weekly or every 4 weeks for extensive small-cell lung cancer (JCOG9902-DI). *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.*, 14: 709-714.
- Sekine, I. Nokihara, H. Takeda, K. Nishiwaki, Y. Nakagawa, K. Isobe, H. Mori, K. Matsui, K. Saijo, N. & Tamura, T. (2008) Randomised phase II trial of irinotecan plus cisplatin vs irinotecan, cisplatin plus etoposide repeated every 3 weeks in patients with extensive-disease small-cell lung cancer. *British Journal of Cancer*, 98: 693-696.
- Socinski, M. A. Weissman, C. Hart, L. L. Beck, J. T. Choksi, J. K. Hanson, J. P. Prager, D. Monberg, M. J. Ye, Z. & Obasaju, C. K. (2006) Randomized phase II trial of pemetrexed combined with either cisplatin or carboplatin in untreated extensive-stage small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 24: 4840-4847.
- Socinski, M. A.; Smit, E. F.; Lorigan, P.; Konduri, K.; Reck, M.; Szczesna, A.; Blakely, J.; Serwatowski, P.; Karaseva, N. A.; Ciuleanu, T.; Jassem, J.; Dediu, M.; Hong, S.; Vissere-Grul, C.; Hanauske, A. R.; Obasaju, C. K.; Guba, S. C.; Thatcher, N. (2009). Phase III study of pemetrexed plus carboplatin compared with etoposide plus carboplatin in chemotherapy-naïve patients with extensive-stage small-cell lung cancer. *Journal of Clinical Oncology*, 27, 4787-92
- Socinski, M. A. Raju, R. N. Neubauer, M. Smith, D. A. Richards, D. A. Savin, M. Ruxer, R. L. Reynolds, C. H. Zhan, F. Bromund, J. L. Chen, R. & Obasaju, C. (2008) Pemetrexed in relapsed small-cell lung cancer and the impact of shortened vitamin supplementation lead-in time: results of a phase II trial. *Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung Cancer*, 3: 1308-1316.
- Slotman, B. Faivre-Finn, C. Kramer, G. Rankin, E. Snee, M. Hatton, M. et al. (2007). Prophylactic cranial irradiation in extensive small-cell lung cancer. *The New England journal of medicine*, 357, 664-672.
- Sundstrøm, S. Bremnes, R. M. Kaasa, S. Aasebø, U. Aamdal, S. & Norwegian Lung Cancer Study Group (2005) Second-line chemotherapy in recurrent small cell lung cancer. Results from a crossover schedule after primary treatment with cisplatin and etoposide (EP-regimen) or cyclophosphamide, epirubicin, and vincristin (CEV-regimen). *Lung cancer (Amsterdam, Netherlands)*, 48: 251-261.
- Thatcher, N. Qian, W. Clark, P. I. Hopwood, P. Sambrook, R. J. Owens, R. Stephens, R. J. & Girling, D. J. (2005) Ifosfamide, carboplatin, and etoposide with midcycle vincristine versus standard chemotherapy in patients with small-cell lung cancer and good performance status: clinical and quality-of-life results of the British Medical Research Council multicenter randomized LU21 trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 23: 8371-8379.

8 Palliative interventions and supportive and palliative care

The 2005 Lung Cancer guideline included a comprehensive section on palliative interventions and supportive and palliative care. This chapter has not undergone a full review as part of this update. The background and recommendations from the 2005 guideline are reproduced here together with an updated section on the treatment of endobronchial obstruction and established cerebral metastases. Aspects relating to communication have been reviewed in chapter 2.

This topic was viewed by the GDG as an area of great importance, particularly because the majority of patients with lung cancer have incurable disease. Supportive care is the multidisciplinary holistic care offered to all patients and their carers throughout the pathway to help them cope with cancer and treatment of it. It includes issues such as information giving, symptom control and psychological, social and spiritual support. Palliative care provides a similar holistic approach, but is specific to those patients with advanced progressive illness.

Prognostic factors such as performance status and extent of disease can identify those patients for whom more aggressive treatment modalities aimed at extending survival may be appropriate, as opposed to those with a poorer prognosis where the focus will be purely palliation and improved quality of life.

National Institute of Clinical Excellence (NICE) recommendations and guidance is available to improve supportive and palliative care for adults with cancer¹. This guidance should be used alongside this document. The guidance provides an evidence base for how services should be organised and delivered using cancer networks to improve the care of patients with cancer. The guidance encompasses co-ordination of care, user involvement, face-to-face communication, information, psychological support services, social support services, spiritual support services, general palliative care services (including the care of dying patients), specialist palliative care services, rehabilitation services, complementary therapy services, services for families and carers (including bereavement care) and workforce development.

Other guidance produced subsequently of relevance to this section include:

- National Cancer Action Team. Holistic common assessment of supportive and palliative care needs for adults with cancer: Assessment guidance. National Cancer Action Team, London., 2007.
- National Cancer Action Team. Supporting and improving Commissioning of Cancer Rehabilitation Services. National Cancer Action Team, London. 2009.
- National Cancer Action Team. Rehabilitation Care Pathway: Lung. National Cancer Action Team, London. 2009.
- http://www.cancer.nhs.uk/rehabilitation/documents/pathways/care_pathways/NCAT_Rehab_Lung.pdf

¹ <http://guidance.nice.org.uk/CSGSP>

- Department of Health. Advance Care Planning: A guide for Health and Social Care Staff. Department of Health, London. 2008.
- Department of Health. End of life care strategy. Promoting high quality care for all adults at the end of life. Department of Health, London. 2008.

Recommendations

- Supportive and palliative care of the patient should be provided by general and specialist palliative care providers in accordance with the NICE guidance 'Improving supportive and palliative care for adults with cancer'. [2005]
- Patients who may benefit from specialist palliative care services should be identified and referred without delay. [2005]

8.1 Common symptoms of lung cancer

Common symptoms of lung cancer include fatigue, loss of appetite, weight loss, breathlessness, cough, haemoptysis, hoarseness, chest pain, bone pain, spinal cord compression, brain metastases and superior vena caval obstruction. Thoracic symptoms have been subdivided into dyspnoea (breathlessness), including malignant pleural effusion, non-obstructive airway symptoms (cough, haemoptysis, hoarseness and chest pain) and superior vena caval obstruction. Neurological symptoms include those arising from brain metastases and spinal cord compression. The treatment of bone pain and pathological fractures is covered under a section on bone metastases. No specific evidence on the treatment of pain has been reviewed as this is a general symptom of cancer and not specific to lung cancer which is outside the scope of this chapter. Nevertheless, the management of pain is recognised by the GDG to be of particular importance and places great emphasis on the prompt evaluation and effective treatment of pain.

Many of these symptoms can be very debilitating and considerably reduce quality of life. Others are life-threatening conditions requiring immediate treatment. Some treatments with palliative intent, in addition to relieving symptoms and improving quality of life, may increase survival; this is particularly so when the underlying cause is life-threatening (e.g. superior vena caval obstruction, hypercalcaemia of malignancy). The GDG examined the various symptoms encountered and assessed the evidence of the effectiveness of interventions to improve symptoms. The symptoms' underlying causal mechanisms and the stage and performance status of the patient also determine the treatment given.

8.2 Palliative Radiotherapy

Palliative radiotherapy remains an important and commonly used form of treatment for patients with lung cancer. Palliative radiotherapy is used to treat symptoms arising from the primary cancer or sites of secondary spread. The primary cancer may be treated when it causes symptoms such as breathlessness due to endobronchial obstruction or vascular obstruction, persistent cough, haemoptysis and chest pain. Radiotherapy regimens vary from single to multiple fractions and are given in high dose where the aim is to substantially reduce the size of the cancer. Secondary sites are normally treated with radiotherapy if they are causing pain. Symptoms respond in around two-thirds of patients.

Recommendation

- Patients who cannot be offered curative treatment, and are candidates for palliative radiotherapy, may either be observed until symptoms arise and then treated, or be treated with palliative radiotherapy immediately. [2005]

8.3 Management of endobronchial obstruction

Clinical topic: How effective are brachytherapy/(airway) stenting/photodynamic therapy/laser/electrocautery/cryotherapy/(surgical) debulking (via rigid bronchoscope) for treatment of patients with lung cancer with endobronchial obstructions?

Endotracheal or endobronchial obstruction can be classified as intrinsic, extrinsic or mixed; intrinsic obstruction is caused by a cancer within the airway lumen and extrinsic obstruction from a cancer externally compressing an airway. Symptoms can include cough, breathlessness and obstructive pneumonia. Tracheal obstruction is a life-threatening condition and requires urgent assessment and treatment.

There are a range of treatments to prevent or treat airway obstruction including conventional external beam radiotherapy, endobronchial surgical debulking of the cancer, stenting and endoscopic endobronchial treatments. Endobronchial surgical debulking of the cancer can be undertaken using either rigid or flexible bronchoscopy. Advantages of rigid bronchoscopic procedures under general anaesthesia include the ability to remove large pieces of cancer, maintain adequate ventilation, and allow control of large volume haemorrhage. Nonetheless, flexible bronchoscopy is increasingly used for debulking procedures. These treatments are usually given to palliate symptoms and improve quality of life, but in some patients relief of endobronchial obstruction will allow assessment for subsequent treatment with curative intent.

Endobronchial techniques available are either a) used to debulk the cancer (brachytherapy, electrocautery, cryotherapy, thermal laser ablation and photodynamic therapy) or b) used to maintain/re-establish airway patency (endobronchial stenting). It was noted that thermal laser ablation, surgical debulking and stent insertion were all favoured options where immediate relief of endobronchial obstruction is required, especially if there is a relatively large cancer. Endobronchial debulking procedures are generally not suitable in cases where the predominant cause of airway obstruction is extrinsic compression. In such cases airway stenting to maintain/re-establish airway patency and/or external beam radiotherapy aimed at treating the surrounding cancer may be considered. External beam radiotherapy is effective in around two-thirds of patients and is less invasive than the other endobronchial treatments. Please see table 8.1.

Table 8.1: Description of endobronchial treatments

Treatment	Description
Brachytherapy	A catheter is placed bronchoscopically and this is used to deliver a radioactive source (most commonly Iridium-192) within or near an endobronchial cancer. This delivers high dose local irradiation.
Electrocautery (diathermy)	High frequency electrical current is used which produces heat from tissue electrical resistance to destroy cancer cells. Argon plasma coagulation (APC) is a non-contact mode of electrocautery that can also be delivered using flexible bronchoscopy. It causes desiccation and coagulation of exophytic endobronchial cancers.
Cryotherapy	Extreme cold is used to cause delayed local destruction of cancer tissue. It is applied in cycles of freezing and thawing, causing tissue necrosis.
Thermal laser ablation	In laser therapy, the heat energy from laser light is used to coagulate and vaporize endobronchial cancer tissue. The majority of publications report use of the Nd-YAG (neodymium-yttrium-aluminium-garnet) laser.
Photodynamic therapy (PDT)	In PDT a systemic photosensitiser which is selectively retained and concentrated in cancer cells is administered. Subsequent exposure to light of a particular wavelength induces cancer cell death.

Table 8.1 (Contd.)

Airway stents	A number of airway stents are available for the palliation of dyspnoea. Tracheal and bronchial stents are commonly used in patients with endoluminal obstruction and extrinsic compression to maintain airway patency and integrity. Plastic (i.e. silicone) and metal stents are available. Silicone stents are deployed using rigid bronchoscopy under general anaesthesia. Metallic airway stents can be deployed by either flexible bronchoscopy or rigid bronchoscopy. The current standard is the self-expanding metallic airway stent made from the alloy nitinol.
----------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Recommendations

- When patients have large airway involvement, monitor (clinically and radiologically) for endobronchial obstruction to ensure treatment is offered early. [NEW 2011]
- Offer external beam radiotherapy and/or endobronchial debulking or stenting to patients with impending endobronchial obstruction. [NEW 2011]
- Every cancer network should ensure that patients have rapid access to a team capable of providing interventional endobronchial treatments. [NEW 2011]

Clinical evidence

The evidence for the effectiveness of different treatments for endobronchial obstructions due to lung cancer consisted of one randomised phase II study (Mallick et al., 2006) which compared three different schedules of endobronchial brachytherapy (EBBT) with or without external radiation (XRT) for the palliation of advanced non-small cell lung cancer. Arm A (N = 15) received XRT to a dose of 30 Gy in 10 fractions over 2 weeks and endobronchial application and brachytherapy on days 6 and 13. External radiation was not given simultaneously with EBBT on the same day. The dose of EBBT was 8 Gy at 1 cm from the source axis on each of these applications. Arm B (N = 15) received the same schedule as Arm A for external radiation in addition to endobronchial application and brachytherapy on day 13 with a single fraction of 10 Gy at 1 cm. Arm C (N = 15) received a single fraction of EBBT to a dose of 15 Gy at 1 cm. The vast majority of patients across all three treatment groups achieved symptomatic relief after treatment, but the extent of symptomatic relief did not differ between the treatment groups. Similarly, the groups did not differ significantly in terms of response rates or response duration. No grade 2-4 acute complications were reported.

Health economic evaluation

This topic was a medium priority for health economic evaluation because endobronchial obstruction affects up to 25% of all lung cancer patients and has a detrimental effect on quality of life. However the GDG were aware that the clinical evidence base was likely to be small and that there would be a lack of comparative evidence. Due to these feasibility issues, no further economic analysis was undertaken.

Qualifying statement

The evidence review found only poor quality studies for the majority of endobronchial treatments and one randomised trial comparing brachytherapy with external beam radiotherapy. The recommendations were therefore based on expert opinion and the randomised trial.

8.4 Other treatments with palliative intent

8.4.1 Pleural Effusion

Breathlessness due to pleural effusion may be relieved by removal of the fluid via needle aspiration or narrow-bore indwelling catheter. However, symptomatic benefit from simple drainage is generally short lived due to re-accumulation of the fluid over days or a few weeks. This topic was not part of the 2011 update so the recommendations from 2005 are reproduced below.

Recommendations

- Pleural aspiration or drainage should be performed in an attempt to relieve the symptoms of a pleural effusion. [2005]
- Patients who benefit symptomatically from aspiration or drainage of fluid should be offered talc pleurodesis for longer-term benefit. [2005]

8.4.2 Non drug treatment for breathlessness

The cause of breathlessness in lung cancer is often multifactorial. It can be caused by the cancer itself, e.g. airway obstruction, the treatment for the cancer, e.g. chemotherapy-related anaemia, or by co-morbidities such as chronic lung or heart disease, anxiety, depression or panic disorder. A thorough evaluation is important to ensure correctable causes are addressed and that appropriate drug therapies are optimised. Non-drug measures include exploring the patient's understanding of breathlessness and its meaning, providing explanation, breathing retraining and anxiety management.

Recommendations

- Non-drug interventions based on psychosocial support, breathing control and coping strategies should be considered for patients with breathlessness. [2005]
- Non-drug interventions for breathlessness should be delivered by a multidisciplinary group, coordinated by a professional with an interest in breathlessness and expertise in the techniques (for example, a nurse, physiotherapist or occupational therapist). Although this support may be provided in a breathlessness clinic, patients should have access to it in all care settings. [2005]

8.4.3 Management of cough

About 80% of patients with lung cancer experience cough and one-third haemoptysis. The mainstay of treatment is external beam radiotherapy and drug therapy. Other anticancer treatments can also bring relief such as palliative chemotherapy and some endobronchial treatments.

Recommendation

- Opioids, such as codeine or morphine, should be considered to reduce cough. [2005]

8.4.4 Management of Hoarseness

About 10% of patients with lung cancer experience some hoarseness of their voice. Teflon stiffening of the vocal cord can prevent paradoxical movement and lead to some improvement in the voice.

Recommendation

- Patients with troublesome hoarseness due to recurrent laryngeal nerve palsy should be referred to an ear, nose and throat specialist for advice. [2005]

8.4.5 Superior Vena Caval Obstruction

Superior Vena Caval Obstruction (SVCO) is due either to cancer arising in the right main or upper lobe bronchus or by the presence of bulky mediastinal lymph nodes typically arising from the right paratracheal or pre-carinal stations. It causes oedema of the face, neck and arms. Distended veins over the chest are also usually apparent. SVCO is present at diagnosis in 10% of patients with SCLC and 2% of patients with NSCLC. Traditional management of SVCO includes systemic corticosteroids (e.g. dexamethasone) and either external beam radiotherapy (more commonly used for NSCLC) or chemotherapy (generally for SCLC). Increasingly, expandable endovascular stents, placed percutaneously in the SVC are used to relieve compression and restore blood flow.

Recommendations

- Patients who present with superior vena cava obstruction should be offered chemotherapy and radiotherapy according to the stage of disease and performance status. [2005]
- Stent insertion should be considered for the immediate relief of severe symptoms of superior vena caval obstruction or following failure of earlier treatment. [2005]

8.5 Management of brain metastases

Brain metastases occur frequently in patients with lung cancer, especially SCLC, and have a profound effect on both quality of life and survival.

Treatments for cerebral metastasis include corticosteroids, radiotherapy (whole brain (WBRT), or stereotactic), cytotoxic chemotherapy, targeted agents and surgical resection.

8.5.1 Treatment of established cerebral metastasis.

Clinical topic: How effective is treatment in the management of brain metastases in lung cancer patients?

Corticosteroids reduce symptoms caused by cerebral metastases by reducing cerebral oedema. Dexamethasone is the most commonly used. The median survival of patients with brain metastases from primary lung cancer is 1–2 months when treated with corticosteroids alone.

Palliative whole brain radiotherapy (WBRT) may be offered to improve symptoms. Improvement in neurological symptoms is seen in half of patients after 2 weeks and three-quarters after 4 weeks.

About one-third of patients presenting with cerebral metastases have a solitary lesion. In patients with NSCLC and a good performance status, prolonged survival has been reported following either neurosurgical resection or stereotactic radiosurgery (SRS).

There is debate about the role of chemotherapy in the treatment of cerebral metastases.

Recommendations

- Offer dexamethasone to patients with symptomatic brain metastases and reduce to the minimum necessary maintenance dose for symptomatic response. [NEW 2011]

- [REDACTED]

Clinical evidence*Radiotherapy treatment of brain metastases from lung cancer*

In an RCT of low quality Aoyama et al. (2007) did not find any statistically significant differences in neurocognitive function in patients with 1-4 brain metastases (the majority of whom from lung cancer) who received either stereotactic radiosurgery (SRS) + whole brain radiotherapy (WBRT) or SRS alone. Sperduto et al. (2010) found in a retrospectively recruited sample of 1888 patients with brain metastases from NSCLC that compared to patients treated for brain metastases with WBRT, patients treated with SRS, WBRT + SRS, surgery + SRS, surgery + WBRT, and surgery + WBRT + SRS all had a reduced hazard of death.

Chemotherapy and whole brain radiotherapy treatment of brain metastases from lung cancer

Eleven studies (Chua et al., 2010; Dae et al., 2008; Guerrieri et al., 2004; Kim et al., 2005; Lee et al., 2008; Liu et al., 2010; Mehta et al., 2003 (including Meyers et al., 2004), 2009; ; Neuhaus et al., 2009; Quantin et al., 2010; Suh et al., 2006) have compared chemotherapy with or without whole brain radiotherapy (with or without gamma-knife radiosurgery; Kim et al., 2005) to whole brain radiotherapy with or without chemotherapy, and tended to report that survival did not differ between the treatment groups. Similar findings were reported for the other outcomes; that is, response and progression/disease-free survival with the exception of Mehta et al. (2003) who found that time to neurologic progression was longer in the chemotherapy with whole brain radiation therapy group compared to the whole brain radiotherapy alone group and with the exception of Liu et al. (2010) who reported higher partial and overall response rates and lower progressive disease rate in the patients who had received tomozolomide + WBRT compared to the patients who had just received WBRT. Overall, the evidence from the majority of these studies is of low to moderate quality.

Prognostic factors for survival in patients with brain metastases from lung cancer

Ten studies (Gerosa et al., 2005; Guerrieri et al., 2004; Kepka et al., 2005; Rades et al., 2007; Serizawa, 2009; Sperduto et al., 2010; Sundaresan et al., 2010; Tang et al., 2005; Videtic et al., 2007, 2009) conducted some analyses on prognostic factors for survival, the majority of which were multivariate analyses. The most consistent findings were that a good performance status was predictive (Gerosa et al., 2005; Guerrieri et al., 2004; Kepka et al., 2005; Rades et al., 2007; Serizawa, 2009; Sperduto et al., 2010; Sundaresan et al., 2010; Tang et al., 2005; Videtic et al., 2007, 2009) and that gender (Guerrieri et al., 2004; Kepka et al., 2005; Rades et al., 2007; Serizawa, 2009) was not predictive of longer survival. Of the prognostic factors addressed by two or three studies, the studies are in agreement that the type of lung cancer (SCLC, NSCLC; Kepka et al., 2005; Serizawa, 2009) is not prognostic for longer survival. A number of prognostic factors were reported by only one study and when considered in concert with the low quality of the evidence assessing prognostic factors in general no conclusions can therefore be made with regards to these variables.

Quality of Life

Only two studies have explicitly reported on quality of life (Slotman et al., 2007, 2009 [same population]; Serizawa, 2009). Slotman et al. found that the patients with extensive disease small cell lung cancer who had received prophylactic cranial irradiation experienced more

Clinical evidence (cont.)

fatigue, hair loss, nausea and vomiting, leg weakness, constipation, headaches, future uncertainty and motor dysfunction than the patients in the control group whose social functioning was also better than that of the prophylactic cranial irradiation patients. The two groups, however, did not differ in their global health status, and emotional-, role-, and cognitive-functioning. Serizawa (2009) found that in a sample of patients with NSCLC (n = 387) or SCLC (n = 56) who had received gamma-knife surgery for brain metastases superior activities of daily living were associated with having 10 or less lesions, a high pre-treatment performance status and no carcinomatous meningitis.

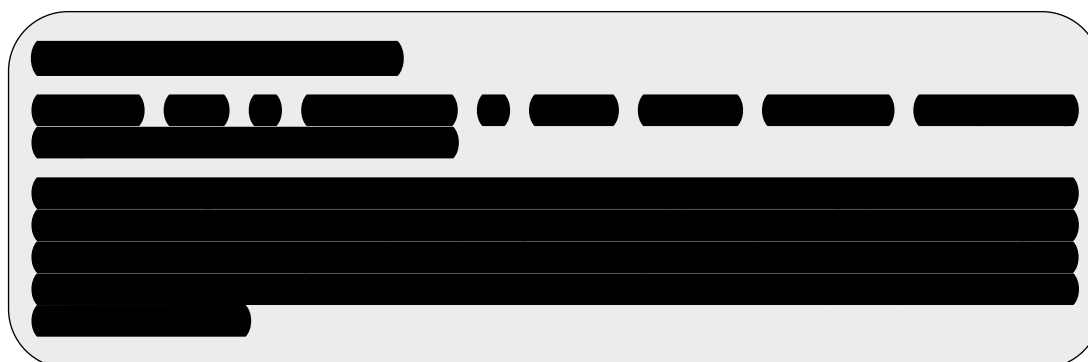
Health economic evaluation

The GDG considered this topic a low priority for health economic analysis.

Qualifying statement

The recommendations concerning corticosteroids are based on expert opinion and evidence from case control and cohort studies, supplemented by extrapolated evidence from RCTs of the use of radiotherapy for cerebral metastases from other disease sites.

The use of targeted agents (for example epidermal growth factor receptor inhibitors) in the treatment of cerebral metastases, has been described in case reports and small series of patients with lung cancer. However, further research is required, and given the low quality of the evidence, no recommendation can currently be made regarding their use.



8.6 Spinal Cord Compression

Compression of the spinal cord, typically by metastatic epidural cancer, can lead to neurological impairment and paraplegia. At the time of diagnosis the most common symptom is pain, followed by weakness, autonomic dysfunction or sensory loss.

This topic was not updated in the 2011 update and the reader is referred to the recently published NICE clinical guideline for Metastatic spinal cord compression: diagnosis and management of patients at risk of or with metastatic spinal cord compression <http://guidance.nice.org.uk/CG75>

8.7 Hypercalcaemia, Bone Pain and Pathological Fractures

A HTA report has been published on treatments for hypercalcaemia². Bone is one of the most frequent sites of metastasis in lung cancer and can result in pain and pathological fracture. Methods of treating bone metastases include radiotherapy, bisphosphonates and nerve blocks. Increasingly, orthopaedic interventions can be considered, e.g. vertebroplasty. This topic has not been updated and the 2005 recommendations are reproduced below.

² Ross JR et al. (2004) A systematic review of the role of bisphosphonates in metastatic disease.

Recommendation

- For patients with bone metastasis requiring palliation and for whom standard analgesic treatments are inadequate, single-fraction radiotherapy should be administered. [2005]

8.8 Other symptoms: weight loss, loss of appetite, difficulty swallowing, fatigue and depression

A thorough assessment is important to guide appropriate management by members of the multidisciplinary team providing holistic supportive and palliative care. The topic was not reviewed as part of the 2011 update.

Recommendation

- Other symptoms, including weight loss, loss of appetite, depression and difficulty swallowing, should be managed by multidisciplinary groups that include supportive and palliative care professionals. [2005]

References

- Aoyama, H. Tago, M. Kato, N. Toyoda, T. Kenjyo, M. Hirota, S. *et al.* (2007). Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *International Journal of Radiation Oncology Biology Physics*, 68, 1388-1395.
- Chua, D. Krzakowski, M. Chouaid, C. Pallotta, M. G. Martinez, J. I. Gottfried, M. Curran, W. and Throuvalas, N. Whole-brain radiation therapy plus concomitant temozolomide for the treatment of brain metastases from non-small-cell lung cancer: a randomized, open-label phase II study. *Clin Lung Cancer* 11[3], 176-181. 2010.
- Dae, H. L. Primary chemotherapy for newly diagnosed nonsmall cell lung cancer patients with synchronous brain metastases compared with whole-brain radiotherapy administered first: Result of a randomized pilot study. *Cancer* 113[1], 143-149. 2008.
- Fuentes, R. Bonfill, C. X, & Expósito, H. J. (2006). Surgery versus radiosurgery for patients with a solitary brain metastasis from non-small cell lung cancer. *Cochrane Database of Systematic Reviews: Reviews*. In *Cochrane Database of Systematic Reviews 2006 Issue 1* (Chichester (UK): John Wiley & Sons, Ltd.
- Gerosa, M. Nicolato, A. Foroni, R. Tomazzoli, L. & Bricolo, A. (2005). Analysis of long-term outcomes and prognostic factors in patients with non-small cell lung cancer brain metastases treated by gamma knife radiosurgery. *Journal of Neurosurgery*, 102 Suppl, 75-80.
- Guerrieri, M. Wong, K. Ryan, G. Millward, M. Quong, G. & Ball, D. L. (2004). A randomised phase III study of palliative radiation with concomitant carboplatin for brain metastases from non-small cell carcinoma of the lung. *Lung cancer (Amsterdam, Netherlands)*, 46, 107-111.
- Kepka, L. Cieslak, E. Bujko, K. Fijuth, J. & Wierzchowski, M. (2005). Results of the whole-brain radiotherapy for patients with brain metastases from lung cancer: the RTOG RPA intra-classes analysis. *Acta Oncologica*, 44, 389-398.
- Kim, D. Y. Lee, K. W. Yun, T. Kim, D. W. Kim, T. Y. Heo, D. S. *et al.* (2005). Efficacy of platinum-based chemotherapy after cranial radiation in patients with brain metastasis from non-small cell lung cancer. *Oncology Reports*, 14, 207-211.
- Lee, D. H. Han, J. Y. Kim, H. T. Yoon, S. J. Pyo, H. R. Cho, K. H. *et al.* (2008). Primary chemotherapy for newly diagnosed nonsmall cell lung cancer patients with synchronous brain metastases compared with whole-brain radiotherapy administered first : result of a randomized pilot study. *Cancer*, 113, 143-149.
- Liu, R. F. Wang, X. H. Ma, B. Yang, K. H. Zhang, Q. N. and Tian, J. H. Concomitant or adjuvant temozolomide with whole-brain irradiation for brain metastases: a meta-analysis. *Anti-Cancer Drugs* 21[1], 120-128. 2010.
- Mallick I, Sharma SC, Behera D, Ghoshal S, Oinam AS. (2006). Optimization of dose and fractionation of endobronchial brachytherapy with or without external radiation in the palliative management of non-small cell lung cancer: A prospective randomized study. *J Can Res Ther* [serial online; cited 2010 Jun 17];2:119-25. Available from: <http://www.cancerjournal.net/text.asp?2006/2/3/119/27586>.
- Mehta, M. P. Rodrigus, P. Terhaard, C. H. Rao, A. Suh, J. Roa, W. *et al.* (2003). Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 21, 2529-2536.
- Mehta, M. P. Shapiro, W. R. Phan, S. C. Gervais, R. Carrie, C. Chabot, P. Patchell, R. A. Glantz, M. J. Recht, L. Langer, C. Sur, R. K. Roa, W. H. Mahe, M. A. Fortin, A. Nieder, C. Meyers, C. A. Smith, J. A. Miller, R. A. and Renschler, M. F. Motexafin gadolinium combined with prompt whole brain radiotherapy prolongs time to neurologic progression in non-small-cell lung cancer patients with brain metastases: results of a phase III trial. *International Journal of Radiation Oncology, Biology, Physics* 73[4], 1069-1076. 2009.

- Meyers, C. A. Smith, J. A. Bezjak, A. Mehta, M. P. Liebmann, J. Illidge, T. *et al.* (2004). Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 22, 157-165.
- Neuhaus, T. Ko, Y. Muller, R. P. Grabenbauer, G. G. Hedde, J. P. Schueller, H. *et al.* (2009). A phase III trial of topotecan and whole brain radiation therapy for patients with CNS-metastases due to lung cancer. *British Journal of Cancer*, 100, 291-297.
- Quantin, X. Bozonnat, M. C. and Pujol, J. L. Recursive Partitioning Analysis Groups II-III Brain Metastases of Non-small Cell Lung Cancer A Phase II Randomized Study Comparing Two Concurrent Chemoradiotherapy Regimens. *Journal of Thoracic Oncology* 5[6], 846-851. 2010.
- Rades, D. Schild, S. E. Lohynska, R. Veninga, T. Stalpers, L. J. & Dunst, J. (2007). Two radiation regimens and prognostic factors for brain metastases in nonsmall cell lung cancer patients. *Cancer*, 110, 1077-1082.
- Serizawa, T. (2009). Metastatic brain tumors: lung cancer. *Progress in Neurological Surgery*, 22, 142-153.
- Slotman, B. J. Mauer, M. E. Bottomley, A. Faivre-Finn, C. Kramer, G. W. Rankin, E. M. *et al.* (2009). Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. *Journal of Clinical Oncology*, 27, 78-84.
- Sperduto, P.W.; Chao, S.T.; Sneed, P.K.; Luo, X.H.; Suh, J.; Roberge, D.; Bhatt, A.; Jensen, A.W.; Brown, P.D.; Shih, H.; Kirkpatrick, J.; Schwer, A.; Gaspar, L.E.; Fiveash, J.B.; Chiang, V.; Knisely, J.; Sperduto, C.M.; Mehta, M. (2010). Diagnosis-Specific Prognostic Factors, Indexes, and Treatment Outcomes for Patients with Newly Diagnosed Brain Metastases: A Multi-Institutional Analysis of 4,259 Patients. *International Journal of Radiation Oncology Biology Physics*, 77, 655-661.
- Suh, J. H. Stea, B. Nabid, A. Kresl, J. J. Fortin, A. Mercier, J. P. *et al.* (2006). Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 24, 106-114.
- Sundaresan, P. Yeghiaian-Alvandi, R. and Gebiski, V. Prognostic index to identify patients who may not benefit from whole brain radiotherapy for multiple brain metastases from lung cancer. *Journal of Medical Imaging and Radiation Oncology* 54[1], 69-75. 2010.
- Tang, S. G. Tseng, C. K. Tsay, P. K. Chen, C. H. Chang, J. W. Pai, P. C. *et al.* (2005). Predictors for patterns of brain relapse and overall survival in patients with non-small cell lung cancer. *Journal of Neuro-Oncology*, 73, 153-161.
- Videtic, G. M. Adelstein, D. J. Mekhail, T. M. Rice, T. W. Stevens, G. H. Lee, S. Y. *et al.* (2007). Validation of the RTOG recursive partitioning analysis (RPA) classification for small-cell lung cancer-only brain metastases. *International Journal of Radiation Oncology, Biology, Physics*, 67, 240-243
- Videtic, G. M. Reddy, C. A. Chao, S. T. Rice, T. W. Adelstein, D. J. Barnett, G. H. Mekhail, T. M. Vogelbaum, M. A. S. and Suh, J. H. Gender, race, and survival: a study in non-small-cell lung cancer brain metastases patients utilizing the radiation therapy oncology group recursive partitioning analysis classification. *International Journal of Radiation Oncology, Biology, Physics* 75[4], 1141-1147. 15-11-2009.

9 Follow-up and patient perspectives

Clinical topic: What is the most effective follow-up model for lung cancer patients?

This section refers to the review of patients following completion of treatment or where patients are given best supportive care. The value of follow-up in lung cancer includes monitoring of treatment outcomes and complications, detection of relapse and recurrence, detection and management of symptoms, provision of information and provision of supportive and palliative care. The emphasis on the purpose of follow-up will differ depending on which modality of treatment has been given. When treatment with curative intent has been given there will be more emphasis on detection of recurrent disease whereas if there has been active treatment with palliative intent there may be a focus on detection of disease progression and symptom control. If no active treatment has been offered then follow-up will be directed towards symptom control. The 2005 guideline included clinical practice recommendations on lung cancer follow-up and noted that there was a paucity of evidence in this field. Some recommendations from the 2005 guideline have been modified and included with the current recommendations.

Recommendations

- Offer all patients an initial specialist follow-up appointment within 6 weeks of completing treatment to discuss ongoing care. Offer regular appointments thereafter, rather than relying on patients requesting appointments when they experience symptoms. [NEW 2011]
- 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. [NEW 2011]
- Ensure that patients know how to contact the lung cancer clinical nurse specialist involved in their care between their scheduled hospital visits. [NEW 2011]

Clinical evidence

The search conducted for this topic identified three retrospective studies of low quality (Nakamura et al., 2010; Virgo et al., 1995; Younes et al., 1999). In a sample of 1398 patients who had undergone surgery for NSCLC Nakamura et al. (2010) found that follow up by thoracic surgeons conferred an independent increased hazard of death relative to follow up by chest physicians. Virgo et al. (1995) examined in patients with stage I-IIIa lung cancer treated with curative intent whether a number of outcomes differed between those who received an intensive follow up schedule (N = 120) and those who received a non-intensive follow up schedule (N = 62). Length of follow up and baseline characteristics of the groups were comparable with the exception that the intensively followed up group had significantly more comorbidities and a significantly longer disease-free interval than the non-intensively followed up patients. Intensity of follow up did not significantly influence time to detection

Clinical evidence (cont.)

of local or regional recurrences, time to detection of second primary, time to detection of metastases, survival (for all patients or for stage I patients only), survival after detection of local or regional recurrence, survival after detection of second primary, survival after detection of metastases, local and regional recurrences, second primaries, metastases, and multiple metastases. In patients who had undergone complete operative and pathologic resection of non small cell lung cancer Younes et al. (1999) found that disease-free survival and survival after recurrence did not differ between patients who had followed a strict (N = 67) or symptom-based (N = 63) follow up schedule, but the patients who received symptom-based follow up experienced more (health problem) episodes detected in the emergency room, had more health problems treated on an inpatient basis and spent more days as an inpatient for health problems compared to the patients receiving a strict follow up schedule, who on the other hand had more health problems treated on an outpatient basis.

Health economic evaluation

This topic was a medium priority for health economic analysis because although intensive follow-up can be expensive, and also has a high opportunity cost, the health benefits of follow-up are difficult to ascertain and high quality clinical evidence is unlikely to be found. Therefore, because of feasibility concerns, no economic analysis was undertaken.

Qualifying statement

These recommendations are based on low quality comparative studies. The paucity of evidence precludes firm evidence-based recommendations. However the evidence did show that regular follow-up results in fewer crisis driven health related episodes. Such episodes are distressing to patients and carers not least because the emergency admission process is often difficult and in the UK at least, often leads to inpatient management by non-specialists. It is therefore likely that this recommendation will benefit patients and lead to more effective use of NHS resources. There were several studies identified that have looked at the use of specific interventions in the setting of follow-up. Unfortunately none of the studies is of sufficient quality to allow evidence based recommendations.

The issue of timing of follow-up remains unclear and hence the Guideline Development Group (GDG) made consensus recommendations.

Research Recommendations

Randomised controlled trials should be conducted to examine the value of imaging modalities and other interventions in the monitoring of response and recurrent disease. **[NEW 2011]**

Randomised controlled trials should be conducted examining the value of different follow-up patterns. **[NEW 2011]**

The use of prognostic factors to develop risk stratification models to determine the optimal follow-up pattern should be examined as part of large clinical trials. **[NEW 2011]**

9.1 The Patient's Perspective

The Department of Health publication recommended that services be 'patient centred'. This document paved the way for cancer patient involvement in service provision.¹ Recently strategies have been produced, setting a framework to achieve this. In England, the relevant document is *Involving Patients and the Public in Healthcare* (2001) and in Wales, *Signposts – A Practical Guide to Public and Patient Involvement in Wales* (2001). These strategies underline the benefits of service user involvement in improving outcomes of health care, increasing patient satisfaction and in strengthening public confidence in the NHS. They provide a framework for patients and the public to be involved both at a collective /strategic level and on an individual basis.

Involvement in service provision is, broadly speaking, achieved in two ways:

- Patient consultation through surveys and questionnaires or through patient focus groups.
- Active partnership with user representatives as members of committees or working groups.

Although lung cancer is the most common cancer diagnosis in the UK, there are currently very few patient representatives involved in service planning and delivery. There are, inherent within this disease, a number of barriers to such patient involvement. With a median survival of four months from diagnosis, around 80% of patients are dead at one year, with only around 7% surviving five years, the average lung cancer patient may not survive the length of the working group. Furthermore, as most people with lung cancer are not only elderly but also less fit than their contemporaries, often suffering from smoking-related illnesses, they may be too ill to attend meetings.

However, certain organisations (such as the Roy Castle Lung Foundation and Macmillan Cancer Support) are involved in patient advocacy issues for lung cancer patients and endeavour to harness the spectrum of patient views with an eye to shaping future cancer services and research.

9.1.1 Lung Cancer Patient Opinions

Within the NHS, the experiences and needs of patients and families living with a diagnosis of lung cancer have been collected in the following initiatives:

Cancer Service Patient Survey

In July 2002 a survey on cancer services eliciting the views of more than 65,000 patients (74% of those approached), was published. 4,000 (6%) of respondents were lung cancer patients. The survey showed that, in most cases, patients were receiving high levels of care - for example, 86% had complete confidence in their doctors; 79% felt they were treated with respect and dignity at all times. However, the survey highlighted variations between Trusts.

The patients surveyed came from 172 NHS Trusts in England and questions related to care received between July 1999 and June 2000. As the National Cancer Plan (2000) was published after the survey was carried out, the findings will act as a baseline, upon which improvements can be measured at the individual Trust level. Of the 65,000 views, only 4000 (6%) were from lung cancer patients.

Patient Reported Outcomes (PROMS)

PROMs are wider than patient experience of care and include measures of activity, specific symptoms, longer term effects of treatment and comprehensive tools to measure quality of life (QOL). Apart from QOL measures (which are difficult to use in routine clinical practice) there are no validated PROMs for lung cancer despite the fact that they could be key to understanding, monitoring and ensuring that patients have the best possible outcomes of care over and above simple survival. PROMs have yet to be developed for specific cancers and

¹ Department of Health (2007) *World class commissioning. Vision*. London. Department of Health. Available from http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_080956

perhaps specific treatment groups. There is an urgent need for the development and validation of useful PROMs for lung cancer.

Cancer Services Collaborative Patient Experience Projects

In England, as part of the Cancer Services Collaborative, a number of projects have measured how patients rate their care and have monitored the impact of system changes. A key area has been to improve communication between patients and their clinical team. This has been achieved in a variety of ways, including written patient information booklets, patient held records and taped consultations. The Service Improvement Manuals (produced by the NHS Modernisation Agency), including the Lung Cancer Manual, give details of individual projects and how changes have resulted in improvement.

Patients with lung cancer have reported experiencing greater levels of unmet psychological, social and economic needs than other cancer groups. They have also been less satisfied, than other people with cancer, with the care received. A national needs assessment of lung cancer patients and carers, undertaken on behalf of Macmillan Cancer Support, identified a myriad of deficiencies in the organisation of care delivery and in areas of information and support.

As part of this Guideline process, The Roy Castle Lung Cancer Foundation (RCLCF), in association with the National Collaborating Centre for Acute Care, collected experiences and opinions from 61 lung cancer patients and carers. Full details of this are available on the RCLCF website (www.roycastle.org). General themes expressed by this group, on the organisation of services, included:

- Accessing services – respondents expressed a desire to have speedy access to specialist services, with the overwhelming majority favouring the rapid access diagnostic clinic approach. Many also reported a willingness to travel considerable distances to access the most specialist services.
- Respondents also placed emphasis on seeing the same doctor at every hospital visit.
- The importance of accessing a lung cancer support nurse, throughout the treatment journey.
- Continuing care – Few in this group had accessed community based support services, those who did rated them highly.

More work is needed to establish the specific opinions of lung cancer patients and carers, on the organisation of lung cancer services.

9.1.2 Monitoring the Effects of Patient Involvement

As with the Cancer Services Collaborative Patient Experience Projects, there are many individual examples of patient views being surveyed and the results contributing to service changes in a number of settings. There is, however, no evidence of such involvement directly improving the quality of care or the outcome for patients. The challenge, therefore, as lay involvement continues to be embedded within health services, is to ensure that it is appropriate, representative and having its impact monitored.

The review of NHS Cancer Care in England and Wales, published in December 2001 and undertaken by the Commission for Health Improvement (CHI) and the Audit Commission (AC), concluded that cancer services still have a long way to go before they are truly 'patient focused'. This review, however, only addressed the progress in implementing recommendations of the 1995 Calman-Hine report, A Policy Framework for Commissioning Cancer Services. It did not take into account the multiple policy changes and initiatives, which have taken place in the intervening years.

At a local level, systems need to be in place to ensure that the opinions and experiences of lung cancer patients and carers are collected. Further work is needed to ensure that such patient involvement is meaningful and that lung cancer services improve as a result. The GDG made a good practice point that the opinions and experiences of lung cancer patients and carers should be collected and used to improve the delivery of lung cancer services. Patients should receive feedback on any action taken as a result of such surveys.

Recommendation

- The opinions and experiences of lung cancer patients and carers should be collected and used to improve the delivery of lung cancer services. Patients should receive feedback on any action taken as a result of such surveys. [2005]

References

- Nakamura, R. Kurishima, K. Kobayashi, N. Ishikawa, S. Goto, Y. Sakai, M. Onizuka, M. Ishikawa, H. Satoh, H. Hizawa, N. & Sato, Y. (2010). Postoperative Follow-Up for Patients with Non-Small Cell Lung Cancer. *Onkologie* 33 (1-2):14-18.
- Virgo, K. S. McKirgan, L. W. Caputo, M. C. A. Mahurin, D. M. Chao, L. C. Caputo, N. A. Naunheim, K. S. Flye, M. W., Gillespie, K. N. & Johnson, F. E. (1995) Posttreatment Management Options for Patients with Lung-Cancer. *Annals of Surgery*, 222: 700-710.
- Younes, R. N. Gross, J. L. & Deheinzelin, D. (1999) Follow-up in lung cancer: how often and for what purpose?[see comment]. *Chest*, 115: 1494-1499.

3. Cardiothoracic (surgical) Nurse Specialist:

- a) Do you have access to a Thoracic Nurse specialist? Yes/no
- b) if so, do they see patients pre-operatively? Yes/no
- c) Does the patient get a telephone number to contact with post-operative concerns? Yes/no
- d) Are there nurse-led post-op clinics? Yes/no

4. Availability of specialist services:

- a) Please confirm which of the following services are available either within your hospital, your NHS Trust, your lung cancer network, or at a higher regional level.
(please tick appropriate column)

If services are **not available** at your hospital; please indicate the distance from your hospital to the treatment site and the approximate waiting time to utilise the specialist service (**1**, < 1 week; **2**, 1-2 weeks; **3**, >2 weeks)

	<i>Available?</i>				Distance (miles)	Waiting time?
	Hospital	NHS Trust	Network	Region		
PET scanning						
<i>Interventional bronchoscopy</i>						
TBNA						
EBUS						
EUS						
Endobronchial stenting						
Electrocautery						
Laser therapy						
Cryotherapy						
Photodynamic therapy (PDT)						
Brachytherapy						
<i>Thoracoscopy</i>						
Medical (LA)						
Surgical (VATS)						
<i>Other services</i>						
Mediastinoscopy						
Pulmonary rehabilitation						
Specialist SOB clinics						
<i>Treatment options</i>						
CHART						
Radical RTx						
Palliative RTx						
Chemotherapy						
Thoracic surgery						

Legend: TBNA; TransBronchial Needle Aspiration;
 EBUS; EndoBronchial UltraSound (needle biopsy)
 EUS; Endoscopic UltraSound (needle biopsy)
 SOB; Shortness of breath
 RTx; Radiotherapy

- b) Please indicate the pathology 'turn around' time;
 Diagnostic samples _____ (days)
 Surgical samples _____ (days)

5. **MDT decision making:**

- a) How many patients were discussed at your MDT in 2009? _____
 b) How many/what percentage of these patients had a PET scan? _____
 c) How many/what percentage of the total number actually received radical treatment? _____
 d) Of those patients receiving radical treatment,
 What percentage received surgery? _____
 What percentage received radical radiotherapy? _____
 e) What percentage of patients enter clinical trials? <5% 5-10% >10%

6. **Administrative support:**

- a) Does your Trust have an MDT co-ordinator? Yes/no
 b) Does your Trust have an electronic database? Yes/no
 c) Does your Trust have a data administrator? Yes/no
 d) Does your Trust routinely upload information to LUCADA? Yes/no

Appendix 2

Summary of the 7th edition of the TNM staging system in comparison with the 6th edition

6 th edition	7 th Edition	
Stage modified	New stage	Descriptor
T1	T1a T1b	maximum dimension ≤2 cm maximum dimension 2-3 cm
T2	T2a T2b T3	maximum dimension 3-5 cm maximum dimension 5-7 cm maximum dimension >7 cm
T4	T3	additional nodule in same lobe
M1	T4	additional nodule in ipsilateral different lobe
M1	M1a	additional nodules in contralateral lung
M1	M1a	ipsilateral pleural effusion

Surgical stage groupings in 7th TNM classification

Stage Group	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1a, b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T1a, b	N1	M0
	T2a	N1	M0
	T2b	N0	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1, T2	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	M1a, b

Appendix 3

Questions for histopathologists regarding update of nice lung cancer guideline

1. In your practice, in what proportion of cases do you think that the following needle aspiration samples will enable you to differentiate between adenocarcinoma and non-adenocarcinoma?
 - a. Blind TBNA
 - b. EBUS and EUS
 - c. Lung needle aspiration
 - d. Cervical / other node sampling and the following biopsy samples?
 - e. Lung needle biopsy
 - f. Cervical/other node sampling
 - g. Bronchoscopic endobronchial biopsy
 - h. Mediastinoscopy
 - i. Surgical resection specimen
2. In your practice, in what proportion of cases do you think that the following needle aspiration samples will enable you to define EGFR status / mutation status?
 - a. Blind TBNA
 - b. EBUS and EUS
 - c. Lung needle aspiration
 - d. Cervical / other node sampling and the following biopsy samples?
 - e. Lung needle biopsy
 - f. Cervical/other node sampling
 - g. Bronchoscopic endobronchial biopsy
 - h. Mediastinoscopy
 - i. Surgical resection specimen
3. Are there any new laboratory techniques developed/in development that will improve this?
4. Are there specific sampling or processing techniques that may improve differentiation of different tumour types?
5. Given that tumour type is likely to influence treatment choice in the future, how do you think that the Tissue Pathways for Pulmonary Pathology will address issues of tumour type?
6. In studies that have defined tumour types, how robust was the typing, in comparison with the methods applied to needle cytology samples?
7. Regarding specialist skills:
 - a. Do most pathologists possess the skills to achieve results of the same order that you describe?
 - b. Are your skills easily transferrable

- c. What is required to provide a basic service?
- d. What is the requirement for a specialist referral service?
- 8. Considering a potential improvement in treatment outcome, under what circumstances would it be appropriate to change or add to the diagnostic pathway so as to provide an additional or larger sample?
- 9. In what way will the reclassification of bronchioloalveolar cell carcinoma influence treatment and samples required?
- 10. Do you have any specific recommendations on tumour typing in relation to cytology samples that you would wish included in the 2011 NICE Lung Cancer Guideline Update?

Appendix 4

Economic model to compare different testing strategies to stage the mediastinum in patients with NSCLC

Background

In the 2005 NICE Lung cancer guideline, the staging of non-small cell lung cancer (NSCLC) was prioritised for independent economic modelling. Several years later, this issue remains high on the agenda in terms of the need to review the latest evidence on the clinical effectiveness of staging procedures and to re-assess their cost-effectiveness, particularly when the tests are considered in sequence.

The annual incidence of lung cancer in the UK currently stands at over 38,000 and the vast majority of these patients (as well as others with suspected lung cancer) will undergo one or more procedures to determine a diagnosis and stage. Accurate diagnostic and staging information, particularly of mediastinal disease, helps the clinician decide which patients are suitable for treatment with curative intent; mediastinal lymph-node involvement reduces the chance of surgery being curative. Since 2005 a number of minimally invasive techniques have started to be used in some centres, but at a higher cost than older biopsy procedures. PET-CT scanners are now routinely available but a question remains over where best to use them in the diagnostic and staging pathway.

As well as influencing the choice of treatment and the resulting effect on health outcomes, there are also differences in health outcomes associated with the diagnostic procedures themselves. Transbronchial needle aspiration (TBNA), endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS) are performed on an outpatient basis and are associated with lower morbidity than surgical procedures. It is also reasonable to assume that there might also be health benefits to patients if they avoid unnecessary diagnostic staging procedures. All these factors will be important to take into account in an independent modelling exercise to evaluate the cost-effectiveness of different staging tests.

Although published economic evaluations assessing the cost-effectiveness of diagnostic tests and staging procedures exist, none adequately investigate the best sequence in which to use them. Uncertainty surrounding utility values used to estimate quality of life remains a concern, and will be explored using sensitivity analysis.

Existing Economic Evidence

As reported in the 2005 guideline, economic evaluations in the literature have focused on assessing the cost-effectiveness of imaging for staging patients with NSCLC, particularly the role of FDG-PET. The general consensus seems to be that PET compared to no PET (or CT) is cost-effective in different settings; Germany, US, the Netherlands, Switzerland, France, Italy, Canada and Australia (Dietlein et al, 2000, Gambir et al, 1996, Scott et al, 1998, Verboom et al 2003, Von Schulthess et al, 1998, Mansueto et al, 2007, Nguyen et al, 2005, Yap et al, 2005).

The economic modelling conducted in the 2005 lung cancer guideline compared PET, mediastinoscopy and thoracotomy for all in patients suitable for surgery and in a separate analysis compared PET with no PET for patients otherwise suitable for radical radiotherapy. The results showed that PET and selective mediastinoscopy was cost-effective compared with the strategy of proceeding directly to thoracotomy in patients with no evidence of mediastinal or metastatic disease on CT, with an incremental cost-effectiveness ratio (ICER) of £7,200 per

QALY gained. The estimated incremental cost-effectiveness of the PET strategy compared with the radical radiotherapy strategy was £9,500 per QALY gained. These models were based on an economic evaluation conducted by the Health Technology Board for Scotland (Bradbury et al, 2002) which has recently been updated to extend the original decision model and include patient-elicited utilities for FDG-PET (+ if negative mediastinoscopy) vs. mediastinoscopy for all (Kee et al, 2010). The updated model confirmed the apparent cost-effectiveness of FDG-PET and indicated that the expected value of perfect information (EVPI) associated with the utility of futile thoracotomy considerably exceeds that associated with measures of test accuracy.

A broad search of the literature revealed no full economic evaluations that have investigated the cost-effectiveness of the less invasive techniques for staging mediastinal disease. The ASTER trial which reported its clinical findings in 2010, has a health economic component which should provide information on the cost-effectiveness of EUS-FNA and EBUS-TBNA compared to mediastinoscopy and report in 2011.

Thus independent economic modelling was judged to be appropriate for this topic given its clinical importance, the potential financial impact on the NHS and in the absence of any published studies investigating the cost-effectiveness of different test sequences. Reasons for the priority given to this topic over others are outlined in detail in the accompanying Economic Plan which can be found in the evidence review which accompanies this guideline.

Aim of analysis

To assess the cost utility of clinically relevant alternative sequences of tests (listed in section 3.2.1) to stage the mediastinum in three subgroups of patients with non-small cell lung cancer (detailed in section 3.1) from a UK NHS perspective. See table A4.1.

Methods

Study population

Separate analyses were carried out on three hypothetical patient populations constructed to represent the spectrum of patients that are diagnosed with NSCLC and require investigations to determine disease stage. These were defined as follows:

- (i) Low prevalence group – patients in this group have no enlarged nodes on CT (may have <10mm short axis nodes)
- (ii) Intermediate prevalence group - patients in this group have small volume nodes on CT (defined as one or more mediastinal lymph nodes of 10-19mm short axis)
- (iii) High prevalence group – patients in this group have bulky N2 disease on CT (defined as any node \geq 20mm)

All patients are assumed to have had a standard diagnostic work-up, including CT.

Diagnostic/staging interventions

The following interventions were considered as part of the staging sequences:

- Surgical procedure:
 - o Mediastinoscopy (Med)
- Bronchoscopy/biopsy procedures:
 - o Transbronchial needle aspiration (TBNA)
 - o Endobronchial ultrasound (EBUS)
- Radiology/Imaging:
 - o PET-CT
- Ultrasound:
 - o of the neck (Neck US)

Other tests considered in the clinical review such as MRI, Bone scintigraphy, SPECT, VATS and TTNA are not commonly used for assessing nodal status so were excluded from the analysis.

Mediastinoscopy (biopsy under general anaesthetic (GA)) is a surgical procedure and is associated with a relatively high morbidity, compared with minimally invasive tests. Tests performed before mediastinoscopy are used with the aim of reducing the number of patients undergoing this procedure.

TBNA is a less invasive alternative to mediastinoscopy, but because it does not involve real-time guidance, is less reliable in sampling smaller nodes. EBUS and EUS are relatively new techniques which are used to sample mediastinal lymph nodes and intra parenchymal parabranchial lung masses. The choice of whether to use EUS or EBUS is determined by the lymph node station where disease is suspected. TBNA, EUS and EBUS are all usually performed under conscious sedation and occasionally a GA is needed for EUS/EBUS, usually as a day case procedure. Neck US is commonly used for picking up advanced disease (it is cheap and highly sensitive for N3 disease).

PET-CT is the only test amongst these that is able to detect metastatic disease (the 'M' of the TNM classification). It also gives the clinician valuable information about the nodal disease status of a patient. However the information provided by PET-CT is not usually definitive and, according to the opinion of the GDG, would almost always be followed by another test. Given that the implications of both a positive and a negative result for N disease are the same – we exclude the test result for N disease from PET-CT in the model. Therefore for the purposes of the model, PET-CT only provides information on the presence of metastatic disease. In clinical reality the information from a PET-CT scan may influence the choice of the next test, but it was not considered possible to include this level of detail in the economic model. It is also worth noting that combined PET-CT has replaced PET alone as the standard PET scanning equipment in the NHS.

CT alone (i.e. a 'no further test' strategy) is not included since surgery would not be carried out on the basis of this information alone. Repeat tests are infrequent, so are not considered in this analysis.

Testing strategies

The testing strategies follow the logic outlined below:

- Tests for nodal disease:
 - o If test is positive – treat as N2/3.
 - o If test is negative – move on to next test.
- Tests for metastatic disease:
 - o If test is positive – treat as M1.
 - o If test is negative – move on to next nodal test or treat as M0,N0/1 (depending on strategy).

Not all staging strategies were considered by the GDG to be clinically relevant alternatives in each population subgroup. Therefore the strategies considered in each analysis differ.

Table A4.1: Strategies considered in each subgroup analysis

Strategies	LOW prevalence group	INTERMEDIATE prevalence group	HIGH prevalence group
X PET-CT	√		
1 PET-CT Med	√	√	√
2 PET-CT TBNA	√	√	
3 PET-CT EBUS	√	√	
4 PET-CT TBNA EBUS	√	√	
5 PET-CT TBNA Med	√	√	
6 PET-CT EBUS Med	√	√	
7 PET-CT TBNA EBUS Med	√	√	
8 TBNA PET-CT		√	√
9 EBUS PET-CT		√	√
10 Med PET-CT		√	√
11 Neck US PET-CT Med		√	√
12 EBUS PET-CT Med		√	√
13 Neck US TBNA PET-CT		√	√
14 Neck US EBUS PET-CT		√	√
15 Neck US Med PET-CT		√	√
16 TBNA EBUS PET-CT		√	√
17 EBUS Med PET-CT		√	√
18 Neck US TBNA PET-CT Med		√	√
19 Neck US EBUS PET-CT Med		√	√
20 TBNA EBUS PET-CT Med		√	√
21 TBNA EBUS Med PET-CT		√	√
22 Neck US TBNA EBUS PET-CT		√	√
23 Neck US TBNA Med PET-CT		√	√
24 Neck US EBUS Med PET-CT		√	√
25 Neck US TBNA EBUS PET-CT Med		√	√
26 Neck US TBNA EBUS Med PET-CT		√	√

Outcome of tests

The aim of the staging tests considered in the model (excluding PET-CT) is to determine the status of nodes in the chest; that is to determine the 'N' of the TNM classification system, presented in table A4.2 below.

Table A4.2: N descriptors from TNM classification (version 6)

N descriptor	Description
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 subcranial lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

The outcomes of the tests are classified as positive if N2/3 disease and negative if N0/1. This classification is the most common method of reporting test accuracy data of mediastinal staging in the published literature. The possibilities of a positive result for a benign diagnosis (very rare in the population of interest) or a non-diagnostic result (i.e. node not adequately sampled) are excluded from the economic model.

The new staging system (Rusch et al., 2007) is unchanged in N descriptors but introduces the concept of zones in N disease. However the clinical evidence does not report results in terms of nodal zones and there remains considerable debate about impact of nodal zones on determining whether patients should or should not be offered treatment with curative intent. Given that the impact of the new staging system is not clear, it has not been considered in the economic model.

PET-CT identifies metastatic disease as shown in table A4.3 below. In the new staging system the fact that patients with distant metastases have a worse prognosis than those with local metastases (contralateral lung nodule(s), ipsilateral malignant pleural disease or pericardial disease) is reflected in the designations M1a for local metastases and M1b for distant. For the purposes of this economic evaluation, M1a and M1b were merged. The results of PET-CT are classed as positive if M1 (both a and b) and negative if M0.

Table A4.3: M descriptors from the TNM classification (version 7, Postmus et al., 2007)

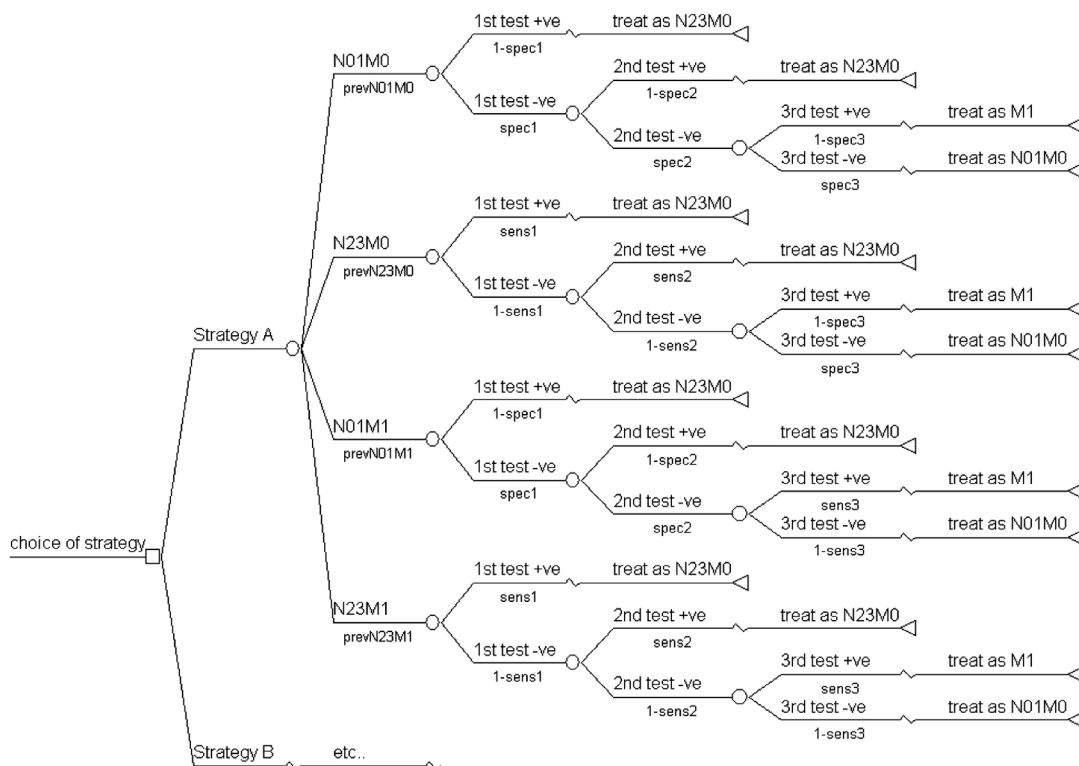
M descriptor	Description
M0	No distant metastasis
M1a	Local metastasis
M1b	Distant metastasis

Structure of the model

The model was built using TreeAge Pro 2009 software. A decision tree approach was taken to model the staging alternatives with an embedded Markov process to model the longer term consequences resulting from treatment. Read from left to right, the decision tree outlines the complex sequences of clinical alternatives for each strategy (see figure A4.1).

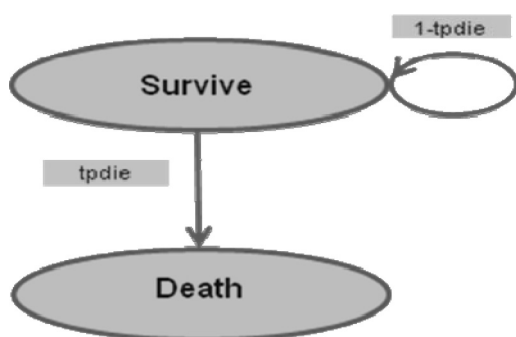
Tree inversion was used to perform Bayes' probability revision (Hunink 2001, p.144). Using this method the decision tree does not depict events in chronological order. Instead the tree starts with the true disease stage defined at the outset (i.e. N0/1 M0, N2/3 M0, N0/1 M1 and N2/3 M1) followed by the possible test results, using the sensitivities and specificities of the tests (as shown in figure A4.1).

Figure A4.1: Decision tree outline for hypothetical strategy A (1st test for N disease, 2nd test for N disease, 3rd test for metastatic disease)



The Markov model at the end of the decision tree branch (not shown in figure A4.1) is a simplified version of the natural progression of disease, accounting only for the possibility of death (see figure A4.2). Different stages of disease progression (and associated reduction in quality of life) are not captured. The cycle length of one month was chosen during which patients face a probability of dying (*tpdie*). A half-cycle correction was applied following standard methodological guidance (Briggs et al, 2006) so that all deaths are assumed to occur halfway through the monthly cycle.

Figure A4.2: Structure of embedded Markov model



Since the NLCA database provided the survival data for the model (described below) death can occur from the disease itself (lung cancer) or any other cause (including surgical complications). Death can also occur in the model (within the decision tree) as a result of mediastinoscopy.

Several assumptions are implicit in the way the model has been structured:

- the diagnostic and staging work-up is rapid, so the length of a testing strategy is assumed to have no influence on overall outcomes for patients
- the choice between EUS and EBUS (e.g. in stations 2L, 4L, 7) is not modelled
- the staging procedures are conditionally independent (that is the results of each test are independent of each other but dependent on the presence or absence of disease)
- if a test is positive, no confirmatory tests are required
- the choice of treatment is solely determined by the result of the final test.

The decision about which treatment to offer patients on the basis of the staging test results will not be evaluated in terms of cost-effectiveness (there are no embedded decision nodes). We have instead tried to capture the downstream consequences of the staging tests as typified in current clinical practice or best practice as defined by relevant NICE guidance, including recommendations within this guideline (modelled using chance nodes).

Patients with no metastatic disease (M0) and no or minimal nodal involvement (N0/1) may receive surgery with or without adjuvant chemotherapy and are more likely than patients with N2/3 M0 disease to receive potentially curative treatment with curative intent. Patients with N2/3 M0 disease will not be offered surgery but may receive potentially curative radiotherapy, though many will only be suitable for treatment with palliative intent. Many patients with either N0/1 M0 or N2/3 M0 stage will receive no active anti-cancer treatment.

Treatment for patients with distant metastatic disease (M1b) is limited to those options given with palliative intent (palliative chemotherapy, palliative radiotherapy or no active anti-cancer treatment). The proportions of patients receiving each treatment option, depending on the stage of their disease are presented under 'treatment options'. All patients will receive active supportive care in addition to any anti-cancer treatment.

Clinical data

The clinical data used to populate the model came from the published literature, the NLCA database (audit data) or was based on GDG expert opinion see table A4.4 below.

Table A4.4: Sources of data for model

Data required for model	Source
Prevalence	NLCA + expert opinion
Test accuracy	Expert opinion (+ published literature)
Treatment options (proportions)	NLCA
Survival estimates	NLCA
Utility weights	published literature + expert opinion
Resource use	expert opinion
Unit costs	NHS Reference costs/Trust level data

Analysis of NLCA

The collection of data for the NLCA database started in 2006 with data so far collected on over 91,000 patients, thus providing a rich source of data for the model (Department of Health, 2009).

NLCA was used to provide several parameters for the model:

- probability of M1 disease given N disease status
- proportions of patients offered various treatment options
- survival associated with each treatment option, by stage.

The analysis was carried out¹ in STATA (StataCorp. 2009) using all years of data (2006-8) but excluding the following categories of patients:

- patients diagnosed on death certificate (N=113)

¹ All the analysis of the NLCA data to inform the economic model was carried out by Anna Rich. Without her considerable efforts the economic work for the guideline would not have been possible.

- patients with SCLC at time of diagnosis (N=8,643)
- patients with mesothelioma at time of diagnosis (N=3,133)
- patients with performance status 4 (N=2,843).

We consider NLCA data to be a more accurate source of data for this model since it captures the real treatment options offered to patients, given the stage of their disease, thus increasing the external validity of the model results.

Prevalence of disease (pre-test probabilities of disease)

Since the model sought to investigate the cost-effectiveness of sequences of staging tests in three hypothetical populations, the prevalence was estimated by GDG expert opinion and the values shown in table A4.5 below were chosen to represent groups with low, intermediate and high prevalence of nodal (N2/3) and metastatic (M1) disease.

Table A4.5: Prevalence of malignancy in lymph nodes by subgroup

SUBGROUP	LOW	INTERMEDIATE	HIGH
Result on CT	CT -ve (N0/1)	CT +ve (N2/3)	CT +ve (N2/3)
Definition of nodes	No enlarged nodes <10mm short axis on CT	Small volume nodes 1+ mediastinal lymph nodes of 10-19mm short axis	Bulky N2 disease Any node ≥20mm
Prevalence N2/3 disease	15% <i>1- Negative predictive value of CT (post-test probability of disease)</i>	50%	85%
Prevalence M1 disease	5%	15%	25%

In addition to the prevalence of nodal disease and the prevalence of metastatic disease, it was also necessary to define the relationship between the two, i.e. how much more likely is a patient with N2/3 disease to have M1 disease than a patient with N0/1 status. We assumed the probability of a patient having metastatic disease, given N disease status, does not vary between the low, intermediate and high prevalence groups. We applied a ratio of 1:1.5 for M1 disease in patients with N0/1: M1 disease in patients with N2/3 disease, which was the ratio observed in pathologically confirmed stage data from NLCA. In other words we assume patients with N2/3 disease are 50% more likely than patients with N0/1 status to have metastatic disease.

Test accuracy

A systematic review was carried out for this topic to identify papers reporting test accuracy data on diagnostic and staging tests that have been published since 2003 (the cut-off date used for the systematic review in the 2005 NICE guideline). This review revealed 75 papers in total, 59 relating to staging tests (note: many of the tests can be used for the purposes of both diagnosis and staging). Despite the apparent volume of evidence, none reported test accuracy in patient populations that mirror the subgroups identified for this economic analysis (with the exception of Gould et al., 2003; Gu et al., 2009; Pozo-Rodriguez et al., 2005, the populations appear to be largely a mix of patients with and without enlarged nodes on initial CT). In order to continue with the proposed tripartite analysis, the GDG agreed to populate the model with test accuracy estimates formed on close inspection of the evidence reviewed for this topic, but which are essentially based on expert opinion see table A4.6.

Table A4.6: Assumptions about test accuracy

Subgroup	LOW		INTERMEDIATE		HIGH	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
PET-CT (M staging)	62.5%	94.5%	62.5%	94.5%	62.5%	94.5%
EBUS	80%	99%	90%	99%	95%	99%
TBNA	30%	99%	40%	99%	70%	99%
Neck ultrasound	N/A	N/A	33%	99%	50%	99%
Mediastinoscopy	80%	99%	90%	99%	95%	99%

Treatment options

Data from NLCA were used to estimate the proportions of patients receiving each treatment option given their pre-treatment nodal status, presented in table A4.7 below. Treatment was considered to have been given only if the date of treatment was recorded and, as such, very few patients that received dual or triple modality treatment can be identified from the NLCA data (we suspect patients may have been offered a combination or sequential treatment but only have the date of the first treatment recorded). Using pre-treatment nodal status is not ideal since we want the treatment options in the model to reflect those offered to patients given their 'true' underlying nodal status. NLCA also collects data on pathological nodal status but this is only available in patients who undergo some form of surgical procedure which introduces a bias into the proportions.

Table A4.7: Treatment options received by patients reported by N-stage and M-stage

Treatment	N0/1 M0 status	N2/3 M0 disease	M1 disease
	%	%	%
Surgery alone	30.9%	N/A	N/A
Surgery + chemo	3.6%	N/A	N/A
RT (curative)	8.0%	3.8%	N/A
CHART	4.0%	1.9%	N/A
Radical RT	4.0%	1.9%	N/A
Chemo alone	9.0%	29.2%	22.7%
RT (palliative)	11.0%	21.6%	23.0%
No recorded treatment	37.5%	45.3%	54.3%

NLCA records radiotherapy as a treatment option, but cannot distinguish between radiotherapy given with curative intent and palliative radiotherapy. We used the 'MDT plan' field to allow us to distinguish between radiotherapy given with curative intent and radiotherapy given with palliative intent. The data recorded in NLCA do not allow us to distinguish between different forms of radiotherapy given with curative intent. Therefore it was assumed 50% of patients receiving radiotherapy with the MDT recording treatment intent as curative receive CHART (54Gy in 36 fractions: three fractions per day for 12 days), and the other 50% receive conventionally fractionated radiotherapy, defined for the purposes of this model as 55Gy in 20 daily fractions. Since the survival data from NLCA is being used to populate the model, these assumptions only impact on the cost used in the model.

We followed the guidance given in NICE TA 181 when defining the palliative chemotherapy regimens. TA 181 states that patients with large cell carcinoma or adenocarcinoma should be offered pemetrexed in combination with cisplatin as first-line treatment for NSCLC. Roughly 29% of patients with non-small cell cancer will meet these criteria and receive pemetrexed in combination with cisplatin, whilst the remaining patients will receive either gemcitabine in

combination with cisplatin (88%) or vinorelbine in combination with cisplatin (22%) (NICE Costing template, TA181).

Survival

The model was populated with survival data from NLCA (converted from days into months). In order to extend the survival curves and calculate transition probabilities a Weibull distribution was assumed and fitted to the data in STATA. Transition probabilities were calculated using the standard formula (Briggs, A et al (eds.), 2006 p.71): $tp(t) = 1 - \exp\{\lambda[(t-1)^y - t^y]\}$ see table A4.8.

Table A4.8: Survival data from NLCA, by stage and treatment

Stage and treatment	Type of staging	N	shape parameter	scale parameter	Mean survival (months)	Median survival (months)
N0/1: Surgery only	Path	2322	0.99865	0.00040	82.4	57.1
N2/3: Surgery only	Path	210	0.98300	0.00104	35.7	24.4
N0/1: Chemotherapy and Surgery	Path	302	1.14901	0.00012	83.6	63.9
N2/3: Chemotherapy and Surgery	Path	82	1.44376	0.00004	35.9	30.8
N0/1: Radiotherapy with curative MDT plan	Pre-Rx	640	1.25774	0.00016	32.0	25.7
N2/3: Radiotherapy with curative MDT plan	Pre-Rx	174	1.12929	0.00070	19.5	14.7
N0/1: Chemotherapy only	Pre-Rx	1103	1.18018	0.00048	20.1	15.6
N2/3: Chemotherapy only	Pre-Rx	2682	1.18519	0.00060	16.1	12.6
M1: Chemotherapy only	Pre-Rx	3779	1.19490	0.00089	11.1	8.7
N0/1: Radiotherapy with palliative MDT plan	Pre-Rx	1035	1.06740	0.00138	15.3	11.1
N2/3: Radiotherapy with palliative MDT plan	Pre-Rx	1511	1.07355	0.00206	10.1	7.4
M1: Radiotherapy only	Pre-Rx	3830	0.99419	0.00592	5.7	4.0
N0/1: No specific anticancer Rx	Pre-Rx	506	0.90908	0.00321	19.0	12.1
N2/3: No specific anti cancer RX	Pre-Rx	382	0.82119	0.00867	11.8	6.8
M1: Nil specific RX	Pre-Rx	873	0.72735	0.02982	5.0	2.5

Key: Path = pathological staging, Pre-Rx= pre-treatment (clinical) staging, N= number of patient records in NLCA

Despite the rich source of data for survival estimates from NLCA, we have no information about patients' survival from treatment given as the result of misleading test results (i.e. false positives or false negatives) so we were required to make some significant assumptions on the basis of expert opinion from the GDG. If patients with metastatic M1 disease were given any form of treatment with curative intent it was assumed they would have similar survival outcomes to a patient with M1 disease given palliative chemotherapy.

If patients with N2/3 disease were offered surgery or surgery and adjuvant chemotherapy, the associated survival was considered to depend on the population subgroup. A patient in the low prevalence group offered surgery with or without chemotherapy would have the survival outcomes that are recorded in the NLCA database for patients with N2/3 disease on the basis of pathological staging. Since surgery is not commonly considered the most appropriate treatment for this group of patients, those that are recorded as received surgery with or without chemotherapy in NLCA are thought to be an atypical subgroup and as such these survival estimates ought not to be applied to all patients with N2/3 disease. With this in mind the GDG made the following assumptions:

- A patient in the intermediate prevalence group offered surgery with or without chemotherapy would have the same survival outcome as a patient with N2/3 disease offered radiotherapy with curative intent (median survival of 14.7 months).
- A patient in the high prevalence group offered surgery with or without chemotherapy would have the same survival outcome as a patient with N2/3 disease offered palliative chemotherapy (median survival of 12.6 months).

In the case of patients with N0/1 disease that was mistakenly staged as N2/3 or M1 the associated survival of the treatment they were then offered would be the same as if that treatment had been based on correct staging information.

Therefore the model does not apply a penalty in terms of worse health outcomes for any patient if they were incorrectly staged. Health outcomes for a patient may in fact be better, on average, than if a patient received treatment given correct staging information. However these assumptions are likely to underestimate costs, as there may be costs associated with picking up mis-diagnoses that are not accounted for.

Safety/adverse events

The only adverse events that were considered in the model were death from mediastinoscopy and death following treatment (by any cause). A 0.5% mortality rate from mediastinoscopy was used, although the GDG thought this was high and was likely to be nearer 0.1%, so a lower rate was considered in the sensitivity analysis. The NLCA survival data accounts for any deaths from surgical complications. EBUS is associated with a very low incidence of pneumothorax, so was excluded from the model.

Quantifying quality of life

NICE states a clear preference for the use of quality adjusted life years (QALYs) to compare the cost-effectiveness of interventions across different disease areas (NICE Guidelines Manual, 2008). A QALY is a measure of a person's length of life weighted by a valuation of their health-related quality of life over that period.

Health related quality of life (HRQL) can be measured in several ways, and different systems produce different utility values; therefore, results from the use of different systems cannot always be compared. Given the comparative nature of NICE's work and the need for consistency across decisions, NICE has stated a preference for the measurement of changes in HRQL to be reported directly from patients and valued using a choice-based method in a representative sample of the UK population to capture public preferences, and states a preference for the use of EQ-5D (NICE Guidelines Manual, 2008). HRQL data is notoriously difficult to collect from patients with lung cancer, due to the severity of the disease. As such, questions have been raised about the robustness of the utility values used to calculate QALYs in all recent NICE guidance on lung cancer (NICE TAs 181, 184, 162, 2005 guideline).

The economic evaluation for TA162 on erlotinib in patients with non-small cell lung cancer used utility values from an unpublished study of EQ-5D health state data from 154 patients. However the focus of this study was on chemotherapy therefore the health state descriptions do not cover the states we are considering within this model structure. Utility values used for the economic evaluation for TA 181 on pemetrexed for the first-line treatment of locally advanced and metastatic NSCLC, came from a manufacturer sponsored study, Nafees et al. (2008), which was commissioned for second-line NSCLC but was considered applicable to a first-line setting. Again this study focused on chemotherapy but the utilities recorded for stable disease and responding disease are similar to values reported for 'advanced disease which responds to treatment' in the Berthelot (2000) study.

For the economic analysis on oral topotecan in TA184, EQ-5D data was taken directly from an RCT (O'Brien, 2006) where patients filled in the EQ5D form at 3 weekly periods. However there was a lot of data missing and concern has been raised about methods used to input the missing values.

The 2005 Lung cancer guideline acknowledged the absence of data on quality of life estimates and used estimates from two studies, Earle (2000) and Berthelot (2000), which elicited health state descriptors from twenty-four oncologists (and not patients) using a visual analogue scale. The 2005 model made two additional assumptions, that both a thoracotomy and CHART were associated with a 50% loss of quality of life for 8 weeks. Following a broad search of the literature, no new information on health related quality of life for lung cancer patients was identified. It seems appropriate to use published utility values that were used in technology appraisal TA 181 (from Nafees et al, 2008) and from the 2005 Lung guideline. However assumptions still had to be made about quality of life, and have been tested with sensitivity analysis see table A4.8.

Table A4.8: Utility assumptions used in the 2010 economic model

Parameter	Assumption	Comments
Loss of health-related quality of life (HRQL) associated with PET-CT and Neck US	0	Non-invasive tests
Loss of HRQL associated with EBUS and EUS	0	Minimally invasive tests
Loss of HRQL associated with mediastinoscopy	1 month with 50% reduction in HRQL	Invasive surgical procedure
Loss of HRQL associated with surgery (lobectomy)	2 months with 50% reduction in HRQL	Assumption made by 2005 GDG was 8 weeks with 50% reduction in quality of life
Loss of HRQL associated with surgery (lobectomy) + adjuvant chemo	2 months with 50% reduction in HRQL	Follows assumption made for surgical treatment by the 2005 GDG (above)
Loss of HRQL associated with treatment with curative intent (CHART or RT)	2 months with 50% reduction in HRQL	Assumption made by 2005 GDG was 8 weeks with 50% reduction in quality of life
HRQL associated with local /advanced disease	0.65	From Berthelot 2000 and Nafees 2008
HRQL associated with no anti-cancer treatment	0.53	Best supportive care HRQL from Berthelot 2000
HRQL associated with the last month of life	0.53	Best supportive care HRQL from Berthelot 2000

Costs

In accordance with the perspective of this analysis, the only costs considered were those relevant to the UK NHS. Costs were estimated in 2008-9 prices (since this is the price year from the most recent edition of NHS Reference costs, published June 2010). Where costs have been taken from sources using a different price year, they have been inflated using the Hospital and Community Health Services Pay and Prices Index (PSSRU, 2010).

There are broadly five categories of costs considered in the model:

- Cost of diagnostic tests
- Cost of treatment
- Cost of treating adverse events
- Cost of follow-up
- Cost of supportive and palliative care

Cost of diagnostic tests

The costs of all diagnostic tests, apart from EBUS, were taken from NHS Reference costs 2008-9 (see table A4.9 below).

Table A4.9: Cost of diagnostic tests in GBP, NHS reference costs 2008-9

Tests	Primary OPCS 4.5 code	Associated HRG 4 code	Type of care	Average unit cost, £	Lower quartile	Upper quartile
Mediastinoscopy	E63.9	DZ04	elective inpatient	3056	2360	3652
TBNA (FNA of mediastinal lymph node)	T87.4	DZ03	outpatient	162	120	155
Neck ultrasound	U21.6	RA23Z	outpatient	53	39	60
PET-CT	U21.3	RA39Z	outpatient	472	339	631
	U21.2	RA50Z	outpatient	195	131	227

OPCS 4.5 - Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures version 4.5, HRG4 - Healthcare Resource Groups version 4

HRG4 - Healthcare Resource Groups version 4

EBUS does not sit comfortably in any HRG category, with some NHS trusts receiving the tariff for standard bronchoscopy, DZ07 (£504 for 2010-11) and others negotiating to receive the tariff for mediastinoscopy, DZ03B, (£3,382 for 2010-11). EBUS is more complex than standard bronchoscopy requiring a longer time (45-60 minutes) to perform it and two highly skilled operators, but is not a surgical procedure requiring a GA like mediastinoscopy. Following the NICE Reference case, we have chosen to use a different source for the cost of EBUS in the model as we do not believe the relevant NHS reference cost to be appropriate. Instead we have used a cost estimate provided by University Hospitals of Leicester Trust (Andrew Medford, UHL Trust, personal communication) which was estimated using a bottom-up approach, as detailed in table A4.10:

Table A4.10: UHL costing of EBUS

Resource use	Unit cost
Components for EBUS and standard bronchoscopy (62.5% of EBUS cases)	
Capital costs of EBUS scope (spread over 5 years, 41 procedures per year)	£510
Pay costs (1 x band 6 nurse, 1 x band 5 nurse, 1 x band 2 HCA, 2 x Consultants: 60 minutes)	£218
Consumables from standard bronchoscopy	£100
Sterilisation (x 2 scopes)	£32
EBUS TBNA needle	£175
Maintenance contract for EBUS scope and processor (assuming 41 procedures per year)	£118
Pathology costs (bronchoscopy samples + TBNA node biopsy)	£131
Support services (admin)	£59
Overheads (facilities and capital charges)	£90
	£1,433
Components for EBUS only (37.5% of EBUS cases)	
Capital costs of EBUS scope (spread over 5 years, 41 procedures per year)	£510
Pay costs (1 x band 6 nurse, 1 x band 5 nurse, 1 x band 2 HCA, 2 x Consultants: 45 minutes)	£164
Consumables from standard bronchoscopy	£100
Sterilisation (x 1 scope)	£16
EBUS TBNA needle	£175
Maintenance contract for EBUS scope and processor (assuming 41 procedures per year)	£118
Pathology costs (TBNA node biopsy only)	£35
Support services (admin)	£44
Overheads (facilities and capital charges)	£90
	£1,252
Average cost of EBUS	£1,365

The cost of the initial diagnostic work-up, including CT if done separately to PET-CT, is excluded as it is common to all strategies (and so would disappear in the incremental analysis).

Cost of treatment

Since lobectomy is the most common surgical procedure (Society for Cardiothoracic Surgery, 2008) we used this cost to represent the cost of surgery. Lobectomy (OPCS-4.5] E54.3, HRG4 DZ02, "complex thoracic procedure without CC") as an elective inpatient procedure was estimated to be £5,704 (NHS Reference costs 2008-9). For radiotherapy with curative intent we assumed 50% of patients received CHART (54 Gy in 12 three-times daily fractions) and the other 50% received standard radiotherapy (55 Gy in 20 daily fractions). CHART, given in an inpatient setting, was estimated to cost £6,296 (1 x SC03Z "define volume for simple radiation therapy with imaging and dosimetry" £205, 1 x SC23Z "Deliver a fraction of complex treatment on a megavoltage machine" £204 and 35x SC22Z "Deliver a fraction of treatment on a megavoltage machine" £168). Radiotherapy with curative intent given in an outpatient setting was estimated to cost £2,840 using NHS reference costs (1 x SC03Z "define volume for simple radiation therapy with imaging and dosimetry" £471, 1 x SC23Z "Deliver a fraction of complex treatment on a megavoltage machine" £129 and 19 x SC22Z "Deliver a fraction of treatment on a megavoltage machine" £112).

Standard costing assumptions made for in the recent NICE Gemcitabine STA such as a mean of 2.79 cycles, frequency and treatment of adverse events and no vial sharing were followed (NICE TA 181). We also assumed a mean body surface area of 1.818m² (Sacco et al., 2010). A standard dosage of 80mg/m² cisplatin delivered on day 1 and 30 mg/m² vinorelbine delivered on days 1 and 8 of a three week cycle was assumed and drug acquisition costs were taken from the British National Formulary (BNF 59, 2010). The total cost of adjuvant chemotherapy (cisplatin and vinorelbine) was therefore £3,629. Three regimens of palliative chemotherapy were costed following the same assumptions. We assumed these regimens would be i.v. administered, first as a daycase and then all subsequent administrations on an outpatient basis (NHS reference costs 2008-9 SB14Z and SB15Z). The total cost of Gemcitabine (1250mg/m²) + cisplatin (75mg/m²) combination therapy was £3,668. The total cost of vinorelbine (25mg/m²) + cisplatin (100mg/m²) combination therapy was £3,243. The total cost of pemetrexed (500mg/m²) + cisplatin (100mg/m²) combination therapy was £4,798. Palliative radiotherapy fractionation schedules vary but we assume a 13 x 36-39 Gy schedule delivered in an outpatient context. Using NHS reference costs (1 x SC03Z £471, 1 x SC23Z £129 and 12 x SC22Z £112) this was estimated to cost £1,940.

Cost of treating adverse events

The cost of death during or immediately following a mediastinoscopy was assumed to be £3,628 which is equivalent to the cost of an intermediate thoracic procedure carried out as an elective inpatient, with co-morbidities and complications (DZ04C NHS Reference costs 2008-9).

Cost of follow-up

Cost of follow-up was assumed to be equivalent to one attendance with a consultant every 2 months, £132 (NHS reference costs 2008-9).

Cost of supportive and palliative care

Active supportive and palliative care was considered to be a cost that would apply to all patients (who died from lung cancer and not surgical complications), regardless of their initial treatment. The average cost of supportive and palliative care per cancer death (including inpatient care, home care, hospital support, day care and bereavement services) was estimated to be £3,581 (NICE 2009, NICE 2004).

Crude assumptions were made about when the direct health costs were accrued; the cost of tests and treatment were assumed to fall in the first year, whilst the cost of follow-up occurred every 2 months and the cost of supportive and palliative care fell in the final month of life.

To summarise, the costs included in the model were estimated as follows, table A4.11:

Table A4.11: Summary of cost inputs

Cost inputs	Cost	Source
Mediastinoscopy	£3,056	NHS Reference costs 2008-9
Non-ultrasound TBNA	£162	NHS Reference costs 2008-9
Neck ultrasound	£53	NHS Reference costs 2008-9
PET-CT	£667	NHS Reference costs 2008-9
EBUS-TBNA	£1,365	UHL Trust (personal communication)
Lobectomy	£5,704	NHS Reference costs 2008-9
CHART	£6,296	NHS Reference costs 2008-9
Radiotherapy with curative intent	£2,840	NHS Reference costs 2008-9
Adjuvant chemotherapy – cisplatin & vinorelbine	£3,629	NHS Reference costs 2008-9/ BNF 59, 2010
Palliative chemotherapy - Gemcitabine + cisplatin	£3,668	NHS Reference costs 2008-9/ BNF 59, 2010
Palliative chemotherapy: vinorelbine + cisplatin	£3,243	NHS Reference costs 2008-9/ BNF 59, 2010
Palliative chemotherapy: pemetrexed + cisplatin	£4,798	NHS Reference costs 2008-9/ BNF 59, 2010
Palliative radiotherapy	£1,940	NHS Reference costs 2008-9
Death during/ following mediastinoscopy	£3,628	NHS Reference costs 2008-9
Follow up	£132 (every 2 months)	NHS Reference costs 2008-9
Supportive and palliative care	£3,581	NICE 2009, NICE 2004

Discounting

In line with the NICE Reference case, both costs and health outcomes were discounted at an annual rate of 3.5% (NICE, 2008a).

Sensitivity analysis

The following parameters were tested using deterministic sensitivity analyses to assess the robustness of the model results:

- Proportions of patients getting each type of treatment
- Survival estimates associated with inappropriate treatment with curative intent for patients with metastatic disease
- Utility values
- Drug discounts/generic prices
- Cost of EBUS-TBNA
- Resource use/cost associated with radiotherapy
- Complication rate of surgery

The proportions of patients receiving treatment may be controversial, despite being based on NLCA data. Whilst unlimited scenarios could be investigated the treatment of patients with N0/1 disease was tested in the scenario that all such patients (based on the test results) would be offered some form of radical anti-cancer treatment, i.e. removing the treatment with palliative intent or 'no specific treatment' options for these patients.

A strong assumption was made that a patient with metastatic disease offered treatment with curative intent would achieve the same survival outcomes as for palliative chemotherapy. This assumption was tested using all survival outcomes recorded in NLCA for metastatic patients (palliative chemotherapy, palliative radiotherapy and no specific treatment).

Another key area of uncertainty was the utility values used in the analysis. A threshold analysis was performed on the utility loss associated with surgery, in each of the three groups to see the point at which the decision might change.

Given the availability of discounts on some chemotherapy agents, the drug acquisition costs were tested using a scenario analysis. Until recently, the NHS Purchasing and Supplies Agency (PASA) published the eMIT database providing data on nationally-available drug discounts. This database is now maintained by the NHS Commercial Medicines Unit, part of the Procurement Investment and Commercial Division of the Department of Health. In a scenario analysis we investigated using the 2009 discounted prices of cisplatin and vinorelbine (no discount is available on gemcitabine or pemetrexed) instead of the list prices published in the BNF see table A4.12.

Table A4.12: Drug acquisition costs for sensitivity analysis

Chemotherapy agent	Dose (mg/m ²)	Cost per cycle from BNF (£)	Cost per cycle with PASA discount (£)
Vinorelbine	25	139.00	25.39
	30	168.00	31.18
Cisplatin	75	736.62	16.51
	80	74.72	12.29
	100	98.15	16.32

Another source of uncertainty in the model was the cost of EBUS. To investigate the impact this might have on the model results a one-way sensitivity analysis was performed, varying it between £480 (Callister, 2008) and £1,433 (higher end of UHL estimate).

The assumptions made about radiotherapy schedules might be controversial, since these vary across the country. In particular the choice of palliative radiotherapy is a high intensity treatment and might be not considered typical. As described in section 3.5.3, these assumptions only impact the cost of treatment. To investigate the impact these assumptions on radiotherapy have on the results of each subgroup analysis, a three-way deterministic sensitivity analysis was conducted by considering alternative fractionation schedules: CHART (54Gy x36 fractions over 12 days or 55Gy in 3 daily fractions for 14 days) between £6,128 and £7,305, Radiotherapy with curative intent (64Gy x 32 daily fractions (international standard) or 55Gy x 20 daily fractions (common in UK)) between £2,722 and £4,398 and palliative radiotherapy (options include 10Gy as a single fraction, 15Gy x 3 fractions, 17Gy x 2 fractions, 20Gy x 5 fractions, 36/39Gy in 12/13 fractions) between £583 and £1,812.

Finally, the impact the complication rate of surgery might have on the results was investigated with a two-way sensitivity analysis. The probability of surgical complications was varied between two extremes of 0%-50% and at the same time the utility loss associated with complications from surgery was varied between the equivalent of 2 months with a 50% reduction in quality of life up to 4 months of zero utility (a state equivalent to death). The sensitivity analysis was repeated in each three of the subgroups.

The limitations of deterministic sensitivity analysis are well documented, particularly for investigating parameter uncertainty. However, it was not possible to conduct probabilistic sensitivity analysis since we had no data on the correlation between the sensitivities and specificities of the tests since these were based on expert opinion, and we were unable to extract data on the correlation between survival estimates from NLCA in time to feed this into the analysis.

Results

The base-case results are reported for each subgroup considered in the model.

Base-case results for the low prevalence population

The results of the model for the low prevalence population show only small differences in the total expected (mean) QALYs per patient, ranging between 1.582 and 1.625. Total expected

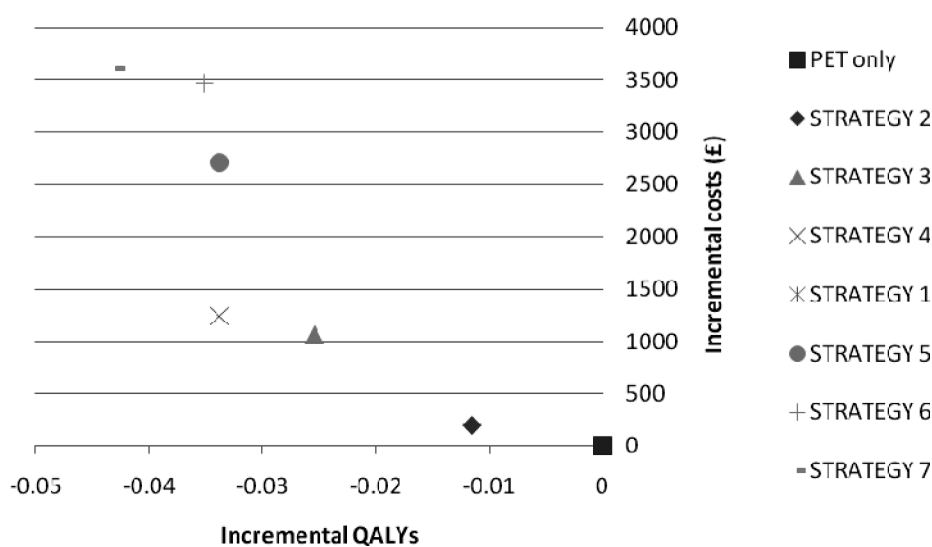
costs per patient ranged from £7,500 - £11,000. Strategy 'X' (PET-CT only) is the most effective strategy, and also the cheapest, thus dominates all the other strategies as seen in table A4.13.

Table A4.13: Total expected costs and QALYs for strategies compared in the model for the low prevalence population

Strategy	Description	Total expected cost (£)	Total expected QALYs	Incremental cost-effectiveness
STRATEGY X	PET-CT only	7,561	1.625	
STRATEGY 2	PET-CT, TBNA	7,756	1.613	(Dominated)
STRATEGY 3	PET-CT, EBUS	8,624	1.599	(Dominated)
STRATEGY 4	PET-CT, TBNA, EBUS	8,802	1.591	(Dominated)
STRATEGY 1	PET-CT, Med	10,174	1.599	(Dominated)
STRATEGY 5	PET-CT, TBNA, Med	10,275	1.591	(Dominated)
STRATEGY 6	PET-CT, EBUS, Med	11,030	1.590	(Dominated)
STRATEGY 7	PET-CT, TBNA, EBUS, Med	11,170	1.582	(Dominated)

In the incremental analysis this strategy, PET-CT only, is located at the origin of the cost-effectiveness plane with all other more costly and less effective strategies represented as points in the north-west quadrant see figure A4.3.

Figure A4.3: Cost-effectiveness plane for the low prevalence subgroup



Base-case results for the intermediate prevalence population

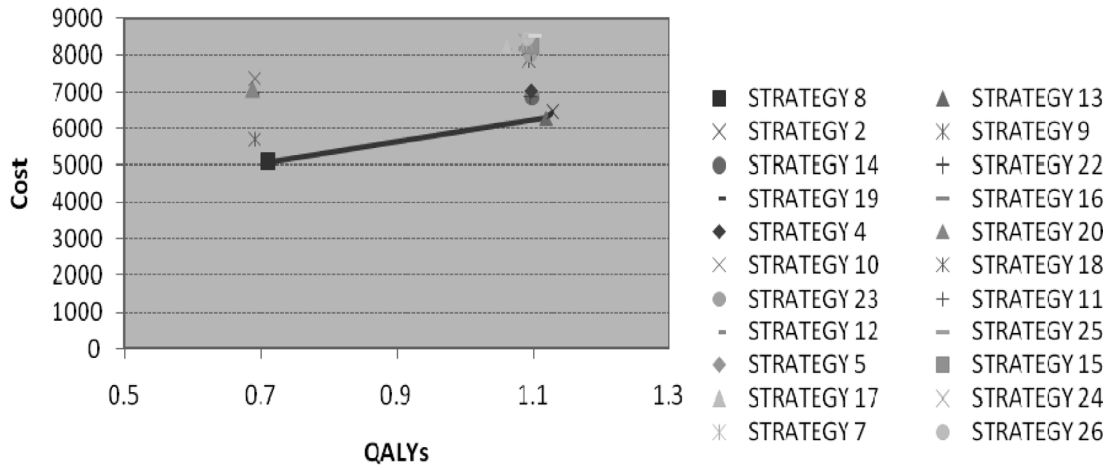
The base-case results for the analysis on the intermediate prevalence group showed larger differences between strategies in terms of health outcomes for patients, with total expected QALYs per patient ranging from 0.688 to 1.128. Total expected costs ranged from just over £5,000 up to £8,500 see table A4.14.

Table A4.14: Total expected costs and QALYs for strategies compared in the model for the intermediate prevalence population

Strategy	Total expected costs	Total expected QALYs	Incremental cost-effectiveness ratio (ICER)
STRATEGY 8	£5,081	0.713 QALYs	
STRATEGY 9	£5,686	0.690 QALYs	(Dominated)
STRATEGY 13	£6,281	1.118 QALYs	£2,958
STRATEGY 2	£6,476	1.128 QALYs	£19,448
STRATEGY 14	£6,844	1.100 QALYs	(Dominated)
STRATEGY 22	£6,863	1.096 QALYs	(Dominated)
STRATEGY 19	£6,928	0.688 QALYs	(Dominated)
STRATEGY 16	£6,966	1.100 QALYs	(Dominated)
STRATEGY 20	£7,046	0.688 QALYs	(Dominated)
STRATEGY 4	£7,053	1.097 QALYs	(Dominated)
STRATEGY 3	£7,070	1.103 QALYs	(Dominated)
STRATEGY 10	£7,377	0.690 QALYs	(Dominated)
STRATEGY 18	£7,862	1.095 QALYs	(Dominated)
STRATEGY 23	£8,030	1.096 QALYs	(Dominated)
STRATEGY 11	£8,074	1.099 QALYs	(Dominated)
STRATEGY 12	£8,112	1.060 QALYs	(Dominated)
STRATEGY 25	£8,171	1.090 QALYs	(Dominated)
STRATEGY 5	£8,214	1.097 QALYs	(Dominated)
STRATEGY 17	£8,233	1.061 QALYs	(Dominated)
STRATEGY 15	£8,244	1.100 QALYs	(Dominated)
STRATEGY 24	£8,355	1.090 QALYs	(Dominated)
STRATEGY 7	£8,390	1.091 QALYs	(Dominated)
STRATEGY 26	£8,415	1.093 QALYs	(Dominated)
STRATEGY 6	£8,448	1.095 QALYs	(Dominated)
STRATEGY 21	£8,473	1.090 QALYs	(Dominated)
STRATEGY 1	£8,523	1.103 QALYs	(Dominated)

Figure A4.4 below shows these results graphically. Since all strategies are being compared to each other, we take strategy 8 (TBNA followed by PET-CT) – the cheapest strategy – as the baseline. In doing so, the majority of the other strategies are ruled out by simple dominance of strategy 2 (PET-CT followed by TBNA), that is they are less effective and more costly. Three strategies are left in the incremental analysis, strategy 8 (TBNA followed by PET-CT) as the baseline, strategy 2 (PET-CT followed by TBNA) and strategy 13 (Neck ultrasound, then TBNA, then PET-CT). Following standard decision rules, strategy 2 (PET-CT followed by TBNA), is the most cost-effective strategy since it is associated with an incremental cost per QALY gained of £19,448 and it maximizes QALYs subject to a £20,000 per QALY threshold. Strategy 13 is not cost-effective despite the fact it is associated with a lower ICER of just under £3,000 per QALY, precisely because strategy 2 is a relevant comparator and provides more QALYs at an acceptable cost to the UK NHS.

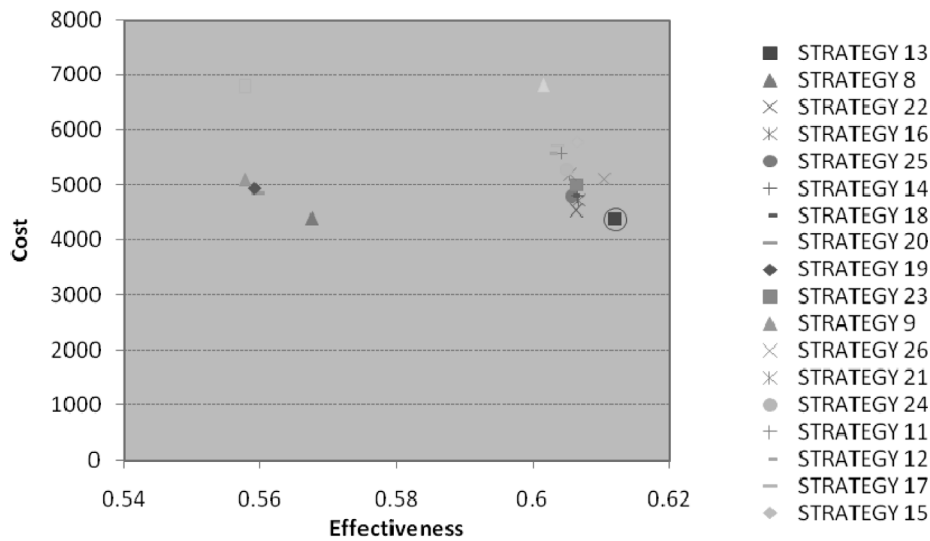
Figure A4.4: Expected costs and expected QALYs for the intermediate prevalence population



Base-case results for the high prevalence population

In the high prevalence population, total expected (mean) QALYs per patient were very similar, ranging from 0.558 - 0.612 see table A4.15. The expected costs (per patient) were between £4,360 and £6,830, so lower than the costs observed in the other two patient populations. In this analysis, strategy 13 (Neck ultrasound, then TBNA, then PET-CT) is the most cost-effective as it dominates all other strategies (i.e. is cheaper and more effective in terms of QALYs) see figure A4.5.

Figure A4.5: Expected costs and expected QALYs for the high prevalence population



Updated 2011

Table A4.15: Total expected costs and QALYs for strategies compared in the model for the high prevalence population

Strategy	Total expected costs	Total expected QALYs	Incremental cost-effectiveness ratio (ICER)
STRATEGY 13	4362	0.612	dominates
STRATEGY 26	5077	0.611	(Dominated)
STRATEGY 16	4712	0.607	(Dominated)
STRATEGY 14	4785	0.607	(Dominated)
STRATEGY 15	5754	0.607	(Dominated)
STRATEGY 22	4521	0.606	(Dominated)
STRATEGY 23	4985	0.606	(Dominated)
STRATEGY 18	4802	0.606	(Dominated)
STRATEGY 25	4778	0.606	(Dominated)
STRATEGY 21	5173	0.605	(Dominated)
STRATEGY 24	5258	0.605	(Dominated)
STRATEGY 11	5588	0.604	(Dominated)
STRATEGY 17	5684	0.604	(Dominated)
STRATEGY 12	5575	0.603	(Dominated)
STRATEGY 1	6833	0.602	(Dominated)
STRATEGY 8	4386	0.568	(Dominated)
STRATEGY 20	4839	0.560	(Dominated)
STRATEGY 19	4924	0.559	(Dominated)
STRATEGY 9	5083	0.558	(Dominated)
STRATEGY 10	6774	0.558	(Dominated)

Sensitivity analysis

There was no change to the decision of which strategy is most cost-effective when changing the structure of the model to necessitate that all patients with test results suggesting N0/1 disease receive treatment with curative intent. The increase in treatment with curative intent for N0/1 resulted in a modest change in price but a dramatic increase in average QALYs per patient. The results of this sensitivity analysis were the same across all three subgroups. The increase in QALYs is not a surprising finding, given the additional survival associated with treatment with curative intent and the potential increase in health-related quality of life, but it is interesting to note that the change in QALYs does not alter the selection of the most cost-effective strategy.

Similarly there was no change to the cost-effectiveness decision when we relaxed the assumption about the survival estimates for patients with metastatic disease wrongly given radical treatment.

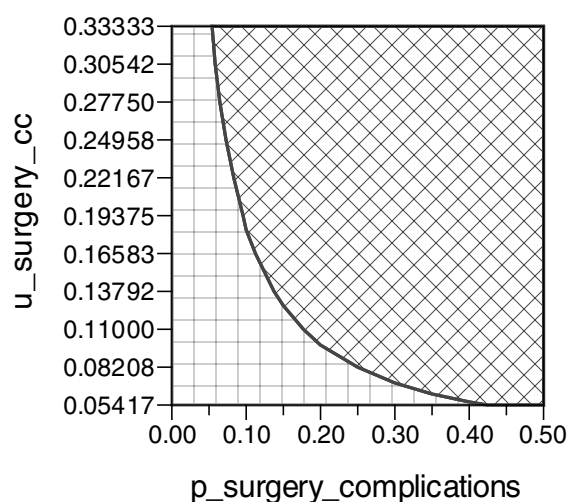
A threshold analysis was performed on the disutility associated with surgery. The value used in the model did not affect the results in either the low prevalence or high prevalence group; however in the intermediate prevalence group a threshold value of 0.06QALYs represents the point at which the most cost-effective strategy changes from strategy 2 to strategy 13. The threshold value 0.06 QALYs is equivalent to just under 2.5 months of 50% reduction in quality of life, which is likely to be a plausible figure and should be taken into account when interpreting the results of the model in this subgroup of patients.

The discounts on drug acquisition costs investigated reduced the cost of the strategies but did not impact the decision of which was most cost-effective in any of the three groups. Similarly the cost of EBUS, when varied between £480 and £1433, did not impact on the cost-effectiveness results in any of the three subgroups. In the high subgroup the decision does not change, but the results of the incremental analysis do differ from the base-case since strategies 9, 14, 22 and 16 are all cheaper than strategy 13. However at a £20,000 per QALY threshold,

strategy 13 is still the most cost-effective (when EBUS costs £480, strategy 13 is associated with an ICER of £15,148).

The joint impact of uncertainty surrounding the resource use associated with the three different radiotherapy schedules (in terms of the differences in cost) had no impact on the results of the model in any of the three subgroup groups. Similarly increasing the surgery complication rate up to 50% and the associated utility loss did not change the most-cost effective strategy in the low or high prevalence subgroups at any point given a £20,000 cost-per-QALY threshold. This shows the results to be robust to large changes in the surgery complication rate and the impact this will have on patients' quality of life between the extreme values tested. However, the strategy did change in the intermediate prevalence group, as shown in figure A4.6. The values tested were extreme and the figure shows that as the surgical complication rate (on the x-axis) increases and the utility loss associated with surgical complications (on the y-axis) increase, the decision of which test sequence to follow changes from the base-case strategy 13 (Neck US, TBNA, PET-CT) changes to strategy 2 (PET-CT, TBNA).

Figure A4.6: Results of 2-way sensitivity analysis (surgical complication rate and associated loss of health-related quality of life) in the intermediate prevalence subgroup



Discussion

The results of the cost-effectiveness analyses show that different sequences of staging tests are likely to be cost-effective in different subgroups of patients. The results show that in the low prevalence population there are only small differences in QALYs between strategies involving PET-CT, roughly equivalent to just over 16 days in full health. However, when this is put in context of lung cancer, where utility values are likely to be much lower than perfect health, this difference is not inconsiderable. The results in the low prevalence group show that PET-CT on its own is clearly the most cost-effective alternative (of the strategies considered) and seems robust to deterministic sensitivity analysis of several parameters. The results of the analysis in the intermediate subgroup showed more variation in overall expected costs and health benefits. The incremental analysis revealed that strategy 2, PET-CT followed by TBNA at an incremental cost-effectiveness ratio of £19,448 per QALY. However, due to the multitude of strategies in the analysis, these results of the analysis in this subgroup need careful interpretation. Since there is little difference in terms of QALYs between several strategies (particularly between strategies 3, 4, 6, 14 and 22) and given the uncertainty surrounding these point estimates, there is likely to be some ambiguity over which strategy dominates, and thus which should be excluded from the incremental analysis.

The results in the high prevalence population showed that strategy 13 is both cheapest and most clinically effective and therefore most cost-effective, dominating all other clinically relevant strategies for that subgroup. The results are summarised below, table A4.16:

Table A4.16: Summary of results

SUBGROUP	LOW	INTERMEDIATE	HIGH
Result on CT	CT –ve (N0/1)	CT +ve (N2/3)	CT +ve (N2/3)
Definition of nodes	No enlarged nodes <10mm short axis on CT	Small volume nodes 1+ mediastinal lymph nodes of 10-19mm short axis	Bulky N2 disease Any node ≥20mm
Preferred strategy	Strategy ‘X’: PET-CT	Strategy 2: PET-CT, TBNA <i>but potential for some strategies to overlap and thus may change the incremental cost-effectiveness results</i>	Strategy 13: Neck US, TBNA, PET-CT
Incremental cost-effectiveness ratio	dominates all relevant comparators	£19,448 per QALY	dominates all relevant comparators

These results may seem on the surface to be counter-intuitive. Those sequences of tests which lead to more accurate staging information do not lead to overall better outcomes for patients. However, test performance is only a surrogate endpoint – and the results of all three analyses are heavily dependent on assumptions made about downstream treatment decisions. Within the context of the model, strategies resulting in a higher number of false negatives allow a great proportion of patients with N2/3 disease to be offered surgery and other treatment with curative intent options. Similarly if metastatic disease is missed, patients still achieve better outcomes with (inappropriate?) treatment with curative intent than with no anti-cancer treatment. These assumptions have been discussed in depth with the GDG, but it was decided that they hold and thus the results of the model logically follow from these assumptions.

There are a number of limitations to the analysis. In dichotomising the test results we may have omitted several important factors. The possibility of a non-diagnostic test is not considered in the model which may bias the results towards EBUS and against mediastinoscopy. In fact we only considered the impact of tests on staging mediastinal disease for resectability, which limits the usefulness of tests like PET-CT. We also made some strong assumptions in order to evaluate test sequences which have not been analysed in the context of randomised controlled trials. For example we assumed if a test is positive, no confirmatory tests are required and additionally that the choice of treatment is solely determined by the result of the final test.

We were not able to model the choice between EBUS and EUS (FNA), which we know in reality are used as complementary tools in assessing stage of disease. In the circumstance where either test is considered appropriate, we would need data on the location of nodes sampled using these tests and test accuracy for each test in order to model the choice between them.

Additionally, despite the wealth of data on test accuracy, we were unable to pool it and use it to populate the model, as the data were not reported in terms of the three different subgroups of interest and instead had to rely on expert opinion.

The survival estimates used in the model were estimates of achieved survival of patients recorded in NLCA. This obviously increases the generalisability of the model results since many lung cancer patients are treated in the NHS that would not be eligible for a randomized clinical trial, however the results might be different if we used data from RCTs to populate the model with achievable survival for each treatment. Additionally, a strong assumption was made in fitting a Weibull distribution to the data. Given time and resource constraints, it was not possible to investigate the impact different distributions might have had the model results.

We accounted for co-morbidities present in real-life patients by using the proportions of patients receiving treatment as recorded in NLCA, which show a high proportion of all patients not receiving treatment with curative intent in all stages of disease. However we did not investigate different sequences of staging tests for patients who could be identified as having co-morbidities upfront.

The sensitivity analysis performed showed the model was reasonably robust to changes in the treatment options, the choice of radiotherapy schedules, the price of chemotherapy drugs, the price of diagnostic tests, the death rate from mediastinoscopy, changes in utility values as well

as some assumptions about the choice of survival estimates for patients incorrectly staged. Other assumptions about utility values could not be tested without changing the model structure. Test accuracy data was not available for the three subgroups identified as relevant to the decision problem; as such we have relied on the expert opinion of the GDG. Ideally we would have wanted to conduct a probabilistic sensitivity analysis and a value of information analysis to quantify the maximum value of conducting research in this area.

The choice of clinically relevant sequences of tests considered in each subgroup analysis was not tested, and due to the incremental nature of the analysis will certainly influence the model results.

Despite these acknowledged limitations, these three analyses provided the GDG with useful information used in its deliberations over the recommendations to be made on this topic, particularly in the absence of any evidence from the UK of clinical as well as cost-effectiveness on the best sequence in which to use tests to stage mediastinal disease, in different subgroups of patients.

References

- ASTER trial: <http://www.hta.ac.uk/project/1603.asp>
- Briggs, A, Claxton, K and Sculpher, M. (2006) *Decision Modelling for Health Economic Evaluation* (Oxford, Oxford University Press).
- Berthelot, J.M. Will, B.P. Evans, W.K. Coyle, D. Earle, C.C. Bordeleau, L. (2000) Decision framework for chemotherapeutic interventions for metastatic non-small cell lung cancer. *Journal of the National Cancer Institute*, 92(16). pp.1321-9.
- Bradbury, I. Bonell, E. Boynton, J. Cummins, E. Facey, K. Iqbal, K. Laking, G. McDonald, C. Parpia, T. Sharp, P. Single, A. and Walker, A. (2002) Health Technology Assessment Report 2 Positron emission tomography (PET) imaging in cancer management. Glasgow: Health Technology Board for Scotland.
- Callister, M. E. J, Gill, A. Allott, W and Plant, P.K. (2008) Endobronchial ultrasound guided transbronchial needle aspiration of mediastinal lymph nodes for lung cancer staging: a projected cost analysis *Thorax* 63;384
- Department of Health (2009) National Lung Cancer Audit 2009 <http://www.ic.nhs.uk/webfiles/Services/NCASP/audits%20and%20reports/NHS%20IC%20Lung%20Cancer%20AUDIT%202009%20FINAL.pdf> accessed: February 2010
- Department of Health (2010) NHS Payment by Results Tariff (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_112284) accessed: Feb 2010
- Department of Health (2010) NHS Reference Costs 2008-9 (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591) accessed: Feb 2010
- Dietlein, M. Weber, K. Gandjour, A. Moka, D. Theissen, P. Lauterbach, K.W et al. (2000) Cost-effectiveness of FDGPET for the management of solitary pulmonary nodules: a decision analysis based on cost reimbursement in Germany. *European Journal of Nuclear Medicine*, 27(10) pp. 1441-56.
- Earle, C. Chapman, R. Baker, C et al. (2000) Systematic Overview of Cost-Utility Assessments in Oncology, *Journal of Clinical Oncology*, Vol 18, Issue 18. pp. 3302-3317
- Gambhir, S.S. Hoh, C.K. Phelps, M.E. Madar, I. Maddahi, J. (1996) Decision tree sensitivity analysis for cost-effectiveness of FDG-PET in the staging and management of non-small-cell lung carcinoma. *Journal of Nuclear Medicine*, 37(9):1428-36.
- Gould, M. K. Kuschner, W. G. Rydzak, C. E. Maclean, C. C. Demas, A. N. Shigemitsu, H. et al. (2003) Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. *Annals of Internal Medicine*, 139, pp. 879-892.
- Gu, P. Zhao, Y. Z. Jiang, L. Y. Zhang, W. Xin, Y. & Han, B. H. (2009). Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. *European Journal of Cancer*, 45, pp. 1389-1396.
- Hunink, M and Glasziou, P. (2001) *Decision making in health and medicine: Integrating evidence and values.* (Cambridge, Cambridge University Press).
- Kee, F. Erridge, S. Bradbury, I. Cairns K. (2010) The value of positron emission tomography in patients with non-small cell lung cancer. *European Journal of Radiology*, 73(1) pp.50-8.
- Mansueto, M. A. Grimaldi, et al. (2007). Cost-effectiveness analysis in the clinical management of patients with known or suspected lung cancer: [18F]fluorodeoxyglucose PET and CT comparison. *The Quarterly Journal of Nuclear Medicine & Molecular Imaging* 51(3): 224-234.
- Nafees, B. Stafford, M. Gavriel, S. et al. (2008) Health state utilities for non small cell lung cancer" *Health and Quality of Life Outcomes*. Vol.6. Issue 84.
- National Institute for Health and Clinical Excellence (2009a) Pemetrexed for the first-line treatment of non-small-cell lung cancer. NICE TA 181 <http://guidance.nice.org.uk/TA181>
- National Institute for Health and Clinical Excellence (2009b) Topotecan for the treatment of relapsed small-cell lung cancer. NICE TA184. <http://guidance.nice.org.uk/TA184>
- National Institute for Health and Clinical Excellence (2008a) Guide to the methods of technology appraisal. <http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp?domeia=1&mid=B52851A3-19B9-E0B5-D48284D172BD8459>

- National Institute for Health and Clinical Excellence (2008b). Erlotinib for the treatment of non-small cell lung cancer. NICE TA 162 <http://guidance.nice.org.uk/TA162>
- National Institute for Health and Clinical Excellence (2005) The diagnosis and treatment of lung cancer. NICE Lung cancer guideline <http://guidance.nice.org.uk/CG24>
- National Institute for Health and Clinical Excellence (2004) Supportive and Palliative care: Economic review <http://guidance.nice.org.uk/index.jsp?action=download&o=28817>
- Nguyen, V. H. S. Peloquin, et al. (2005) Cost-effectiveness of positron emission tomography for the management of potentially operable non-small cell lung cancer in Quebec (Structured abstract). *Canadian Respiratory Journal* 12(1) pp.19-25.
- O'Brien, M. Ciuleanu, T. Tsekov, H. et al. (2006) Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *Journal of Clinical Oncology* pp.5441-5447
- Postmus, Pieter, E. Brambilla, Elisabeth; Chansky, Kari; Crowley, John; Goldstraw, Peter; Patz, Edward F; Yokomise, Hiroyasu (2007). The IASLC Lung Cancer Staging Project: proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM Classification of Lung Cancer. *Journal of Thoracic Oncology*. 2(8) pp.686-693.
- Pozo-Rodriguez, F. Martin de Nicolas, J. L. Sanchez-Nistal, M. A. Maldonado, A. Garcia de, B. S. Calero-Garcia, R. et al. (2005) Accuracy of helical computed tomography and [18F] fluorodeoxyglucose positron emission tomography for identifying lymph node mediastinal metastases in potentially resectable non-small-cell lung cancer. *Journal of Clinical Oncology*, 23, 8348-8356.
- Rusch, Valerie, W. Crowley, John, Giroux, Dorothy, J. Goldstraw, Peter. Im, Jung-Gi. Tsuboi, Masahiro. Tsuchiya, Ryosuke; Vansteenkiste, Johan (2007). The IASLC Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming seventh edition of the TNM Classification for Lung Cancer. *Journal of Thoracic Oncology*. 2(7) pp.603-612
- Sacco, J.J. Botten, J. Macbeth, F. Bagust, A. Clark, P. (2010) The Average Body Surface Area of Adult Cancer Patients in the UK: A Multicentre Retrospective Study. *PLoS ONE* 5(1): e8933. doi:10.1371/journal.pone.0008933
- Scott, W.J. Shepherd, J. Gambhir, S.S. (1998) Cost-effectiveness of FDG-PET for staging non-small cell lung cancer: a decision analysis. *Annals of Thoracic Surgery*, 66(6) pp.1876-83.
- StataCorp. 2009. *Stata Statistical Software*: Release 11. College Station, TX: StataCorp LP.
- TreeAge Pro v.2009 (2009) Boston, MA: TreeAge Software.
- Verboom, P. van Tinteren, H. Hoekstra, O.S. Smit, E.F. Van den Bergh, JHAM. Schreurs, A.J.M. et al. (2003) Cost-effectiveness of FDG-PET in staging non-small cell lung cancer: The PLUS study. *European Journal of Nuclear Medicine & Molecular Imaging*, 30(11): 1449.
- von Schulthess, G.K. Steinert, H.C. Dummer, R. Weder, W. (1998) Cost-effectiveness of whole-body PET imaging in non-small cell lung cancer and malignant melanoma. *Academic Radiology*, 5(Suppl 2), pp. S300-S302.
- Wolstenholme, J.L. & Whymes, D.K (1999) The hospital costs of treating lung cancer in the UK, *British Journal of Cancer* (80) pp.215-218
- Yap, K. K. K. S. Yap, et al. (2005) Positron emission tomography with selected mediastinoscopy compared to routine mediastinoscopy offers cost and clinical outcome benefits for pre-operative staging of non-small cell lung cancer. *European Journal of Nuclear Medicine and Molecular Imaging* 32(9) pp.1033-1040.

Appendix 5

Abbreviations

ACCP	American College of Chest Physicians
AJCC	American Joint Committee on Cancer
CHART	Continuous Hyperfractionated Accelerated Radiotherapy
CI	Confidence Interval
CT	Computerised tomography
CXR	Chest x-ray
DA	Decision aid
DVH	Dose-volume histogram
EBUS	Endobronchial ultrasound
ED	Extensive stage disease
EBUS	Endobronchial ultrasound
EUS	Endoscopic ultrasound
FEV	¹⁸ F-deoxyglucose
FNA	Fine needle aspiration
FP	False positive
GDG	Guideline Development Group
GP	General Practitioner
HTA	Health Technology Assessment
IASLC	International Association for the Study of Lung Cancer
ICER	Incremental Cost Effectiveness Ratio
LD	Limited stage disease
LY	Life-year
MDT	Multidisciplinary Team
MLD	Mean lung dose
MRI	Magnetic Resonance Imaging
NLCA	National Lung Cancer Audit
NSCLC	Non-Small Cell Lung Cancer
PCI	Prophylactic Cranial Irradiation
PDT	Photodynamic therapy
PET	Positron Emission Tomography
PPV	Positive predictive value
PTV	Planning target volume
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RT	Radiotherapy
SBRT	Stereo-tactic body radiotherapy
SCLC	Small cell lung cancer
SEER	Surveillance epidemiology and end results
SRS	Stereotactic radiosurgery
SVCO	Superior vena caval obstruction
TBNA	Transbronchial needle aspiration
UICC TNM	Union Internationale Contre le Cancer
US	Ultrasound
VALSG	Veterans Administration Lung Study Group
VATS	Video assisted thoracoscopy
WHO	World Health Organisation

Appendix 6

Glossary

Absolute risk

Measures the probability of an event or outcome occurring (e.g. an adverse reaction to the drug being tested) in the group of people under study. Studies that compare two or more groups of patients may report results in terms of the *Absolute Risk Reduction*.

Absolute Risk Reduction (ARR)

The ARR is the difference in the risk of an event occurring between two groups of patients in a study – for example if 6% of patients die after receiving a new experimental drug and 10% of patients die after having the old drug treatment then the ARR is $10\% - 6\% = 4\%$. Thus by using the new drug instead of the old drug 4% of patients can be prevented from dying. Here the ARR measures the risk reduction associated with a new treatment. See also *Absolute risk*.

Adjuvant chemotherapy

The use of chemotherapy, after initial treatment by surgery and/or radiotherapy, to reduce the risk of recurrence of the cancer.

Adjuvant radiotherapy

The use of radiotherapy after treatment by surgery to reduce the risk of recurrence of the cancer.

Asymptomatic

Without obvious signs or symptoms of disease. Cancer may cause symptoms and warning signs, but, especially in its early stages, cancer may develop and grow without producing any symptoms.

Benign

Non-cancerous. Does not metastasise (spread to other organs) and treatment or removal is usually curative.

Bias

Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually doesn't. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data.

Biopsy

Removal of a sample of tissue from the body to assist in diagnosis of a disease.

Blinding or masking

The practice of keeping the investigators or subjects of a study ignorant of the group to which a subject has been assigned. For example, a clinical trial in which the participating patients or their doctors are unaware of whether they (the patients) are taking the experimental drug or a placebo (dummy treatment). The purpose of 'blinding' or 'masking' is to protect against *bias*.

Brachytherapy

A form of radiotherapy in which the radiation is given using a radioactive source using wires inserted into the airways, delivering the radiation to a very localised area of lung.

Bronchoplasty

Plastic surgery of a bronchus; surgical closure of a bronchial fistula.

Bronchoscopy

An examination of the major air passages of the lungs.

Broncho-angioplastic

A surgical technique involving the main arteries and air passages in the lungs.

Cancer networks

The organisations for cancer services to implement the NHS Cancer Plan and Cancer Reform Strategy, bringing together health service commissioners and providers, the voluntary sector and local authorities.

Case-control study

A study that starts with the identification of a group of individuals sharing the same characteristics (e.g. people with a particular disease) and a suitable comparison (control) group (e.g. people without the disease). All subjects are then assessed with respect to things that happened to them in the past, e.g. things that might be related to getting the disease under investigation. Such studies are also called *retrospective* as they look back in time from the outcome to the possible causes.

Case report (or case study)

Detailed report on one patient (or case), usually covering the course of that person's disease and their response to treatment.

Case series

Description of several cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (*control*) group of patients.

Chemotherapy

The use of drugs that kill cancer cells, or prevent or slow their growth.

Chemo-radiotherapy

The planned use of a combination of chemotherapy and radiotherapy in combination in the treatment of cancer.

Chronic Obstructive Pulmonary Disease (COPD)

An 'umbrella' term for people with chronic bronchitis, emphysema, or both. With COPD the airflow to the lungs is restricted (obstructed).

Cohort study

An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, e.g. comparing mortality between one group that received a specific treatment and one group which did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

Combined modality

Use of different treatments in combination (for example surgery, chemotherapy and radiotherapy used together) (see chemo-radiotherapy).

Co-morbidity

Co-existence of a disease or diseases in the people being studied in addition to the health problem that is the subject of the study.

Computed tomography (CT)

An x-ray imaging technique, which allows detailed investigation of the internal organ of the body.

Control group

A group of patients recruited into a study that receives no treatment, a treatment of known effect, or a placebo (dummy treatment) - in order to provide a comparison for a group receiving an experimental treatment, such as a new drug.

Controlled clinical trial (CCT)

A study testing a specific drug or other treatment involving two (or more) groups of patients with the same disease. One (the experimental group) receives the treatment that is being tested, and the other (the comparison or control group) receives an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. A CCT where patients are randomly allocated to treatment and comparison groups is called a *randomised controlled trial*.

Cost benefit analysis

A type of economic evaluation where both costs and benefits of health care treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

Cost-effectiveness

Value for money.

Cost effectiveness analysis

A type of economic evaluation that compares the costs and benefits of different treatments. In cost-effectiveness analysis benefits are measured in clinical outcome units, for example, additional heart attack prevented, life years gained, etc. When a new treatment is compared with current care, its additional costs divided by its additional benefits is called the cost effectiveness ratio.

Cost utility analysis

A special form of *cost effectiveness analysis* where benefit is measured in *quality adjusted life years*. A treatment is assessed in terms of its ability to extend or improve the quality of life.

Cross-sectional study

The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a *longitudinal study* which follows a set of people over a period of time).

Cryotherapy

A treatment which aims to eradicate cancer by freezing.

Decision aids

Booklets or videos/DVDs that provide information about the disease, treatment options and outcomes, and help patients to explore how their individual values impact on their treatment decision.

Decision analysis

A systematic way of reaching decisions, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.

Diaphragm

A large dome-shaped muscle at the bottom of the chest cavity that is the primary breathing muscle.

Diagnostic study

A study to assess the effectiveness of a test or measurement in terms of its ability to accurately detect or exclude a specific disease.

Double blind study

A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.

Economic evaluation

Economic evaluation is a comparative analysis of costs and consequences of each alternative in order to provide explicit criteria for making choices.

Elective

Name for planned clinical procedures that are regarded as advantageous to the patient but not urgent.

Electrocautery

A treatment which aims to eradicate cancer by burning with electrical energy.

Emphysema

A long-term, progressive disease of the lung that primarily causes shortness of breath and whose main cause is tobacco smoking.

Endobronchial ultrasound (EBUS)

The use of ultrasound to examine either the airway wall or lymph nodes/masses in and around the airways. An ultrasound transducer is mounted on a specially adapted bronchoscope and the examination is performed during a bronchoscopic procedure.

Endoscopic ultrasound (EUS)

The use of ultrasound to examine lymph nodes/masses around the oesophagus. An ultrasound transducer is mounted on a specially adapted endoscope and the examination is performed during an endoscopy procedure.

Epidemiology

The study of populations in order to determine the frequency and distribution of disease and measure risks.

Evidence based

The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.

Evidence based clinical practice

Evidence based clinical practice involves making decisions about the care of individual patients based on the best research evidence available rather than basing decisions on personal opinions or common practice (which may not always be evidence based). Evidence based clinical practice therefore involves integrating individual clinical expertise and patient preferences with the best available evidence from research.

Evidence table

A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

Exclusion criteria

See Selection criteria.

Extensive stage disease

A term used to define the extent of small cell lung cancer. Broadly this includes all small cell lung cancers that have metastasised outside of the thorax. See Chapter 7 and definition of limited stage disease for further details. Using the 7th edition of the TNM classification this now includes T1-4, N1-3, M1a/b disease.

Fine needle aspiration (FNA)

The use of a fine needle (usually 21G or 22G) to sample a lymph node or mass. Commonly this is performed to sample lymph nodes in the neck. During the procedure, a syringe on the end of the needle is used to suck cells into the needle as it is moved backwards and forwards inside the target. This can be performed with or without ultrasound guidance.

Fluoroscopy

An imaging technique commonly used by physicians to obtain real-time moving images of the internal structures of a patient through the use of a fluoroscope. In its simplest form, a fluoroscope consists of an X-ray source and fluorescent screen between which a patient is placed.

Focus group

A *qualitative research* technique. It is a method of group interview or discussion of between 6–12 people focused around a particular issue or topic. The method explicitly includes and uses the group interaction to generate data.

Gold standard

A method, procedure or measurement that is widely accepted as being the best available.

Gray (Gy)

Unit of absorbed radiation dose.

Haemoptysis

Coughing up of blood or of blood-stained sputum from the bronchi, larynx, trachea, or lungs.

Health economics

The study of the allocation of scarce resources among alternative health care treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.

Heterogeneity

Or lack of *homogeneity*. The term is used in *meta-analyses* and *systematic reviews* when the results or estimates of effects of treatment from separate studies seem to be very different – in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur as a result of differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.

Histological

Relating to the study of cells and tissue at the microscopic level.

Homogeneity

This means that the results of studies included in a *systematic review* or *meta analysis* are similar and there is no evidence of *heterogeneity*. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.

Hypercalcaemia

A medical condition in which abnormally high concentrations of calcium compounds are found in the bloodstream.

In situ

A cancer that is in the natural place, is non-invasive without invading neighbouring tissue.

Lobectomy

A surgical procedure that is used to take out part of the lung (called a lobe).

Life year

A measure of health outcome which shows the number of years of remaining life expectancy.

Limited stage disease

A staging classification for small cell lung cancer developed by the Veterans' Administration Lung Study Group. Limited stage disease small cell lung cancer is characterised by tumours confined to one hemi-thorax; local extension and ipsilateral supraclavicular lymph nodes can be present if they can be encompassed in a potentially curative radiotherapy volume. No extra-thoracic metastases should be present. Using the 7th edition of the TNM staging system this broadly includes T1-4, N1-3, M0 disease.

Lymph

Almost colourless fluid that bathes body tissues and is carried by lymphatic vessels. Contains cells that help fight infection and disease.

Lymph nodes or glands

Small bean-shaped organs located along the lymphatic system. Nodes filter bacteria or cancer cells that might spread through the lymphatic system and to other parts of the body.

Magnetic Resonance Imaging (MRI)

A special imaging technique used to image internal structures of the body, particularly the soft tissues. An MRI image is often superior to a normal plain x-ray image. It uses the influence of a large magnet to polarize hydrogen atoms in the tissues and then monitors the summation of the spinning energies within living cells. Images are very clear and are particularly good for soft tissue, brain and spinal cord, joints and abdomen. These scans may be used for detecting some cancers or for following their progress.

Malignant

Cancerous. Malignant tumours can invade and destroy surrounding tissue and have the capacity to spread.

Mediastinoscopy and Mediastinotomy

Type of 'keyhole' surgery that allow doctors to look inside the chest. It can be used to take samples of tissue for further testing. Often used to assess the stage of the cancer in the chest.

Meta analysis

Results from a collection of independent studies (investigating the same treatment) are pooled, using statistical techniques to synthesise their findings into a single estimate of a treatment effect. Where studies are not compatible e.g. because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to statistically pool results in this way. See also *Systematic review & Heterogeneity*.

Metastases/metastatic disease

Spread of cancer away from the primary site to somewhere else via the bloodstream or the lymphatic system.

Morbidity

The state of being diseased.

Mortality

Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in any specific region, age group, disease or other classification, usually expressed as deaths per 1000, 10,000 or 100,000.

Multi Disciplinary Team (MDT)

A team with members from different health care professions (e.g. surgery, oncology, pathology, radiology, nursing).

Negative lymph nodes

Lymph nodes showing no signs of cancer.

Neoadjuvant chemotherapy

Chemotherapy that is given before the treatment of a primary tumour with the aim of reducing the size of the cancer and preventing the development of metastases.

Nodule

A spherical or near-spherical abnormality in an organ, often seen in the lungs. They may be benign or malignant and can represent metastatic disease.

Non-experimental study

A study based on subjects selected on the basis of their availability, with no attempt having been made to avoid problems of bias.

NSCLC

Non-Small Cell Lung Cancer. A group of different types of lung cancer, including Squamous Cell Carcinoma, Adenocarcinoma and Large Cell Carcinoma.

Observational study

In research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies.

Odds ratio

Odds are a way of representing probability, especially familiar for betting. In recent years odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a *confidence interval*) for the effect of a treatment. Odds are used to convey the idea of 'risk' and an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks and not odds) will be very similar.

Oncology

The study of cancers.

Opioids

A chemical substance that has a morphine-like action in the body. The main use is for pain relief.

Palliative

One which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it.

Palliative care

The active holistic care of patients with advanced, progressive illness. Management of pain and other symptoms and the provision psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality of life for patients and families. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with other treatments.

Parenchymal sparing

Surgical or radiotherapy techniques aimed at minimising damage to the normal tissues.

Performance status

A measure of how well a patient is able to perform ordinary tasks and carry out daily activities. (PS WHO score of 0=asymptomatic, 4=bedridden, or a Karnofsky score of 0=dead, 100=asymptomatic.

Photodynamic therapy (PDT)

Uses laser, or other light sources, combined with a light-sensitive drug (sometimes called a photosensitising agent) to destroy cancer cells.

Pneumonectomy

Surgical procedure to remove a whole lung.

Pneumothorax

Air that is trapped on the outside of a lung that impairs its full function.

Positron emission tomography (PET)

A specialised imaging technique using a radioactive tracer to produce a computerised image of metabolic activity in body tissues and find abnormalities. PET scans may be used to help diagnose cancer, to see how far it has spread and to investigate response to treatment. Since PET looks at function, it is often combined with CT [PET-CT] which reveals the underlying structure.

Pilot study

A small scale 'test' of the research instrument. For example, testing out (piloting) a new questionnaire with people who are similar to the population of the study, in order to highlight any problems or areas of concern, which can then be addressed before the full scale study begins.

Placebo

Placebos are fake or inactive treatments received by participants allocated to the *control group* in a clinical trial which are indistinguishable from the active treatments being given in the experimental group. They are used so that participants are ignorant of their treatment allocation in order to be able to quantify the effect of the experimental treatment over and above any *placebo effect* due to receiving care or attention.

Placebo effect

A beneficial (or adverse) effect produced by a *placebo* and not due to any property of the *placebo* itself.

Pleural effusion

A collection of fluid between the lung and the rib cage and diaphragm often resulting in some loss of volume of the lung.

Pleurodesis

A collection of techniques which result in adherence of the lung to the inside of the chest wall to prevent its collapse, due to either a pleural effusion or a pneumothorax.

Pneumonitis

Inflammation of lung tissue.

Positive lymph nodes

Lymph nodes that contain cancer cells.

Predictive factor

A condition or finding that can be used to help predict whether a person's cancer will respond to a specific treatment. Predictive factors may also describe something that increases a person's risk of developing a condition or disease.

Primary care

Healthcare delivered to patients outside hospitals. Primary care covers a range of services provided by GPs, nurses and other health care professionals, dentists, pharmacists and opticians.

Primary tumour

Original site of the cancer.

Prognostic factor

Patient or disease characteristics, e.g. age or *co-morbidity*, which influence the course of the disease under study. In a randomised trial to compare two treatments, chance imbalances in variables (prognostic factors) that influence patient outcome are possible, especially if the size of the study is fairly small. In terms of analysis these prognostic factors become *confounding factors*.

Progression

A term used to indicate that a primary cancer or metastases have increased in size or new metastases have developed.

Prophylactic Cranial Irradiation

Radiotherapy to the brain with the intention of reducing the risk of developing brain metastases.

Prospective study

A study in which people are entered into the research and then followed up over a period of time with future events recorded as they happen. This contrasts with studies that are *retrospective*.

Psychological support

Professional support which can help people with a wide range of psychological problems such as anxiety and depression, and can provide emotional assistance during times of distress.

P value

If a study is done to compare two treatments then the *P* value is the probability of obtaining the results of that study, or something more extreme, if there really was no difference between treatments. (The assumption that there really is no difference between treatments is called the 'null hypothesis'.) Suppose the *P*-value was $P=0.03$. What this means is that if there really was no difference between treatments then there would only be a 3% chance of getting the kind of results obtained. Since this chance seems quite low we should question the validity of the assumption that there really is no difference between treatments. We would conclude that there probably is a difference between treatments. By convention, where the value of *P* is below 0.05 (i.e. less than 5%) the result is seen as statistically significant. Where the value of *P* is 0.001 or less, the result is seen as highly significant. *P* values just tell us whether an effect can be regarded as statistically significant or not. In no way do they relate to how big the effect might be, for which we need the *confidence interval*.

Qualitative research

Qualitative research is used to explore and understand people's beliefs, experiences, attitudes, behaviour and interactions. It generates non-numerical data, e.g. a patient's description of their pain rather than a measure of pain. In health care, qualitative techniques have been commonly used in research documenting the experience of chronic illness and in studies about the functioning of organisations. Qualitative research techniques such as *focus groups* and in depth interviews have been used in one-off projects commissioned by guideline development groups to find out more about the views and experiences of patients and carers.

Quality adjusted life years (QALYS)

A measure of health outcome. QALYS are calculated by estimating the number of years of life gained from a treatment and weighting each year with a quality of life score between zero and one.

Quantitative research

Research that generates numerical data or data that can be converted into numbers, for example clinical trials or the national Census which counts people and households.

Radiotherapy

The use of radiation, including x-rays, gamma rays or electrons, to kill cancer cells and treat tumours.

Randomised controlled trial (RCT)

A study to test a specific drug or other treatment in which people are randomly assigned to two (or more) groups: one (the experimental group) receiving the treatment that is being tested, and the other (the comparison or control group) receiving an alternative treatment, a placebo (dummy treatment) or no treatment. The two groups are followed up to compare differences in outcomes to see how effective the experimental treatment was. (Through randomisation, the groups should be similar in all aspects apart from the treatment they receive during the study.)

Relapse

A term that is sometimes used when a previously treated cancer recurs at the same site or elsewhere as a metastasis. In some situations it may also be used when a cancer that has previously been controlled by treatment starts to increase in size.

Retrospective study

A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are *prospective*.

SCLC

Small Cell Lung Cancer.

Secondary care

Care provided in hospitals.

Selection criteria

Explicit standards used by guideline development groups to decide which studies should be included and excluded from consideration as potential sources of evidence.

Sensitivity

In diagnostic testing, it refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a ‘false positive’. The sensitivity of a test is also related to its ‘negative predictive value’ (true negatives) – a test with a sensitivity of 100% means that all those who get a negative test result do not have the disease. To fully judge the accuracy of a test, its *Specificity* must also be considered.

Sleeve resection

Surgery to remove a lung tumor 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.

Specificity

In diagnostic testing, it refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a ‘false negative’. The specificity of a test is also related to its ‘positive predictive value’ (true positives) – a test with a specificity of 100% means that all those who get a positive test result definitely have the disease. To fully judge the accuracy of a test, its *Sensitivity* must also be considered.

Staging

Process of describing to what degree cancer has spread from its original site to another part of the body. Staging involves clinical, surgical and pathology assessments.

Stereotactic radiosurgery (SRS)

The precise delivery of a single fraction of an ablative dose of irradiation to an image-defined intracranial lesion.

Stereotactic body radiotherapy (SBRT)

SBRT is a form of external beam radiotherapy using specialised equipment to precisely deliver highly focused radiation to benign or malignant tumours in the body. This technique enables a high dose of radiotherapy to be delivered to tumours in a small number of treatments, whilst sparing the surrounding healthy tissue. It usually requires specialist positioning equipment'

Stridor

A high pitched sound resulting from turbulent air flow in the upper airway (usually trachea or main bronchi).

Superior vena caval obstruction (SVCO),

The result of the direct obstruction of the superior vena caval (the main vein in the upper chest) usually as a consequence of compression or destruction by malignant tumours.

Supportive care

'...helps the patient, partners, carers and their family to cope with cancer and treatment of it – from pre-diagnosis, through the process of diagnosis and treatment, to cure, continuing illness, palliative care or death and into bereavement. It helps the patient to maximise the benefits of treatment and to live as well as possible with the effects of the disease. It is given equal priority alongside diagnosis and treatment.'

Survival

Survival is the probability of surviving with a diagnosis of a disease.

Systematic review

A review, in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. May or may not include a *meta-analysis*.

Thermal laser ablation

A treatment which aims to remove cancer tissue by laser energy.

Thoracoscopy

An examination of the space between the rib cage and the lung by inserting an endoscope (a narrow diameter tube with a viewing mirror or camera attachment) through a very small incision (cut) in the chest wall.

Thoracscore

A scoring tool to estimate operative mortality in thoracic surgery. www.sfar.org./scores2/thoracscore2.php

TNM classification

TNM classification provides a system for staging the extent of cancer. T refers to the size of the primary tumour. N refers to the involvement of the lymph nodes. M refers to the presence of metastases or distant spread of the disease.

Transbronchial needle aspiration (TBNA)

The use of a fine needle (usually 21G or 22G) to sample a lymph node or mass by passing the needle through an airway wall. During the procedure, a syringe on the end of the needle is used to suck cells into the needle as it is moved backwards and forwards inside the target. This can be performed with or without ultrasound guidance.

Tumour

A mass of tissue formed by a new growth of cells, normally independent of the surrounding structures.

Ultrasound

A painless test that uses sound waves to create images of organs and structures inside your body. It is a very commonly used test.

Vertebroplasty

Vertebroplasty is an image-guided, minimally invasive, nonsurgical therapy used to strengthen a broken vertebra (spinal bone) that has been weakened by osteoporosis or, less commonly, cancer. Percutaneous vertebroplasty involves the injection of acrylic bone cement into the vertebral body in order to relieve pain and/or stabilise the fractured vertebrae and in some cases, restore vertebral height.

X-ray

A radiograph made without use of a contrast medium.

Appendix 7

Guideline Scope

Guideline title

The diagnosis and treatment of lung cancer (update of NICE clinical guideline 24).

Short title

Lung cancer update.

Background

The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Cancer to review recent evidence on the management of lung cancer and to update the existing guideline 'The diagnosis and treatment of lung cancer' (NICE clinical guideline 24, 2005) for use in the NHS in England and Wales. The update will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

NICE clinical guidelines support the implementation of National Service Frameworks (NSFs) in those aspects of care for which a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by NICE after an NSF has been issued have the effect of updating the Framework.

NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, if appropriate) can make informed decisions about their care and treatment.

Clinical need for the guideline

There are more than 38,000 new cases of lung cancer in the UK each year and more than 35,000 people die from the condition; more than for breast cancer and colorectal cancer combined.

Lung cancer is now the leading cause of cancer death in women.

About 90% of lung cancers are caused by smoking. Now that fewer men smoke, lung cancer deaths in men have decreased by more than a quarter in the UK (a 27% reduction between 1971 and 2006). However, the number of women who smoke has risen and deaths from lung cancer in women have increased.

Only about 5.5% lung cancers can be cured. Although the cure rate is rising slowly, the rate of improvement has been slower than that for other common cancers.

Outcomes in the UK are worse than those in some European countries and North America.

There is evidence that outcomes vary within the UK, which – among other factors – may be explained by variations in the standard of care.

NICE clinical guidelines are regularly reviewed, and updated as necessary. As part of its review of NICE clinical guideline 24, the National Collaborating Centre for Cancer convened a Lung Cancer Expert Advisory Group in June 2007 to discuss whether any part (or all) of the existing

guideline needed updating. The advisory group comprised members of the original Guideline Development Group and other invited specialists involved in the delivery of lung cancer services.

The Advisory Group identified significant progression and expansion of the evidence base since the publication of NICE clinical guideline 24, indicating that a large number of recommendations would need to be updated. It also identified new topics not included in the original guideline.

In September 2007 the NICE Guidance Executive agreed to a partial update of the guideline (including new topics where appropriate) with an 18 month development time. In order to produce a high quality update within the allotted time, in line with the methods set out in 'The guidelines manual' (2009), it will not be possible to update the entire lung cancer guideline. Therefore we intend to focus on topics:

- for which there is important new published evidence
- that are still controversial or uncertain
- in which there continues to be identifiable variation in practice, and
- that will have the most significant impact on the clinical service and management of patients with lung cancer.

A draft list of the prioritised clinical topics to be included in the updated guideline were then developed using advice from the Advisory Group, the GDG chair, the GDG clinical lead and attendees at the stakeholder scoping workshop. These topics were included as an Appendix in the draft scope that was issued to stakeholders for consultation in November 2008.

The guideline

The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.

This scope defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider.

The guideline update will include:

- updated topics and recommendations, and supporting evidence
- new topics and recommendations, and supporting evidence
- 'old' topics and recommendations that do not need updating and are therefore still valid.

The evidence that supported these recommendations will not be updated.

There will be some important topics that need updating but are not part of the final prioritised list. These will be added to a holding list for future consideration and the final guideline will make this clear to the reader.

The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

Adults (18 years and older) with newly diagnosed non-small-cell lung cancer (NSCLC).

Adults with newly diagnosed small cell lung cancer (SCLC).

Adults with relapsed NSCLC.

Adults with relapsed SCLC.

Groups that will not be covered

Adults with mesothelioma.

Adults with lung metastases arising from primary cancers originating outside the lung.

Children (younger than 18) with lung cancer.

Adults with rare lung tumours (for example, pulmonary blastoma).

Adults with benign lung tumours (for example, bronchial adenoma).

Healthcare setting

Primary care – excluding population-based and opportunistic screening and prevention.

Secondary care.

Tertiary care by services offering specialist care (for example, thoracic surgery, radiotherapy and interventional bronchoscopy).

Clinical management (including service delivery where appropriate)

- Diagnosis and staging.
- Information for patient and carers.
- Radical treatment of patients with NSCLC.
- Palliative endobronchial therapies.
- Management of patients with SCLC.
- Follow up.
- Service organisation and inequality of management at key decision points to be addressed by the needs assessment Status

Status

Scope

This is the final scope.

Guideline

The development of the guideline recommendations will begin in February 2009.

Related NICE guidance

Published guidance

The following guidance will be cross referred to as appropriate:

- Bevacizumab for the treatment of non-small-cell lung cancer (terminated appraisal). NICE technology appraisal 148 (2008). See www.nice.org.uk/TA148
- Erlotinib for the treatment of non-small cell lung cancer. NICE technology appraisal guidance 162 (2008). Available from www.nice.org.uk/TA162
- Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for mediastinal masses. NICE interventional procedure guidance 254 (2008). Available from www.nice.org.uk/IPG254
- Pemetrexed for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance 124 (2007). Available from www.nice.org.uk/TA124
- Percutaneous radiofrequency ablation for primary and secondary lung cancers. NICE interventional procedure guidance 185 (2006). Available from www.nice.org.uk/IPG185
- Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005). Available from www.nice.org.uk/CG027

- Photodynamic therapy for localised inoperable endobronchial carcinoma. NICE interventional procedure guidance 137 (2005). Available from www.nice.org.uk/IPG137
- Photodynamic therapy for advanced bronchial carcinoma. NICE Interventional procedure guidance 87 (2004). Available from www.nice.org.uk/IPG087
- Cryosurgery for malignant endobronchial obstruction. NICE interventional procedure guidance 142 (2005). Available from www.nice.org.uk/IPG142
- Improving supportive and palliative care for adults with cancer. Guidance on cancer services (2004). Available from www.nice.org.uk/csgsp
- Docetaxel, paclitaxel, gemcitabine and vinorelbine for the treatment of non-small cell lung cancer. NICE technology appraisal guidance 26 (2001). Available from www.nice.org.uk/TA26 (updated by and incorporated into NICE clinical guideline 24).

Relevant guidance published by other organisations

- Department of Health (1998) Guidance on commissioning cancer services: improving outcomes in lung cancer: the manual. London: Department of Health. Available from: www.dh.gov.uk

Under development

NICE is in the process of developing the following guidance (details available from www.nice.org.uk). Recommendations from these technology appraisals will be incorporated in the lung cancer guideline update.

- Pemetrexed for the first-line treatment of non-small cell-lung cancer. NICE technology appraisal guidance. Publication expected August 2009.
- Topotecan for the treatment of small-cell-lung cancer (second line treatment). NICE technology appraisal guidance. Publication expected November 2009.
- Cetuximab for the treatment of advanced non-small-cell lung cancer. NICE technology appraisal guidance. Publication expected November 2009.
- Gefitinib for the treatment of non-small-cell lung cancer. NICE technology appraisal guidance. Publication expected January 2010.
- Erlotinib, in combination with bevacizumab for the maintenance treatment of non-squamous advanced or metastatic non-small-cell lung cancer after previous platinum-containing chemotherapy. NICE technology appraisal guidance. Publication expected October 2010.
- Pemetrexed for maintenance treatment following first-line chemotherapy for non-small-cell lung cancer. NICE technology appraisal guidance. Publication date to be confirmed.
- Erlotinib monotherapy for the maintenance treatment of non-small-cell lung cancer after previous platinum containing chemotherapy. NICE technology appraisal guidance. Publication date to be confirmed.
- Vandetanib within its licensed indications, for the second and subsequent line treatment of non-small-cell lung cancer after previous platinum containing chemotherapy. NICE technology appraisal guidance. Publication date to be confirmed.

Further information

- The guideline development process is described in: 'How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS'
- 'The guidelines manual'.

These are available from www.nice.org.uk/guidelinesmanual. Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix 8

List of topics covered by each chapter

Chapter 3 – Communication

- For patients with lung cancer and their carers, what is the effectiveness of communication methods to support decisions regarding treatment options?

Chapter 4 – Diagnosis and staging

- How effective are diagnostic and staging investigations in patients with suspected/confirmed lung cancer?

Chapter 5 – Treatment with curative intent for NSCLC

- Key measures of fitness that predict whether or not patients with lung cancer can be treated with curative intent
- What is the most effective treatment for patients with resectable non-small cell lung cancer?
- Does pre-operative smoking cessation/pre-operative pulmonary rehabilitation improve outcomes following lung cancer surgery?
- Combination treatment for patients with non-small cell lung cancer

Chapter 7 – Treatment of SCLC

- What is the most effective first line treatment for patients with limited disease small cell lung cancer?
- What is the most effective first line treatment for patients with limited disease small cell lung cancer?
- What is the most effective regimen of chemotherapy for patients with extensive disease small cell lung cancer?
- Which group of patients with small cell lung cancer are suitable for second line treatment?
- How effective is surgical treatment for patients with small cell lung cancer?

Chapter 8 – Palliative interventions and Supportive and Palliative Care

- How effective are brachytherapy/(airway) stenting/photodynamic therapy/laser/ electrocautery/ cryotherapy/(surgical) debulking (via rigid bronchoscope) for treatment of patients with lung cancer with endobronchial obstructions?
- How effective is treatment in the management of brain metastases in lung cancer patients?

Chapter 9 – Follow up and patient perspectives

- What is the most effective follow-up model for lung cancer patients?

Appendix 9

People and organisations involved in production of the guideline

- 9.1 Members of the Guideline Development Group
- 9.2 Organisations invited to comment on guideline development
- 9.3 Individuals carrying out literature reviews and complementary work
- 9.4 Expert advisers to the Guideline Development Group
- 9.5 Members of the Guideline Review Panel

Appendix 9.1

Members of the Guideline Development Group (GDG) 2011

GDG Chair

Mr Barrie White	Neurosurgeon, Queens Medical Centre, Nottingham
Professor Mark Baker ¹	Divisional Medical Director for Oncology and Surgery and Lead Cancer Clinician, Leeds Teaching Hospitals NHS Trust

GDG Lead Clinician

Dr David Baldwin	Consultant Physician, Nottingham University Hospital NHS Trust
------------------	----------------------------------------------------------------

Group Members

Barry Attwood	Patient/Carer Representative
Mr Sion Barnard	Consultant Thoracic Surgeon, Freeman Hospital, Newcastle-upon-Tyne
Dr Jeremy Braybrooke	Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust
Dr Paul Cane	Consultant Histopathologist, Guys & St Thomas' NHS Foundation Trust
Dr James Entwisle	Consultant Radiologist, Glenfield Hospital, University Hospitals of Leicester NHS Trust
Dr Jesme Fox	Patient/Carer Representative, The Roy Castle Lung Cancer Foundation
Thomas Haswell	Patient/Carer Representative
Mr Matthew Hatton	Consultant Clinical Oncologist, Weston Park Hospital, Sheffield
Dana Knoyle	Macmillan Lung Cancer Nurse Specialist, Prince Charles Hospital, Cwm Taf Health Board
Dr Richard Neal	Senior Lecturer in General Practice, North Wales Clinical School, Cardiff University
Mr Richard Page	Consultant Thoracic Surgeon, Liverpool Heart and Chest Hospital
Bob Park	Director, North East London Cancer Network
Sue Pascoe	Lung Cancer Clinical Nurse Specialist, Royal Cornwall Hospital
Dr Michael Peake	Consultant and Senior Lecturer in Respiratory Medicine, Glenfield Hospital, University Hospitals of Leicester NHS Trust
Dr Robert Rintoul	Consultant Respiratory Physician, Papworth Hospital NHS Foundation Trust, Cambridge
Dr Andrew Wilcock	Macmillan Clinical Reader in Palliative Medicine and Medical Oncology, Nottingham University Hospitals NHS Trust
Dr Abebaw Yohannes	Reader in Physiotherapy, Manchester Metropolitan University

¹ November 2008 – June 2009

Declarations of interest

The Guideline Development Group were asked to declare any possible conflicts of interest which could interfere with their work on the guideline. The interests that were declared are as follows:

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Mark Baker	Fees from unrestricted educational grants for contributions to conferences funded by members of the pharmaceutical industry.	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics
Jeremy Braybrooke	American Society of Clinical Oncology (ASCO), Orlando (2009), Chicago (2010). Grants to cover travel plus registration and accommodation. Roche and Pfizer respectively.	Personal pecuniary, non-specific	Declare and can participate in discussions
	Received an honorarium from Boehringer Ingelheim for attending an advisory board on afatinib for second/third line treatment of advanced NSCLC in December 2010.	Personal pecuniary, specific	Declare and must withdraw from discussion on all topics that include afatinib until December 2011 ¹
Jesme Fox	Employer has received grants from pharmaceutical and commercial businesses. Have also attended conferences and participated in advisory boards organised by pharmaceutical companies. Donations have been given by the company to RCLCF in lieu of time	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics
Tom Haswell	Given media interviews on personal views as a lung cancer patient.	Personal non-pecuniary	Declare and can participate in discussions on all topics
Robert Rintoul	Papworth Hospital NHS Trust acts as a reference centre for bronchoscopy equipment for Olympus KeyMed and as such are in receipt of loan equipment used for the diagnosis of lung cancer. Olympus KeyMed have also provided unrestricted educational grants to support annual endobronchial ultrasound course.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics
Matthew Hatton	Advisory Board Consultancy fee received from GSK. Travel bursary to attend ASCO conference 2008 from Roche	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include GSK and Roche interventions
Michael Peake	Fellow of the RCP and RCR. Member of NCRI Lung cancer Clinical Research Group and member of the British Thoracic Oncology Group Steering Committee	Personal non-pecuniary	Declare and can participate in discussions on all topics
	American Society of Clinical Oncology (ASCO), Chicago. Grant to cover travel plus registration and accommodation. Roche	Personal pecuniary, non-specific	Declare and can participate in discussions
	World Lung Cancer Conference, Seoul, Korea. Grant to cover travel plus registration and accommodation. Roche	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts

¹ Afatinib was not included in any of the topics investigated by the guideline and was therefore not discussed by the GDG

GDG Member	Interest Declared	Type of Interest	Decisions Taken
	British Thoracic Society Winter Meeting, London. Registration fee and accommodation. Boehringer Igelheim Ltd	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	British Thoracic Oncology Group Annual Meeting, Dublin. Grant towards travel and accommodation. Eli Lilly & Co	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	American Society for Clinical Oncology Annual Meeting, Chicago. Grant towards travel, accommodation and registration. Roche	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	European Respiratory Society Annual Meeting, Berlin. Travel grant plus registration and accommodation. Boehringer Igelheim Ltd	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	In the Institute for Lung Health in Leicester I run an annual 2 day educational course on lung cancer for which we receive sponsorship from Eli Lilly & Co, Pierre Fabre Oncology, Sanofi Aventis and Roche Pharmaceuticals	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
	Remunerated lectures: 1. "The Lung Cancer and Mesothelioma Advisory Group and the Cancer Reform Strategy. The practical management of thoracic cancers, British Library, London, 21st November 2007 Sponsored by Eli Lilly – title and content chosen entirely by myself.	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include Eli Lilly interventions
	2. "The value of second line chemotherapy in Small Cell Lung Cancer." British Thoracic Oncology Group National Conference on Small Cell Lung Cancer. Christie Hospital, Manchester, 25th September 2008. Speaker fee covered by a grant from GSK pharmaceuticals. Title and content chosen entirely by myself and an independent conference organising group.	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include GSK interventions
	Advisory Board for Roche Pharmaceuticals, Manchester	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include Roche interventions
	Advisory Board for Roche Pharmaceuticals, Cambridge	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include Roche interventions
	Advice to GSK regarding health economics of lung cancer	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include GSK interventions

GDG Member	Interest Declared	Type of Interest	Decisions Taken
	Advice to Pfizer Ltd regarding health economics of lung cancer	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include Pfizer interventions
	Advisory Board for Astra Zeneca pharmaceuticals	Personal pecuniary, specific	Declare and must withdraw from discussions on all topics that include AstraZeneca interventions

Members of the Guideline Development Group (GDG) 2005

GDG Chair

Dr Jesme Baird (Chair) Director of Patient Care, The Roy Castle Lung Cancer Foundation; patient representative

Group Members

Ms Caroline Belchamber* Senior Oncology Physiotherapist, Poole Hospital, Dorset; Chartered Society of Physiotherapy

Dr David Bellamy General Practitioner, Bournemouth, Dorset; Standing Committee of General Practitioners, Royal College of Physicians, London

Ms Denise Blake Lead Pharmacist, North London Cancer Network, and Chair British Oncology Pharmacy Association; Royal Pharmaceutical Society of Great Britain

Dr Colin Clelland Consultant Pathologist, John Radcliffe Hospital, Oxford; Royal College of Pathologists

Dr Dennis Eraut Consultant Chest Physician, Southend Hospital, Essex; British Thoracic Society

Dr Fergus Gleeson Consultant Radiologist, Churchill Hospital, Oxford; Royal College of Radiologists

Dr Peter Harvey Consultant Clinical Psychologist, St James's University Hospital, Leeds; British Psychosocial Oncology Society

Ms Patricia Hunt Palliative Care Nurse Specialist – Lung Cancer, Royal Marsden Hospital, London; Royal College of Nursing

Ms Barbara Leung Clinical Nurse Specialist – Lung Cancer, Birmingham, Heartlands Hospital; Royal College of Nursing

Ms Katherine Malholtra* Superintendent Physiotherapist, Royal Marsden Hospital, London; Chartered Society of Physiotherapy

Ms Theresa Mann‡ Formerly Cancer Support Service Specialist Nurse, CancerBACUP; patient representative

Ms Maureen McPake Lecturer in Radiotherapy, Glasgow Caledonian University; Society of Radiographers

Ms Catriona Moore‡ Cancer Support Service Specialist Nurse, CancerBACUP; patient representative

Dr Martin Muers Consultant Physician, The General Infirmary at Leeds; British Thoracic Society

Dr Mike O'Doherty Senior Lecturer in Imaging Sciences, Guys, Kings and St Thomas' School of Medicine, and Consultant in Nuclear Medicine, Guy's and St Thomas' NHS Foundation Trust, London; British Nuclear Medicine Society

* Shared seat on Guideline Development Group

Dr Nick Rowell	Clinical Oncologist, Maidstone Hospital, Kent; Royal College of Radiologists, Faculty of Clinical Oncology, and Cochrane Lung Cancer Group
Ms Denise Silvey	Clinical Nurse Specialist – Lung Cancer, Birmingham Heartlands Hospital; Royal College of Nursing
Dr Colin Sinclair	Consultant Anaesthetist, Cardiothoracic Surgery, Royal Infirmary of Edinburgh; Royal College of Anaesthetists
Mr Peter Tebbit	National Policy Adviser, National Council for Hospice and Specialist Palliative Care
Professor Tom Treasure	Consultant Thoracic Surgeon, Guy's and St Thomas' Hospital, London; Society of Cardiothoracic Surgeons
Dr Andrew Wilcock	Reader and Consultant in Palliative Medicine and Medical Oncology, Royal College of Physicians Clinical Effectiveness Unit
Ms Judy Williams*	Senior Physiotherapist, Poole Hospital, Dorset; Chartered Society of Physiotherapy
Professor Penella Woll	Consultant Medical Oncologist, Weston Park Hospital, Sheffield; Royal College of Physicians

Conflict of Interests

The Guideline Development Group were asked to declare any possible conflict of interest and none that could interfere with their work on the guideline were declared. All documentation is held by the National Collaborating Centre for Acute Care.

* Shared seat on Guideline Development Group

Appendix 9.2

Organisations invited to comment on guideline development

Abbott Laboratories Limited	Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)
Action on Smoking and Health (ASH)	Chartered Society of Physiotherapy (CSP)
Air Products PLC	CMMC NHS Trust
Almac Diagnostics	College of Emergency Medicine
Anglia cancer network	College of Occupational Therapists
Arden Cancer Network	Connecting for Health
Association for Palliative Medicine of Great Britain and Ireland	Department of Health
Association for Respiratory Technology & Physiology	Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)
Association of British Insurers (ABI)	Derby-Burton Cancer Network
Association of Chartered Physiotherapists in Oncology and Palliative Care	Derbyshire Mental Health Services NHS Trust
AstraZeneca UK Ltd	Dorset Cancer Network
Birmingham cancer network	East Lancashire Hospitals NHS Trust
BOC Healthcare	East Midlands Cancer Network
Boehringer Ingelheim Ltd	Essex Cancer Network
Boston Scientific	Eusapharma (Europe) Ltd
Brighton and Sussex University Hospitals Trust	Foundation Trust
British Association of Otolaryngologists Head and Neck Surgeons (ENT UK)	GE Healthcare
British Geriatrics Society	General Practice Airways Group
British Lung Foundation	GlaxoSmithKline UK
British National Formulary (BNF)	Greater midlands cancer network
British Nuclear Medicine Society	Harrogate and District NHS Foundation Trust
British Thoracic Oncology Group	Heart of England NHS Foundation Trust
British Thoracic Society	Hospira UK Limited
BUPA	Humber and Yorkshire Coast Cancer Network
Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)	Imperial College Healthcare NHS Trust
Cancer Services Co-ordinating Group	Institute of Biomedical Science
Care Quality Commission (CQC)	Leeds Irish Health and Homes
Central South Coast Cancer Network	Leeds PCT

Leicestershire Northamptonshire and Rutland Cancer Network	NICE – IMPLEMENTATION CONSULTANT Region West Midlands
Lilly UK	NICE - Technical Appraisals (Interventional Procedures) FOR INFO
Luton & Dunstable Hospital NHS Foundation Trust	North East London Cancer Network
Macmillan Cancer Support	North East London Cancer Network
Manchester Metropolitan University	North London Cancer Network
Marie Curie Cancer Care	North Trent Cancer Network
Medicines and Healthcare Products Regulatory Agency (MHRA)	North Trent Cancer Network
Merck Serono	North Yorkshire and York PCT
Merck Sharp & Dohme Ltd	Northern Ireland Cancer Network
Ministry of Defence (MoD)	Nottingham University Hospitals NHS Trust
MRC-CTU	Novartis Pharmaceuticals UK Ltd
National Lung Cancer Forum for Nurses	Nucletron B.V
National Patient Safety Agency (NPSA)	OSI Pharmaceuticals
National Public Health Service for Wales	Patients Council
National Treatment Agency for Substance Misuse	PERIGON Healthcare Ltd
NCC – Cancer	Pfizer Limited
NCC – Mental Health	Philips Healthcare
NCC – National Clinical Guidance Centre (NCGC)	Pierre Fabre Ltd
NCC – Women & Children	Poole and Bournemouth PCT
NCRI – Lung Clinical Studies Group	Roche Diagnostics
NETSCC, Health Technology Assessment	Roche Products Limited
Newham Primary Care Trust	Roy Castle Lung Cancer Foundation
NHS Clinical Knowledge Summaries Service (SCHIN)	Royal College of General Practitioners
NHS Direct	Royal College of General Practitioners Wales
NHS Improvement	Royal College of Nursing
NHS Kirklees	Royal College of Pathologists
NHS Knowsley	Royal College of Physicians London
NHS Plus	Royal College of Radiologists
NHS Quality Improvement Scotland	Royal Pharmaceutical Society of Great Britain
NHS Sheffield	Royal Society of Medicine
NHS Western Cheshire	Sandwell PCT
NICE – CPHE	Sanofi-Aventis
NICE – CPHE Methodology – Simon for info	Scottish Intercollegiate Guidelines Network (SIGN)
NICE – Guidelines Coordinator – for info	Sedgefield PCT
NICE – Guidelines HE for info	Sheffield PCT
NICE – IMPLEMENTATION CONSULTANT Region – East	Sheffield Teaching Hospitals NHS
NICE – IMPLEMENTATION CONSULTANT – Region SW	Smokefree North West
NICE – IMPLEMENTATION CONSULTANT – SE/London	Social Care Institute for Excellence (SCIE)
NICE – IMPLEMENTATION CONSULTANT Region NW/NE	Society and College of Radiographers

Society for Acute Medicine	The Society and College of Radiographers
Society for Cardiothoracic Surgery	The Transplant Trust
Society of Cardiothoracic Surgeons	UK Lung Cancer Coalition
South Asian Health Foundation	University College London
South East Wales Cancer Network	University College London Hospitals (UCLH) Acute Trust
St Ann's Hospital	University Hospital Birmingham NHS Foundation Trust
St Helens Hospital	University Hospitals Birmingham NHS Foundation Trust
Sussex Cancer Network	Welsh Assembly Government
Takeda UK Ltd	Welsh Scientific Advisory Committee (WSAC)
Teva UK Limited	Western Cheshire Primary Care Trust
Thames Valley Cancer Network	Western Health and Social Care Trust
The Roy Castle Lung Cancer Foundation	York NHS Foundation Trust
The Royal College of Radiologists	

Appendix 9.3

Individuals carrying out literature reviews and complementary work 2011

Overall Co-ordinators

Dr John Graham ¹	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Angela Bennett	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff
Dr Fergus Macbeth ²	Clinical Practice Centre Director, NICE

Project Manager

Katrina Asquith-Coe	National Collaborating Centre for Cancer, Cardiff
---------------------	---------------------------------------------------

Senior Researcher

Angela Melder ³	National Collaborating Centre for Cancer, Cardiff
----------------------------	---------------------------------------------------

Researcher

Mia Schmidt-Hansen	National Collaborating Centre for Cancer, Cardiff
--------------------	---------------------------------------------------

Information Specialist

Elise Collins	National Collaborating Centre for Cancer, Cardiff
Sabine Berendse	National Collaborating Centre for Cancer, Cardiff

Health Economist

Sarah Willis	Research Fellow, London School of Health and Tropical Medicine
--------------	----------------------------------------------------------------

Needs Assessment

Dr Anna Rich	RCP (LUCADA) Research Fellow, Nottingham University Hospital NHS Trust
Dr Paul Beckett ⁴	Burton Hospital

¹ From March 2009 – present

² From July 2008 – September 2008

³ From July 2008 – December 2009

⁴ The NCC-C would like to acknowledge and thank Dr Beckett for his help with the on-line MDT survey

Individuals carrying out literature reviews and complementary work 2005

Project Manager

Dr Jennifer Hill

Clinical Consultant

Mr Ian Hunt

Research Associate

Ms Veena Mazarello Paes

Ms Louise Thomas

Information Scientist

Ms Rachel Southon

Health Economist

Ms Guldem Okem

Mr David Wonderling

Acknowledgements

The development of this guideline was greatly assisted by the following people:

- From the NCC-AC: Jennifer Wood, Jacqueline Rainsbury, Carlos Sharpin, Gemma Kothari, Adrian Brown, James Barnard, Christine Pennington, Sue Langham, Artyom Sedrakyan, James Lewsey, Funsho Akinluyi, Susan Murray, Arash Rashidian, Jan van der Meulen, Peter B. Katz and Rifna Aktar.
- The staff and lung cancer guideline development group at the Scottish Intercollegiate Guidelines Network (SIGN)
- Jill Cooper – HOPE the College of Occupational Therapists Specialist Section for HIV/AIDS, Oncology, Palliative Care and Education
- Mick Peake- Royal College of the Physicians, for assistance with drafting the section on audit criteria.

Appendix 9.4

Expert advisers to the Guideline Development Group 2011

Professor Andrew G Nicholson	Consultant Histopathologist, Royal Brompton and Harefield NHS Trust and Professor of Respiratory Pathology, National Heart and Lung Institute Division of Imperial College School of Medicine, London
Professor Keith Kerr	Consultant Pathologist, Aberdeen Royal Infirmary and Professor of Pulmonary Pathology, Aberdeen University Medical School, Scotland
Dr Doris Rassl	Consultant Histopathologist, Papworth Hospital NHS Foundation Trust, Cambridge

Appendix 9.5

Members of the Guideline Review Panel 2011

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The members of the Guideline Review Panel were as follows:

Dr John Hyslop – Chair

Consultant Radiologist, Royal Cornwall Hospital NHS Trust

Mrs Sarah Fishburn

Lay member

Mr Kieran Murphy

Health Economics & Reimbursement Manager, Johnson & Johnson Medical Devices & Diagnostics (UK)

Dr Ash Paul

Deputy Medical Director, Health Commission Wales

Professor Liam Smeeth

Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine

Members of the NICE project team

Dr Fergus Macbeth

Director, Centre for Clinical Practice

Claire Turner

Guideline Commissioning Manager

Nicole Elliott

Associate Director

Emma Banks

Guidelines Coordinator

Anne-Louise Clayton

Editor

Barbara Meredith

Patient Involvement Lead

Members of the Guideline Review Panel 2005

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The members of the Guideline Review Panel were as follows:

Mr Peter Robb (Chair)	Consultant ENT Surgeon, Epsom and St Helier University Hospitals and The Royal Surrey County NHS Trusts
Joyce Struthers	Patient representative, Bedford
Dr Peter Duncan	Consultant in Anaesthetics and Intensive Care Medicine, Royal Preston Hospital, Preston
Anne Williams	Deputy Director of Clinical Governance, Kettering General Hospital NHS Trust

Members of Expert Advisory Group 2007

The expert advisory group's responsibility is to review the NICE Lung Cancer Guideline 2005 and decide which topics require either no update, a partial update or a full update of the guideline.

Dr Fergus Macbeth	Director, Centre for Clinical Practice (previously Director NCC-C)
Dr Mike O'Doherty	Consultant in Nuclear Medicine, Guy's and St Thomas' NHS Foundation Trust, London
Dr Jesme Fox	The Roy Castle Lung Cancer Foundation
Dr Mick Peake	Consultant and Senior Lecturer in Respiratory Medicine, Glenfield Hospital, University Hospitals of Leicester NHS Trust.
Mr Ian Hunt	Consultant Thoracic Surgeon, St George's Hospital, London
Barbara Leung	Clinical Nurse Specialist – Lung Cancer, Heartlands Hospital, Birmingham
Dr Martin Muers	Consultant Physician, Leeds General Infirmary
Professor Allan Price	Radiation oncology, University of Edinburgh, Scotland
Denise Silvey	Clinical Nurse Specialist – Lung Cancer, Heartlands Hospital, Birmingham
Dr Fergus Gleeson	Consultant Radiologist, Churchill Hospital, Oxford
Professor Penella Woll	Consultant Medical Oncologist, Weston Park Hospital, Sheffield
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Angela Melder	Senior Researcher, National Collaborating Centre for Cancer, Cardiff