National Collaborating Centre for Acute Care

The Diagnosis and Treatment of Lung Cancer

METHODS, EVIDENCE & GUIDANCE

FEBRUARY 2005

Commissioned by the National Institute for Clinical Excellence

The Diagnosis and Treatment of Lung Cancer

METHODS, EVIDENCE & GUIDANCE

Published by the National Collaborating Centre for Acute Care at The Royal College of Surgeons of England, 35-43 Lincoln's Inn Fields, London, WC2A 3PE

First published 2005

© National Collaborating Centre for Acute Care 2005

Apart from any fair dealing for the purposes of research or private study, criticism or review, as permitted under the Copyright, Designs and Patents Act, 1988, 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 licences 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.

The rights of National Collaborating Centre for Acute Care to be identified as Author of this work have been asserted by them in accordance with the Copyright, Designs and Patents Act, 1988.

ISBN 0-9549760-0-2

Citing this document: National Collaborating Centre for Acute Care, February 2005. Diagnosis and treatment of lung cancer. National Collaborating Centre for Acute Care, London. Available from www.rcseng.ac.uk

Foreword

Lung cancer remains the UK's commonest cause of cancer death. It is now over 50 years since Sir Richard Doll's seminal paper linked tobacco smoking to lung cancer. Although tobacco consumption has fallen overall since then, with a resultant fall in the male incidence of lung cancer, smoking has increased in women, having the effect of increased lung cancer in females. Tobacco control remains the crucial factor in reducing future lung cancer rates.

It is clear to everyone involved in lung cancer care that the public concept of this disease is characterised by much negativity. There is too much emphasis generally on the relatively poor outcomes of treatment, there is a lack of sympathy for the patients deemed to have brought the disease on themselves through tobacco use, and there is an impression which is unwarranted, that some professionals have a nihilistic attitude about the treatment of lung cancer patients. There are few patient advocates, and the disease has a low public profile in respect of media coverage, general awareness and research funding.

However, in reviewing the research, and preparing this guideline, the Development Group were encouraged by many positive developments such as the emergence of the lung cancer specialist nurse service, the creation of Lung Cancer Multi-Disciplinary teams, and the improvement in the evidence base for treatment, especially chemotherapy. We would also wish to highlight developments in technology, such as FDG-PET scanning in disease staging and the use of the CHART regimen for the delivery of radical radiotherapy in suitable patients.

The Development Group were charged to consider "the diagnosis and treatment of lung cancer". This is a huge topic overall. To consider every nuance of presentation and management in this guideline would have been a formidable and impossible task. We have not set out to write a text book of lung cancer care. Rather, we have attempted to review the main outlines of lung cancer presentation, diagnosis and treatment, with particular emphasis on areas where there has been new evidence, or, where it seems to us, carefully evaluated guidance, which will improve patient care.

It has been a difficult decision for the group as to which aspects to include, which to omit and which to highlight. It has been particularly difficult too to narrow down our original 94 recommendations to 10 key items, which we believe if implemented, will have the greatest impact on patient outcomes. We hope however that the research review in this document and the conclusions we have drawn from it will continue the improvements which are taking place in the care of patients with this common and important disease.

Jesme Baird,
Chair, Guideline Development Group.

Contents

Appendicies 1-8, including the evidence tables, are on the attached CD-ROM.

Guideline Development Group membership and acknowledgments

Guideline Development Group

Dr Jesme Baird (Chair)	Director of Patient Care, The Roy Castle Lung Cancer Foundation; patient representative
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
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

* Shared seat on Guideline Development Group ‡ Shared seat on Guideline Development Group

NCC-AC staff on the Guideline Development Group

Dr Jennifer Hill	Project Manager
Mr Ian Hunt	Clinical Consultant
Ms Veena Mazarello Paes	Research Associate
Ms Guldem Okem	Health Economist
Ms Rachel Southon	Information Scientist
Ms Louise Thomas	Research Associate
Mr David Wonderling	Health Economist

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.

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.

Guideline Review Panel

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

Stakeholder Involvement

The following stakeholders registered with NICE and were invited to comment on draft versions of these guidelines:

Abbott Laboratories Limited (BASF/Knoll)
Action on Smoking and Health (ASH)
Afiya Trust, The
Aintree Hospitals NHS Trust
Airedale General Hospital
Amersham Health
Amgen UK Ltd
Anglesey Local Health Board
Association for Palliative Medicine of Great Britain and Ireland
Association for Respiratory Technology & Physiology
Association of Hospice and Specialist Palliative Care Social Workers
Association of the British Pharmaceuticals Industry (ABPI)
AstraZeneca UK Ltd
Aventis Pharma
Bard Limited
Bath and North East Somerset PCT
Baxter Oncology
Bayer PLC
Bedfordshire & Hertfordshire NHS Strategic Health Authority
Biolitec Pharma Ltd (formerly QuantaNova Limited)
Birmingham Heartlands & Solihull NHS Trust
Blaenau Gwent Local Health Board
Bolton Hospitals NHS Trust
Boston Scientific Limited
Brighton & Sussex University Hospitals Trust
Bristol-Myers Squibb Pharmaceuticals Ltd
British Association for Counselling and Psychotherapy
British Association for Parenteral & Enteral Nutrition (BAPEN)
British Association of Art Therapists
British Dietetic Association
British Geriatrics Society
British Lung Foundation
British National Formulary (BNF)
British Nuclear Medicine Society
British Psychological Society, The
British Psychosocial Oncology Society
British Thoracic Society
BUPA
Cancer Research UK
Cancer Services Co-ordinating Group
Cancer Voices
CancerBACUP
Chartered Society of Physiotherapy
Chesterfield and North Derbyshire Royal Hospital NHS Trust
Clatterbridge Centre for Oncology NHS Trust
College of Occupational Therapists
Countess of Chester Hospitals NHS Trust
Craven Harrogate & Rural District PCT
Department of Health
Eisai Limited
Elan Pharmaceuticals Ltd
Eli Lilly and Company Ltd
Faculty of Public Health
Gateshead Health NHS Trust
GE Health Care
General Medical Council
General Practice Airways Group Limited
General Practice and Primary Care
GlaxoSmithKline UK
Guerbet Laboratories Ltd
Hammersmith Hospitals NHS Trust
Healthcare Commission
Help Adolescents with Cancer
Help the Hospices
Intercollegiate Lung Cancer Group
Isle of Wight Healthcare NHS Trust
Joint Committee on Palliative Medicine
Leeds North East PCT
Leeds Teaching Hospitals NHS Trust
Lifesyne
Liverpool Reviews and Implementation Group
Long Term Medical Conditions Alliance
Macmillan Cancer Relief
Maidstone and Tunbridge Wells NHS Trust
Marie Curie Cancer Care
Medeus Pharma Ltd
Medical Research Council Clinical Trials Unit
Medicines and Healthcare Products Regulatory Agency (MHRA)
Merck Pharmaceuticals
Mid Essex Hospitals NHS Trust
Mid Staffordshire General Hospitals NHS Trust
National Audit Office
National Cancer Alliance
National Cancer Network Clinical Directors Group
National Cancer Research Institute (NCRI) Clinical Studies Group
National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)
National Council for Hospice and Specialist Palliative Care Services
National Lung Cancer Forum for Nurses
National Patient Safety Agency
National Public Health Service - Wales
Newcastle Upon Tyne Hospitals NHS Trust
NHS Modernisation Agency, The
NHS Quality Improvement Scotland
North Glamorgan NHS Trust – Merthyr Tydfil
Novartis Pharmaceuticals UK Ltd
Ortho Biotech
Papworth Hospital NHS Trust
Pfizer Limited
Pierre Fabre Limited
Princess Alexandra Hospital NHS Trust
Roche Products Limited
Rotherham Primary Care Trust
Roy Castle Lung Cancer Foundation
Royal Brompton and Harefield NHS Trust
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners Wales
Royal College of Nursing – Lung cancer
Royal College of Nursing (RCN)
Royal College of Pathologists
Royal College of Physicians of London
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal College of Surgeons of England / Thoracic Forum
Royal Pharmaceutical Society of Great Britain
Salford Primary Care Trust
Sanofi-Synthelabo
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield Teaching Hospitals NHS Trust
Society and College of Radiographers
Society of Cardiothoracic Surgeons
South & Central Huddersfield PCTs
Tameside and Glossop Acute Services NHS Trust
Teenage Cancer Trust, The
Thames Valley Strategic Health Authority
The Dudley Group of Hospitals NHS Trust
The Medway NHS Trust
The National Association of Assistants in Surgical Practice
The Royal Society of Medicine
The Royal West Sussex Trust
UK Pain Society
University College London Hospital NHS Trust
Velindre NHS Trust
Wareney PCT
Welsh Assembly Government (formerly National Assembly for Wales)
Wessex Cancer Trust

Abbreviations

ASC	Active Supportive Care
BSC	Best Supportive Care
BTS	British Thoracic Society
CCOPGI	Cancer Care Ontario Practice Guidelines Initiative
CEA	Cost Effectiveness Analysis
CHART	Continuous Hyperfractionated Accelerated Radiotherapy
CI	Confidence Interval
CT	Computerised tomography
CWU	Conventional Work Up
CXR	Chest X-Ray
DEALE	Declining Exponential Approximation of Life Expectancy
DS	Diagnostic Studies
ED	Extensive disease
EUS	Endobronchial ultrasound
EUS-NA	Endoscopic ultrasound guided needle aspiration
FDG	^{18}F-deoxyglucose
FNA	Fine needle aspiration
FP	False positive
GDG	Guideline Development Group
GP	General Practitioner
GPP	Good Practice Point
HRQL	Health Related Quality of Life
HTA	Health Technology Assessment
HTBS	Health Technology Board for Scotland
ICER	Incremental Cost Effectiveness Ratio
IP	Inpatient
LD	Limited disease
LN	Lymph node

LY	Life-year
MDT	Multidisciplinary Team
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MVP	mitomycin-vindecine-cisplatin
NCC-AC	National Collaborating Centre for Acute Care
ND-YAG	Neodymium-Yttrium Aluminum Garnet
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NNH	Number needed to harm
NNT	Number needed to treat
NPV	Negative predictive value
NSCLC	Non-Small Cell Lung Cancer
OP	Outpatient
OR	Odds ratio
PCI	Prophylactic Cranial Irradiation
PDT	Photodynamic therapy
PET	Positron Emission Tomography
PPV	Positive predictive value
PS	Performance status
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RT	Radiotherapy
SCLC	Small Cell Lung Cancer
SIGN	Scottish Intercollegiate Guidelines Network
SLN	Subcarinal Lymph Nodes
SPECT	Single Photon Emission Computerised Tomography
SPN	Solitary Pulmonary Nodules
SROC	Summary Receiver Operating Characteristic
SVCO	Superior vena cava obstruction
TTNA	Transthoracic needle aspiration
UK	United Kingdom
US	Ultrasound
VATS	Video assisted thoracoscopy
WHO	World Health Organisation

Glossary of Terms

Amended from a glossary produced by the Patient Involvement Unit, NICE.

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.

Adjuvant radiotherapy

The use of radiotherapy after treatment by surgery.

Benign

Non-cancerous. Does not metastasise and treatment or removal is 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.

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*.

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.

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).

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.

Confidence interval

A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95%' confidence interval as the range of effects within which we are 95% confident that the true effect lies.

Confounder or confounding factor

Something that influences a study and can contribute to misleading findings if it is not understood or appropriately dealt with. For example, if a group of people exercising regularly and a group of people who do not exercise have an important age difference then any difference found in outcomes about heart disease could well be due to one group being older than the other rather than due to the exercising. Age is the confounding factor here and the effect of exercising on heart disease cannot be assessed without adjusting for age differences in some way.

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)

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.

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 an explicit criteria for making choices.

Elective Name for clinical procedures that are regarded as advantageous to the patient but not urgent.

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.

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.

Good Performance Status Performance Status 0/ 1 WHO/ Zubrod scale or 80-100 Karnofsky scale (see Appendix 2, Figure 4)

Gray (Gy) Unit of absorbed radiation dose

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.

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.

Inclusion criteria See Selection criteria.

In situ A cancer that is in the natural place, is non-invasive without invading neighbouring tissue

Intervention Healthcare action intended to benefit the patient, e.g. drug treatment, surgical procedure, psychological therapy, etc.

Life year A measure of health outcome which shows the number of years of remaining life expectancy

Longitudinal study A study of the same group of people at more than one point in time. (This type of study contrasts with a *cross sectional study* which observes a defined set of people at a single point in time)

Lymph Almost colourless fluid that baths 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 travel through the lymphatic system.

Malignant Cancerous. Malignant tumours can invade and destroy surrounding tissue and have the capacity to spread

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*.

Metastasis Spread of cancer from one part of the body to another.

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 improving the results and preventing the development of metastases.

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

Number Needed to Treat (NNT) This measures the impact of a treatment or intervention. It states how many patients need to be treated with the treatment in question in order to prevent an event which would otherwise occur. E.g. if the NNT=4, then 4 patients would have to be treated to prevent one bad outcome. The closer the NNT is to 1, the better the treatment is. Analogous to the NNT is the Number Needed to Harm (NNH), which is the number of patients that would need to receive a treatment to cause one additional adverse event. e.g. if the NNH=4, then 4 patients would have to be treated for one bad outcome to occur.

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.

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.

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.

Positive lymph nodes Lymph nodes that contain cancer cells.

Power See Statistical power.

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*.

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*.

***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.

Random allocation or Randomisation A method that uses the play of chance to assign participants to comparison groups in a research study, for example, by using a random numbers table or a computer-generated random sequence. Random allocation implies that each individual (or each unit in the case of cluster randomisation) being entered into a study has the same chance of receiving each of the possible interventions.

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.)

Relative risk A summary measure which represents the ratio of the risk of a given event or outcome (e.g. an adverse reaction to the drug being tested) in one group of subjects compared to another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for *risk ratio*.

Retrospective study A retrospective study deals with the present/ past and does not involve studying future events. This contrasts with studies that are *prospective*.

Risk ratio Ratio of the risk of an undesirable event or outcome occurring in a group of patients receiving experimental treatment compared with a comparison (control) group. The term *relative risk* is sometimes used as a synonym of risk ratio.

Sample A part of the study's target population from which the subjects of the study will be recruited. If subjects are drawn in an unbiased way from a particular population, the results can be generalised from the sample to the population as a whole.

SCLC Small Cell Lung Cancer

Scottish Intercollegiate Guidelines Network (SIGN) SIGN was established in 1993 to sponsor and support the development of evidence-based clinical guidelines for the NHS in Scotland.

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.

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.

Statistical power The ability of a study to demonstrate an association or causal relationship between two variables, given that an association exists. For example, 80% power in a clinical trial means that the study has a 80% chance of ending up with a *P* value of less than 5% in a statistical test (i.e. a statistically significant treatment effect) if there really was an important difference (e.g. 10% versus 5% mortality) between treatments. If the statistical power of a study is low, the study results will be questionable (the study might have been too small to detect any differences). By convention, 80% is an acceptable level of power. See also *P value*.

Summary Receiver Operating Characteristic curve (sROC) A statistical method to combine the results of multiple studies assessing the diagnostic performance of a test. It takes into account the relationship between sensitivity and specificity among the individual studies by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity)

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*.

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.

1 Introduction

1.1 Background

1.1.1 Epidemiology

In 2002, lung cancer accounted for nearly 29,000 deaths in England and Wales. It is the most common cause of cancer death for men, who account for 60% of lung cancer cases. In women it is the second most common cause of cancer death after breast cancer[1].

Past trends of lung cancer incidence reflect the changes in smoking habits over the last century[2]. The age-standardised incidence rates show a long-term decrease in cases among males but an increase in cases among women. Under the age of 40 lung cancer is rare, but incidence rises sharply with age and the most common age group at diagnosis is 70-74[2].

Survival rates for lung cancer are very poor. In England, for patients diagnosed between 1993 and 1995 and followed up to 2000, 21.4% of men and 21.8% of women with lung cancer were alive one year after diagnosis and only 5.5% of both men and women were alive after five years[3]. For Wales, the latest figures on survival, for people diagnosed between 1994 and 1998, showed 1-year relative survival of 20.5% for both males and females and five year relative survival figures of 6% for both males and females[4]. These figures are around 5 percentage points lower than the European average and 7-10 percentage points lower than the USA. Five year survival rates vary between different English health authorities, ranging from 2.2% to 8.9%, for patients diagnosed with lung cancer between 1993 and 1995[5]. Although 1-year survival has improved by about five percentage points since the early 1970s, there has been little improvement in 5-year survival.

Lung cancers are classified into two main categories: small-cell lung cancers (SCLC), which account for approximately 20% of cases, and non-small cell lung cancers (NSCLC), which account for the other 80%. Non-small cell lung cancer includes squamous cell (35%), adenocarcinomas (27%) and large cell (10%) carcinomas[6]. In practice however, not all patients receive histological confirmation of the cell type of their disease. Figures recorded by NYCRIS (North Yorkshire Cancer Registry and Information Service), from a registry-based population study conducted during 1986-1994, showed that 55% were confirmed as NSCLC, 11% as SCLC and 34% had no histological confirmation of cell type[7].

1.1.2 Risk Factors

Smoking is by far the greatest cause of lung cancer, accounting for an estimated 85 to 90% of cases, but the precise relationship with smoking is probably complex[6]. The age-adjusted relative risk of developing lung cancer, for people that smoke more than 20 cigarettes a day, is 20 times that compared with lifelong non-smokers (or a 2000% increased risk), and many studies have reported that women who smoke are more likely to develop lung cancer than male smokers[6]. Stopping smoking earlier is associated with greater benefit[8], stopping before middle age means that an individual can avoid almost 90% of the risk[9], although the risk never drops to the level it was prior to smoking. A number of studies, presented in a recent review[10], have shown the danger of environmental tobacco smoke or passive smoking and have examined its links with lung cancer. It has been estimated that in the UK passive smoking could account for several hundred cases of lung cancer each year[11]. A meta-analysis of 37 studies of non-smokers who lived with smokers showed an increased risk of lung cancer of 24% (95% CI 13-36%)[12].

A number of other occupational and environmental factors are risk factors for lung cancer. Asbestos is the greatest occupational risk factor[13]. Other known occupational carcinogens include arsenic, beryllium, bis (chloromethyl) ether, cadmium, chromium, nickel, polycyclic aromatic hydrocarbons, vinyl chloride and radon. Radon is also an environmental carcinogen as it is the decay product of naturally occurring uranium in the earth and can accumulate in buildings. Radon is estimated to account for around 2000 lung cancer deaths per year in the UK, or about 6% of the total[14]. Other studies have identified air pollution, poor nutrition, previous and coexisting lung disease and genetic predisposition as risk factors for lung cancer.

1.2 What is a guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care though primary and secondary care to more specialised services. Clinical guidelines are based on the best available evidence, and are produced to help health care professionals and patients make informed choices about appropriate health care. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Clinical guidelines for the NHS in England and Wales are produced as a response to a request from the Department of Health and the Welsh Assembly Government. They select topics for guideline development and before deciding whether to refer a particular topic to the National Institute for Clinical Excellence (NICE) they consult with the relevant patient bodies, professional organisations and companies. Once a topic is referred, NICE then commissions one of seven National Collaborating Centres to produce a guideline. The Collaborating Centres are independent of government and comprise partnerships between a variety of academic institutions, health profession bodies and patient groups.

1.3 Remit of the Guideline

The following remit was received from the Department of Health and National Assembly for Wales in July 2001 as part of NICE's 6th wave programme of work:

"To prepare clinical guidelines for the NHS in England and Wales for the diagnosis and treatment of lung cancer. This is to supplement the existing service guidance published by the Department of Health in 1998 and this commission replaces the earlier commission to update that guidance".

The previous cancer service publications referred to, in this remit, is the NHS Executive (1998) Guidance on commissioning cancer services: improving outcomes in lung cancer: the research evidence. London: Department of Health[15].

It was expected that this previous work should be "updated to reflect recent evidence", in the form of a clinical guideline.

The recommendations in this guideline were arrived at following careful consideration of the available evidence.

1.4 What the guideline covers

This guideline:

> is relevant for adults over the age of 18 years who are suspected as having, or are diagnosed with, lung cancer.

> addresses diagnosis, staging and treatment. Where there are issues specific to lung cancer, it will also address palliative care, psychological impact and day-to-day functioning.

> offers guidance on care provided in primary care, secondary care, outpatient and day treatment services, tertiary care, specialist services and the interface with the voluntary and social services where relevant.

> is relevant to multidisciplinary teams involved in the diagnosis and care of patients with suspected or diagnosed lung cancer. These teams may include, for example, general physicians and nurses, chest physicians, palliative care physicians, clinical and medical oncologists, thoracic surgeons, geriatricians, cellular pathologists, radiologists, radiographers, occupational therapists, specialist nurses, physiotherapists, dietitians, pharmacists and clinical psychologists.

1.5 What the guideline does not cover

The guideline will not cover:

> The care of patients with mesothelioma

> The care of patients with lung metastases from cancer arising from outside the lung

> The prevention of lung cancer.

1.6 Collaboration with the Scottish Intercollegiate Guideline Network

In 2002, NICE received a referral from the Department of Health and Welsh Assembly Government to produce a guideline on the diagnosis and management of lung cancer. This occurred at approximately the same time that the Scottish Intercollegiate Guideline Network (SIGN) was preparing a similar guideline on lung cancer. In order to avoid duplication of work, NICE and SIGN decided to share the workload relating to searching and reviewing the literature. NICE commissioned the National Collaborating Centre for Acute Care to develop this guideline and the Centre thus took on the responsibility of working with SIGN.

Although the NCC-AC and SIGN shared certain aspects of the search, retrieval and review of the literature, they had autonomy in developing their own clinical questions and final recommendations. The areas of literature reviewed by the NCC-AC and SIGN are outlined in Table 1.

The NCC-AC was solely responsible for reviewing the literature on diagnosis and the treatment of NSCLC, while SIGN was solely responsible for the literature on the treatment of SCLC, palliative care, follow up and communication. Both the NCC-AC and SIGN reviewed the literature (independently) on background information, access to services, staging, palliative interventions, and service organisation.

TABLE 1: Division of work between NCC-AC and SIGN

NCC-AC	SIGN
Background Information	Background Information
Access to Services	Access to Services
Diagnosis	
Staging	Staging
Treatment of NSCLC	
	Treatment SCLC
Palliative Interventions	Palliative Interventions
	Palliative Care
	Follow Up
	Communication
Service Organisation	Service Organisation

Each group summarised their respective literature reviews in evidence tables and exchanged those related to the topics that each had focused solely upon.

1.7 Who developed the guideline?

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline (see Guideline Development Group Membership and acknowledgements).

The National Institute for Clinical Excellence funds the National Collaborating Centre for Acute Care and thus supported the development of this guideline. The GDG was convened by the National Collaborating Centre for Acute Care (NCC-AC) and chaired by Dr. Jesme Baird. In accordance with guidance from the National Institute for Clinical Excellence (NICE)[16], 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.

The Group met on a monthly basis during development of the guideline. Staff from the NCC-AC provided methodological support and guidance for the development process, undertook systematic searches, retrieval and appraisal of the evidence and drafted the guideline. The Glossary to the guideline contains definitions of terms used by staff and the GDG.

1.8 Summary of the recommendations and the algorithm

1.8.1 The Key Recommendations for Implementation

The following recommendations have been selected from the full list (see 1.8.2) as priorities for implementation:

Access to services

1. All patients diagnosed with lung cancer should be offered information, both verbal and written, on all aspects of their diagnosis, treatment and care. This information should be tailored to the individual requirements of the patient, and audio and videotaped formats should also be considered.

2. Urgent referral for a chest X-ray should be offered when a patient presents with:

   > haemoptysis, or

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

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

3. If a chest X-ray or chest computed tomography (CT) scan suggests lung cancer (including pleural effusion and slowly resolving consolidation), patients should be offered an urgent referral to a member of the lung cancer multidisciplinary team (MDT), usually a chest physician.

Staging

4. Every cancer network should have a system of rapid access to

   ^{18}F-deoxyglucose positron emission tomography (FDG-PET) scanning for eligible patients.

Radical radiotherapy alone for treatment of non-small-cell lung cancer

5. Patients with stages I and II non-small-cell lung cancer (NSCLC) who are medically inoperable but suitable for radical radiotherapy should be offered the continuous hyperfractionated accelerated radiotherapy (CHART) regimen.

Chemotherapy for non-small-cell lung cancer

6. Chemotherapy should be offered to patients with stages III and IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) to improve survival, disease control and quality of life.

Palliative interventions and supportive and palliative care

7. Non-drug interventions for breathlessness should be delivered by a lung cancer multidisciplinary group, co-ordinated 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.

Service organisation

8. The care of all patients with a working diagnosis of lung cancer should be discussed at a lung cancer multidisciplinary team (MDT) meeting.

9. Early diagnosis clinics 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.

10. All cancer units/centres should have one or more trained lung cancer 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.

1.8.2 The Clinical Practice Recommendations

Recommendations are graded A, B, C, D or D(GPP) according to the level of evidence on effectiveness that the recommendation is based on. Studies of diagnostic accuracy are graded A(DS), B(DS), C(DS) or D(DS). Some recommendations are based on both diagnostic and effectiveness evidence and therefore receive two grades to reflect this. Please see Chapter Two for grading information.

1.8.2.1 Access to Services

All patients diagnosed with lung cancer should be offered information, both verbal and written, on all aspects of their diagnosis, treatment and care. This information should be tailored to the individual requirements of the patient, and audio and videotaped formats should also be considered. [D(GPP)]

Treatment options and plans should be discussed with the patient and decisions on treatment and care should be made jointly with the patient. Treatment plans must be tailored around the patient's needs and wishes to be involved, and his or her capacity to make decisions. [D(GPP)]

The public needs to be better informed of the symptoms and signs that are characteristic of lung cancer, through co-ordinated campaigning to raise awareness. [D(GPP)]

Urgent referral for a chest X-ray should be offered when a patient presents with: [D]

> haemoptysis, or

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

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

If a chest X-ray or chest computerised tomography (CT) scan suggests lung cancer (including pleural effusion and slowly resolving consolidation), patients should be offered an urgent referral to a member of the lung cancer multidisciplinary team (MDT), usually a chest physician. [D]

If the chest X-ray is normal but there is a high suspicion of lung cancer, patients should be offered urgent referral to a member of the lung cancer MDT, usually the chest physician. [D]

Patients should be offered an urgent referral to a member of the lung cancer MDT, usually the chest physician, while awaiting the result of a chest X-ray, if any of the following are present: [D]

> persistent haemoptysis in smokers/ex-smokers older than 40 years

> signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure)

> stridor

Emergency referral should be considered for patients with superior vena cava obstruction or stridor.

1.8.2.2 Diagnosis

Where a chest X-ray has been requested in primary or secondary care and is incidentally suggestive of lung cancer, a second copy of the radiologist's report should be sent to a designated member of the lung cancer MDT, usually the chest physician. The MDT should have a mechanism in place to follow up these reports to enable the patient's GP to have a management plan in place. [D(GPP)]

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 adrenals. [D(GPP)]

Chest CT should be performed before:

> an intended fibreoptic bronchoscopy [A; C(DS)]

> any other biopsy procedure. [D(GPP)]

Bronchoscopy should be performed on patients with central lesions who are able and willing to undergo the procedure. [B(DS)]

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. [B(DS)]

Percutaneous transthoracic needle biopsy is recommended for diagnosis of lung cancer in patients with peripheral lesions. [B(DS)]

Surgical biopsy should be performed for diagnosis where other less invasive methods of biopsy have not been successful or are not possible. [B(DS)]

Where there is evidence of distant metastases, biopsies should be taken from the metastatic site if this can be achieved more easily than from the primary site. [D(GPP)]

An ^{18}F-deoxyglucose positron emission tomography (FDG-PET) scan should be performed to investigate solitary pulmonary nodules in cases where a biopsy is not possible or has failed, depending on nodule size, position and CT characterisation. [C; B(DS)]

1.8.2.3 Staging

Non-Small Cell Lung Cancer

In the assessment of mediastinal and chest wall invasion:

> CT alone may not be reliable [B(DS)]

> other techniques such as ultrasound should be considered where there is doubt [D(GPP)]

> surgical assessment may be necessary if there are no contraindications to resection. [D(GPP)]

Magnetic resonance imaging (MRI) should not routinely be performed to assess the stage of the primary tumour (T-stage) in NSCLC. [C(DS)]

MRI should be performed, where necessary to assess the extent of disease, for patients with superior sulcus tumours. [B(DS)]

Every cancer network should have a system of rapid access to FDG-PET scanning for eligible patients. [D(GPP)]

Patients who are staged as candidates for surgery on CT should have an FDG-PET scan to look for involved intrathoracic lymph nodes and distant metastases. [A(DS)]

Patients who are otherwise surgical candidates and have, on CT, limited (1–2 stations) N2/3 disease of uncertain pathological significance should have an FDG-PET scan. [D(GPP)]

Patients who are candidates for radical radiotherapy on CT should have an FDG-PET scan. [B(DS)]

Patients who are staged as N0 or N1 and M0 (stages I and II) by CT and FDG-PET and are suitable for surgery should not have cytological/histological confirmation of lymph nodes before surgical resection. [A]

Histological/cytological investigation should be performed to confirm N2/3 disease where FDG-PET is positive. This should be achieved by the most appropriate method. Histological/cytological confirmation is not required: [B(DS)]

> where there is definite distant metastatic disease

> where there is a high probability that the N2/N3 disease is metastatic (for example, if there is a chain of high FDG uptake in lymph nodes).

When an FDG-PET scan for N2/N3 disease is negative, biopsy is not required even if the patient's nodes are enlarged on CT. [B(DS)]

If FDG-PET is not available, suspected N2/3 disease, as shown by CT scan (nodes with a short axis > 1cm), should be histologically sampled in patients being considered for surgery or radical radiotherapy. [D(GPP)]

An MRI or CT scan should be performed for patients with clinical signs or symptoms of brain metastasis. [D(GPP)]

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 considered. [D(GPP)]

Small cell lung cancer

SCLC should be staged by a contrast-enhanced CT scan of the patient's chest, liver and adrenals and by selected imaging of any symptomatic area. [D(GPP)]

1.8.2.4 Surgery with curative intent for patients with NSCLC

Surgical resection is recommended for patients with stage I or II NSCLC who have no medical contraindications and adequate lung function. [D]

For patients with stage I or II NSCLC who can tolerate lobar resection, lobectomy is the procedure of choice. [C]

Pending further research, patients with stage I or II NSCLC who would not tolerate lobectomy because of comorbid disease or pulmonary compromise should be considered for limited resection or radical radiotherapy. [D]

For all patients with stage I or II NSCLC undergoing surgical resection – usually a lobectomy or a pneumonectomy – clear surgical margins should be the aim. [D(GPP)]

Sleeve lobectomy offers an acceptable alternative to pneumonectomy for patients with stage I or II NSCLC who have an anatomically appropriate (central) tumour. This has the advantage of conserving functioning lung. [C]

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. [C]

All patients undergoing surgical resection for lung cancer should have systematic lymph node sampling to provide accurate pathological staging. [D(GPP)]

In patients with stage IIIA (N2) NSCLC detected through preoperative staging, surgery alone is associated with a relatively poor prognosis. Therefore, these patients should be evaluated by the lung cancer MDT. [D(GPP)]

1.8.2.5 Radical radiotherapy alone for treatment of NSCLC

Radical radiotherapy is indicated for patients with stage I, II or III NSCLC who have good performance status (WHO 0, 1) and whose disease can be encompassed in a radiotherapy treatment volume without undue risk of normal tissue damage. [D(GPP)]

All patients should undergo pulmonary function tests (including lung volumes and transfer factor) before having radical radiotherapy for NSCLC. [D(GPP)]

Patients who have poor lung function but are otherwise suitable for radical radiotherapy should still be offered radiotherapy, provided the volume of irradiated lung is small. [D(GPP)]

Patients with stage I or II NSCLC who are medically inoperable but suitable for radical radiotherapy should be offered the CHART regimen. [A]

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. [A]

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. [D(GPP)]

1.8.2.6 Chemotherapy for NSCLC

Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life. [A]

Chemotherapy for advanced NSCLC should be a combination of a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. [D(GPP)]

Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug. [A]

Docetaxel monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy. [A]

The development of this section included a review of the following technology appraisal. "Doxetaxel, paclitaxel, gemcitibine and vinorelbine for non-small-cell lung cancer. NICE Technology Appraisal No. 26 (2001)". The appraisal is therefore now obsolete and has been replaced by the guideline.

1.8.2.7 Combination treatment for NSCLC

Patients with stage I, II or IIIA NSCLC who are suitable for resection should not be offered preoperative chemotherapy unless it is part of a clinical trial. [B]

Preoperative radiotherapy is not recommended for patients with NSCLC who are able to have surgery. [A]

Postoperative radiotherapy is not recommended for patients with NSCLC after complete resection. [A]

Postoperative radiotherapy should be considered after incomplete resection of the primary tumour for patients with NSCLC, with the aim of improving local control. [D]

Adjuvant chemotherapy should be offered to NSCLC patients who have had a complete resection, with discussion of the risks and benefits. [A]

Patients who are pathologically staged as II and III NSCLC following resection should not receive postoperative chemoradiotherapy unless it is within a clinical trial. [B]

Patients with stage III NSCLC who are not suitable for surgery but are eligible for radical radiotherapy should be offered sequential chemoradiotherapy. [A]

1.8.2.8 Treatment of Small Cell Lung Cancer

Patients with SCLC should be offered an assessment that includes evaluation of the major prognostic factors: performance status, serum lactate dehydrogenase, liver function tests, serum sodium, and stage. [D]

All patients with SCLC should be offered:

> platinum-based chemotherapy [A]

> multidrug regimens, because they are more effective and have a lower toxicity than single-agent regimens. [A]

Four to six cycles of chemotherapy should be offered to patients whose disease responds. Maintenance treatment is not recommended. [A]

Patients with limited-stage SCLC should be offered thoracic irradiation concurrently with the first or second cycle of chemotherapy or following completion of chemotherapy if there has been at least a good partial response within the thorax. For patients with extensive disease, thoracic irradiation should be considered following chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax [A]

Patients undergoing consolidation thoracic irradiation should receive a dose in the range of 40 Gy in 15 fractions over 3 weeks to 50 Gy in 25 fractions over 5 weeks. [D(GPP)]

Patients with limited disease and complete or good partial response after primary treatment should be offered prophylactic cranial irradiation. [A]

Second-line chemotherapy should be offered to patients at relapse only if their disease responded to first-line chemotherapy. The benefits are less than those of first-line chemotherapy. [D(GPP)]

1.8.2.9 Palliative Interventions and Supportive and Palliative care

This section focuses on palliative interventions and supportive and palliative care for patients with lung cancer and therefore only evidence specific to lung cancer was reviewed. An absence of evidence does not imply that nothing can be done to help, and supportive and palliative care multidisciplinary teams- in particular specialist palliative care teams- have an important role in symptom control.

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'. [D(GPP)]

Patients who may benefit from specialist palliative care services should be identified and referred without delay. [D(GPP)]

External beam radiotherapy should be considered for the relief of breathlessness, cough, haemoptysis or chest pain. [A]

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

Debulking bronchoscopic procedures should be considered for the relief of distressing large-airway obstruction or bleeding due to an endobronchial tumour within a large airway. [D]

Patients with endobronchial symptoms that are not palliated by other means may be considered for endobronchial therapy. [D]

Patients with extrinsic compression may be considered for treatment with stents. [D]

Non-drug interventions based on psychosocial support, breathing control and coping strategies should be considered for patients with breathlessness. [A]

Non-drug interventions for breathlessness should be delivered by a multidisciplinary group, co-ordinated 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. [D(GPP)]

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

Patients who present with superior vena cava obstruction should be offered chemotherapy and radiotherapy according to the stage of disease and performance status. [A]

Stent insertion should be considered for the immediate relief of severe symptoms of superior vena caval obstruction or following failure of earlier treatment. [B]

Corticosteroids and radiotherapy should be considered for symptomatic treatment of cerebral metastases in lung cancer. [D]

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. [D(GPP)]

Pleural aspiration or drainage should be performed in an attempt to relieve the symptoms of a pleural effusion. [B]

Patients who benefit symptomatically from aspiration or drainage of fluid should be offered talc pleurodesis for longer-term benefit. [B]

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

Spinal cord compression is a medical emergency and immediate treatment (within 24 hours), with corticosteroids, radiotherapy and surgery where appropriate, is recommended. [D]

Patients with spinal cord compression should have an early referral to an oncology physiotherapist and an occupational therapist for assessment, treatment and rehabilitation. [D(GPP)]

1.8.2.10 Service organisation

All patients with a likely diagnosis of lung cancer should be referred to a member of a lung cancer MDT (usually a chest physician). [D]

The care of all patients with a working diagnosis of lung cancer should be discussed at a lung cancer MDT meeting. [D]

Early diagnosis clinics 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. [A]

All cancer units/centres should have one or more trained lung cancer 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. [D]

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). [D]

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. [A]

When patients finish their treatment a personal follow-up plan should be discussed and agreed with them after discussion with the professionals involved in the patient's care. GPs should be informed of the plan. [D(GPP)]

After completion of their treatment, patients with an expectation of life of more than 3 months should have access to protocol-controlled, nurse-led follow-up. [A]

Patients who have had attempted curative surgery for NSCLC, or radical radiotherapy should be followed up routinely by a member of the MDT for up to 9 months to check for post-treatment complications. Thoracic imaging should be part of the review. [D]

For patients who have had attempted curative surgery for NSCLC, any routine follow-up should not extend beyond 5 years. [D]

Patients who have had palliative radiotherapy or chemotherapy should be followed up routinely at 1 month after completion of treatment. A chest X-ray should be part of the review if clinically indicated. [D]

Patients with lung cancer – in particular those with a better prognosis – should be encouraged to stop smoking. [D]

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. [D(GPP)]

1.8.3 Research Recommendations

The guideline development group made a number of recommendations for research in areas where research is lacking. They selected 5 of these that were considered to be the highest priority. These are:

- Further research is needed into whether the use of low-dose CT in early diagnosis of patients at high risk of developing lung cancer has an effect on the mortality of lung cancer. A randomised trial should compare no intervention with low-dose CT performed at baseline and then annually for 5 years.

- Further research is needed into the symptoms and signs associated with early- and late-stage lung cancer and the factors associated with delay in presentation. For patients diagnosed with lung cancer, analysis should be undertaken of the symptoms at presentation, the time between onset of symptoms and presentation, the stage at presentation and the reasons for delay in presentation.

- Further research is needed into whether chemotherapy or active supportive care result in better symptom control, quality of life and survival for patients with advanced NSCLC of performance status 2.

- Research is needed to compare concurrent chemoradiotherapy with alternative fractionation schedules (such as 55 Gy in 20 fractions or CHART) with sequential chemoradiotherapy for patients with NSCLC. Outcomes measured should include detailed recording of the impact on quality of life and on toxicity.

- The management of common symptoms such as cachexia, anorexia fatigue and breathlessness experienced by patients with lung cancer needs further research. Specifically, research is required into clinically meaningful outcome measures for the treatment of the cachexia-anorexia syndrome. For example, does the level of physical activity as measured by an activity meter relate to performance status, quality of life and use of health and social care services?

The following research recommendations were also made:

1.8.3.1 Staging

- Further research is needed into the diagnostic accuracy and efficacy of FDG-PET scanning in follow-up of patients after radical treatment for lung cancer to investigate possible recurrence of the disease.

- Further research is needed into the diagnostic accuracy and efficacy of FDG-PET scanning in staging patients with SCLC.

- Further research is required to assess the diagnostic accuracy and efficacy of FDG-PET in the assessment of tumour response to chemotherapy and radiotherapy.

1.8.3.2 Surgery for NSCLC

- In stage I (IA and IB) NSCLC, further randomised trials on the survival and morbidity after limited resection in comparison to lobar resection for small lung tumours (less than 2 cm) are needed.

> In patients with clinical stage I (IA and IB) NSCLC who are suitable for surgical resection, further research on the survival and morbidity after anatomical resection by thoracoscopic techniques in comparison to open resection is needed.

> In patients with stage IIIA (N2) NSCLC detected through preoperative staging, surgery alone is associated with a relatively poor prognosis. Research should be conducted in a multidisciplinary setting into the survival and morbidity after surgery alone in comparison with multi-modality treatments.

1.8.3.3 Radical Radiotherapy for NSCLC

> Research should be conducted into whether NSCLC patients with poor lung function have better survival, morbidity and quality of life when treated with radical radiotherapy alone compared to no treatment or treatment with chemotherapy or chemoradiotherapy .

1.8.3.4 Chemotherapy for NSCLC

> Further trials should invesigate the optimum timing, combination, dosage and duration of chemotherapy for patients with NSCLC who are candidates for chemotherapy. These should include assessment of quality of life and survival.

1.8.3.5 Combination treatment for NSCLC

> Further large-scale prospective trials should be conducted into the effect on survival and quality of life of postoperative radiotherapy compared to surgery alone in the treatment of completely resected stage III NSCLC patients.

> Prospective randomised controlled trials should be conducted into the effect on survival and quality of life of treatment with preoperative radiotherapy and chemotherapy in the treatment of patients with Pancoast tumours compared to surgery alone.

1.8.3.6 Endobronchial Therapy with curative intent for NSCLC

> Further randomised trials should be conducted on the effect on survival and quality of life of endobronchial techniques (photodynamic therapy, brachytherapy, cryotherapy, electrocautery, Nd-YAG laser ablation) used as curative treatment in patients with early-stage NSCLC not suitable for conventional treatment.

1.8.3.7 Small Cell Lung Cancer

> Clinical trials should be conducted to determine to benefit of prophylactic cranial irradiation compared to no prophylactic treatment in terms of survival and quality or life for patients with extensive disease SCLC and a complete response at distant metastatic sites and a complete or good partial response within the thorax after treatment.

1.8.3.8 Palliative Interventions and Supportive and Palliative care

> Further research is required to determine the benefit of non-drug treatments for breathlessness, compared to no treatment or other drug based treatments, in terms of symptom relief and performance status for patients with lung cancer.

> The effect of bisphosphonates in the relief of pain and skeletal morbidity from bone metastasis in lung cancer needs further research.

1.8.3.9 Service Organisation

> For patients who have had attempted curative treatment and have completed their initial follow up, trials should examine the duration of follow-up and whether regular routine follow-up is better than symptom-led follow-up in terms of survival, symptom control and quality of life.

> The impact of the time between first symptom (or first detection if asymptomatic) and the treatment of lung cancer on patients' survival and quality of life should be investigated.

1.8.4 Algorithm

General Principles

Information and support

- Give all patients diagnosed with lung cancer verbal and written information on all aspects of their diagnosis, treatment and care, in a form that is tailored to their needs. **D (GPP)**
- Discuss treatment options and plans with the patient, and make decisions on treatment and care jointly with the patient. Treatment plans should be tailored around the patient's needs and wishes to be involved and his or her capacity to make decisions. **D (GPP)**
- Encourage patients with lung cancer – particularly those with a better prognosis – to stop smoking. **D**

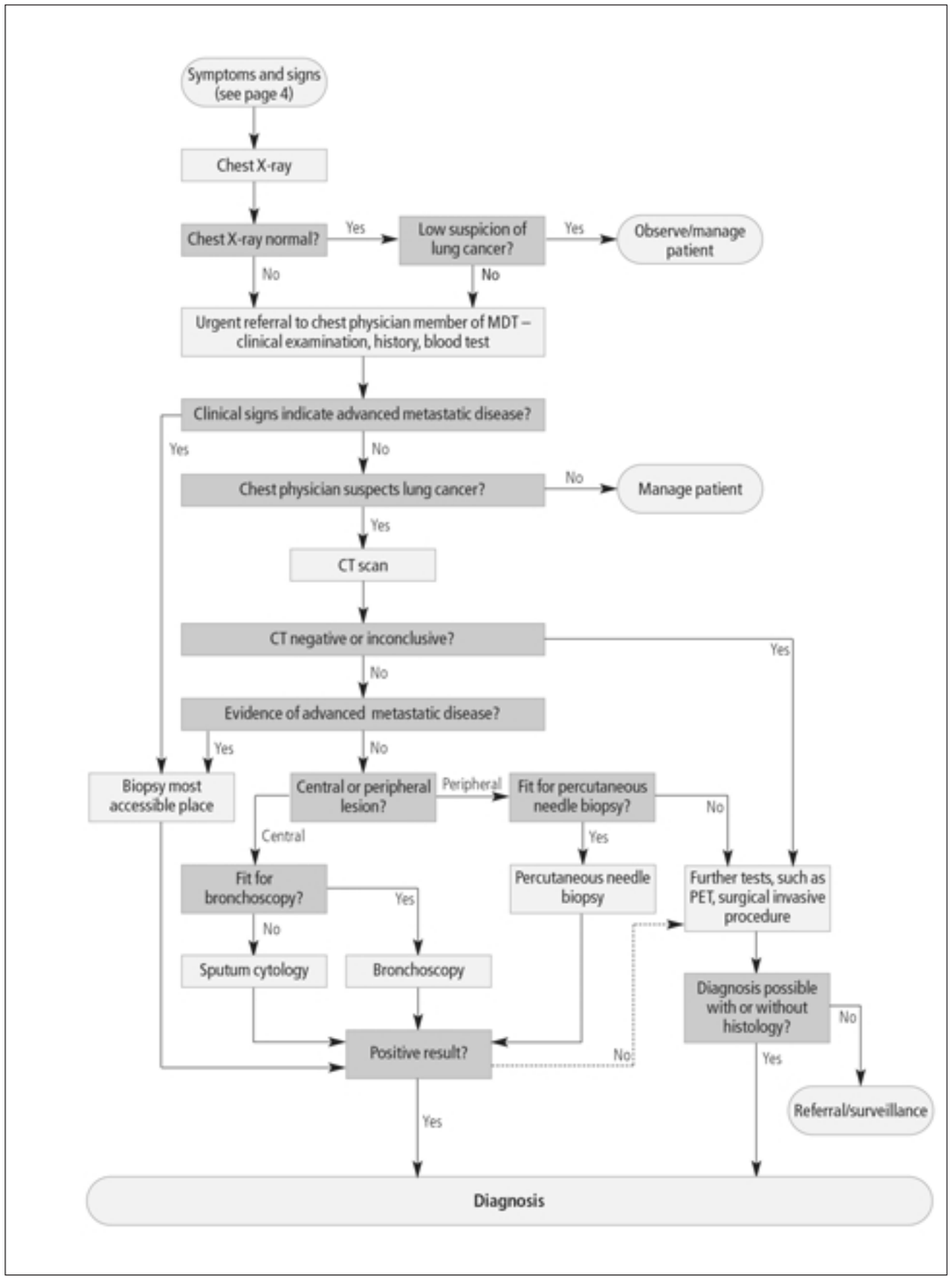
Referral

- Offer urgent chest X-ray to patients presenting with haemoptysis, or any of the following if unexplained or present for more than 3 weeks: D
  - cough
  - chest/shoulder pain
  - dyspnoea
  - weight loss
  - chest signs
  - hoarseness
  - finger clubbing
  - signs suggesting metastases (for example, in brain, bone, liver or skin)
  - cervical/supraclavicular lymphadenopathy.
- Offer urgent referral to lung cancer MDT (usually the chest physician) while waiting for chest X-ray results if any of the following are present: **D**
  - persistent haemoptysis in a smoker or ex-smoker older than 40 years
  - signs of superior vena cava obstruction (swelling of the face and/or neck with fixed elevation of jugular venous pressure – consider emergency referral)
  - stridor (consider emergency referral).

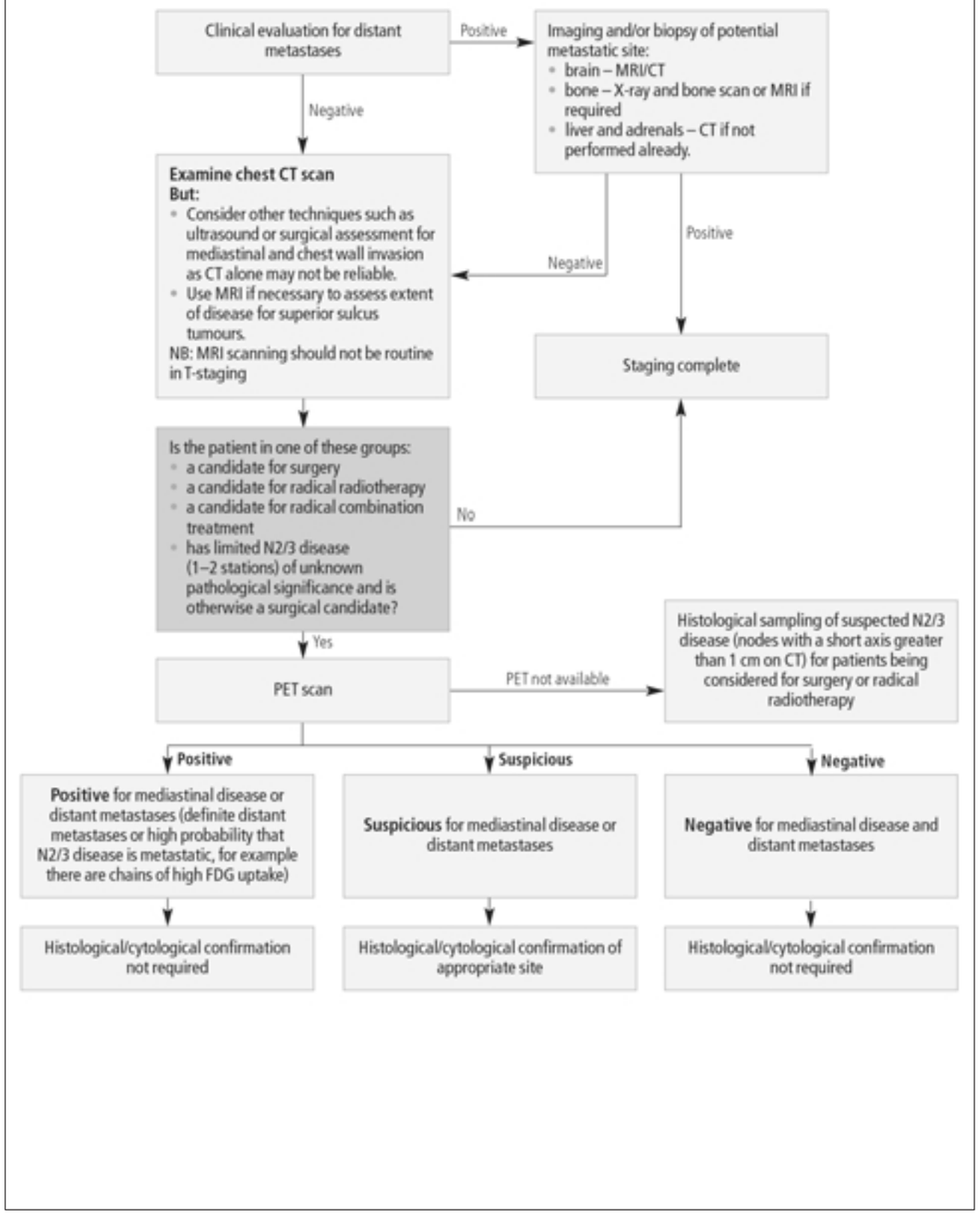
Organisation of care – key features

- Lung cancer as an incidental finding: a second copy of the chest X-ray report should be sent to a member of the MDT – usually the chest physician. **D (GPP)**
- MDTs: discuss care of all patients with a working diagnosis of lung cancer. **D**
- Early diagnosis clinics: provided where possible, to speed up diagnosis and reduce patient anxiety. **A**
- PET scanning: every cancer network should have a system of rapid access to FDG-PET scanning for eligible patients. **D (GPP)**
- Lung cancer nurse specialists: each cancer unit/centre should have one or more trained nurse specialists to provide continuing support to patients, and to facilitate communication between healthcare professionals. **D**
- Timing of treatment: patients suitable for radical treatment or chemotherapy, or needing radiotherapy or ablative treatment for symptom relief, 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). **D**
- Patients' views: use the opinions and experiences of patients and carers to improve the delivery of lung cancer services, and give patients feedback on any action taken as a result. **D (GPP)**

Diagnosis of Lung Cancer



Staging of non-small cell lung cancer



Surgery (stages I to III)

Stages I and II

- Surgical resection is recommended for patients with no medical contraindications and adequate lung function. **D**
- Lobectomy is the procedure of choice for patients who can tolerate it. **C**
- Consider limited resection or radical radiotherapy for patients who would not tolerate lobectomy because of comorbid disease or pulmonary compromise. **D**
- Aim for clear surgical margins in all patients with stage I or II NSCLC undergoing surgery – usually lobectomy or pneumonectomy. **D (GPP)**
- Sleeve lobectomy is an acceptable alternative to pneumonectomy for patients with central tumour, and conserves functioning lung. **C**

Stages II and III

- Aim for complete resection for patients with T3 NSCLC with chest wall involvement who are undergoing surgery, by either extrapleural or en bloc chest wall resection. **C**
- The MDT should assess patients with stage IIIA (N2) NSCLC because surgery alone is associated with a relatively poor prognosis. **D (GPP)**

All patients having surgery

- Perform systematic lymph node sampling to provide accurate pathological staging. **D (GPP)**

Radiotherapy alone (stages I to III)

- Radical radiotherapy is indicated for patients with stage I, II or III NSCLC who have good performance status (WHO 0, 1) and whose disease can be encompassed in a radiotherapy treatment volume without undue risk of normal tissue damage. **D (GPP)**
- All patients should undergo pulmonary function tests (including lung volumes and transfer factor) before having radical radiotherapy. **D (GPP)**
- Patients who have poor lung function but are otherwise suitable for radical radiotherapy should still be offered radiotherapy, provided the volume of irradiated lung is small. **D (GPP)**
- Offer the CHART regimen to:
  - patients with stage I or II NSCLC who are medically inoperable but suitable for radical radiotherapy. **A**
  - patients with stages IIIA or IIIB NSCLC who are eligible for radical radiotherapy and who cannot tolerate or do not wish to have chemoradiotherapy. **A**
- If CHART is not available, offer conventionally fractionated radiotherapy to a dose of 64–66 Gy in 32–33 fractions over 6 1 /2 weeks or 55 Gy in 20 fractions over 4 weeks. **D (GPP)**

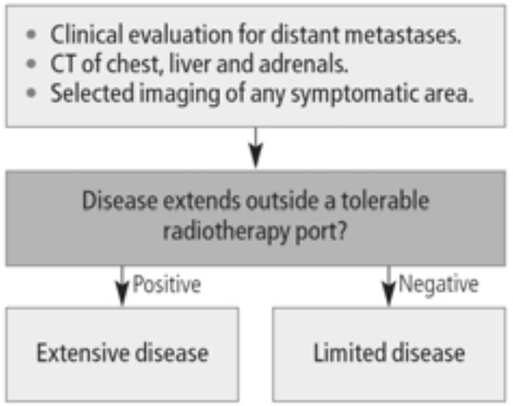
Chemotherapy for patients with NSCLC (stages III and IV)

- Offer chemotherapy to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life. **A**
- Chemotherapy should be a combination of: **D (GPP)**
  - a single third-generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine), plus
  - a platinum drug – carboplatin or cisplatin, taking account of their toxicities, efficacy and convenience.
- Single-agent chemotherapy with a third-generation drug can be offered to patients who cannot tolerate a platinum combination. **A**
- Consider docetaxel monotherapy if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy. **A**

Combination treatment

- The following treatments are not recommended:
  - preoperative chemotherapy (except as part of a clinical trial) **B**
  - preoperative radiotherapy **A**
  - postoperative radiotherapy after complete resection **A**
  - postoperative chemoradiotherapy for patients whose NSCLC is pathologically staged as II and III (except as part of a clinical trial). **B**
- Consider postoperative radiotherapy after incomplete resection of the primary tumour, to improve local control. **D**
- Offer adjuvant chemotherapy to patients who have had a complete resection, with discussion of the risks and benefits. **A**
- Offer sequential chemoradiotherapy to patients with stage III NSCLC who are not suitable for surgery but are eligible for radical radiotherapy. **A**

Staging of small-cell lung cancer



Treatment of small-cell lung cancer

- Assessment includes evaluation of the major prognostic factors: performance status, serum lactate dehydrogenase, liver function tests, serum sodium, and stage. **D**
- Offer all SCLC patients multidrug platinum-based chemotherapy. **A**
- If the disease responds, offer four to six cycles of chemotherapy. Maintenance treatment is not recommended. **A**
- Offer patients with limited-stage SCLC thoracic irradiation concurrently with the first or second cycle of chemotherapy or after completion of chemotherapy if there has been at least a good partial response within the thorax. For patients with extensive disease, consider thoracic irradiation after chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax. **A**
- The dose for consolidation thoracic radiotherapy should be between 40 Gy in 15 fractions over 3 weeks and 50 Gy in 25 fractions over 5 weeks. **D (GPP)**
- Consider prophylactic cranial irradiation for patients with limited disease and complete or good partial response after primary treatment. **A**
- At relapse, offer second-line chemotherapy only if the disease responded to first-line chemotherapy. The benefits are less than with first-line chemotherapy. **D (GPP)**

Treatent of non-small-cell lung Cancer

	Stage I	*Stage II*	*Stage IIIA*	*Stage IIIB*	*Stage IV, WHO 0–1*	*Stage IV, WHO 2*	*Stage IV, WHO > 2*
Surgery							
Radiotherapy followed by surgery							
Surgery followed by radiotherapy							
Preoperative chemotherapy and surgery	a	a	a				
Surgery followed by chemotherapy							
Surgery then chemo- and radiotherapy		a	a				
Radical radiotherapy							
Chemotherapy and radical radiotherapy				b			
Chemotherapy						a	
Symptomatic treatment, including palliative radiotherapy							

Key	
	First choice for eligible patients
	Suitable for some patients (see recommendations)
	Not recommended

a Except within a clinical trial.

b May be first choice of treatment for patients with good performance status and localised disease that can be safely encompassed in a radical radiotherapy treatment volume.

Surgery (Stages I to III)

- This section focuses on palliative interventions and supportive and palliative care for patients with lung cancer and therefore only evidence specific to lung cancer was reviewed. An absence of evidence does not imply that nothing can be done to help, and supportive and palliative care multidisciplinary teams – in particular specialist palliative care teams – have an important role in symptom control.
- Supportive and palliative care should be provided by general and specialist palliative care providers in accordance with the NICE Cancer Service Guidance 'Improving supportive and palliative care for adults with cancer' (available from www.nice.org.uk/csgsp). **D (GPP)**
- Identify and refer without delay patients who may benefit from specialist palliative care services. **D (GPP)**
- Patients who cannot be offered curative treatment, and are candidates for palliative radiotherapy, can be either observed until symptoms arise and then treated or treated immediately. **A**
- Non-drug interventions for breathlessness should be delivered by a multidisciplinary group, co-ordinated by a professional with expertise in the techniques (such as a nurse, physiotherapist or occupational therapist). Patients should have access to this support in all care settings. **D (GPP)**
- Patients should be offered general supportive measures – including drugs – for symptom control, in addition to the specific interventions listed in the table below.

Symptom	Management
Breathlessness	• External beam radiotherapy. **A** • Non-drug interventions (psychosocial support, breathing control and coping strategies). **A** **Intrinsic airway obstruction** • De-bulking bronchoscopic procedures. **D** • Endobronchial therapy (photodynamic therapy, brachytherapy) for endobronchial symptoms not palliated by other means. **D** **Extrinsic airway compression** • Stents. **D** **Pleural effusion** • Pleural aspiration/drainage for pleural effusion. **B** • Talc pleurodesis if symptoms improve after aspiration/drainage of fluid. **B**
Cough	• External beam radiotherapy. **A**
Haemoptysis	• External beam radiotherapy. **A**
Chest pain	• External beam radiotherapy. **A**
Hoarseness	• Referral to ear, nose and throat specialist. **D (GPP)**
Superior vena cava obstruction	• Chemotherapy and radiotherapy, depending on stage of disease and performance status. **A** • Stent insertion for immediate relief of severe symptoms or after failure of earlier treatment. **B**
Symptoms from brain metastases	• Corticosteroids and radiotherapy. **D**
Spinal cord compression	• Corticosteroids, radiotherapy and surgery where appropriate, within 24 hours. **D** • Early referral to oncology physiotherapist and occupational therapist. **D (GPP)**
Symptoms from bone metastases	• Single-fraction radiotherapy if standard analgesic treatments are inadequate. **B**
Other symptoms	• Management by multidisciplinary groups including supportive and palliative care professionals should address other symptoms, including weight loss, loss of appetite, difficulty swallowing, and depression. **D(GPP)**

Follow-up

- When patients finish their treatment, a personal follow-up plan should be discussed and agreed with them, after discussion with other professionals involved in the patient's care. The patient's GP should be informed of the plan. D (GPP)
- After completion of treatment, patients with an expectation of life greater than 3 months should be offered the option of protocol-controlled nurse-led follow-up. A
- Patients who have had attempted curative surgery for NSCLC or radical radiotherapy should be followed up routinely by a member of the MDT for up to 9 months, to check for post-treatment complications. The review should include thoracic imaging. D
- Routine follow-up should not extend beyond 5 years after attempted curative surgery for NSCLC. D
- Patients who have had palliative radiotherapy or chemotherapy should be followed up routinely 1 month after completion of treatment. The review should include a chest X-ray if clinically indicated. D

2 Methodology

2.1 Guideline Methodology

The guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups[16].

2.2 Review of the clinical literature

The aim of the literature review was to identify and synthesise relevant evidence within the published literature, in order to answer specific clinical questions. Searches were performed using generic and specific filters, relevant medical subject heading terms and free text terms. Only studies on patients with lung cancer (or where the majority of patients recruited were those with lung cancer) were included, with one exception. When we considered the treatment of pleural effusion, studies on patients with mixed primary sites were included as specific data was not available and the GDG agreed that the site of the primary tumour would not determine treatment in this case. Details of all literature searches are available in appendix six. The scope and the clinical questions can be found in appendix seven and eight respectively.

Search filters to identify systematic reviews, randomised controlled trials and observational studies were adapted from the SIGN methodological search filters (http://www.sign.ac.uk/methodology/filters.html). The lung cancer search strategy stem was devised in collaboration with SIGN. It was then combined with independently devised search strategies for each section of the guideline. The following databases were searched for all section:

> The Cochrane Library (up to Issue 4, 2003)

> Medline (OVID) 1966-2003 (week 52)

> Embase (OVID) 1980-2003 (week 52)

The Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PsychInfo were also searched for relevant clinical questions. Identification of high quality systematic reviews determined the date ranges searched for each clinical question. No language restrictions were applied to the search but identified foreign papers were not requested or reviewed. The cut off date for the NCC-AC literature search was 31st December 2003. In order to be consistent and systematic we did not consider papers after this date. This decision was made for pragmatic reasons of work load and means that very current data will be missed.

There was no systematic attempt to search for all the 'grey literature' (conferences, abstracts, theses and unpublished literature). However, we searched ASCO (http://www.asco.org) for interventional abstracts to identify and verify published papers. We searched for guidelines and reports from relevant websites, including the following listed below. Bibliographies of identified reports and guidelines were also checked to identify relevant literature.

> National Institute of Clinical Excellence (NICE) (www.nice.org.uk)

> National electronic Library for Health (NeLH) (http://www.nelh.nhs.uk/)

> National Institutes of Health Consensus Development Program (consensus.nih.gov)

> New Zealand Guidelines Development Group (NZGG) (http://www.nzgg.org.nz/)

> Scottish Intercollegiate Guideline Network (SIGN) (www.sign.ac.uk)

> US National Guideline Clearing House (www.guidelines.gov)

> Google (www.google.com)

All retrieved articles have been methodologically appraised using checklists developed by SIGN.

2.3 Hierarchy of clinical evidence

There are many different methods of ranking the evidence and there has been considerable debate about what system is best. A number of initiatives are currently under way to find an international consensus on the subject, but until a decision is reached on the most appropriate system, for the NICE guidelines the Institute advises the National Collaborating Centres to use the system for evidence shown in Table 2. This is the same system that the Scottish Intercollegiate Guideline Network (SIGN) used to evaluate the evidence in the areas they reviewed. For more details on the methods used by SIGN, please see their website (www.sign.ac.uk).

TABLE 2: Levels of evidence for intervention studies (reproduced with permission of the Scottish Intercollegiate Guidelines Network)

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion

The ranking system described above covers studies of treatment effectiveness and is less appropriate for studies reporting diagnostic tests of accuracy. Since there is no validated ranking system for diagnostic tests, NICE has developed a hierarchy for evidence of this nature which takes into account factors likely to affect the validity of these studies (Table 3). The NCC-AC was the first Centre to pilot this hierarchy and it has yet to be systematically tested.

TABLE 3: Levels of evidence for studies of the accuracy of diagnostic tests. Adapted from The Oxford Centre for Evidence-based Medicine Levels of Evidence (2001)[17] and the Centre for Reviews and Dissemination Report Number 4 (2001)[18]

Levels of Evidence	Type of Evidence
Ia	Systematic review (with homogeneity)* of level-1 studies**
Ib	Level-1 studies**
II	Level-2 studies*** Systematic reviews of level-2 studies
III	Level-3 studies**** Systematic reviews of level-3 studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience without explicit critical experience, based on physiology, bench research, or first principles.

*Homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

**Level-1 studies are studies:

> That use a blind comparison of the test with a validated reference standard (gold standard)

> In a sample of patients that reflects the population to whom the test would apply.

***Level-2 studies are studies that have **only one** of the following:

> Narrow population (the sample does not reflect the population to whom the test would apply)

> Use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')

> The comparison between the test and reference is not blind

> Case-control studies

****Level-3 studies are studies that have **at least two or three** of the features listed above.

For each clinical question the highest level of evidence was sought. Where an appropriate systematic review, meta- analysis or randomised controlled trial exist, we did not search for studies of a weaker design.

Studies that were assessed to be of adequate quality were summarised in evidence tables. All the evidence tables can be found in appendix one.

2.4 Health economics methods

It is important to investigate whether health services are clinically effective and also cost-effective (that is, value for money). If a particular diagnostic or treatment strategy were found to yield little health gain relative to the resources used, then it could be advantageous to re-deploy resources to other activities (either in lung cancer or beyond) that yield greater health gain.

To assess the cost-effectiveness of each recommendation, a comprehensive systematic review of the economic literature relating to lung cancer was conducted. For selected components of the guideline original cost-effectiveness analyses were performed.The primary criteria applied for an intervention to be considered cost-effective were either:

a) the intervention dominated other relevant strategies (that is it is both less costly in terms of resource use and more clinically effective compared with the other relevant alternative strategies); or

b) the intervention cost less than £30,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy (and compared with best supportive care). However, between £20,000 and £30,000 per QALY, judgements about the acceptability of the intervention as an effective use of NHS resources will make more explicit reference to such factors as the degree of uncertainty surrounding the calculation of cost-effectiveness, the innovative nature of the intervention and the particular features of the condition and the population receiving it.

2.4.1 Literature review for Health Economics

We obtained published economic evidence from a systematic search of the following databases:

> Medline (Ovid) (1966-2003)

> Embase (1980-2003)

> Health Economic Evaluations Database (HEED)

> NHS Economic Evaluations Database (NHS EED)

For those clinical area's we reviewed, the information scientists used the same search strategy as for the clinical questions, substituting an economics filter for a study type filter. For those clinical area's SIGN reviewed, the information scientistics had to design a filter specifically for the health economists.

Each search strategy was designed to find any applied study estimating the cost or cost-effectiveness of some aspect of lung cancer. A health economist reviewed abstracts and database reviews of papers. Relevant references in the bibliographies of reviewed papers were also identified and reviewed.

Given the diversity of economic studies, it was not possible to determine a general exclusion criterion based on study quality. Hence all studies were included in the evidence tables (including abstracts) and study quality and applicability are discussed in the review. Papers were only excluded from the evidence tables and review if:

> Results were not reported specifically for lung cancer patients (Although occasionally studies were found and included, where most but not all patients had lung cancer, e.g. in comparisons of different types of thoracic surgery).

> The study did not contain any original data on cost or cost-effectiveness (i.e. it was a review or a clinical paper).

> The analysis was not incremental and was not described adequately to allow incremental analysis (so studies reporting only average cost-effectiveness ratios were excluded unless they provided data to allow the calculation of incremental cost-effectiveness ratios).

For one topic – treatment of pleural effusion - it was decided to include data not specific to lung cancer. In this case, all studies were reviewed for malignant pleural effusion, on the assumption that the site of the primary tumour would not determine treatment.

For key papers where costs were in a currency other than pounds sterling, US dollars or euros, the results were converted to pounds sterling using the relevant purchasing power parity for the study year. Most studies were recent during a period of relatively low inflation, therefore inflation to current prices was not considered necessary.

Each study was categorised as one of the following: cost analysis, cost-effectiveness analysis or cost-utility analysis (i.e. cost-effectiveness analysis with effectiveness measured in terms of QALYs). We did not find any cost benefit analyses (studies that put a monetary value on health gain). Studies labelled as 'cost consequences analysis' or 'cost minimisation analysis' were simply categorised as cost analyses, since the lack of an overall measure of health gain prevents such studies being considered full economic evaluations.

2.4.2 Cost-effectiveness modelling

Specific topics were selected for original economic analysis if there was a likelihood that the recommendation made would substantially change clinical practice in the NHS and have important consequences for resource use.

In three cases there was not a relevant economic evaluation in the published literature: CHART versus conventional radical radiotherapy for NSCLC; FDG-PET in the work-up to radical radiotherapy for NSCLC; and platinum versus non-platinum drug regimens in the treatment of SCLC.

In a fourth case, economic evaluations had been previously published but had substantial limitations - FDG-PET in the work-up to curative surgery for NSCLC.

Methods used depended on the question being analysed, however, the following principles were followed:

> The GDG was consulted during the construction and interpretation of each model.

> Each model was based on the best evidence from the systematic review.

> Model assumptions were reported fully and transparently.

> The results were subject to thorough sensitivity analysis and limitations discussed.

> Costs were calculated from a health services perspective.

2.5 Forming and grading the recommendations

NICE guideline recommendations are graded according to the strength of the supporting evidence, which is assessed from the design of each study (see Table 2 and Table 3). The grading system currently used is presented in Table 4 and Table 5.

The Guideline Development Group was presented with summaries (text and evidence tables) of the best available research evidence to answer the clinical questions. Recommendations were based on, and explicitly linked to, the evidence that supported them. The evidence tables can be found in appendix one.

TABLE 4: Grading of recommendations**

Grade	Evidence
A	> At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population, or > A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results > Evidence drawn from a NICE technology appraisal
B	> A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results, or > Extrapolated evidence from studies rated as 1++ or 1+
C	> A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or > Extrapolated evidence from studies rated as 2++
D	> Evidence level 3 or 4, or > Extrapolated evidence from studies rated as 2+, or > Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group

The Group worked on an informal consensus basis. The recommendations were then graded according to the level of evidence upon which they were based.

Recommendations based on studies assessing the diagnostic accuracy of tests are also classified according to the strength of the supporting evidence. The classification system used for this guideline is presented in

Table 5. It is currently being piloted and has not yet been systematically tested by NICE. Some recommendations in this guideline have two grades because they are based on both diagnostic and effectiveness evidence.

TABLE 5: Classification of recommendations for studies of the accuracy of diagnostic tests. (DS = diagnostic studies)

Class	Level of Evidence (See Table 3)
A (DS)	Studies with levels of evidence Ia or Ib
B (DS	Studies with levels of evidence II
C (DS)	Studies with levels of evidence III
D (DS)	Studies with levels of evidence IV

The usefulness of a classification system based solely on the level of evidence has been questioned because it does not take into consideration the importance of the recommendation in changing practice and improving patient care. It is worth noting that NICE is currently assessing the best way of presenting recommendations for future guidelines.

3 Access to Services

3.1 Introduction

In this chapter we examine access to services. In particular we examine the delay between patients first experiencing symptoms and their presentation at their general practitioner (GP), interventions that may encourage patients to present sooner and the key symptoms and signs for which a GP should make a referral. This latter issue is particularly problematic because the symptoms of lung cancer, such as cough, are common among smokers and patients with chronic obstructive pulmonary disease (COPD). Information on the delays before treatment of lung cancer and the effect of using rapid access clinics are discussed in chapter 13 (Service organisation). Although this chapter discusses presentation to and referral by GPs it should be noted that many other management pathways for lung cancer patients exist. A regional randomised stratified analysis of the management pathways of 400 patients, found 80 such pathways and that more than 50% of patients did not present to hospital with a chest x-ray suspicious of lung cancer[19].

Patient communication and support are discussed more fully in chapter 12 (Palliative Interventions and Supportive and Palliative Care). It is, however, important to stress that at diagnosis and throughout treatment and care, patients are given information, both verbal and written, on aspects of their disease such as prognosis, treatment options and anticipated benefits and side effects in a form that is tailored to the needs of the individual patient. Good communication between patients and professionals must be encouraged and patients involved in the decision making process on their personal treatment and care plan.

3.2 Methodology

We conducted a systematic literature search and review according to the methods described in chapter 2. The search strategy is shown in appendix six.

3.3 Patient delay in presentation to general practitioners

We found no research that specifically addressed the effect of delay in presentation to GPs on the outcome for patients with lung cancer. However, a survey of lung cancer patients and carers in the UK looked at the delay between patients first experiencing symptoms of lung cancer and reporting them to a GP[20]. The survey revealed that for patients who reported visiting their GP because of chest symptoms there was a wide variation in delay in presentation between 3 weeks and 3 months (Level 3). One Swedish study of 134 patients noted similar results (see Table 7) finding that the mean delay from first symptom to presentation was 43 days (median 21 days)[21] (Level 3).

We searched for studies on the effectiveness of interventions at encouraging patients to present to healthcare services sooner with symptoms of lung cancer. 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[20,22]. Campaigns such as 'lung cancer awareness month' (The Roy Castle Lung Cancer Foundation and Macmillan Cancer Relief) have been run to address this and although outcomes are difficult to assess and have not been formally evaluated, an increase in callers to telephone helplines was noted[23]. There is scope for additional innovative and imaginative ways to engage those at risk.

The effect of delays in treatment on patient outcomes and the effect of using rapid access clinics or fast track systems are discussed in chapter 13 on service organisation.

3.4 Key Symptoms and Signs

The symptoms and signs of lung cancer can be difficult for the GP to distinguish from those of other diseases. The main symptoms and signs at presentation have been collected in case series and are shown in Table 6 (Level 3). We identified no evidence on whether any symptoms, or combinations of symptoms, can be used to predict the presence of lung cancer.

TABLE 6: Range of frequency of initial symptoms and signs of lung cancer (Source: Beckles et al. 2003[24])

Symptoms and Signs	Range of frequency,%
Cough	8-75
Weight Loss	0-68
Dyspnoea	3-60
Chest Pain	20-49
Haemoptysis	6-35
Bone Pain	6-25
Clubbing	0-20
Fever	0-20
Weakness	0-10
Superior Vena Cava Obstruction (SVCO)	0-4
Dysphagia	0-2
Wheezing and stridor	0-2

The Department of Health have issued referral guidelines for suspected cancer in 2000[25] and we found no recent evidence with which to update these guidelines. The guideline development group support these recommendations (Level 4). These guidelines state that:

Urgent referral for a chest x-ray should be made when a patient presents with:

> Haemoptysis

Or unexplained or persistent (more than 3 weeks)

> Cough

> Chest/shoulder pain

> Dyspnoea

> Weight loss

> Chest signs

> Hoarseness

> Finger clubbing

> Features suggestive of metastasis from a lung cancer (e.g. brain, bone, liver or skin)

> Persistent cervical/supraclavicular lymphadenopathy

The Department of Health Guidelines[25] note that in most cases where lung cancer is suspected it is appropriate to arrange for an urgent chest x-ray before urgent referral to a chest physician.

Chest x-ray (CXR) findings are abnormal in the vast majority of symptomatic patients. However, a normal CXR does not exclude a diagnosis of lung cancer[25]. The guideline development group support the Department of Health guidelines in stressing that where the GP is suspicious of lung cancer a referral should be offered even if the chest x-ray is normal.

If a chest x-ray or chest CT is suggestive or suspicious of a lung cancer (including pleural effusion and slowly resolving consolidation), patients should be offered urgent referral to a chest physician who is a member of the multidisciplinary lung cancer team.

In a limited number of circumstances, patients should be offered an urgent referral to a member of the MDT, usually the chest physician while awaiting the result of a chest x-ray, if any of the following are present:

> Persistent haemoptysis in smokers/ex-smokers over 40 years of age

> Signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure)

> Stridor

Emergency referral should be considered for patients with superior vena caval obstruction or stridor.

This has been adapted from the Department of Health guidelines on referral[25]. No economic evidence was found in this area.

The Department of Health has commissioned NICE to produce an update of the original GP referral guidelines for suspected cancers, including lung cancer, and these are due to be published in March 2005. NICE commissioned the National Collaborating Centre for Primary Care to produce evidence based guidelines on referral.

3.5 Recommendations

3.5.1 Clinical Practice Recommendations

All patients diagnosed with lung cancer should be offered information, both verbal and written, on all aspects of their diagnosis, treatment and care. This information should be tailored to the individual requirements of the patient, and audio and videotaped formats should also be considered. [D(GPP)]

Treatment options and plans should be discussed with the patient and decisions on treatment and care should be made jointly with the patient. Treatment plans must be tailored around the patient's needs and wishes to be involved, and his or her capacity to make decisions. [D(GPP)]

The public needs to be better informed of the symptoms and signs that are characteristic of lung cancer, through co-ordinated campaigning to raise awareness. [D(GPP)]

Urgent referral for a chest x-ray should be offered when a patient presents with: [D]

- **haemoptysis, or**
- **any of the following unexplained or persistent (that is, lasting more than 3 weeks) symptoms or signs:**
  - **cough**
  - **chest/shoulder pain**
  - **dyspnoea**
  - **weight loss**
  - **chest signs**
  - **hoarseness**
  - **finger clubbing**
  - **features suggestive of metastasis from a lung cancer (for example, in brain, bone, liver or skin)**
  - **cervical/supraclavicular lymphadenopathy.**

If a chest x-ray or chest computerised tomography (CT) scan suggests lung cancer (including pleural effusion and slowly resolving consolidation), patients should be offered an urgent referral to a member of the lung cancer multidisciplinary team (MDT), usually a chest physician. [D]

If the chest x-ray is normal but there is a high suspicion of lung cancer, patients should be offered urgent referral to a member of the lung cancer MDT, usually the chest physician. [D]

Patients should be offered an urgent referral to a member of the lung cancer MDT, usually the chest physician, while awaiting the result of a chest X-ray, if any of the following are present: [D]

- **persistent haemoptysis in smokers/ex-smokers over 40 years of age**
- **signs of superior vena caval obstruction (swelling of the face/neck with fixed elevation of jugular venous pressure)**
- **stridor.**

Emergency referral should be considered for patients with superior vena caval obstruction or stridor.

3.5.2 Research Recommendations

Further research is needed into whether the use of low-dose CT in early diagnosis of patients at high risk of developing lung cancer has an effect on the mortality of lung cancer. A randomised trial should compare no intervention with low-dose CT performed at baseline and then annually for 5 years.

Further research is needed into the symptoms and signs associated with early- and late-stage lung cancer and the factors associated with delay in presentation. For patients diagnosed with lung cancer, analysis should be undertaken of the symptoms at presentation, the time between onset of symptoms and presentation, the stage at presentation and the reasons for delay in presentation.

4 Diagnosis

4.1 Introduction

Patients with lung cancer generally present with symptoms and signs of the tumour as described previously (e.g. cough, dyspnoea, weight loss, anorexia, chest pain, haemoptysis and hoarseness). These symptoms are characteristic of lung cancer but many can be indicative of a number of other more minor diseases or ailments. It is possible for a tumour to grow quite large before causing any symptoms. In addition, a proportion of patients are diagnosed after their tumour is picked up incidentally on CXR and may not present with any of the classic symptoms of lung cancer. Solitary pulmonary nodules (SPN) are commonly encountered in clinical practice and are usually defined as lesions up to 3cm in size. Determining whether a solitary pulmonary nodule is benign or malignant is a frequently encountered problem requiring a multidisciplinary approach, often involving further imaging and intervention.

A CXR is almost invariably performed as the initial investigation. The vast majority of patients will then have both a computerised tomography (CT) scan and either bronchoscopy or image guided biopsy to obtain a tissue diagnosis. The patients' clinical status, the tumour stage, the cell type and patient preferences determine the diagnostic and staging tests that are most suitable. Accurate diagnosis is important for the future management for the patient.

In this chapter we review the evidence for the main diagnostic tests that can aid the clinician to establish a diagnosis. Formal staging will be discussed in the next chapter. However, in practice, staging is performed alongside diagnosis and some of the techniques discussed will provide both diagnostic and staging information.

4.2 Techniques included in this review

In this review we have examined the following techniques used for diagnosing lung cancer: CXR, CT, radionuclide imaging, positron emission tomography (PET), sputum cytology, bronchoscopy, percutaneous needle biopsy, biopsies of sites other than lung, anterior mediastinotomy, surgical thoracoscopy with biopsy and thoracotomy. Diagnostic techniques that examine mediastinal lymph nodes (e.g. mediastinoscopy) will be covered in the chapter on staging.

In this chapter we discuss imaging modalities used to diagnose lung cancer followed by techniques that aim to achieve tissue confirmation.

4.3 Methodology

The guideline review team undertook new systematic reviews of all of the techniques listed above. Guidelines on diagnosis issued by the American College of Chest Physicians in 2003 were included as the review was judged to have been systematic[26,27]. A comprehensive systematic review published in 2001 was also considered[28] but was less up to date for most topics. Studies of diagnostic accuracy were quality assessed using a system being piloted (described in the chapter on methodology) and studies of the effectiveness of the test at changing patient management were assessed as for all other studies of clinical effectiveness. For studies of diagnostic accuracy we report the sensitivity, specificity, positive predictive value (PPV) and the negative predictive value (NPV). Papers were rejected if the true positives, true negatives, false positives and false negatives could not be calculated.

The search strategy is described in appendix six.

4.4 Imaging

4.4.1 Chest X-Ray

When there is a suspicion of lung cancer, the CXR is usually the first investigation performed. Lung cancer usually presents itself radiographically as a solitary pulmonary nodule or pulmonary mass, pulmonary collapse, mediastinal lymphadenopathy, a pleural effusion or as an area of consolidation.

We identified one systematic review on the topic[28] that searched literature from 1966 to 2000. We conducted our own systematic review in which we searched for literature back to1994. However, although CXR is in common usage throughout the world as a diagnostic technique for lung cancer there has been little work on the subject. The systematic review[28] found only a small number of studies, which included patients of all stages and cell types and the sensitivity and specificity of chest x-rays could not be derived for a population applicable to UK patients awaiting diagnosis

The typical effective dose received by the patient undergoing a chest x-ray is 0.02mSv, which is equivalent to a lifetime additional risk of fatal cancer per examination of 1 in a million[29].

Although there is a lack of published evidence, the guideline development group considered that the CXR is a mandatory first line of investigation, enabling decisions on the next choice of investigation to be made. It is unfortunately an insensitive method of examination, and as such, if lung cancer is suspected clinically and the CXR is negative the patient should still be referred to a chest physician. Where a CXR is incidentally suggestive of lung cancer, the guideline development group agreed that patients should be identified to a chest physician within the local lung cancer multidisciplinary team (MDT) so that their further management can be initiated as soon as possible and to prevent an oversight occurring from an unexpected malignancy. The MDT should have a mechanism in place to follow up these reports to ensure the patient's GP has a management plan in place. This is discussed in more detail in chapter 3 on Access to Services.

4.4.2 Computerised tomography (CT)

A diagnosis of lung cancer can be achieved in a number of ways using CT. Firstly, the overall CT appearances may enable a diagnosis of malignancy to be made, such as identifying either metastatic disease or evidence of local tumour invasion into the chest wall or mediastinum. In addition, careful examination of the morphology of the lung lesion, its degree of enhancement or demonstration of growth on sequential examinations may allow a presumptive radiological diagnosis of malignancy.

Morphological Features

Previous researchers have suggested a number of morphological features particularly characteristic of benign solitary pulmonary nodules (SPN). These include various patterns of calcification such as diffuse, concentric, laminar, dense central or a 'popcorn' pattern of calcification. However, we identified only two studies that examined the accuracy with which these features could be used to predict whether a nodule is malignant (Table 8-Appendix 1 separate document). One study found that nodules with diffuse calcification were benign in 100% of 154 cases, (Specificity 63%, PPV 77.5%, NPV 100%)[30] (Level II). A more recent study[31] examined various morphological signs of 104 patients with SPNs, using spiral CT and high resolution CT (HRCT). They found that the sensitivity was 89% and 91% with spiral CT and HRCT respectively and that the specificity was 61% (spiral CT) and 57% (HRCT) (Level 1b). These figures were based on using any one of the following features: presence of spicules, the vessel sign, necrotic areas, circumscribed pleural thickening, inhomogeneity, ground-glass opacity of lung parenchyma adjacent to SPN, lesion density, pleural retraction or bronchus sign. Thus, sensitivity and specificity when using morphological features of SPNs on CT to predict malignancy does not seem to be good enough to allow confident decisions about whether to pursue further investigation of a suspect SPN.

Growth Rate

The growth rate of lesions has been used as a predictor of malignancy, in particular stability of the lesion size over time has been reported as a reliable sign that the lesion is benign although this too has been challenged. There are also major practical difficulties in measuring small size changes. Firstly, the average life expectancy of SCLC patients is too short to allow long-term assessment (the average doubling time of SCLC is 30 days compared to 100 days for NSCLC[32]). Secondly, long evaluation times mean that there is a risk of tumour spread. Lastly, accurate measurement of small changes is affected by exact positioning of the nodule. Two recent studies[33,34] of SPNs in small groups of patients found that a repeat scan could detect growth rate indicative of malignancy with a sensitivity and a specificity both of 100%. These encouraging preliminary results, if confirmed, indicate that repeated thin section could be used to detect lung malignant SPNs (Level IIDS).

Contrast Enhancement

Two studies examined the differential uptake of contrast agent in determining the diagnosis of an SPN[35,36]. The sensitivity and specificity ranged between 88-100% and 36-76.9% respectively. The PPV and NPV ranged between 62.3-90.2% and 71.4-100% respectively (Level II). As with the other CT methods of diagnosis, the low specificity is problematic.

Overall, CT provides anatomical information enabling the exact positioning of the lesion, and some results have shown that CT can have a high sensitivity. However, the specificity is poor in a number of studies. The typical effective dose received by the patient undergoing a chest CT is 8mSv, which is equivalent to a lifetime additional risk of fatal cancer per examination of 1 in 2500[29].

A CT scan provides useful information that can be used for decisions on further investigations such as bronchoscopy or needle biopsy in the establishment of a diagnosis of lung cancer.

4.4.3 Positron Emission Tomography

Unlike imaging with X-rays or MRI, positron emission tomography allows functional information of cells to be collected. ^{18}F-deoxyglucose (FDG) is generally used in the evaluation of lung cancer patients. FDG is a glucose analogue labelled with positron emitting fluorine. Most malignant tumours have a higher glucose metabolism than normal tissue and therefore take up more FDG than the surrounding tissue and emit a greater number of positrons. Thus, areas of malignancy show up as areas of greater activity on the scan. The majority of the PET evidence is from dedicated full ring PET scanners. In this document the use of PET therefore excludes gamma camera PET and half ring systems. The data is derived from scanning patient from the brain to at least mid thigh and using local views of thorax. The development of PET-CT systems is likely to result in the need for a single scan from skull vertex to mid thigh and may not need local views of the chest.

Presently there are few PET scanners in English and Welsh hospitals and the technique is not widely used for the diagnosis of lung cancer patients. There is however interest in its use in the investigation of solitary pulmonary nodules and other focal lung lesions and a number studies have investigated its use in diagnosis.

A meta-analysis[37] was found for which a systematic review of literature was performed from January 1966 and September 2000 using the Medline and Cancerlit databases. This review included studies that 1) included at least 10 subjects with pulmonary nodules or masses (at least 5 with malignant lesions), and 2) included enough data to allow calculation of sensitivity and specificity. We updated this review by searching for papers published after September 2000 on Medline and searching all years of Embase as this database had not been covered by the earlier review.

As well as the meta-analysis by Gould et al[37], we found 13 other papers that met our inclusion criteria[38-50]. These are shown in Table 9. Gould et al[37] found 40 studies which met their inclusion criteria. They found the sensitivity to be 96.8% (read from a receiver operator characteristic curve) at the median specificity of 77.8%. (Level II). The range of sensitivities in the 13 additional diagnostic studies is 72-100% and the specificity ranges from 67-100%[38-50]. (Level II)

The spatial resolution of full ring PET scanners is about 7-8mm and thus there has been some concern that PET would not be effective at imaging smaller

nodules (<1.5cm). We have no evidence to confirm this as the studies either did not test nodules smaller than 1.5cm or did not break down the results sufficiently to allow this analysis. However, the metabolic activity of the tumour is likely to be the major determinant rather than size alone.

One study assessed management change due to the use of PET in diagnosis by using a before and after questionnaire approach[50] (Table 10). According to referring physicians, PET resulted in beneficial change of treatment in 50% of patients. Cancelled surgery was the most frequent change in treatment after PET (35% of patients) and improved diagnostic understanding solely based on PET was reported in 26% of patients[50]. (Level 2+)

An added advantage of FDG-PET in SPN assessment is that metastatic disease can also be assessed at the one scanning visit and either provide an alternative site to biopsy or confirm whether a patient, who is proven to have NSCLC, can proceed to operation (see chapter 5 on staging).

The typical effective dose received by the patient undergoing a PET scan with 400MBq of FDG is 10mSv, which is equivalent to a lifetime additional risk of fatal cancer per examination of 1 in 2000 (compared with a natural lifetime risk of 1 in 3).

In summary, PET appears to have a good sensitivity and a reasonable specificity for detection of malignant SPNs and masses. However, for small nodules <1.5cm the results may be less reliable. Whether the specificity of PET is acceptable is debatable. However, since prevalence affects the probability of finding malignancy in the test, PET may therefore be useful for low risk patients, meaning that one could be quite confident about accepting the results of a negative scan. In practice, for those of intermediate risk, a tissue biopsy would be performed, but if this was not possible or had failed then PET may be useful as an additional technique of investigation. The risk is dependent on a variety of clinical and radiographic variables, such as smoking history, haemoptysis, and size. As such, duration of follow up and decision on biopsy will vary, although the presence of a negative PET scan enables a watch and wait policy to be implemented.

If the FDG PET is positive then further confirmatory investigation is required (see sections below on tissue sampling).

It is anticipated that the next wave of FDG-PET scanners will be integrated PET-CT scanners and it is likely that the diagnostic accuracy will continue to improve.

4.4.4 NeoSPECT

NeoSPECT is a radiopharmaceutical containing Tc-99m depreotide and is able to bind to somatostatin receptors in tumour tissue to a greater extent than normal tissue. This localisation to tumour should result in more gamma photons being emitted from the tumour than surrounding tissue and therefore make the tumour capable of being localised by a gamma camera.

Two prospective diagnostic studies[51,52] examined the use of NeoSPECT in the differential diagnosis of solitary pulmonary nodules on a total of 153 patients. (Table 11) The sensitivity, specificity, PPV and NPV for the first study are 97%, 73%, 92% and 86%[51] respectively and for the second study 100%, 43%, 64% and 100%[52] respectively. (Level 1b and II)

The typical effective dose received by the patient undergoing a NeoSPECT scan with Tc-99m is 11.84 mSv for a typical injected activity of 740 MBq, which is equivalent to a lifetime additional risk of fatal cancer per examination of 1 in1700.

There is limited evidence available on NeoSPECT at the present time. The results in one study[52] show reasonable diagnostic accuracy, although the specificity is poor. At present, there is insufficient data to comment on the utility of NeoSPECT.

4.5 Tissue confirmation

4.5.1 Sputum cytology

Sputum cytology can occasionally detect pulmonary tumours in the asymptomatic patient and is one of the least invasive methods of detecting lung cancer.

Our literature search identified a recent systematic review[26] and one further diagnostic study that was not included in the review[53]. Pooled data from 28,477 patients in 16 studies in the review gave a sensitivity of 66%, a specificity of 99%, a PPV of 91% and a NPV of 94%[26]. However, the indication for performing sputum cytology in these patients was mixed, which may have led to the large degree of heterogeneity in the results (Table 12). In the same review, a selection of 8 studies with 2455 patients, tested prior to bronchoscopy (and therefore with a suspicion of lung cancer), gave a pooled sensitivity of 22% (Level II). The additional diagnostic study, not included in the review[53], tested 60 consecutive patients suspected of lung cancer. Again, in this population of suspected lung cancer patients, the sensitivity was found to be rather low at 33%, the specificity was 94%, the PPV was 93% and the NPV was 38% (Level II).

The systematic review[26] included 17 studies that examined the effect of location of the pulmonary nodule or mass. Most studies showed better sensitivity for centrally located masses compared to peripheral masses (pooled sensitivity 71% vs. 49% respectively) (Level II).

In conclusion, it appears that sputum cytology has a rather low sensitivity for detecting malignancy of peripheral masses but for central masses it may be a useful diagnostic technique, particularly for those patients unable to tolerate or unwilling to have bronchoscopy or other invasive diagnostic tests. We found no studies on morbidity associated with the technique.

4.5.2 Bronchoscopy

Confirmation of a diagnosis of lung cancer can be achieved by using bronchoscopy for patients who are able and willing to tolerate the procedure. Guidelines on assessment of patients' fitness for bronchoscopy have been published by the British Thoracic Society[54]. Imaging prior to bronchoscopy can help to locate the position of the lesion and will improve the success of the technique (see section 4.5.2.1).

We identified one systematic review[26] and two additional diagnostic studies[55,56] on the use of bronchoscopy in diagnosing lung cancer. As histocytology is the gold standard in diagnosis, there are no false positive results but some studies do include a follow-up to support their outcomes. We divided the outcomes into those reporting for central masses (endobronchial) and those reporting results for peripheral masses (beyond the segmental bronchus). We also examined the effect of the size of the lesion on the sensitivity of the technique.

Central Disease

The results for central and peripheral lesions are shown in Table 13. Bronchoscopy has a higher sensitivity for central masses as sampling methods are likely to be more accurate when the lesion is visible. The results are broken down by sampling method. The systematic review[26] reported the results from 3754 patients and found that endobronchial biopsy provided the best sensitivity (74%, 20 studies), followed by brushings (59%, 18 studies) and washings (48%, 12 studies). (Level II) The study by Hashmi et al[56] also found a high sensitivity for endobronchial biopsy (82%, 88 patients). (Level II) The sensitivity for bronchoscopic needle aspiration in the review[26] was 56%, (8 studies) but there was a high degree of heterogeneity in the methods and the results. The study by Xie et al[55] found a sensitivity of 67% for bronchoscopy guided transtracheal and transbronchial biopsy. (Level II). Fourteen studies in the systematic review examined the sensitivity of combining different methods (endobronchial biopsy, brushing, washing and endobronchial/transbronchial needle aspiration) and found it to be 88% for centrally located lesions[26].

Peripheral Disease

The systematic review by Schreiber et al[26] reported the pooled results of 4136 patients in 30 studies on the sensitivity of flexible bronchoscopy for peripheral lesions beyond the visual segmental bronchi (Table 13). Brushings have the highest sensitivity (52%, 15 studies), followed by transbronchial biopsy (46%, 18 studies) and broncoalveolar lavage/washings (43%, 13 studies). Transbronchial needle aspiration had a pooled sensitivity of 67%, but this was calculated from only five studies and there was a large degree of heterogeneity in the sample sizes. Twelve studies in

the systematic review[26] examined the use of all modalities combined, giving a pooled sensitivity of 69%, again much lower than the sensitivity for diagnosis of central disease. Eight studies in the systematic review[26] presented results by size of lesion for peripheral disease. Bronchoscopy (brushings and/or biopsy) of lesions greater than 2cm in diameter had a pooled sensitivity of 62%, whereas for lesions smaller than 2cm in diameter the sensitivity was 33%. (Level II)

Typical complications figures for bronchoscopy are reported in the British Thoracic Society guidelines for diagnostic flexible bronchoscopy[54]:

- Mortality Rate in UK: 0.04%
- Major Complication rate in UK (including respiratory depression, airway obstruction and pneumonia): 0.12%
- Transbronchial biopsy: pneumothorax 1-5% cases
- Haemorrhage (usually mild): 9%

Overall, bronchoscopy provides a reasonably accurate method of determining a diagnosis in patients with central disease and with lesions over 2 cm in diameter. For peripheral disease, the sensitivity is too low to recommend this technique for diagnosis in preference to the other techniques available.

4.5.2.1 Should CT be performed prior to Bronchoscopy?

We investigated whether it was appropriate to perform a CT scan of the thorax prior to bronchoscopy. Despite organisational barriers (such as longer waiting times for scans than for bronchoscopies), a CT scan prior to bronchoscopy could not only provide valuable information regarding the tumour position but could highlight the presence of any metastatic disease. This would allow recommendations for an alternative diagnostic procedure to be made if clinically more appropriate.

There is some evidence to suggest that the additional imaging data significantly increases the likelihood of obtaining a diagnosis at bronchoscopy (Table 14). Only two studies report on the accuracy of bronchoscopy performed with and without information from a CT scan in obtaining a diagnosis. Laroche et al[57] found that the sensitivity of bronchoscopy performed blind to CT information was 71% and the sensitivity of bronchoscopy performed with knowledge of CT information was 89%, a statistically significant difference (p=0.012). (Level III DS). The study by Bungay et al[58] found that when bronchoscopy was performed before CT the sensitivity was 56% and when CT was performed before bronchoscopy the sensitivity was 80%, although this was not a statistically significant difference. (Level III DS). The different results reported by these studies may be a reflection of the differences in the patient populations. The study by Bungay et al[58] excluded patients with pulmonary collapse and included some patients with peripheral lesions, whereas the study by Laroche et al[57] included some patients with distal collapse but excluded peripheral lesions.

The study by Laroche[57] also reported changes in management that resulted from the difference in performing the tests in a different order. Of the patients that had a CT scan first, 7% required no further investigation as the CT scan was either normal, consistent with benign disease or consistent with widespread metastatic disease, and 18% had an alternative procedure (e.g. needle biopsy) instead of bronchoscopy due to the CT results (Level 1+). However, the reasons for changes in management were not always fully specified.

Overall, the evidence indicates that by performing a CT prior to an intended bronchoscopy, some unnecessary bronchoscopies can be prevented and the accuracy of bronchoscopy is improved.

There is no evidence on the use of CT before other biopsy procedures. However, the GDG wished to make a good practice point that CT should also be performed before other biopsy procedures.

4.5.3 Percutaneous Transthoracic Needle Aspiration/ Biopsy

Transthoracic needle aspiration or biopsy involves insertion of a small needle percutaneously to remove fluid or tissue from the lung, which is then examined for malignancy. Fluoroscopy, CT or ultrasound can be used to guide the insertion of the needle to the site of disease.

The literature search identified one systematic review[26] and four other studies of diagnostic accuracy, that were not included in the review[59-62]. The systematic review excluded studies with less than 50 patients, and we used the same exclusion criteria for our review. The data are reported in Table 15. The pooled sensitivity for 61 studies included in the systematic review is 90% (95% CI: 88-92%) and the specificity is 97% (95%CI: 96-98%)[26]. The PPV and the NPV range from 82-100% and 0-96% respectively. (Level II DS)The four additional studies that we identified found similar results, reporting sensitivities between 95-97% and specificities between 96-100%[59-62].(Level Ib and II DS) The systematic review found two studies that compared the use of cutting needle core biopsy to needle aspiration and found that they had similar sensitivities but that core biopsy had a better specificity[26]. (Level II).

A systematic review of case series reporting mortality and morbidity for a total of 4527 patients found that a chest drain was needed in 10.4% of patients, haemoptysis occurred in 3.6% of patients and there was a mortality of 0.04%[28]. One additional case series of 506 patients, not included in the review, reported similar results (chest drain in 7.9% of patients and mortality in 0%)[63]. Pneumothorax was observed in 31 % of patients in the systematic review[26] and 23% of patients in the additional study[63](Level III).

The British Thoracic Society and the Royal College of Radiology have also issued guidelines on radiologically guided lung biopsy, which provide further detail on the indications for the test, complications that may arise and the technique to use[64]. (Level IV)

In summary, the evidence suggests that transthoracic needle aspiration and biopsy have a good sensitivity and specificity for diagnosis of lung cancer. The complication rate is acceptable. For peripheral lung lesions, it provides a more accurate way of diagnosing lung cancer than bronchoscopy.

4.5.4 Biopsies of sites other than the lung

In some cases, for example patients presenting with stage IIIb or IV disease or symptoms that suggest metastases in specific organs (e.g. the liver), or in patients with clinical or radiographic evidence of SCLC, it may be more convenient to take a biopsy from the chest wall, pleural effusion or the site of distant metastasis. The site may be easier to biopsy than the primary tumour and this technique has the advantage of allowing confirmation of the stage of disease at the same time. A search was performed, but no studies were found that provided information on the sensitivity and specificity for suspected lung cancer.

The guideline development group decided to make a good practice point that biopsies should be taken from the site of a metastases where this can be achieved more easily than from the primary site.

4.5.5 Surgical techniques

Surgery plays an important role in the diagnosis and accurate staging of lung cancer. However, a decision to include a surgical procedure in the diagnostic work-up must anticipate associated risks as well as potential benefits. These benefits are closely tied to the likely stage of the disease. This section examines surgical methods of diagnosis. Evidence relating to staging and techniques examining the lymph nodes (e.g. mediastinoscopy) are discussed in the chapter 5 on staging.

4.5.5.1 Anterior Mediastinotomy

Anterior (parasternal) mediastinotomy has developed primarily as a means of staging carcinoma of the lung located in the left upper lobe[65]. It has also been advocated to establish the diagnosis of primary masses in the anterosuperior mediastinum, especially in the setting of superior vena cava obstruction when needle biopsy may be contraindicated[66].

We identified only one study that reported results of diagnostic accuracy for anterior mediastinotomy[67] (Table 16). The overall sensitivity and specificity of the technique for diagnosing various diseases was 98% and 65% respectively for 62 patients with hilar or mediastinal masses. This study reported a morbidity of 16% and a mortality of 1.6%. (Level II)

There is very limited evidence on the use of anterior mediastinotomy in the diagnosis of lung cancer, although the sensitivity appeared high from the one study that evaluated it[67]. Its role is far more clearly defined as a staging technique (see chapter 5 on staging).

4.5.5.2 Thoracoscopy

The use of video-assisted thoracoscopy (surgical thoracoscopy) is a useful means of obtaining a diagnosis of indeterminate solitary pulmonary nodules without the need for thoracotomy when less invasive methods may have failed to identify the lesion. The surgical thoracoscopy approach is particularly valuable in this setting because thoracotomy can be avoided for the removal of nodules that ultimately prove to be benign. A relatively small, typically less than <3cm in diameter, and peripherally located nodule in the outer third of the lung may be resected using such thorascopic methods[68].

The literature search identified three fairly large series that examined the diagnostic accuracy of thoracoscopy in assessing the status of solitary pulmonary nodules (Table 17). Two studies reported high sensitivities of 97%[69] and 100%[70] and one study found a lower sensitivity of 41%[71]. (Level II DS) The complication rate, reported by one study only, is low, with conversion to thoracotomy occurring in two patients (<1% conversion rate)[70] Other studies with much smaller number of patients have reported significantly higher conversion rates [72,73] (Table 18). No deaths occurred as a result of the diagnostic thoracoscopy and morbidity ranged from 3.6% - 22% and included significant lobar atelectasis, pneumonia and prolonged leak. Chest drains were used in all procedures. Postoperative length of stay was 2- 4 days.

The results are mixed for the accuracy of thoracoscopy in the diagnosis of solitary pulmonary nodules. However, the technique appears to have a moderately low complication rate.

4.6 Economics of diagnosis of lung cancer

The papers[42,57,74-89] selected for economics of lung cancer diagnosis are shown in Table 19 and Table 20.

4.6.1 Health Economics analysis of FDG-PET in diagnosis

The value of FDG-PET lies in its ability to reduce the number of futile (diagnostic) surgical operations by diagnosing non-cancer cases earlier. This should reduce surgical morbidity and surgical cost. FDG-PET may misdiagnose some cancer cases (c.f. surgical biopsy) and therefore PET negative cases may have to be systematically followed up. FDG-PET scanning is expensive compared with CT scanning but is less costly than surgical biopsy (see Table 21) and therefore in some circumstances PET could in theory reduce health service costs by eliminating episodes of futile surgery.

There are nine cost-effectiveness analyses (one from Germany[75], two from Japan[82,83], four from the USA[77-79,88] and two from Australia[42,74]) that have evaluated the use of FDG-PET scanning in solitary pulmonary nodules. In addition, three more studies estimated incremental cost but not effectiveness. All cost analysis resulted in cost savings per patients examined by FDG-PET for investigation of SPNs[81,84,89] (see Table 20).

The cost-effectiveness studies used a variety of comparator strategies including 'watch and wait', CT alone, transthoracic needle biopsy and thoracotomy.

Gambhir et al[77], evaluated thoracic FDG-PET after indeterminate/positive CT, with wait and watch after negative CT or negative PET. They looked at five scenarios for example, 64-year-old, 1.5 pack per day smoker (prevalence=0.83). For this group, CT scanning had a lower cost and longer life expectancy compared with the PET strategy. Generally, they found that the optimal strategy depends on the underlying prevalence (P) of cancer as follows:

> 0.12<P<0.69: CT→ FDG-PET→ Transthoracic needle biopsy/surgery is optimal

> 0.69<P<0.90: CT→ Transthoracic needle biopsy/surgery is optimal

> p>0.90: Transthoracic needle biopsy/surgery is optimal

Keith et al[42] adapted this model and concluded that PET after indeterminate CT would dominate CT for their hospital population in Australia.

Dietlein et al[75] found that whole-body PET scanning dominates both transthoracic needle biopsy and surgery. Compared with watch and wait it costs around £2,000 per life year gained (LY gained). Kosuda et al[82] looked at CT *and* chest-PET for all SPNs versus CT alone. They found that chest-PET added around £1,100 per life-year gained. They use a rather low unit cost for a PET scan of $700. Kosuda et al[83] examined full-body-PET and CT vs CT alone and conversely showed a cost-saving of around £1,000 but a drop in life-expectancy of 0.01 years. Shepherd[88] estimated that PET after indeterminate CT would cost approximately £7,000 per LY gained compared with watch and wait; however, extra caution should be applied to this study, since it has not subsequently been published as a full report.

The decision analysis of Gould et al[79] on cost effectiveness for five diagnostic strategies (computed tomography, FDG-PET, transthoracic needle biopsy, surgery and watchful waiting) showed the choice of strategy depended on the pre-test probability of malignancy and to a lesser extent the risk for surgical complications. The use of FDG-PET was most cost-effective when pre-test probability and CT results were conflicting. In addition, use of FDG-PET was also cost-effective in patients with intermediate pre-test probability (55%) who are at high risk for surgical complications.

Comber et al.[74] evaluated whether the cost-effectiveness of FDG-PET could be improved by using it with quantitative contrast-enhanced computed tomography (QECT). The baseline results (55% prevalence of malignancy) showed that QECT with FDG-PET strategy was the most cost effective strategy (AUS$12,059/patient-£5,111/patient) followed by the FDG-PET strategy (AUS$12,300/patient-£5,212/patinet) for the evaluation of solitary pulmonary nodules.

The published evidence from overseas seems to show that for some patient subgroups PET scanning after CT is cost-effective. The cost-effectiveness depends on the prevalence of cancer among the patient group. If the prevalence of cancer in the patient group is very high, then PET is both more costly and less effective than going straight to surgery. If the prevalence of cancer is very low then PET is more effective then watchful waiting but unlikely to be cost-effective. If the prevalence of cancer is slightly higher, then PET could be cost-effective. The studies differed in terms of where the cut-offs should be, for example, the upper prevalence cut-off beyond which PET is not cost-effective varied between 0.4 and 0.9 between studies.

None of the published studies evaluated the use of PET scanning within the NHS in the UK. They all showed that cost-effectiveness is dependent on the prevalence of cancer in the patient group, which can vary between settings. Cost-effectiveness will also depend on the precise sensitivity and specificity and on the exact pathway to be followed subsequent to scanning; these factors also vary between health systems. This includes patients with a strong suspicion of lung cancer and where surgical biopsy has failed or is not possible.

This section has only considered the cost-effectiveness of PET with regard to *diagnosing* lung cancer; evidence for the cost-effectiveness of PET in the staging of NSCLC is appraised in the following chapter.

4.6.2 Health Economics analysis of Sputum Cytology

Only one economic evaluation explicitly explored the role of sputum analysis in the diagnosis of lung cancer. Raab et al[86] conducted 9 decision analyses that compared the use of sputum analysis as the first procedure with no sputum analysis, in a US context. The analyses differed according to whether the lesion was central or peripheral and to the sequence of the other diagnostic tests. For example, one analysis for peripheral lesions compared the sequence in the order of the tests undertaken:

> Sputum analysis → Fine needle aspiration (FNA) → thoracoscopy

Compared with

> FNA → thoracoscopy

For all but one of the analyses the sputum analysis arm dominated its comparator (i.e. with a lower cost and a slightly increased life expectancy). This was

because some surgical procedures were avoided through the use of sputum analysis. The main sensitivity analysis concerned the prevalence of lung cancer in the patient group. Essentially they found that sputum analysis dominates in patient groups with a prevalence of cancer greater than 0.5.

4.6.3 Health Economics Analysis of Bronchoscopy

There was a single eligible study examining the cost-effectiveness of bronchoscopy. The US study by Govert et al[80] compared the following strategies using decision analysis:

- Flexible bronchoscopy alone
- Flexible bronchoscopy with washings *or* brushings
- Flexible bronchoscopy with washings *and* brushings.

They ascribed seven days of additional morbidity to a complication arising from a surgical lung biopsy, with a complication rate 0.03, a cost of this complication of $20,000 and a cost of cytology of $177. On this basis, and using retrospective diagnostic data they estimated that the addition of washings *or* brushings cost an additional $308 per reduced quality day avoided. The addition of washings *and* brushings cost an additional $5,500 per reduced quality day avoided. They concluded that the cytology of either washings or brushings was cost-effective but not both. By usual conventions (i.e. a threshold of $50,000 per QALY gained), even this seems to be poor value for money. However, given that the cost of cytology in the USA is substantially higher than in the UK, it is still likely that either washings or brushings (as an adjunct to forceps biopsy) is cost-effective in the NHS compared with a £30,000 per QALY threshold.

4.6.4 Health Economics analysis of performing CT prior to Bronchoscopy

Chest CT is widely considered an essential diagnostic procedure for most patients with suspected lung cancer, hence only one relevant economic evaluation was found. Laroche et al[57] conducted a randomised controlled trial (n=171) in the UK to compare the consequences of CT versus flexible bronchoscopy as the first investigation for patients with suspected lung cancer. They found that CT first has the following advantages:

- Avoids some invasive investigations - 19% avoid bronchoscopy (12% FNA and 7% no invasive investigation)
- Improves accuracy of first invasive investigation – (90% vs. 71% of malignancies were detected with the first invasive investigation). Hence, overall 11% avoided having a second invasive procedure (19% vs. 8%).
- Reduces length of hospital stay (data not presented)

The trial was not powered to detect differences in the number of surgical complications. In theory, one would expect fewer complications in the CT arm but this is partially offset by the higher incidence of pneumothorax for thoracic needle biopsy compared with bronchoscopy.

The trial was not able to determine whether overall health service costs were reduced or increased because it was not known how many CT scans would normally take place after bronchoscopy. However, based on other costs the authors estimated that if CT scanning after bronchoscopy is normally 60% or more, routine CT scanning would reduce costs (otherwise it would increase costs).

The study was an RCT but there is a potential for selection bias, as the inclusion/exclusion criteria are unclear. The authors note that they 'attempted to exclude patients with an obvious peripheral mass amenable to percutaneous needle biopsy'. One factor that diluted the outcomes measured is that all patients in the trial underwent CT and even in the bronchoscopy arm, subsequent intervention was based not only on the results of the bronchoscopy but also on the results of the CT scan.

In summary, the consequences of routine CT scanning for suspected lung cancer are:

- Chest CT as the initial investigation (after CXR) for patients with suspicion of lung cancer can reduce the number of invasive investigations (by an estimated 17%).
- It could potentially reduce NHS costs if the current CT rate (after bronchoscopy) is greater than approximately 60%.
- If the current CT rate is below 60% then it could still be cost-effective, if there are associated improvements in patient outcomes. There is no evidence for this at present.
- The incremental cost-effectiveness of CT before bronchoscopy could vary considerably across the NHS because it is determined by usual CT scanning practice.

4.6.5 Health Economics analysis of Surgical Biopsy

One paper was identified that considered the cost of different surgical diagnostic strategies. Osada et al[85] were concerned with patients who had suspected malignancy in CT but were undiagnosed after bronchoscopy. They were attempting to determine whether thoracotomy alone without needle or surgical thoracoscopy biopsy based solely on chest CT scan was feasible. They found that for this group, 93% (38/41) of these patients went on to thoracotomy after surgical thoracoscopy biopsy and therefore costs could be reduced by going straight to thoracotomy. They added that even in the three patients who did not show appropriate indicators for thoracotomy in their surgical thoracoscopy biopsy would have benefited from going straight to thoracotomy because they required wedge resection to be declared cancer-free.

4.6.6 Summary of Health Economics Findings

Sputum cytology as the first diagnostic investigation could potentially improve patient outcomes and reduce costs.

The cytological analysis of *both* washings and brushings after non-diagnostic forceps bronchoscopy biopsy is not likely to be cost-effective.

Routine chest CT before bronchoscopy can reduce the number of invasive procedures. It is likely to reduce surgical morbidity and could reduce health service costs if the pre-test prevalence is relatively high (> about 60%).

In patients with a suggestion of malignancy on CT but no diagnosis after bronchoscopy, surgical thoracoscopy biopsy to eliminate unnecessary thoracotomies is unlikely to be cost-effective compared with going straight to thoracotomy.

Diagnostic PET scanning could potentially both reduce costs and improve patient outcomes for some patients with SPNs. Further research is required to establish cost effectiveness in a UK setting.

We should be cautious in interpreting the results of studies in this review because:

All the studies except one were non-UK studies. There are a number of problems associated with using overseas studies. Estimates of effectiveness may be inappropriate because of differences in the population. The cost of resources used can vary considerably between countries, for example, the cost of clinical staff is lower in the UK than in some countries. The resources used in the subsequent treatment will vary between countries according to local protocols. This may also impact on the estimated health gain for patients diagnosed.

Studies varied in their assumptions. For example for surgical complications Govert et al (1996)[80] estimated only the morbidity whereas, Raab et al (1997)[86] estimated reduction in life expectancy. Furthermore, all the studies compared often quite complicated pathways. Patient selection would also have affected the cost-effectiveness.

One study has evaluated the importance of patient preferences for diagnostic strategy. Raab et al[87] incorporated into their analysis the quality of life of patients. They concluded that overall patient outcome could be substantially affected by an individual patient's anxiety. They considered two types of patients with the same risk of cancer. For a patient who is averse to surgical risk, watchful waiting gave the best overall quality of life and was the most cost-effective strategy. In contrast, for the patient who is less risk averse but averse to waiting, going straight to surgery could be the most cost-effective strategy.

4.7 Recommendations

4.7.1 Clinical Practice Recommendations

Where a chest X-ray has been requested in primary or secondary care and is incidentally suggestive of lung cancer, a second copy of the radiologist's report should be sent to a designated member of the lung cancer MDT, usually the chest physician. The MDT should have a mechanism in place to follow up these reports to enable the patient's GP to have a management plan in place. [D(GPP)]

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 adrenals. [D(GPP)]

Chest CT should be performed before:

- **an intended fibreoptic bronchoscopy [A; C(DS)]**
- **any other biopsy procedure. [D(GPP)]**

Bronchoscopy should be performed on patients with central lesions who are able and willing to undergo the procedure. [B(DS)]

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. [B(DS)]

Percutaneous transthoracic needle biopsy is recommended for diagnosis of lung cancer in patients with peripheral lesions. [B(DS)]

Surgical biopsy should be performed for diagnosis where other less invasive methods of biopsy have not been successful or are not possible. [B(DS)]

Where there is evidence of distant metastases, biopsies should be taken from the metastatic site if this can be achieved more easily than from the primary site. [D(GPP)]

An ^{18}F-deoxyglucose positron emission tomography (FDG-PET) scan should be performed to investigate solitary pulmonary nodules in cases where a biopsy is not possible or has failed, depending on nodule size, position and CT characterisation. [C; B(DS)]

5 Staging of Lung Cancer

5.1 Introduction

Once a diagnosis of Lung Cancer has been made it is essential that the stage of the disease is ascertained to enable decisions to be made about the future management of the patient.

Patients should have had established, where possible, a histological diagnosis of the cell type of the lung cancer. Clinical examination is likely to give some indication of the stage of the disease but normally further tests are necessary to determine the exact status.

Treatment is dependent on histology and on the size and location of the primary tumour, the presence and location of involved lymph nodes and the occurrence of distant metastases. A number of other prognostic factors may also influence the choice of treatment. These include performance status, co-morbidity, age, gender and biochemistry. Information on the stage of the disease will be used in addition to these factors to determine patient management.

A variety of investigations can be used to establish the stage of the disease and in practice staging is often carried out alongside diagnosis.

5.2 Techniques included in this Review

Non-invasive methods used to stage lung cancer included in this review are Computerised Tomography (CT), Positron Emission Tomography (PET) (excluding gamma camera PET) and more recently PET-CT, Magnetic Resonance Imaging (MRI), Bone Scintigraphy (BS) and Ultrasound (US). Invasive staging techniques evaluated include mediastinoscopy, thoracoscopy, Video Assisted Thoracic Surgery (VATS), Endoscopic Ultrasound guided Fine Needle Aspiration (EUS-FNA) and percutaneous Trans-Thoracic Needle Aspiration biopsy.

5.3 Methodology

Guidelines produced by the American College of Chest Physicians (ACCP) on the staging of lung cancer were retrieved and found to be relevant for this review, in addition to a Health Technology Board for Scotland (HTBS) report. New systematic reviews were undertaken on all of the techniques listed above.

The full search strategy can be found in appendix six.

5.4 Staging Classifications

5.4.1 Non-Small Cell Lung Cancer (NSCLC)

The basis of staging in lung cancer is the relationship between the anatomical extent of the tumour at diagnosis and survival outcome. In 1973 the American Joint Committee on Cancer (AJCC) proposed a scheme for lung cancer based on this TNM system. The system was revised in 1986 and most recently in 1997 being published on behalf of the AJCC and the Union Internationale Contre le Cancer (UICC). In the TNM classification system for NSCLC (appendix two, figures one and two), the T-factor represents the extent of the primary tumour, the N-factor denotes the extent of regional lymph node involvement, and the M-factor corresponds to the presence of extra-thoracic metastasis.

5.4.2 Small Cell Lung Cancer (SCLC)

The simple staging system introduced by the Veterans Administration Lung Cancer Study Group (VALG) of 'limited' and 'extensive' disease is generally applied in clinical practice and has proven adequate for most clinical situations (appendix two, figure three). In addition the revised TNM system has limited use in SCLC, except in those patients undergoing surgical resection.

5.5 T-Stage Assessment

Despite many prognostic factors, stage at presentation has significant bearing on the lung cancer patient's eventual outcome. The T-stage involves predominantly intra-thoracic assessment of the primary tumour in terms of size, location and relationship to surrounding structures.

Accurate discrimination between T1 and T2 has limited clinical relevance, as it does not significantly affect the choice of treatment. However, differentiation between T2 and T3 disease, and T3 and T4 involvement will have important prognostic and therapeutic implications.

CT remains the mainstay of radiological clinical staging though MRI has been advocated as an alternative. In assessing the current role of CT and MRI in the T-staging of lung cancer appropriate studies were systematically reviewed with consideration to the reliability of differentiating T2 and T3, and T3/4 status, reflecting the presence of invasion of mediastinal and chest wall structures which has significant implications on whether or not the tumour is resectable. Study inclusion was based on patients with histologically proven NSCLC without distant metastases who were being assessed for surgery. All studies evaluated CT in assessing T-stage either alone or against another modality (usually MRI). Pathological staging following surgical resection was the usual comparison.

An alternative to radiological staging is surgical staging with video-assisted thoracoscopy (VATS) used specifically to assess pleural and chest wall involvement. Few studies have been published in this area.

5.5.1 Computerised Tomography (CT) in T-Staging

A recent systematic review of 15 studies evaluating the reliability of CT in predicting T2/T3 and T3/4 status divided studies according to whether the CT study assessed for chest wall invasion, or mediastinal involvement or both[90] (see Table 22). Within these groups, studies showed similarity in patient groups, location of tumour, radiological criteria for assessment and outcome measures. The overall reliability of CT in predicting T3 or T4 disease is quite poor with a sensitivity 55%, specificity 89%, NPV 82% and PPV 68% (Level II DS) with significant variability (range 38-100%).

In considering whether there is specifically local chest wall invasion the reliability of CT was similar with a sensitivity 64%, specificity 74%, NPV 91% and PPV 56%. For central T3/4 tumours, reliability of CT in assessing whether there is mediastinal involvement was limited with a sensitivity of 76%, specificity 80%, NPV 86% and PPV 67% (Level II DS).

The False Positive (FP) rate (1- PPV) is probably the most important factor in determining whether or not to consider surgical resection. It was relatively high for both central and peripheral tumour groups (FP rate of 23% and 44% respectively) and therefore CT does not appear to be reliable in assessing chest wall or mediastinal tumour involvement unless overt evidence of invasion is demonstrated, such as bone destruction or vascular invasion (Level II DS).

In conclusion, to stage the extent of the primary tumour a chest CT should be performed for patients with lung cancer, although CT alone should not be relied upon to assess chest wall and mediastinum invasion. A recommendation to support this is in the diagnosis chapter.

5.5.2 Magnetic Resonance Imaging in T-Staging

Our search retrieved one paper examining the reliability of MRI in assessing T-status, (Table 23). This study (N=170) showed no significant difference between the two modalities (CT and MRI) in detecting chest wall involvement (P=0.77)[91]. However, MRI was marginally more accurate than CT in diagnosing mediastinal invasion (Level III DS) (P=0.047)[91]. For MRI the overall sensitivity was 56%, specificity 80%, PPV 24% and NPV 22%, the prevalence was 29%. The systematic review assessing the reliability of MRI in predicting T3 or T4 status showed no significant advantages over CT[90] (Level II DS).

Overall, in regard to MRI and T3/4 assessment, from the few studies in this area there appears to be no general advantage over CT scanning. However, there may be specific circumstances whereby MRI scanning may provide additional information over and above CT, although care should be exercised in interpreting these studies as they were performed prior to the advent of spiral and multislice CT (see 5.5.5).

5.5.3 Thoracoscopy in T-Staging

With the development of Video-Assisted Thoracoscopic Surgery (VATS), staging thoracoscopy may allow assessment of visceral pleural involvement by tumour and provide information on T-status beyond standard assessment.

Much of the literature on VATS has dealt with its role in the diagnosis and management of the solitary pulmonary nodule (see chapter 4 Diagnosis). Several small retrospective series have examined the role of VATS prior to formal thoracotomy in looking for pleural and chest wall involvement (T-status) with or without N-stage assessment (see section 5.6). VATS was found to be a safe procedure (see chapter 6 Surgery) but because of significant heterogeneity in patient selection, methodology described and comparisons used these papers were discarded. Unfortunately no conclusions can be made regarding the effectiveness of VATS in detecting radiologically occult chest wall disease owing to the limited trial data available. Further research in the use of VATS as a staging tool is required.

5.5.4 Future Considerations for T-Staging

Recent technical improvement in CT imaging with helical and multi-detector CT leading to faster scanning times whilst using thin sections leading to and reduced motion/ respiratory artefacts, together with vascular enhancement techniques, are likely to improve current delineation of tumour invasion. Multiplanar reconstruction methods with isometric voxels in multislice CT are likely to provide improved diagnostic information over conventional imaging. Clinical evaluation is awaited.

5.5.5 Pancoast tumours

Pancoast tumours arise in the apex of the chest, often invading the lower portion of the brachial plexus, the upper thoracic ribs and vertebral bodies, the stellate ganglion and the sub-clavian vessels.

There is little data on the staging of Pancoast tumours. One paper was retrieved. Heelan et al[92] measured the diagnostic accuracy of MRI and CT in the T-staging of Pancoast tumours (Table 25) and reported that MRI provided better detail of tumour involvement around the brachial plexus and vertebral bodies.

5.5.6 Pleural Effusion

Malignant pleural effusions are classed as T4 disease in the NSCLC staging classification system. It is important to determine the extent of the effusion so that the appropriate treatment strategy can be determined. The British Thoracic Society (BTS) have developed guidelines based on a systematic review of the literature[93] and these should be referred to in the management of patients with (suspicious) malignant pleural effusions.

5.6 N-Stage Assessment

The most important aspect of intrathoracic staging is the determination of nodal (N) involvement. N-staging not only establishes the treatment that the patient will be offered (perhaps most importantly, if they are eligible for curative surgery) but in addition, the prognosis of the patient. This review is concerned with the accuracy of staging N2 and N3 disease. In current clinical practice, apart from a sub-section of patients with N2 disease, patients with mediastinal disease are not eligible for curative surgery.

CT and MRI scans, which represent conventional imaging technologies for staging the mediastinum, rely on an anatomic assessment of the area, specifically, the size of the lymph node to predict malignancy. While the cut-off size for lymph node malignancy can vary from study to study, there is a general consensus within the literature that 1cm on the short axis is the threshold used to differentiate non-malignant nodes from enlarged, malignant nodes[94]. There has been recent interest in Positron Emission Tomography (PET) scans for staging the mediastinum. PET scans permit a metabolic assessment of the region under suspicion by relying on tumour cells metabolising an injected radioactive tracer faster than non-malignant cells. The scanner is able to detect such areas of high metabolic activity. This review is restricted to the use of ^{18}F-deoxyglucose positron emission tomography (FDG-PET).

5.6.1 Computerised Tomography in N-Staging

We retrieved a recent systematic review that evaluated the diagnostic accuracy of CT for staging the mediastinum[95]. This was updated with our own search, which located three new trials (Table 24). Pooled sensitivity, specificity, PPV and NPV figures from the review were 57% (95% CI 49-66%), 82% (95% CI 77-86%), 56% (range 26-84%) and 83% (range 63-93%) respectively (Level III DS), although there was marked heterogeneity between the individual reported figures. The additionally retrieved studies ranged from 37-60% sensitivity, 73-91% specificity, 51-85% PPV and 56-81 NPV (Level Ib and II DS).

In conclusion, CT enables the detection of enlarged mediastinal nodes, but the poor specificity makes tissue sampling necessary to determine the patients true nodal status if surgery is a therapeutic option (Level Ib, II and III DS). A recommendation to support this is in the diagnosis chapter.

5.6.2 FDG-PET in N-Staging

A recent systematic review on mediastinal staging using FDG-PET was retrieved and updated[95]. We retrieved three additional studies[96-98] that met the inclusion criteria (see Table 26). Pooled weighted averages calculated from the review reported sensitivity and specificity as 84% (CI 0.78-0.89) and 89% (CI 0.83-0.93) respectively and PPV and NPV as 79% (range 0.4-1.0) and 93% (range 0.75-1) respectively (Level II DS). The additional studies reported sensitivities and specificities in the range of 61-68% and 72-84% and PPVs and NPVs in the range of 56-88% and 64-87% (Level II DS). The sensitivity and specificity of FDG PET is therefore better than CT.

In conclusion, FDG-PET allows a reasonably accurate determination of mediastinal disease. It is reasonable not to proceed with tissue sampling in the presence of a negative study of the mediastinum, but a positive study may require tissue sampling because there are false positive results associated with infection and inflammation (Level II DS).

5.6.3 Combined use of CT prior to FDG-PET in N-Staging

There has been recent interest in combining the results of CT and PET to increase diagnostic accuracy in mediastinal staging. By using the results of a CT scan prior to that of PET scans, it is possible to assess both the anatomical and metabolic features of the nodes.

A recent Heath Technology Board for Scotland (HTBS) represents the most appropriate and up-to date systematic review of potential candidates for surgery[99,100]. The NCC-AC review team undertook a search to update this review of 17 observation trials and retrieved one additional paper that has been incorporated into the results[101] (Table 27).

Appendix three, Figure 1 shows the diagnostic accuracy of combined use of CT and FDG-PET of all retrieved studies, which is divided into those patients who were designated CT negative at initial CT and those deemed CT positive for lymph nodes. We calculated the pooled weighted specificity and read off the sensitivity from the summary receiver operating characteristic (sROC) curve. While sensitivity for diagnosing mediastinal disease is high in both groups of patients, 90% and 94% for CT negative and CT positive groups, respectively, the specificity of CT positive patients was much lower (71%) than CT negative patients (93%). This was also reflected in the PPV and NPV of the groups being 57% and 96% respectively, for patients who were CT negative for lymph nodes and 76% and 92% respectively, for patients with a positive CT for mediastinal lymph nodes. Thus, the high false positive rate in CT positive patients means that a positive PET result cannot be relied upon for accuracy (Level Ib and II (DS).

There were several methodological weaknesses in the studies included in this analysis. The majority of studies were not controlled trials and tended to focus on diagnostic accuracy rather than patient outcomes such as surgery rates, survival or quality of life. Despite this however, the consistency of results reported from the studies suggest they are reliable. Therefore there is evidence to support the use of FDG-PET for potential candidates for surgery who are negative for mediastinal disease on CT (Level II DS).

5.6.4 Endoscopic Ultrasound (EUS) in N-Staging

EUS provides high-resolution images that can be used for the detection of accessible mediastinal lymph nodes, which are commonly located in the posterior mediastinum. Studies used a combination of shape irregularity and echo heterogeneity to establish the presence of malignancy.

The NCC-AC retrieved a systematic review which incorporated five studies that assessed the use of EUS to stage the mediastinum [95]. We retrieved one additional paper which met our inclusion criteria[102]. Both are shown in Table 28.

The pooled weighted sensitivity, specificity, PPV and NPV for this modality from the systematic review was 78% (95% CI 61-89), 71% (95% CI 56-82), 75% (range 38-100) and 79% (range 25-76%), respectively (Level II DS). The additional study retrieved reported 70% (95% CI 50.6-85.3), 81% (95% CI 68.6-89.6), 64% and 85%, respectively (Level Ib DS). EUS alone has a better sensitivity than CT for those nodes that can be visualised.

In conclusion, EUS allows a reasonable evaluation of accessible mediastinal lymph nodes (Level Ib and II DS).

5.6.5 Endoscopic Ultrasound Guided Fine Needle Aspiration (EUS-FNA) in N-Staging

EUS-FNA is commonly performed by oesophagoscopy under conscious sedation. As a tissue sample is taken during the procedure, the technique can act as its own gold standard to verify the presence of malignant disease.

A systematic review of five studies, which had little variation in performance characteristics[103], was updated with one additional paper [98](Table 29). The sensitivity, specificity, PPV and NPV of the review was 88% (95% CI, 82-93), 91 (95% CI 77-97), 98% (range 96-100%) and 77% (range 68-100%) respectively (Level II DS) compared to 63%, 100%, 100% and 68% in the additional study (Level II DS).

EUS-FNA allows a reasonably accurate assessment of accessible mediastinal lymph nodes (Level II DS). These results however, come from studies of patients commonly with radiographic evidence of mediastinal lymphadenopathy accessible by a biopsy needle. The results reported should be interpreted in light of the fact that the high sensitivity may be due to an unusually small number of false negatives.

5.6.6 Transbronchial Needle Aspiration (TBNA) in N-Staging

TBNA, or the Wang technique as it is also known, removes aspirate material or paratracheal or subcarinal lymph nodes using a flexible bronchoscope. This has a good specificity but is not sensitive (Table 30).

Twelve studies were retrieved in a recent systematic review [103] and no additional studies were found (see Table 30). A total of 910 patients were included, 99.7% of whom had lung cancer. The overall sensitivity and specificity was reported as 76% (95% CI 72-79) and 96% (95% CI 91-100%). The prevalence varied among the studies, from between 30 and 88% which may be responsible for the large range of NPVs. The average weighted NPV and PPV was 71% (range 36-100%) and 100%, respectively. TBNA has a better sensitivity and specificity than EUS-FNA which has 88% sensitivity and 91% specificity (Table 29). In conclusion, TBNA allows an accurate assessment of accessible mediastinal nodes (Level II DS).

5.6.7 Image Guided Transthoracic Needle Aspiration (TTNA) in N-Staging

A variety of approaches can be utilised to perform TTNA which may involve traversing lung parenchyma to obtain histological proof of malignancy. It is most commonly used to confirm mediastinal involvement in patients who are not surgical candidates as it is limited by an inability to sample multiple node stations. Our search retrieved a systematic review of five studies[103] to which no additional studies were added (Table 31).

A total of 215 evaluable people were included, 96% of whom were confirmed to have lung cancer. The overall sensitivity and specificity were 91 (95% CI 74-97%) and 100%. The NPV again was inversely correlated with the prevalence, the pooled weighted average being 83% (range 65-91%) (Level III DS).

TTNA allows an assessment of mediastinal nodes (Level III DS).

5.6.8 Mediastinoscopy in N-Staging

Cervical mediastinoscopy gives access to the pre-tracheal and para-tracheal lymph nodes, as well as lymph nodes between the left and right main bronchus. Alternatively, an anterior mediastinotomy via the second or third intercostal space on the left side allows exploration of the aorto-pulmonary window, particularly in patients with tumours of the left lung. A modified technique, an extended cervical mediastinoscopy has been described for assessing the same region. In addition, video-assisted techniques in combination with standard cervical or extended mediastinoscopy have also been described in small series.

Previous guideline recommendations concerning mediastinoscopy have reinforced the belief that it is the "gold standard" among staging tests of mediastinal lymph nodes. It is performed under a general anaesthetic, either as a day-case or short stay procedure, with low rates of morbidity and mortality (see chapter 4 on Diagnosis).

Study inclusion for our review was based on patients with histologically proven NSCLC without distant metastases who were being assessed for surgery. All studies evaluated mediastinoscopy in assessing N2/3 disease either alone or against another modality (usually CT).

The most recent systematic review of mediastinal staging by standard cervical mediastinoscopy included 14 studies (N=5867) (Table 32). The overall sensitivity was 81% (95% CI, 0.76-0.85). The overall NPV was 91% (range, 58-97%) with a prevalence of 37% (range, 21-54%). This gives an average false negative (FN) rate of approximately 10%. However, in at least four of the studies reviewed, the FN rate was affected by detection of positive nodes at surgery that were inaccessible by conventional mediastinoscopy. In addition, the FN rate is likely to be affected by the diligence with which nodes are sampled at mediastinoscopy[90].

The specificity and PPV for mediastinoscopy were both reported to be 100%. These values cannot be assessed as patients with positive lymph nodes were not subject to any further procedures. However, several commentators have suggested that the FP rate is likely to be low [90,103].

In conclusion, it is often difficult to compare invasive staging methods as the patients having one test may differ from patients having another. However, standard cervical mediastinoscopy appears to have reasonable sensitivity, a high NPV, and the ability to assess directly the clinically relevant nodal stations.

5.6.9 Anterior Mediastinotomy and Extended Cervical Mediastinoscopy

In the context of left upper lobe tumours, limited information is available on the two additional methods that allow access to the aortopulmonary window (but not other stations particularly), anterior mediastinotomy and extended cervical mediastinoscopy. The American College of Chest Physicians' (ACCP) systematic review[103] evaluated two small observational studies (N=206) (Table 32 and Table 34) and noted that both methods had low sensitivity (for anterior mediastinotomy 63% and 83%, and extended mediastinoscopy, 45% and 51%) compared with other invasive tests. But as an adjunct to standard mediastinoscopy there was improved sensitivity (for anterior mediastinotomy 87% in both studies, and extended mediastinoscopy 82% and 89%) and NPV (for anterior mediastinotomy 89% and 92%, and extended mediastinoscopy 82% and 89%) in patients with left upper lobe tumours.

5.6.10 Thoracoscopy in N-Staging

Staging thoracoscopy or VATS provides access to nodal stations that are not accessible by standard mediastinoscopy, such as the aortopulmonary window. In addition, it may allow assessment of visceral pleural involvement by tumour and provide information on T-status beyond standard assessment.

Several observational papers examined the role of VATS prior to formal thoracotomy in assessing mediastinal lymph node stations that are generally inaccessible to standard cervical mediastinoscopy. Patient selection, lymph node station selection and comparison groups were variable and so no studies passed our quality assessment criteria. Therefore, no conclusions can be made regarding its role and further research is needed.

5.6.11 Future Considerations

There has been recent interest in improving assessment on CT by including morphological features of the nodes i.e. contour and heterogeneity[90].

The current wave of FDG-PET scanners are integrated PET-CT scanners and it is likely that the diagnostic accuracy of these machines will better than the estimates from the published literature.

There has been interest in recent years in the detection and diagnosis of non-palpable supraclavicular lymph nodes using CT and US, with promising results[104].

5.7 M-Stage Assessment

Distant metastases are present in most SCLC patients and around 40% of NSCLC patients at presentation[105]. The presence of distant metastases leads to a classification of stage IV disease and these patients are no longer candidates for radical therapy. It is therefore important that metastases are identified prior to treatment planning to minimise the number of futile radical therapies.

Approximately 90% of NSCLC and SCLC patients with distant metastases have symptoms indicative of these sites[105]. In many ways this makes M-staging straightforward although no test is 100% accurate and patients without symptoms may still have occult metastases. The clinician therefore faces a number of decisions for the most efficient way to carry out M-stage assessment.

5.7.1 Clinical Evaluation

The clinical evaluation is an essential part of the M-stage assessment. Not only will clinical investigations indicate the presence of distant metastases but will also direct further investigative tests.

Clinical examination consists of a history and physical examination to include routine haematological and biochemical blood tests and a CXR. As common practice many patients will also have had a CT scan of the chest and liver for diagnostic purposes. The clinical signs that suggest the presence of distant metastases are shown below.

Clinical findings that suggest the presence of distant metastasis

General findings	weight loss ≥10%; fatigue; decreased albumin; decreased hematocrit; increased white blood cell count; increased platelets
Indication of brain metastases	headache; nausea; other neurological symptoms or signs
Indication of bone metastases	skeletal pain; elevated alkaline phosphatase (ALK-P); hypercalcemia
Indication of liver metastases	Right upper quadrant pain; hepatomegaly; elevated ALK-P, serum glutamic-oxaloacetic transaminase, lactate dehydrogenase or bilirubin
Indication of adrenal metastases	none

5.7.2 Clinical Evaluation to Detect Specific Sites of Metastasis

5.7.2.1 Brain

A recent review was retrieved by our search that comprised 17 studies which compared the ability of the clinical examination against CT, MRI or PET (reference standard) to detect brain metastases[95]. Our update search retrieved no additional papers (Table 35). Nine studies within the review included patients with a negative clinical evaluation while the remainder included patients with both positive and negative evaluations. For both groups of patients the pooled sensitivity was 76% (95% CI 64-84), the specificity 87% (95% CI 74-94), PPV 54% (range 21-100%) and NPV (range 79-100%). Cerebral metastases are more likely in patients with adenocarcinomas, N2 disease or large primary tumours and therefore careful clinical examination for cerebral metastases in this group should be undertaken.

In conclusion, clinical evaluation detects around 76% of patients with brain metastases (level III DS).

5.7.2.2 Bone

A recent review was retrieved by our search which comprised 17 studies that had each compared clinical examination against radionuclide bone

scanning (reference standard) for the detection of bone metastases[95]. Our update search retrieved no additional papers (Table 36).

The sensitivity, specificity, PPV and NPV of the clinical evaluation to detect bone metastasis is 87%, 67%, 36% and 90%, respectively.

The clinical evaluation allows a reasonably accurate determination of the presence of bone metastasis (Level III DS).

5.7.2.3 Liver and Adrenal

Our search retrieved a recent review which comprised 12 studies that compared the ability of the clinical examination against CT (reference standard) to detect both liver and adrenal metastasis[95]. Our update search retrieved no additional papers (Table 37).

In conclusion, while the sensitivity and NPV of the clinical evaluation is high for the detection of abdominal metastasis (92% and 95% respectively), the specificity and PPV is low (49% and 32% respectively) (Level III DS).

5.7.3 Imaging of Distant Metastasis

Studies that looked at the effectiveness of imaging techniques to detect the presence of distant metastasis can be split into two broad areas. Firstly, we retrieved studies that evaluated the ability of a whole body FDG-PET scan to detect the presence of all distant metastasis and the subsequent management changes which ensue. Secondly, studies were evaluated that reported the diagnostic accuracy of imaging techniques including CT, MRI and FDG-PET to detect the most common sites of lung cancer metastasis in the brain, liver, adrenals and bone, this is discussed from 5.7.4 onwards.

5.7.3.1 All Sites

The HTBS systematic review of around 17 observational trials was the most recent and comprehensive evidence of the effectiveness of a whole body FDG-PET scan to detect distant metastasis[99]. The literature mostly concerned patients who were candidates for surgery (and was not split into CT positive and negative groups). Our update search retrieved two additional papers[96,106] that met our inclusion criteria and are included in the results reported below (Table 38).

The summary receiver operator characteristic curve (appendix three, Figure two) illustrates the distribution of values for the detection of distant metastasis. We calculated the pooled weighted specificity and read off the sensitivity from the sROC curve. This gave a sensitivity of 93% and specificity 96%. It seems conclusive that FDG-PET had a high sensitivity and specificity for the detection of extrathoracic disease (Level III DS).

In addition to the diagnostic accuracy of FDG-PET, 17 observational studies were included in the HTBS report which reported the rate of unexpected distant metastasis detected and subsequent patient management changes[99]. The studies recruited a combination of patients eligible for radical therapy (surgery: three studies, radiotherapy: one study and both: five studies). One additional paper[96] that comprised potentially surgical candidates, was retrieved and incorporated into the results reported in this section (Table 39).

From the review and additional studies, an average of 15% of patients had unexpected distant metastases detected by FDG-PET (range 8-39%), which resulted in management changes (as a result of detected metastasis only) in 25% of patients (Level 2++).

5.7.4 Imaging of Specific Sites of Metastasis

Studies that report on imaging modalities for detecting distant metastases vary widely in quality and results. The type of reference standard used (which may be a repeat scan, alternative scan, follow-up, histology or a combination of this list) and the heterogeneity in patient populations both contribute to the variety in results for each test. Papers with reference standards other than at least a follow-up of 6 months or histology were excluded. It should also be noted that, in the majority of instances, the literature fails to report either the results broken down by stage (clinical or pathological) or to compare the results of those patients with symptoms against those without. More research is needed in this area.

5.7.4.1 Brain

The brain is one of the most common sites of metastasis for lung cancer patients; the incidence of brain metastasis in necropsy studies vary from 30%-50%[107]. While screening for cranial metastasis has been investigated, the low pick up rate of positive scan without neurological signs and symptoms and the high cost of scanning all patients, means it is not thought to be either clinically or financially worthwhile[108]. This section will review the evidence of CT and FDG-PET to accurately diagnose cranial metastasis.

One paper was retrieved that measured the ability of CT to detect disease in potentially operable patients free from sign and symptom of cranial metastasis[108] (Table 40). An additional paper reports the accuracy of FDG-PET (Table 41) and MRI plus CT in newly diagnosed NSCLC patients[109] (Table 42). The diagnostic accuracy of CT plus MRI was the most accurate imaging modality for the detection of distant metastasis (sensitivity: 100%, specificity: 100%, PPV: 100% and NPV: 100%), followed by FDG PET and finally CT (Grade III DS). Although these results are encouraging, the heterogeneity of the patients both across and within each study and the small number of patients within each study make it difficult to reach any firm conclusions. MRI is believed to be the most sensitive technique to demonstrate metastases in the brain and would be the modality of choice, followed by CT if the patient cannot tolerate the MRI scanner.

5.7.4.2 Liver

Due to its anatomical location, the liver is now routinely imaged in combination with the patient's initial chest CT in the initial staging protocol. Despite having relatively low incidence (in clinically staged I-III patients, liver metastasis occur in approximately 2% of patients)[105], metastatic imaging at such an early stage in the pathway can immediately identify those not going onto a radical treatment. Perhaps because of this low incidence there are comparatively few studies with adequate reference standards which evaluate CT, FDG-PET and ultrasound for the detection of liver metastasis.

Three papers, with a total of 312 patients, reported results on the ability of CT to detect malignancy in the liver (Table 43)[109-111]. The pooled weighted results from these studies were a sensitivity 97% and specificity of 94% (Grade III DS). One paper, with 78 patients, reviewed the ability of PET to detect liver metastasis[109] (Table 44). It reported a sensitivity of 100% and a specificity of 100% (Grade III DS). These results were compared to that of one paper with 77 patients which reported results of ultrasound[110], sensitivity 92% and specificity 96% (Table 45) (Grade II DS). Although the results from these studies appear encouraging, it is difficult to draw any firm conclusions from this small number of heterogeneous participants. There is not sufficient evidence to depart from the current practice of routinely scanning the liver during the initial staging CT.

5.7.4.3 Adrenals

Many of the issues surrounding the detection of adrenal metastases are associated with distinguishing metastatic disease from adenomas, which are also common in lung cancer patients. The incidence of abnormal and subsequently malignant adrenal glands appears to be exponentially linked to clinical stage. We compared FDG-PET[109,112,113] (Table 48), CT[109,114,115] (Table 46), and MRI[116-118] (Table 47) against gold standard histology to determine the status of adrenal metastases in lung cancer patients.

In summary, the sensitivity of FDG-PET is in the range from 84% to 100%, whilst the specificity is in the range from 80% to 100% (Grade III DS) compared to MRI, sensitivity: 100%, specificity: 59% (Grade II DS) and CT scans, sensitivity: 93% and specificity: 92% (Grade II DS), yet it is important to remember the heterogeneity of patients in each study. The available evidence in this area is not sufficient to depart from the current practice of routinely scanning the adrenals during the initial staging CT.

5.7.4.4 Bone Metastasis

Current methods of detecting bone metastases include X-ray of the local area, bone scintigraphy, CT, MRI and FDG-PET scans.

This review undertook the comparison of bone scintigraphy[109,119-121] (Table 49) and FDG-PET[109,119,120] (Table 50) and MRI[121] (Table 51) to diagnose bone

metastases within groups of lung cancer patients. Again, the breakdown of results was not specific enough to include results by specific stage or symptoms. However, the reported results from all retrieved studies concluded that FDG-PET was the most accurate (sensitivity: 93%, specificity: 98% (Grade III DS)) followed by MRI (sensitivity: 92%, specificity: 94% (Grade III DS)) and finally bone scanning (sensitivity: 88%, specificity: 64% (Grade III DS)). These results however, are based on small numbers and heterogeneous groups of patients and cannot be relied upon to make a recommendation that departs from current clinical practice.

5.7.5 The Addition of FDG-Pet to Work-up to Radical Therapy

The earlier evidence regarding FDG-PET reported on the effect of the technology on both N and M staging. There are however, some studies looking at the outcome of FDG-PET on patient management change, bringing together N and M staging during work-up to surgery and radical radiotherapy.

5.7.5.1 Potential Candidates for Surgery

One RCT[122] reported futile thoracotomy rate as its primary outcome. This study has an unusually high surgery rate considering the group of patients recruited for it and included a high incidence of thoracotomy for benign disease when compared to current UK practice. In addition the comparator CT scans were performed suboptimally in half of the patients, without intravenous contrast, excluded the liver and were non spiral. Nevertheless the results can be interpreted as five patients need an FDG-PET scan to avoid one futile thoracotomy. In addition, one observational study[123] incorporated patients eligible for both surgery and radical RT reported that 83% of patients undergoing a pre-treatment FDG-PET underwent a management change (i.e. change from one radical treatment to another or from a radical treatment to a palliative one) (Table 52).

In conclusion, potential candidates for surgical resection would benefit from a FDG-PET scan (Level 2+).

5.7.5.2 Potential Candidates for Radical Radiotherapy

No systematic reviews were retrieved for this section and a full literature search retrieved four observational studies[124-127] that reported therapy changes (Table 53). A pooled weighted average for therapy changes that ensued as a result of the FDG-PET scan during work-up to radical radiotherapy was 42%. In addition to this, one study reported that 23% of patients were downstaged as a result of the FDG-PET scan while two studies reported that between 27-45% of patients were upstaged.

In conclusion, those patients who are potential candidates for radical radiotherapy would benefit from a FDG-PET scan prior to their treatment (Level 2+).

5.8 Staging of Small Cell Lung Cancer

Small cell lung cancer (SCLC) patients are staged, as described earlier, into two categories: limited and extensive disease. Extensive disease refers to cases where there is metastatic spread. Thus intrathoracic staging in SCLC has little clinical relevance.

Most SCLC patients present with symptoms of metastases and a systematic review found that two thirds have extensive disease on presentation[105]. This review also found, from combining the figures from five studies with a total of 1,806 patients, that the most common sites of metastases at presentation were the liver and bone. Thus further investigation for distant metastases is always indicated in SCLC.

For symptomatic patients the choice and site of staging examination should be guided by clinical examination. For asymptomatic patients a history and physical examination should be followed by a choice of one or more of the following tests: CT of chest, upper abdomen (liver and adrenals) or bone scan. Tests should be performed sequentially and the testing stopped once a metastatic site is found[128] (see 5.9.5). Detterbeck et al looked at the reliability of neurological examinations for staging SCLC and concluded that CT or MRI of the brain was not worthwhile in asymptomatic patients[105].

5.9 Economics of Lung Cancer Staging

5.9.1 Search Results

The studies on economic analysis pertaining to PET scanning are summarised in Table 54 and Table 55. The rest of the staging economics studies[118,128-141] are summarised in Table 56 and Table 57.

There were a number of cost-effectiveness studies evaluating PET scanning; however, we focused more on the report of the HTBS, the only one from a UK context.

The evidence concerning the cost-effectiveness of PET scanning was largely inconclusive or inapplicable. Given its potential clinical importance and substantial cost, an original cost-effectiveness study from an NHS perspective was conducted to enable the GDG to make a decision in this area.

5.9.2 Report of the Health Technology Board for Scotland (Bradbury et al, 2002)

Bradbury et al[99] conducted a cost-effectiveness analysis to evaluate different strategies for staging NSCLC. They used a decision tree, which calculated cost-effectiveness in terms of the cost per quality-adjusted life-year (QALY) gained.

The model evaluated the use of PET in patients that had the following characteristics:

> Definite diagnosis of NSCLC

> Fit for surgery

> Have already had CXR, bronchoscopy & chest CT

Therefore the model does not consider the use of PET in patients who have symptoms that might indicate metastasis and it does not assume that routine scanning for metastasis has taken place (other than with chest CT). However, it is assumed that 10% have distant metastases that are only detected by PET.

Appendix one, figure two shows strategies evaluated for the patient group. The cost-effectiveness of each strategy was evaluated separately for patients that had enlarged nodes on their CT scan (CT node positive) and those that had normal-sized nodes on CT (CT node negative).

Bradbury et al conducted their own meta-analyses to estimate the sensitivity and specificity of PET, as reported above (see sections 5.6.2, 5.6.3, 5.7.3, 5.7.4 and 5.7.5). The unit cost of a PET scan (high resolution with attenuation correction) was estimated from a detailed costing of proposed Scottish PET facility. Estimates of the other model parameters (probabilities, life expectancies, quality of life valuations and unit costs) were extracted from the literature, mainly from Dietlein et al[142].

Results - CT Node-positive

It was found that strategies 3 and 7 dominate the other strategies, that is to say that compared with one of these two, each of the other strategies was both more costly and less effective. Strategy 3 (mediastinoscopy all and no PET) had second best outcome. Only strategy 7 (mediastinoscopy after positive PET) had a higher expected level of QALYs at an incremental cost of £59,000 per QALY gained. Hence PET scanning does not appear to be cost-effective in CT positive patients, when using a threshold of £30,000 per QALY gained. None of the strategies were clearly differentiated apart from strategy 2, which had the worst outcome and highest cost.

Results - CT Node-negative

Strategies 1, 3 and 7 were found to dominate the others. Strategy 3 had second best outcome. Only strategy 7 had a higher expected level of QALYs at an incremental cost of £10,500 per QALY gained. Hence PET scanning appears to be cost-effective in CT negative patients, however the model suggests that those who are PET positive should be given a follow-up mediastinoscopy, given its 100% specificity for N2/3 disease.

The overall health outcome in terms of life-expectancy or quality-adjusted life expectancy was very similar for all strategies (except strategy 2, where everybody receives only best supportive care). This suggests that the cost-effectiveness results are not robust to changes in the model parameters.

5.9.3 Overseas Economic Evidence for the use of FDG-PET in Staging NSCLC

The other economic analyses are presented in Table 54 and Table 55. Of the eight previously published studies, there were six cost-effectiveness, one cost-accuracy and one cost analysis.

The three cost-effectiveness studies were all based on decision analyses[142-144]. Their results were similar in that all four studies seem to show that mediastinoscopy after a positive PET was the most effective strategy. Dietlein[142] found that this strategy is highly cost-effective in CT negative patients and fairly cost-effective in CT positive patients. Scott et al[144] found, as did the HTBS report[99], that this strategy is only cost-effective in CT negative patients. Gambhir et al[143] did not evaluate PET separately for CT negative and CT positive patients.

As with the HTBS report Bradbury et al[99], Dietlein et al[142], Scott et al[144], and Gambhir et al[143] found very little difference in life expectancy (or in cost) between strategies, implying that the models are sensitive to the model parameters.

The cost-effectiveness analysis of Verboom et al.,[145] based on a Dutch RCT, compared conventional work up (CWU) with CWU+PET. Their results showed that additional use of PET in the staging of patients with NSCLC reduced unnecessary thoracotomies by 20% when compared to CWU alone and was cost-saving.

Among the cost-effectiveness analysis, two were based on prospective studies. Von Schulthess et al.[146] compared CT and bone scanning with whole body PET. They found that whole-body PET staging was a dominant strategy over the other as PET staging was more effective in terms of reducing unnecessary operations and was cost-saving. Fritscher-Ravens et al's [98] analysis based on two-year prospective study comparing computed tomography, PET and endoscopic ultrasound (EUS) with FNA for the staging of potentially operable patients with suspected or proven lung cancer. The results indicated that PET strategy was cost-effective.

Hetzel et al's,[147] cost-accuracy analysis compared the use of F-18 NaF PET with planar bone scintigraphy (BS) and single photon emission tomography (SPECT) for detection of bone metastases in patients with initial diagnosis of lung cancer. F-18 NaF PET had greater accuracy and higher costs compared to other methods. However, this study evaluated the use of the procedure in detecting bone metastases only and took into account direct costs of these procedures only. Therefore, the results are not comparable to other studies reported where FDG-PET was used for detecting nodal involvement and all distant metastases.

Harewood et al.[148] evaluated the costs of alternative staging evaluations of enlarged subcarinal lymph nodes (SLNs) in patients with NSCLC using decision analysis. EUS-FNA biopsy has the least cost but the study did not take into account the clinical effectiveness and quality of life of patients.

5.9.4 Original Economic Evaluation of FDG-PET in Staging NSCLC

We conducted an economic evaluation for two groups of NSCLC patients that were identified as having the most to gain from PET scanning:

- Potentially operable patients with normal sized lymph nodes on CT being considered for surgery
- Patients being considered for radical radiotherapy (mainly with enlarged nodes on CT)

For both patient groups we have estimated costs and health outcomes for different strategies using decision analysis. Our decision analytic models are adapted from those previously reported in the literature, especially the HTBS model [99] and Dietlein et al[142]. For each strategy the primary outcomes are:

- Health service cost per patient
- QALYs per patient.

For the patients being considered for surgery, three strategies were compared:

- Patients go straight to thoracotomy
- Patients have a mediastinoscopy and then receive either radical radiotherapy (Med=N2/3) or thoracotomy (Med=N0/1)
- Patients have a PET scan and then receive either active supportive care (PET=M1+) or thoracotomy (PET=M0 N0/1) or go on to mediastinoscopy (PET=M0 N2/3)

For the patients being considered for radical radiotherapy, only two strategies were compared:

- Patients go straight to radical radiotherapy
- Patients have a PET scan and then receive either active supportive care (PET=M1+) or thoracotomy (PET=M0 N0/1) or radical radiotherapy (PET=M0 N2/3)

It is assumed that all patients (except those that have successful surgery) go on to have active supportive care including chemotherapy.

A detailed description of methods and results can be found in appendix four. Some of the assumptions remain unchanged from the HTBS model. Substantial changes are as follows:

- When replicating their model, we found that the authors of the HTBS model had (inadvertently) used sensitivity and specificity that had been calculated for CT positive patients when they should have those figures calculated for CT negative patients. We corrected this.
- PET sensitivity and specificity in the HTBS model were based on nodes alone (not on distant metastases). For the detection of distant metastases, in their base case analysis, they had in effect assumed that the sensitivity was the same for distant metastases as it was for nodes in N0/1 patients but a 0% sensitivity in N2/3 patients. We have calculated sensitivity and specificity specifically for detecting distant metastases (see 5.7.3.1) and have applied them consistently. We have also sought to take account of the (modest) cost of following up false positive PET scans for distant metastases with biopsies.
- We have updated the unit costs, including the cost of a PET scan. The cost of mediastinoscopy in the HTBS model seemed unrealistically low.
- We have re-estimated the underlying distribution of disease. In particular, unlike the HTBS model we do not assume that distant metastases have the same prevalence in N0/1 patients as in N2/3 patients.
- For patients with numerous enlarged lymph nodes on their CT scan we considered the most appropriate comparator to be radical radiotherapy, rather than thoracotomy or mediastinoscopy.
- In both our models we explicitly estimate the number of patients receiving radical radiotherapy, and we estimate the corresponding implications for cost, survival and toxicity. The LY gained from radical radiotherapy compared with active supportive care was estimated to be 9 months.
- For both thoracotomy and radical radiotherapy we assume a conservative 50% reduction in quality of life for eight weeks attributable to the temporary effects of treatment.

Appendix four shows the main outcomes for patients being considered for surgery. The Mediastinoscopy strategy is dominated by PET strategy (i.e. it is both more costly and less effective). Compared with the thoracotomy strategy, the PET strategy had:

- fewer futile thoracotomies (avoided in 22% of patients),
- fewer surgical deaths (1% of patients are spared a surgical death) and
- more appropriate selection of patients for radical radiotherapy.

This resulted in:

- improved life expectancy (0.04 years per patient) and
- quality-adjusted life expectancy (0.04 QALYs per patient).

Cost savings, mainly from thoracotomies averted, offset much but not all of the cost of PET scanning. The estimated incremental cost-effectiveness of the PET strategy compared with the thoracotomy strategy was £7,200 per QALY gained.

Appendix four shows the main outcomes for patients being considered for radical radiotherapy. Compared with the radical radiotherapy strategy, the PET strategy had:

> fewer courses of futile radical radiotherapy,

> some patients benefiting from curative surgery,

but,

> some missed radical radiotherapy courses, and

> some futile surgery.

This resulted in:

> improved life expectancy (0.01 years per patient) and

> quality-adjusted life expectancy (0.04 QALYs per patient).

Again cost savings, this time mainly from radical RT courses averted, offset much but not all of the cost of PET scanning. The estimated incremental cost-effectiveness of the PET strategy compared with the radical radiotherapy strategy was £9,500 per QALY gained.

For both groups of patients, the results were robust to sensitivity analysis and the PET strategy is unlikely to cost more than £30,000 per QALY gained in either case (see appendix four). Therefore PET scanning appears to be more cost-effective than a number of treatments recommended by NICE.

5.9.5 Routine Extrathoracic Screening in Lung Cancer

Three studies have evaluated routine extrathoracic screening using technologies other than PET in patients with potentially operable NSCLC Table 56 and Table 57).

Colice et al[132] constructed a decision analysis to evaluate routine head CT compared to symptomatic head CT to detect brain metastasis. The model was developed for a US context. The details of the model are not reported entirely transparently. They found that routine scanning added just 1.1 days to the life expectancy of the average patient. This gain was found to be not cost-effective at a cost of about £44,000 per QALY gained.

Tanaka et al[141] and Canadian Lung Oncology Group (Guyatt et al[136]) both evaluated routine CT (abdomen & brain) & bone scan versus symptomatic scanning, from a Japanese and Canadian perspective respectively. Tanaka's results were based on a retrospective cohort, whereas the Canadian study was RCT-based. The Canadian study saw a bigger reduction in the number of thoracotomies than the Japanese study (5/318 versus 3/755) and hence they differed considerably in their cost implications; Can$819 (£332) per patient cost saving versus US$1,226 (£677) additional cost. However, this might not be down to inconsistency, as the Canadian group had a broader patient selection than Tanaka et al[141], who considered only T1-2/N0 patients.

Richardson et al[128] presented the cost of different permutations of the following tests: bone scan, abdominal CT, cranial CT and bone marrow aspiration and biopsy (Table 56 and Table 57). At the end of each permutation were chest CT plus pulmonary function test. The population was all patients with newly diagnosed SCLC and no clinical evidence of extensive disease. In each case testing was halted once evidence of extensive disease was found. If all six tests did not indicate extensive disease then the diagnosis was limited disease. The lowest cost permutation was bone scan and the order of the tests undertaken is as follows:

Bone scan → Abdominal CT → Bone marrow aspirate & biopsy → cranial CT → thoracic CT → pulmonary function test.

At $2,817, this was only $130 lower than the most expensive permutation but was $1,400 less than routinely conducting all six tests. Hence they included that it matters more that tests are performed sequentially and the testing stopped once a metastatic site is found than the exact sequence of the test.

Houston et al[137] performed a cost analysis comparing Ga scanning versus conventional routine testing for distant metastases (radionuclide liver and bone scans, brain CT scan) in the staging of lung cancer patients. The decision analysis showed that the Ga scan was more costly than routine staging procedures. However, it should be noted that FDG PET has superceded Gallium, if any radionuclide is used, and Gallium is not used routinely for lung cancer staging in the UK.

On the basis of the limited evidence here, there is not a strong case for extrathoracic screening in patients that are asymptomatic for metastasis. It is possible then that scanning of asymptomatic patients is cost-effective in some subgroups but not in others. None of the above studies explicitly considered PET scanning for extrathoracic screening. The studies in 5.9.2-5.9.4 evaluated PET both for intrathoracic and extrathoracic staging. If PET were to become routine for some patients then this would almost certainly preclude the need for other extrathoracic imaging for these patients, although there may still be a role for CT scanning of the head, given the lack of accuracy of PET in this area.

5.9.6 MRI Scanning in the Staging of Lung Cancer

There have been four studies (all from the USA) that have evaluated MRI scanning in the staging of lung cancer, two with regard to adrenal gland evaluation, one on brain metastasis and one investigating the use of MRI in staging SCLC.

Mayr et al[139] found that high-dose MRI (0.3mmol/kg) for brain metastasis could save about $2,251 per patient compared with low-dose MRI (0.1mmol/kg) by averting 3 craniotomies and 2 aggressive courses of radiation therapy in 27 patients with CT evidence of bone metastasis.

Jelinek et al[138] compared MRI with CT, bone scan and bone marrow biopsy. In a prospective cohort of 25 patients diagnosed with SCLC. They estimated that the use of MRI could save approximately $481 per patient and an extra 5 patients were found to have extensive disease.

Schwartz et al[118] conducted a decision analysis based on a prospective cohort (n=42) to compare chemical shift MRI with CT-guided biopsy in patients with an enlarged adrenal gland on CT. They included only staging costs and found a saving of $15 per patient with MRI due to 55% of patients avoiding biopsy.

Remer et al[140] also carried out a decision-analysis of different strategies for evaluating adrenal masses including:

a) CT with an adenoma or non-adenoma threshold of 10H followed by MRI; and

b) CT with an adenoma or non-adenoma threshold of 0H followed by CT biopsy.

They found that a) was most the cost-effective strategy at a cost of $16,370 per LY gained compared with b). As with Schwartz et al[118], they only included the costs of staging and not treatment costs.

In summary, the studies' results suggest that MRI of the adrenal gland after CT could be cost-effective. So could the use of high-dose contrast MRI.

5.9.7 Thoracic CT and Mediastinoscopy

There has been a recent cost-effectiveness analysis[135] and three older cost analyses[129,131,134] evaluating the use of chest CT before mediastinoscopy. Two are Canadian studies[131,134] and the others relate to the USA[129,135]. The study by Black et al[129] found cost savings but is of minor interest given that the comparison was with surgery not mediastinoscopy. Both of the Canadian studies found modest cost savings attributable to the introduction of CT scanning to select patients for mediastinoscopy.

Esnaoloa et al[135] also found cost savings attributable to the use of CT before mediastinoscopy, however, they found that mediastinoscopy without CT had better patient outcomes and was more cost-effective than CT for T2/3. The greater effectiveness of routine mediastinoscopy is not surprising given that it is considerably more accurate than CT. In T1 patients, where there is a lower risk of nodal involvement the incremental effect of routine mediastinoscopy was small (0.022 LY gained) and not cost-effective (c£49,000 per QALY gained). They recommend that mediastinoscopy be used selectively in T1 patients; however, it is possible that the modest health gains are cost-effective using UK unit costs instead of US costs.

Hence the studies show that routine mediastinoscopy is more effective but also more

costly than selecting patients for mediastinoscopy on the basis of their CT results. Routine mediastinoscopy may not be cost-effective in T1 patients even if it is cost-effective for T2 and T3 patients. However, this has not been evaluated using UK NHS costs.

Bonadies et al[130] showed that, in a US context at least, outpatient mediastinoscopy is substantially less costly than inpatient mediastinoscopy.

As with all studies that are not UK-based, and US studies in particular, we need to be cautious about transferring the results; certainly prices but also other parameters may be very different. The studies compared different strategies, were based on small sample sizes and had limited follow-up.

5.9.8 Conclusions and Discussion

The published evidence is inconclusive for the UK but suggests the following:

> PET scanning to select patients for surgery is most effective and cost-effective in patients with normal-sized lymph nodes on CT.

> Routine scanning for extrathoracic metastases (with imaging modalities other than PET) is not evidently cost-effective (especially in N0 patients).

> Routine mediastinoscopy is more effective than mediastinoscopy on patients selected by CT scanning. It appears cost-effective for T2/3 patients but may not be for T1 patients.

We should be cautious in interpreting the results of studies in this review because of:

a) *The setting of the studies was overseas in all but one case.* There are a number of problems associated with using cost-effectiveness studies set in health systems overseas. Estimates of effectiveness may be inappropriate because of differences in the population. The cost of resources used can vary considerably between countries. For example, the cost of clinical staff is lower in the UK than in certain other countries. The resources used in the subsequent treatment will vary between countries according to local protocols. This may also impact on the estimated health gain for patients diagnosed.

b) *Studies varied in their assumptions.* Not all studies followed-up patients so that treatment costs could be included and, among those that did, treatment pathways varied. Patient selection could also have affected the estimates of cost-effectiveness.

Our own economic model shows that PET scanning reduces the amount of futile surgery and futile radical radiotherapy but is unlikely to reduce the overall cost of staging and treatment. PET is likely to be cost-effective in patients with normal-sized lymph nodes on CT (this is supported by the published health economic evidence). We also found that PET scanning is cost-effective in patients being considered for radical radiotherapy because some patients will be down-staged and others can avoid the morbidity associated with radical radiotherapy.

5.10 Recommendations

5.10.1 Clinical Practice Recommendations for NSCLC

In the assessment of mediastinal and chest wall invasion:

> CT alone may not be reliable [B(DS)]

> other techniques such as ultrasound should be considered where there is doubt [D(GPP)]

> surgical assessment may be necessary if there are no contraindications to resection. [D(GPP)]

Magnetic resonance imaging (MRI) should not routinely be performed to assess the stage of the primary tumour (T-stage) in NSCLC. [C(DS)]

MRI should be performed, where necessary to assess the extent of disease, for patients with superior sulcus tumours. [B(DS)]

Every cancer network should have a system of rapid access to FDG-PET scanning for eligible patients. [D(GPP)]

Patients who are staged as candidates for surgery on CT should have an FDG-PET scan to look for involved intrathoracic lymph nodes and distant metastases. [A(DS)]

Patients who are otherwise surgical candidates and have, on CT, limited (1–2 stations) N2/3 disease of uncertain pathological significance should have an FDG-PET scan. [D(GPP)]

Patients who are candidates for radical radiotherapy on CT should have an FDG-PET scan. [B(DS)]

Patients who are staged as N0 or N1 and M0 (stages I and II) by CT and FDG-PET and are suitable for surgery should not have cytological/histological confirmation of lymph nodes before surgical resection. [A]

Histological/cytological investigation should be performed to confirm N2/3 disease where FDG-PET is positive. This should be achieved by the most appropriate method. Histological/cytological confirmation is not required: [B(DS)]

> where there is definite distant metastatic disease

> where there is a high probability that the N2/N3 disease is metastatic (for example, if there is a chain of high FDG uptake in lymph nodes).

When an FDG-PET scan for N2/N3 disease is negative, biopsy is not required even if the patient's nodes are enlarged on CT. [B(DS)]

If FDG-PET is not available, suspected N2/3 disease, as shown by CT scan (nodes with a short axis > 1cm), should be histologically sampled in patients being considered for surgery or radical radiotherapy. [D(GPP)]

An MRI or CT scan should be performed for patients with clinical signs or symptoms of brain metastasis. [D(GPP)]

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. [D(GPP)]

5.10.2 Clinical Practice Recommendations for SCLC

SCLC should be staged by a contrast-enhanced CT scan of the patient's chest, liver and adrenals and by selected imaging of any symptomatic area. [D(GPP)]

5.10.3 Research Recommendations

Further research is needed into the diagnostic accuracy and efficacy of FDG-PET scanning in follow-up of patients after radical treatment for lung cancer to investigate possible recurrence of the disease.

Further research is needed into the diagnostic accuracy and efficacy of FDG-PET scanning in staging patients with SCLC.

Further research is required to assess the diagnostic accuracy and efficacy of FDG-PET in the assessment of tumour response to chemotherapy and radiotherapy.

6 Surgery with Curative Intent for Patients with Non-Small Cell Lung Cancer

6.1 Introduction

Surgery plays an important role in the treatment of non-small cell lung cancer (NSCLC). This section reviews this role in relation to the stage of cancer and in isolation from other treatment modalities such as chemotherapy and radiotherapy. In later sections (see chapter 9 Combination therapy) surgery is considered within multimodality therapies.

6.2 Techniques included in this review

The systematic review considered surgical procedures commonly used in treating lung cancer patients with an intention to cure. They include pneumonectomy; standard and extended lobectomies and sub lobar resection particularly wedge resection. In addition, the use of a minimally invasive technique such as Video-Assisted Thoracoscopy (VATS) is reviewed.

6.3 Methodology

A systematic review of the literature relating to the surgical management of NSCLC was undertaken. In addition, guidelines from the British Thoracic Society (BTS) and the American College of Chest Physicians (ACCP) and a systematic review by Detterbeck et al.[149-152] were reviewed.
The search strategy is listed in detail in the appendix six.

6.4 Preoperative selection of patients with Non Small Cell Lung Cancer for surgery

Recent BTS guidelines[153] covering specifically fitness for surgery, regarding age; pulmonary function; cardiovascular fitness; nutrition and performance status (see appendix 2, Figure 4 for comparison of Karnofsky and WHO/ Zubrod performance status scales) were reviewed. The guideline development group has accepted the recommendations reached in the BTS publication.

6.5 Risk of Surgery

6.5.1 Mortality

The standard definition of operative death includes mortality within the immediate 30 days following surgery. Based on a recent systematic review[154] of sixteen studies[155-170] in combination with a further four papers[171-174] reported from 1980 to 2002 including >250 patients undergoing open thoracic procedures for resection of NSCLC, the weighted average operative mortality for patients undergoing all forms of pulmonary resection (N=41105) was 3.5% (range, 1.0 – 7.6%) (Table 58) (Level 3).

The issue of operative mortality and advancing age was recently addressed in a non-systematic review of 37 studies of surgery in the elderly with NSCLC (Level 3) [175]. Though no pooled average was calculated, and the populations were somewhat heterogeneous, a trend was noted toward increasing surgical mortality with increasing age (Table 58) (Level 3).

Operative mortality following lung resections for specific surgical procedures will be discussed under the appropriate sections (Table 58) (Level 3).

6.5.2 Morbidity

Morbidity refers to adverse effects caused by an intervention. Though poorly defined by most authors, surgical morbidity can be further divided according to major or minor complications. Based on studies[155,157,159,162,166,169,176-182] from a recent systematic review[154] in combination with three further papers[172,173,183] reported from 1980 to 2002 including >150 patients undergoing open thoracic procedures for resection of NSCLC, the overall weighted average morbidity rate for patients undergoing all types of pulmonary resections (N=10098) was 30% (Table 60) (Level 3). Highest morbidity rates were seen in patients undergoing extended resections and undergoing pneumonectomy[176,177] (Level 3).

6.6 Surgery for Stage I Non Small Cell Lung Cancer

6.6.1 Introduction

Stage I disease is defined as NSCLC in the parenchyma of the lung, no more proximal then 2 cm from the carina, not invading the chest wall or parietal pleura and without nodal involvement (N0) or metastatic disease (M0).

Stage I is further subdivided into IA (T1N0M0) and IB (T2N0M0) and reflects differences in survival, with the former having better 5-year survival. The relationship between tumour size, patient prognosis, and the appropriate cut-off for tumour size (currently 3cm) to classify T1 and T2 tumours is still a matter of controversy[184]. Patients with stage I NSCLC, provided they are medically fit, should be considered for radical local therapy with curative intent[185]. Expert opinion from a previous guideline on diagnosis and treatment of lung cancer found that surgical resection is the generally accepted treatment of choice[186] (Level 4). Adjuvant or neo-adjuvant therapy will be reviewed in chapter 9 on combination treatment.

6.6.2 Patient Eligibility

An important distinction is whether patients are classified as stage I using clinical staging (c), before any treatment is carried out, or pathological staging (p), with information available after surgical resection. As clinical staging most often refers to radiological staging with CT, clearly the accuracy with which CT detects the presence of mediastinal lymph node involvement (N1, N2 or N3 disease) will influence reliability of clinical staging. The use of mediastinoscopy may improve clinical staging, but methods of staging are often not reported in studies on stage I patients.

The accuracy of pathological staging can also be affected by the extensiveness of the nodal dissection[152]

Based on a recent systematic review of eleven studies[170,187-190,190-195] that examined 5-year survival after open resection of pathological stage IA and IB NSCLC[152] in combination with two further papers[196,197] reported from 1980 to 2003 including >250 patients (N=8037), the weighted average mean 5-year survival was 69% for stage IA and 52% for stage IB NSCLC (Table 61) .For stage I NSCLC, T status has prognostic significance, with every study reported showing a survival average for T1 compared to T2 patients. The survival difference ranged between 12-23% for T1 versus T2 patients (Table 61).

Patient selection in terms of the type of procedure carried out will reflect the patient's fitness to withstand such a procedure. In studies comparing lobectomy versus a limited resection (Table 62), the selection criteria for a limited resection are often vague, based on the surgeon's experience, co-morbid disease or parameters (such as pulmonary function) that are not clearly stated.

6.6.3 Type of Surgical Resection

Lobectomy, the removal of a lobe of the lung, and pneumonectomy, removal of a whole lung define the anatomical resection. Lobectomy has been the standard surgical treatment for lung cancer even for small tumours[198,199] and is regarded as the procedure of choice for patients with stage I NSCLC[152]. Limited resection has mainly been performed in compromised patients with impaired lung function[200].

There are several types of limited lung resection described. A segmental resection or segmentectomy refers to anatomical dissection and complete removal of a bronchopulmonary segment of lung. A wedge resection is just what it says, and involves securing the air leak and bleeding by suturing or 'stapling' across non-anatomic planes of the lung. As a procedure it is most suitable in the context of thoracoscopy.

6.6.4 Limited Resection versus Lobectomy

A systematic review of the literature identified one recent review that included thirteen observational studies[152]. A further three non-randomised studies are also reported[201-203] (Table 62) (Level 3). Only one prospective, randomised trial of limited resection versus lobectomy was identified [204] (Table 62) (Level 1+).

6.6.4.1 Effectiveness

Amongst the observational studies reported, we found significant heterogeneity. Several studies looked at only segmentectomy with or without lymph node exploration [201-203,205-207]. A number of studies included some stage II patients. Inclusion of a comparison group (lobectomy) was variable. Limited resection was performed as the procedure of choice as most patients would have tolerated a lobectomy. Size of tumour reported amongst studies varied, with most including tumours of <2cm, reflecting increasing interest in whether the survival advantage of lobectomy over limited resection is less marked with smaller tumours[201-203,206]. The weighted average 5-year survival for segmentectomy versus lobectomy was 62% versus 80% respectively (Table 62) (Level 3). Two studies reported on loco-regional recurrence at 5-years[201,206], showing local recurrences to be more frequent after segmentectomy.

Seven observational studies reported on wedge resection as a compromise operation as compared to lobectomy[163,179,200,208-211]. Heterogenity was noted in what constituted a poor risk patient. The weighted average 5-year survival for wedge resection as a compromise procedure versus lobectomy was 51% versus 63% respectively (Table 62) (Level 3).

The only prospective, randomised trial of limited resection versus lobectomy allocated 247 eligible patients to either approach[204] (Table 62) (Level 1+). Lobectomy had a non-significant survival benefit at 5-years (73% versus 56%, P=0.06), and though the rate of distant recurrence was not significantly different, the loco-regional recurrence rate for the limited resection group was 75% greater than the lobectomy group (Level 1+).

6.6.4.2 Mortality and Morbidity

A limited resection, such as a segmentectomy or a non-anatomic wedge resection may be performed through either a standard thoracotomy or using a video-assisted thorascopic (VATS) approach. A systematic review of the literature identified one recent review[154] that included fourteen observational studies[155,156,159,161,163,166,168,170,200,205,211-214] undergoing wedge resection by a standard thoracotomy. In addition, three further observational studies were included[172,174,215] (N=6550) (Table 59). The weighted average 30-day or in-hospital mortality was 3% (range, 0-6%). The authors did not report on morbidity.

Lobectomy is the most common procedure employed for resection of lung cancer. A systematic review of the literature regarding morbidity and mortality associated with open lobectomy for lung cancer identified one recent review[154] that included eighteen observational studies[155,156,159-161,163,165-170,200,211-214,216] and a further three series[172,174,215] (N=24221) (Table 59). The weighted average 30-day or in-hospital mortality was 3% (range, 0-9%) (Table 59) (Level 3). The authors did not report on morbidity, though one series reported a complication rate of 28% for lobectomy[157] (Table 60) (Level 3).

6.6.4.3 Conclusions

Based on the completed systematic review for stage I (IA & IB) NSCLC patients with no medical contraindications, surgery is the primary treatment choice (Level 4), aiming for clear surgical margins. For patients who are able to tolerate a lobar resection, lobectomy rather than a limited resection (wedge resection or segmentectomy) is an acceptable alternative (Table 62) (Level 1+). Pending further research, patients with stage I or II non small cell lung cancer who would not tolerate lobectomy because of comorbid disease or pulmonary compromise, should be considered for limited resection or radical radiotherapy. (Table 62) (Level 3). Further research on the role of limited resection in comparison to lobar resection for small lung tumours is required.

6.6.5 Mediastinal lymph node evaluation in stage I NSCLC

Various surgical techniques for mediastinal lymph node evaluation at the time of limited or lobar resection have been developed. Options include

- No mediastinal lymph node biopsies
- Mediastinal lymph node sampling of suspicious lymph nodes
- Systematic mediastinal lymph node sampling
- Radical en bloc resection of mediastinal lymph nodes and surrounding mediastinal fat (lymphadenectomy)[186].

However, in systematically reviewing studies comparing techniques (Table 63), variations in definition of lymph node dissection were apparent. The importance of which technique is employed refers to differential benefit to definitive staging and survival and the potential associated morbidity.

The outcomes of interest are

- A beneficial difference in survival attributable to lymphadenectomy
- A beneficial difference in loco regional recurrence
- A difference in morbidity
- Better staging data

6.6.5.1 Effectiveness

The systematic review identified five RCTs that included stage I patients and evaluated the role of routine or systematic mediastinal lymph node sampling and radical lymphadenectomy in relation to survival difference and pathological staging (Table 63). Observational studies were disregarded.

One prospective RCT comparing radical mediastinal lymphadenectomy with mediastinal lymph node sampling (N=182, all stages) found no differences in survival or loco-regional recurrence in stage matched patients[217] (Level 1+). However, in regard to staging, the same author later analysed the data[218]. Though no differences were found between the two techniques in identifying pN2 disease, more patients with multi-station nodal involvement were found as expected in the radical lymphadenectomy group (57% versus 17%, P=0.007) (Level 1+). The same authors, Izbicki et al[219], in a further RCT (N=169, all stage) confirmed early findings, and also showed no survival difference in the pN0 subgroup. However, they did show a marginal benefit in patients with pN1 or limited pN2 (one station involved only) with radical lymphadenectomy improving survival (p=0.058) (Level 1+). An RCT that specifically evaluated the two techniques in relation to small peripheral tumours (<2cm) and clinical stage I patients found no survival difference and advocated no radical systematic mediastinal node sampling in such patients (Level 1+)[220].

Two recent RCTs did find a survival advantage for a more radical approach to mediastinal node dissection. One RCT compared radical mediastinal lymphadenectomy with mediastinal lymph node sampling in 169 eligible patients with stage I-IIIA NSCLC[221]. Amongst stage I patients (N= 42 versus. 31) 5-year survival was 62% versus 42% (P=0.044) for radical lymphadenectomy and mediastinal lymph node sampling respectively (Level 1+). A further RCT compared systematic mediastinal lymph node sampling to mediastinal sampling of suspicious nodes in 471 eligible patients with stage I-IIIA NSCLC[222]. Amongst stage I patients (N= 58 versus. 98) 5-year survival was 82% versus 58% (P=0.0104) (Level 1+). Both studies found a survival benefit toward more aggressive techniques of mediastinal lymph node evaluation in stage I patients.

6.6.5.2 Morbidity

In comparing complications associated with the various techniques employed to evaluate mediastinal lymph nodes, one RCT found no significant difference between radical lymphadenectomy and mediastinal nodal sampling (38% versus 47%, P=NS)[217] (Level 1+). However, in looking at specific postoperative complications, haemorrhage (>2units) and air leak (>5days) were more commonly recorded following radical lymphadenectomy (11 versus 5 patients with haemorrhage (P=0.051) and 9 versus. 4 patients with air leaks (P=0.075)) (Level 1+). In contrast, an RCT comparing the two methods in patients with small peripheral tumours[220] noted the morbidity of the radical lymphadenectomy group was significantly higher (27% versus 3% P-value not stated) (Level 1+).

6.6.5.3 Conclusions on mediastinal lymph nodes evaluation in stage I NSCLC

Due to the inconsistency of the results, we cannot conclude that one technique has an advantage over the other in terms of survival (Level 1+). Furthermore, no conclusion can be drawn regarding whether one technique of mediastinal node dissection has greater morbidity than another (Level 1+). However, based on consensus opinion in the literature regarding improved accuracy of staging with a systematic approach to lymph node sampling, the group have included a good practice point on its use.

The results of a RCT which began in 1999 to re-evaluate the therapeutic benefits of radical lymphadenectomy in patients with N0,1 NSCLC is awaited.

6.6.6 Open resection versus thorascopic resection

The development of minimally invasive Video-Assisted Thoracic Surgery (VATS) has significantly altered the management of patients with undiagnosed indeterminate or solitary pulmonary nodules. Increasingly, VATS is being used for resections in lung cancer. A systematic review of the literature identified papers that examined the role of VATS in lung resections, most of which were concerned with technique, feasibility and safety of the procedure. Few papers examined the effectiveness of VATS resection as compared to conventional open lung resection. We noted a degree of variability in the techniques used to perform the thorascopic resection in papers identified. Because of problems associated with clarity of definitions used for VATS, Video-assisted mini-thoracotomy was included in review, though we found few papers.

6.6.6.1 Effectiveness

The systematic review identified nine observational studies but no RCTs that included stage I patients and evaluated the role of thorascopic resection as compared to open resection in relation to survival difference and pathological staging[223-231] (Table 64).

The average weighted 5-year survival in patients with stage I NSCLC following VATS lobectomy was 76% in the four studies that had followed-up patients for that length of time[227-230] (Table 64) (Level 3). It compares favourably with 5-year survival following open resection (69% for stage IA and 52% for stage IB, Table 62). However patient selection based on the observational studies reviewed, is likely to be highly selective (size of tumour <5cm in most of the studies reviewed). Furthermore, the extent of lymph node sampling and reporting of sampling varied amongst the studies.

6.6.6.2 Morbidity

The intra- and postoperative outcomes, including complications associated with VATS, reported in two RCTs[232,233] and eight observational retrospective case series are presented[223-230] (Table 65). One prospective RCT[232] comparing VATS lobectomy with muscle-sparing thoracotomy and lobectomy (N=55) found no differences in operative time, intra-operative complications or blood loss between the two techniques (Level 1+). Postoperative complications were higher in the thoracotomy group (53% versus 24%, P<0.05), but the length of stay, and incidence of post-thoracotomy pain was not significantly different (Level 1+). The other RCT[233] compared Video-assisted mini-thoracotomy with muscle sparing thoracotomy for performing lobectomy in 67 patients. No significant differences in postoperative complications, postoperative pulmonary function and length of hospital stay were noted (Level 1+). However, postoperative thoracotomy pain, as measured in the first 8 days using a visual analogue scale was significantly different (P<0.006) in favour of the minimal-invasive procedure (Level 1+).

Eight retrospective case series (N=1469) with >50 patients reported on VATS lobectomy in terms of its technical feasibility and safety. One other smaller study (N=44) was included as it had evaluated pulmonary function in the two groups[234]. Overall, the weighted average operative mortality of VATS lobectomy was 0.7% (range 0 –3%) and a weighted average postoperative morbidity of 12% (range 2-21%). This compares favourably to the average weighted mortality and morbidity for conventional open lobectomy of 3% (range, 0-9%), and 28% (from one series[157]) respectively (Level 3).

The average weighted conversion to open procedure was 11% (range 0-17%), and the average weighted mean operating time was 127mins (range, 75-144mins) with significant variability in operating time noted (Level 3). The weighted average length of stay was 5 days (range, 3-7days). One study reported on pre- and postoperative pulmonary function in patients undergoing either VATS lobectomy or open lobectomy. Though not stated by the author, Kaseda (1998) in the original paper, preservation of pulmonary function was better in the VATS group (P<0.0001)[234] (Level 3). One RCT however found no significant difference[233] (Level 1+).

6.6.6.3 Conclusions

VATS lobectomy as compared to conventional open lobectomy appears to be a safe procedure with comparable, and maybe lower morbidity and mortality (Level 3). Regarding its perceived benefits over conventional surgery there is currently little evidence to support significant preservation in pulmonary function with VATS[233,234] or a shorter length of stay (Level 1+). Early postoperative thoracotomy pain was reported as significantly less in one RCT[233] and a non-significant trend toward less pain in the VATS group in another[232] (Level 1+). Further evaluation of the short-term outcomes of minimally invasive thorascopic resection is required.

Based on observational studies only, survival following VATS resection seems to be equally favourable as compared to open resection (Level 3), though the VATS resection groups are likely to be a highly selective group. Further evaluation, through prospective, randomised trials is required

6.7 Surgery for Stage II Non Small Cell Lung Cancer (N1 disease)

6.7.1 Introduction

Stage II NSCLC is defined as a T1 or T2 cancer with N1 nodal involvement but no distant metastasis, or a T3 cancer with no nodal or distant metastasis. It is further divided into IIA (T1N1M0) and IIB (T2N1M0 and T3N0M0).

Though T3N0 tumours are included in the IIB stage, this section deals primarily with T1 and T2 cancers with N1 nodal disease. This was because it was felt by the guideline group that the biological implications of direct invasion of chest wall or mediastinum without nodal involvement (T3N0), may not be the same as tumours which have spread to intrapulmonary nodes but do not involve chest wall or mediastinum directly (T1,2N1) despite similar survival. Furthermore, T3N0 make up only a small proportion of stage II cancers[149]. Thus in essence this section deals with N1 disease with T3N0 tumours discussed in section 6.8.

As with stage I NSCLC, patients with stage II NSCLC, provided they are medically fit, should be considered for radical local therapy with curative intent. Surgical resection with clear surgical margins is currently the generally accepted treatment of choice[235] though no RCTs were identified that directly compared surgery against other modalities.

6.7.2 Patient Eligibility

The number of lung cancer patients with clinical stage II disease is small, representing 5-10% of patients treated in the most recent surgical series[190,193]. They have therefore, often been included in studies with either stage I or stage IIIA patients. However, pathologically stage II NSCLC represents approximately 15-25% of resected cancers[187]. Direct comparison of studies is made difficult by several revisions of the staging system affecting the definitions of what constitutes stage II disease. Only papers that clearly distinguished stage II patients were included. As with stage I NSCLC, differences between clinical and pathological staging influence apparent outcomes.

Based on a recent systematic review[149] of eleven studies[170,188,190,193,236-242] that examined 5-year survival after resection of pathological stage IIA and IIB (N1) NSCLC in combination with two further papers[187,243] (Table 66) including >50 patients (N=3495), the weighted average mean 5-year survival was 45% for stage IIA and 33% for stage IIB (N1) NSCLC (Level 3). As with stage I, for stage II NSCLC, T status has prognostic significance, with every study except one[243] showing a survival advantage for T1 compared to T2 patients (Level 3). The survival difference ranged between 2-19% for T1 versus T2 patients.

6.7.3 Sleeve Resection versus Pneumonectomy

A sleeve lobectomy offers an alternative surgical technique in centrally located tumours where otherwise pneumonectomy would be necessary. Bronchial sleeve resection was introduced as a means of conserving lung parenchyma in patients with compromised pulmonary function. More recently, sleeve resection has been proposed routinely in the management of patients with anatomically appropriate centrally located tumours, even in patients with sufficient pulmonary reserve to permit pneumonectomy [244].

In identifying appropriate studies comparing sleeve lobectomy with pneumonectomy, we found difficulties in the classification of tumours resected by a sleeve lobectomy and subsequent staging.

Effectiveness

The NCC-AC identified two recent systematic reviews that examined studies comparing sleeve lobectomy with pneumonectomy[149,244]. One review included studies examining the role of sleeve lobectomy as a compromise procedure[149], the other considered only studies where the majority of patients undergoing sleeve lobectomy had acceptable lung function[244]. Only three studies appeared in both analyses (Table 67). The studies included comprised retrospective analyses of outcomes in patients treated with sleeve lobectomy with matched or unmatched control subjects who underwent pneumonectomy. The number of patients undergoing sleeve lobectomy as a compromise procedure was variably reported. We identified no RCTs in the literature search.

The first systematic review examined comparative studies of >50 patients undergoing sleeve resection (excluding sleeve pneumonectomy) for NSCLC[149] (Table 67). In total, ten studies were included (N=1083), though difficulties in comparing such studies were identified. In particular, the stage of tumour resected was often unclear with little detail given on T and N status. Five of the studies noted >90% of patients undergoing sleeve resection as a compromise procedure. The weighted average 5-year survival for stage II disease was 41% (Level 3). The weighted average for local recurrence following sleeve resection was 15% (Level 3). However, the author noted that most studies have reported data using the 1976 staging system (TINI included in stage I; only T2NI in stage II).

The second systematic review and meta-analysis compared outcomes of sleeve lobectomy (N= 860) with pneumonectomy (N= 746) in twelve studies for stage I and II NSCLC in patients who had acceptable lung function[244] (Table 67). The distribution of stages between the two groups differed significantly ($p<0.001$). The mean age did not differ (61.0yrs versus 60.5yrs respectively). There was no difference in mean 5-year survival (51.4+/-10.1% for sleeve lobectomy versus 49.1+/-5.5% for pneumonectomy; p=0.6) (Level 3). The mean median survivals were 70.5+/-16.2 months for sleeve lobectomy and 55.2+/- 6.6 months for pneumonectomy (p=0.024) (Level 3). The systematic review noted the likelihood of isolated local and regional recurrence was substantially higher after sleeve lobectomy (20%) than it was after pneumonectomy (10%) (Level 3). Further economic analysis of this review is presented in section 6.11.

6.7.4 Morbidity

Based on a recent systematic review of twelve studies, the average weighted operative mortality was 4.1% (CI, 2.3-5.9%) after sleeve lobectomy and 6% (CI, 1-11%) after pneumonectomy (p=0.3)[244] (Table 67) (Level 3). Operative mortality for sleeve lobectomy appears similar to standard lobectomy (see section 6.6.4). Details of postoperative morbidity were not given.

6.7.5 Conclusions

The advantage of sleeve resection over pneumonectomy is the preservation of lung tissue that is uninvolved with cancer. It has, therefore, traditionally been advocated as a compromise procedure in patients with limited pulmonary reserve who are unable to tolerate a pneumonectomy[245]. However, from the systematic review that included studies with significant numbers of patients undergoing sleeve resection as a compromise procedure, the weighted average 5-year survival was less (41%) compared to a review of studies of patients who undergo elective sleeve resection as an alternative to pneumonectomy (51%)(Level 3).

The operative mortality and long-term outcome of sleeve lobectomy were comparable to pneumonectomy in patients with acceptable lung function (Level 3). Isolated local and regional recurrences were higher in the sleeve lobectomy group (Level 3). Therefore, sleeve lobectomy offers an acceptable alternative to pneumonectomy for stage I and II patients who have an anatomically appropriate (central) tumour and for reasons of lung function, pneumonectomy is more hazardous (Level 3).

6.8 Surgery for Stage IIB-IIIA Non Small Cell Lung Cancer (T3 disease)

6.81 Introduction

NSCLC classified as T3 disease includes tumour that has extended into the chest wall, diaphragm or mediastinum, as well as tumour involving a main stem bronchus. In addition, involvement of the lower brachial plexus at the apex of the lung (Pancoast tumours) is also included, but as curative treatment usually involves combination modalities it is considered in chapter 9.

The current classification system incorporates T3 disease within stage IIB (T3N0M0), stage IIIA (T3N1-2M0) and stage IIIB (T3N3M0) based on survival outcomes. Though the overall survival appears to support the current classification, issues related to tumour behaviour, recurrence patterns and treatment strategies may be different from that of T2N1 (stage IIB) or T1-2N2 (stage IIIA)[246]. The behaviour and survival of different categories of T3N0-1 tumours may also be different. Therefore, the systematic review of literature regarding the surgical treatment of T3 tumours divided the search results according to chest wall, mediastinal or main stem bronchus involvement. The NCC-AC reviewers searched the published data on T3 tumours based on stage, according to local involvement or surgical technique (such as extended resection).

6.8.2 Patient Eligibility

T3N0-1 tumours comprise about 5% of NSCLC and in resected patients about 10% of NSCLC[246]. Furthermore, in four surgical case series (N=492) involving >75 unselected patients with T3 disease who were found to be pathologically N0,1, approximately 60% of the patients have N0 disease and 40% N1 disease[246] (Table 68) (Level 3). The same series found the weighted average with chest wall involvement was 51%, compared to 29% for mediastinal involvement and 16% for main stem bronchus involvement (Level 3).

Accuracy of staging and variable reliability of modalities such as CT and MRI in assessing clinical T3 disease and likely local invasion has been discussed in chapter 5.

We identified a recent systematic review[246] that included twelve studies which reported 5-year survival after resection of pathological staged T3 patients, and reviewed this in combination with one further paper [243] including >40 patients (N=1499) (Table 69). The weighted average mean 5-year survival was 40% for all T3 disease, 44% for T3N0 and 26% for T3N1 (Level 3).

6.8.3 Chest Wall involvement

Studies examining outcome in patients with a peripheral lung tumour invading the parietal pleura or deeper into the chest wall muscle or ribs were reviewed by the NCC-AC team. Approximately 17 retrospective series[188,247-262] reporting actuarial survival of >20 patients have been systematically reviewed[246], with two further studies included[263,264]. Overall, regardless of completeness of resection, the weighted average five-year survival for all T3 patients with chest wall involvement was 33% (Table 70) (Level 3). The weighted average five-year survival for T3N0 patients with chest wall involvement was 40% and for T3N1 patients 22% (Table 70) (Level 3). Therefore, predictably, an important prognostic factor appears to be the presence or absence of lymph node metastases.

Despite difficulties in comparing series because of differences in inclusion criteria, the systematic review[246] noted a trend to higher survival in those studies reporting on only patients who had complete resections compared with those that included patients with incompletely resected tumours. In a recent non-systematic review of four studies that studied patients undergoing complete versus incomplete resection of T3 chest wall NSCLC[235] weighted average 5-year survival following incomplete resection was 7% compared to 27% for complete resection (Table 71) (Level 3).

Long-term survival therefore appears to be influenced by the completeness of the resection, with very few patients surviving beyond two years with micro- or macroscopic residual disease[235,246].

6.8.3.1 Effectiveness

Two retrospective studies[263,264] have shown that, in patients undergoing complete resection, the depth of

chest wall invasion, as determined histologically, may affect prognosis, with better five-year survival when the invasion did not extend beyond the parietal pleura (Table 72) (Level 3). Furthermore, the technique of resection of chest wall lesions that are not clearly deeply invasive has also been examined. Several small case series showed a more aggressive approach (en-bloc resection) had better survival as compared to less aggressive method (extra-pleural resection)[249,261] (Table 72) (Level 3) However, a later series found no difference among patients who were resected by either technique provided a complete resection was achieved[247] (Table 72) (Level 3).

In terms of operative morbidity of chest wall resection incorporating either technique, no study demonstrated a significant difference statistically[247,261,264] (Table 72) (Level 3).

Currently there is no evidence apart from a few contradictory retrospective series supporting either approach to resection of T3 NSCLC with chest wall involvement that is not clearly deeply invasive (Level 3).

6.8.4 Mediastinal involvement

The most common mediastinal structures involved in patients with NSCLC T3 disease are the main pulmonary vessels, the pericardium and the mediastinal pleura or fat[246]. The prognosis in such patients appears to be worse than in patients with peripheral tumours[243,246] (Table 70) (Level 3). Few studies were identified that examined this group of patients specifically. Furthermore, very few studies have considered outcome based on structures involved. The largest case series (N=151) showed no significant difference in 5-year survival based on what site was primarily involved[265].

On the little evidence available, no conclusions can be drawn on the management of T3 disease with mediastinal involvement.

6.8.5 Main Bronchus invasion

Only 16% of patients with T3N0-1 disease reported in a four case series review had main bronchus invasion[246] (Table 68) (Level 3). Therefore, studies examining five-year survival in patients with involvement of the main stem bronchus within 2cm of the carina are few in number. As with mediastinal invasion, little data is available on prognostic factors, and no conclusions can be drawn.

6.8.6 Conclusions

The completeness of resection appeared to be an important prognostic factor for both central and peripheral T3 tumours (Level 3). In addition, lymph node status is also important, though the evidence for this is stronger and more consistent in the context of chest wall involvement (Level 3). The depth of chest wall invasion may influence prognosis, though the surgical technique of choice in relation to parietal pleura invasion only remains debatable (Level 3). Studies of central T3 tumours involving mediastinum and main bronchus were fewer in number and more difficult to assess, mainly because of problems in accurate staging. Overall, the prognosis was poorer for central T3 tumours as compared to peripheral T3 tumours (Level 3).

6.9 Surgery for Stage IIIA Non Small Cell Lung Cancer (N2 disease)

6.9.1 Introduction

Stage IIIA NSCLC is a heterogeneous group that includes patients with ipsilateral mediastinal (N2) disease, but also includes T3N1 patients. This subgroup of T3N1, because of its likely biological behaviour was reviewed along with T3N0 under surgery for T3 disease (section 6.8). Based on one case series[190], 10% of all patients had local advanced stage IIIA N2 disease at initial presentation. This group is probably the most challenging and controversial subsets of NSCLC both from a perspective of staging as well as treatment[266]. As such, stage IIIA (N2) patients are often regarded as on the border between the generally resectable stage I and II patients and the unresectable stage IIIB patients.

6.9.2 Patient Eligibility

The NCC-AC reviewers examined papers dealing with the surgical treatment of T1-3N2 disease. Most publications were retrospective, based on pathologically staged patients and therefore not easily applied prospectively to preoperative patients outcome. Another concern was the lack of rigorous pre-treatment staging, with preoperative patient selection in most retrospective series involving combinations of radiological staging with CT alone or with mediastinoscopy on selected cases. Papers that assessed curative surgical intent in N2 patients were included. Studies examining the role of a combined modality approach were not included but are reviewed under Combination therapy (chapter 9).

Several differences were noted among patients classified as stage IIIA (N2) that added to the general heterogeneity of studies reviewed. In particular, whether patient selection was in a surgical series, and therefore based generally on postoperative pathological staging, as opposed to non-surgical series with patient selection based on radiology. In addition, patients in surgical series are likely to have a better performance status than patients in non-surgical reports.

Wide ranges of approaches to preoperative patient selection were identified. At one extreme are patients undergoing minimal selection, with positive N2 disease (usually on mediastinoscopy) who have had attempted resection; compared to a highly select group of patients with obscure N2 disease and negative mediastinoscopy who had N2 disease discovered at the time of resection. Many studies fall somewhere between the two, with staging based on CT and selective mediastinoscopy. The guideline development group believes the use of PET will alter staging methods and criteria and it is likely that fewer N2 cases will be discovered at surgery.

6.9.3 Effectiveness

The likelihood of being able to achieve a complete resection would appear to depend on the degree of selection of patients preoperatively. A recent review examined resectability by reviewing 14 studies of greater than 20 pN2 patients from 1980 to 2000[151] (Table 73). The studies were broadly divided according to whether the studies were relatively selective (five studies, N=554) or not (nine studies, N=1287). This was generally based on radiographic criteria (cN2 versus cN0,1), and mediastinoscopy on selected patients. The average weighted percentage of patients who were N2 positive on CT but who did not have a complete resection was 36% as compared to 16% of patients who had undergone a more rigorous selection (negative CT +/- negative mediastinoscopy). However, little difference was found between the two approaches in relation to weighted percentage undergoing complete resection (23% versus 25%) with only a quarter of patients with N2 disease undergoing a complete resection. The authors concluded that a less rigorous approach to stage IIIA (N2) patients in terms of selection for surgery makes little difference to the number of complete resections achieved but does increase the number of patients who underwent an exploratory thoracotomy without complete resection [151].

The overall weighted 5-year survival of stage IIIA (N2) patients in the non-selective group of studies who had undergone complete resection was 26% as compared to 21% in studies which adopted a relatively selective preoperative staging assessment[151] (Table 73) (Level 3)

Recognition of the importance of different approaches to patient selection is reflected in survival data, with patients having favourable or 'occult' (minimal N2) disease appearing to have improved survival as compared to those patients with clinically 'bulky' nodal disease. Some authors,[266-268] in attempting to develop rational treatment guidelines have chosen to classify N2 disease into four subsets. These are shown below.

Subsets of Stage IIIA (N2) (Source: Robinson et al, 2003[266])

Subset	Description
$IIIA_1$	incidental nodal metastases found on final pathological examination of resection specimen
$IIIA_2$	Nodal (single station) metastases recognised intra-operatively
$IIIA_3$	Nodal metastases (single or multiple station) recognised by pre-thoracotomy staging
$IIIA_4$	Bulky or fixed multi-station N2 disease

The benefits of resection are discussed in relation to these four subsets of N2 disease.

6.9.3.1 Incidental N2 disease ($IIIA_{1-2}$)

Incidental N2 disease includes patients who are found to have N2 disease only on a final pathological examination of the resected specimen (stage $IIIA_1$) or as a single nodal station metastasis unexpectedly found at the time of resection (stage $IIIA_2$) despite careful preoperative staging with CT and mediastinoscopic evaluation of suspicious lymph nodes[266]. In three studies (N=182) in which patients had no radiological evidence of N2 disease the average weighted 5-year survival was 33%[151] (Table 73) (Level 3). Furthermore, in two studies (N=85) that required a negative mediastinoscopy, weighted 5-year survival was slightly better at 35%[151] (Table 73) (Level 3).

6.9.3.2 Potentially Resectable N2 disease ($IIIA_3$)

The presence of N2 disease detected radiographically or at mediastinoscopy had generally been regarded as a sign of inoperable lung cancer [266]. Two studies (N=79) within a systematic review[151] have examined survival of patients following complete resection who were positive at mediastinoscopy. The studies showed a 5-year survival of between 9% and 18% (Table 73) (Level 3). It is less than the outcome of N2 patients with negative mediastinoscopy but involves few patients. A systematic review of five studies (N= 735)[151] that radiologically identified N2 disease prior to resection found a variable 5-year survival ranging from 8-31% (weighted average 23%) (Table 73) (Level 3). However, three of the studies included used adjuvant radiotherapy +/- chemotherapy in addition. The stage $IIIA_3$ subset has been targeted for combination therapy and is reviewed further in chapter 9 (Combination therapy).

6.9.3.3 Unresectable, Bulky N2 disease ($IIIA_4$)

Generally regarded as the presence of lymph nodes >2cm in short-axis diameter measured by CT, and including multi-station nodal disease, extra-nodal involvement and groupings of multiple, positive lymph nodes. This subset is reviewed in chapter 9 (Combination therapy).

6.9.4 Conclusions

Regardless of the method of preoperative staging, only a quarter of all clinical N2 patients are completely resectable. Based on data from studies of surgery alone, 5-year survival of N2 patients who are macroscopically completely resectable at operation is approximately 25% (Level 3), with best outcome in patients with minimal disease and complete resection (Level 3).

6.10 Surgery for stage IIIB (N3 and T4 disease) Non Small Cell Lung Cancer

6.10.1 Introduction

Stage IIIB NSCLC incorporates patients with N3 disease and T4 tumours. It is generally considered to be inoperable, though surgery with curative intent has been applied to patients with T4N0,1 disease, typically in the context of carinal resections. This section deals primarily with this subgroup of patients, with further consideration of stage IIIB is given in the radiotherapy (chapter 7) and combination therapy chapters (chapter 9).

6.10.2 Patient Eligibility

T4 disease includes primary tumour involvement of the trachea or carina, superior vena cava, aorta, intra-pericardial pulmonary arteries, oesophagus and vertebral bodies. One systematic review[150] was identified that included eight surgical case series (N=322) of T4 patients undergoing carinal resections (Table 74).

6.10.3 Effectiveness

The weighted operative mortality was 18% (range, 4-30%) (Level 3). The weighted 2-year and 5-year survival was 41% and 27% respectively (Table 74) (Level 3). Little information regarding prognostic factors was identified from the literature search.

6.10.4 Conclusions

No conclusions can be drawn from the little data available on the curative surgical treatment of patients with stage IIIB NSCLC.

6.11 Economics of surgery for Non Small Cell Lung Cancer

The papers that were found compared VATS with open thoracotomy, sleeve resection versus pneumonectomy or else evaluated lung surgery clinical care pathways. There were no papers evaluating surgery compared with best supportive care.

6.11.1 VATS versus. open thoracotomy

Minimally invasive VATS surgery has been advocated as a cost-effective advance on open lung surgery. However, the assessment of cost-effectiveness is not straightforward. Although some cost savings might be achieved if patients spend less time in the intensive care unit (ICU) and less time in hospital[227] these might be offset by an increase in the cost of the operation itself. VATS can take longer than open surgery[227,269] and requires expensive equipment and consumables[270,271]. If VATS is more costly then it could still be justified economically but only if there are associated improvements in patient outcomes.

Four studies[269-273] reported in Table 75 and Table 76 compared the cost of VATS with that of open thoracotomy from retrospective studies that included all or mostly NSCLC patients. Lewis et al[272] and Nakajima et al[273] found a lower cost for VATS, however in both cases there was a strong suggestion that the case-mix was very different in each arm, therefore these studies are not suitable for comparative purposes. This bias is not present in the study by Sugi et al[269], which finds VATS to be more costly than open thoracotomy. However this study had a sample size of just 30. Liu et al[270,271] also find VATS to be more costly, however they recommend a less costly modified version of VATS, of their own devising. They reduce costs by using a form of conventional suturing that avoids excessive use of expensive endoscopic stapling devices. The methods used by Liu et al to cost the different surgical options were not reported, so it is not easy to assess whether this study is also susceptible to the bias observed in some of the other studies.

6.11.2 Sleeve Lobectomy versus. pneumonectomy

Ferguson and Lehman[244] constructed a decision model to assess the cost-effectiveness of sleeve lobectomy versus pneumonectomy for patients with stage I and II disease. Hospital costs for surgery and other therapies (chemo-radiotherapy, radiotherapy, and resection) were calculated retrospectively. But details of other therapies were not given. There was no difference in mean five-year survival (51.4 ± 10.1% for sleeve lobectomy versus 49.1 ± 5.5% for pneumonectomy). The QALY calculations favoured sleeve lobectomy over pneumonectomy (4.37 versus. 2.84 QALY) due to the higher utility associated with sleeve lobectomy. Sleeve lobectomy was cost-effective compared with pneumonectomy at $1,300 per additional QALY gained.

6.11.3 Clinical care pathways

Three US studies[274-276] conducted before-and-after evaluations of clinical care pathways for lung surgery (Table 75 and Table 76). Most but not all patients had NSCLC. They achieved reductions in length of stay of up to 10 days and cost savings of up to $12,000. Wright et al[275] described the components of their clinical pathway as:

- Institution of chest physiotherapy
- Patient instruction in the pre-admission testing area (opposed to the first visit postoperatively)
- Early discontinuation of prophylactic antibiotics
- Epidural catheters are removed usually the day before the chest tubes are removed so that adequate time is available to adjust to oral analgesic medication
- Improved pain control
- Aggressive nausea control policy
- Printed patient info
- Surgeon-led MDT meetings

Cost savings were mainly attributable to the reduced bed use. Zehr et al[276] attributed their reductions in resource use and cost to: early mobilisation; prudent use of x-ray & lab analysis; and early post-op extubation. Patton and Schaerf[274] gave the following as factors contributing to the success of their clinical pathway:

- Close coordination between surgeons and other hospital departments
- Intensive preoperative education to reduce patient anxiety and reduce recovery time
- Patient-controlled analgesia, nerve blocks, non-narcotic analgesia and pre-emptive rehabilitation, which limits the risk of complication
- The use of thoracoscopy to reduce recovery time.

6.11.4 Conclusions & discussion

There is no direct evidence that curative surgery for NSCLC is either cost-effective or not cost-effective compared with best supportive care, however one can infer that this is the case for patients at early stages of disease given that surgery adds years to life expectancy.

There is not strong evidence that VATS is either more costly or less costly than open thoracotomy. Thoracic surgery is undergoing innovations at the current time. It is important that future developments are properly evaluated in terms of both patient outcomes and resource use.

One study showed that sleeve resection was more cost effective than pneumonectomy. The quality of life of patients might have been improved through sleeve resection as the quality of life might be related to the amount of lung resected. Despite similar five-year survival rates obtained for these procedures, the result of incremental cost effectiveness was dominated by improvements in quality of life of patients who had sleeve resection.

The cost of lung cancer surgery is substantial and much of the cost is associated with postoperative care. It has been shown that clinical care pathways can enable the reduction of length of stay and health service costs in certain US contexts. The magnitude of such reductions is unlikely to be achievable in the UK NHS, where length of stay is already shorter than in the USA. However, the notion that by reducing surgical complications we might be able to reduce service costs as well as improve patient outcomes is seductive. Further research is needed to identify interventions that could speed up recovery time in the context of the UK NHS.

6.12 Recommendations

6.12.1 Clinical Practice Recommendations

Surgical resection is recommended for patients with stage I or II NSCLC who have no medical contraindications and adequate lung function. [D]

For patients with stage I or II NSCLC who can tolerate lobar resection, lobectomy is the procedure of choice. [C]

Pending further research, patients with stage I or II NSCLC who would not tolerate lobectomy because of comorbid disease or pulmonary compromise should be considered for limited resection or radical radiotherapy. [D]

For all patients with stage I or II NSCLC undergoing surgical resection – usually a lobectomy or a pneumonectomy – clear surgical margins should be the aim. [D(GPP)]

Sleeve lobectomy offers an acceptable alternative to pneumonectomy for patients with stage I or II NSCLC who have an anatomically appropriate (central) tumour. This has the advantage of conserving functioning lung. [C]

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. [C]

All patients undergoing surgical resection for lung cancer should have systematic lymph node sampling to provide accurate pathological staging. [D(GPP)]

In patients with stage IIIA (N2) NSCLC detected through preoperative staging, surgery alone is associated with a relatively poor prognosis. Therefore, these patients should be evaluated by the lung cancer MDT. [D(GPP)]

6.12.2 Research Recommendations

In stage I (IA and IB) NSCLC, further randomised trials on the survival and morbidity after limited resection in comparison to lobar resection for small lung tumours (less than 2 cm) are needed.
In patients with clinical stage I (IA and IB) NSCLC who are suitable for surgical resection, further research on the survival and morbidity after anatomical resection by thoracoscopic techniques in comparison to open resection is needed.

In patients with stage IIIA (N2) NSCLC detected through preoperative staging, surgery alone is associated with a relatively poor prognosis. Research should be conducted in a multidisciplinary setting into the survival and morbidity after surgery alone in comparison with multi-modality treatments.

7 Radical Radiotherapy Alone for Treatment of Non-Small Cell Lung Cancer

7.1 Introduction

Radical radiotherapy is external beam radiotherapy delivered to a high dose. This may be delivered "conventionally" in daily 2Gy fractions (treatments) five days per week to a total dose of 60Gy or more, or with radiobiologically equivalent doses using fractions of more than 2Gy per day, for example, in daily fractions of 2.5-2.75Gy to a total dose of 50-55Gy over four weeks. Hyperfractionation refers to the use of two or more fractions daily using fractions of less than 2Gy. Accelerated treatments are those completed in a shorter overall time than conventional treatments.

Increased radiation doses may, in theory, result in both improved tumour control and increased normal tissue damage. The use of techniques to minimise normal tissue damage, particularly lung damage as pneumonitis, may enable a higher dose to be delivered to the tumour. The current standard is to use custom-made lead blocks or a multi-leaf collimator to minimise the dose to adjacent normal tissue in conjunction with three-dimensional (3-D) treatment planning where the target volume is contoured directly onto CT slices. This conformal therapy has now replaced older 2-D CT and non-CT based planning techniques. Newer techniques to improve dose delivery (e.g. intensity-modulated radiotherapy, IMRT, or stereotactic radiotherapy) or which minimise the impact of tumour motion during treatment are under evaluation.

The aim of radical radiotherapy is to obtain control of the primary tumour and involved hilar or mediastinal nodes. In general, the impact of radical radiotherapy on overall survival is less in more advanced disease where the incidence of distant metastases is higher[277]. The risk of lung damage when larger volumes are treated means that there is a limit of tumour bulk above which the risks become unacceptable[278].

Radical radiotherapy is suitable for treating a wide variety of non-small cell lung cancer (NSCLC) patients. As well as being used alone, it can be used postoperatively or in combination with chemotherapy. Radical radiotherapy may be the treatment of choice for patients where, due to comorbid disease, other types of treatment are not tolerated or where the patient chooses not to have surgery or chemotherapy.

In this chapter, we describe the use of radical radiotherapy where it is the only treatment modality given for patients with NSCLC. Combination treatments (e.g. sequential or concurrent chemoradiotherapy or where radiotherapy is used in combination with surgery) will be discussed in chapter 9. We discuss lower dose (palliative) radiotherapy administered for the relief of symptoms in chapter 12. The chapter is in two parts, reflecting two distinct patient groups, those with stage I and II disease and those with stage III NSCLC, as the prognosis and the approach to treatment differs between these groups.

7.2 Techniques included in this review

In this chapter, we investigated the treatment of NSCLC patients with radical radiotherapy. We searched for literature that provides evidence for the use of radiotherapy alone in treating NSCLC. We did however consider papers that compared the use of two different regimens of radiotherapy, where the same chemotherapy drugs and dose are used in both arms of the trial. We considered all types of fractionation and both conformal and non-conformal techniques.

7.3 Methodology

We excluded papers that reported treatment doses of less than 40Gy, those that only provided evidence on the use of radiotherapy in combination with other treatment modalities and those that included patients without pathologically confirmed NSCLC.

In our initial search, we found a Cochrane Review on radical radiotherapy for stage I/II NSCLC in patients not sufficiently fit for or declining surgery[279] and a systematic review on the use of radical radiotherapy alone for treatment of stage IIIA and IIIB NSCLC[280]. The NCC-AC team undertook additional searches to update these reviews.

The search strategy is listed in appendix six.

7.4 Assessment of patients for Radical Radiotherapy

The suitability of patients for radical radiotherapy depends on a number of factors including stage and performance status (see appendix 2, Figure 4 for comparison of Karnofsky and WHO/ Zubrod performance status scales). Our literature search found no studies or systematic reviews for inclusion on pre-treatment assessment. The guideline development group decided to highlight some good practice points in this area. They considered that it was good practice to ask all patients to undergo pulmonary function tests, including lung volumes and transfer factor, prior to consideration of radical radiotherapy. Although no satisfactory "cut-off" for FEV_1 (either as an absolute value or as % predicted) has been established, clinical oncologists recognise the need for caution in those with particularly low FEV_1. In practice, patients with an FEV_1 <1.0 can be treated with radical radiotherapy provided the amount of normal lung irradiated is small. In the absence of precise limits of lung function or the volume of lung that may safely be irradiated, clinical oncologists exercise clinical judgement in determining where radical radiotherapy may not be appropriate for patients with bulky tumours because of the excessive risk of lung damage. Because it is likely in the future that many screen-detected tumours will be in patients with poor lung function, this topic will become increasingly important and is an area where further research is needed.

Patients should be encouraged not to smoke during radical radiotherapy. A detrimental effect of smoking has been clearly demonstrated in other cancers including small cell lung cancer (chapter 11), although this has not yet been shown for NSCLC patients.

7.5 Radical Radiotherapy for Stage I and II Medically Inoperable Non Small Cell Lung Cancer Patients

7.5.1 Introduction

Although surgery offers the best outcome in terms of survival for patients with stage I and II NSCLC (see chapter 6), radical radiotherapy has an important role in the management of medically inoperable patients. The term 'medically inoperable' refers to a diverse group of patients who are either considered unfit for surgery (due to insufficient respiratory reserve, cardiovascular disease or general frailty) or who decline surgery.

7.5.2 Effectiveness

We examined the effectiveness of radiotherapy alone in treating stage I and II medically inoperable NSCLC patients. We considered the use of conventional radiotherapy treatment, optimal dose, the volume of chest to be irradiated and the effectiveness of alternative fractionation regimens.

We found no evidence comparing radical radiotherapy to no treatment or palliative radiotherapy, or comparing surgery with radiotherapy. However, one study performed multivariate analysis on data from patients treated in the same centre with radiotherapy or surgery and found that treatment modality did not have an effect on survival[281] (see Table 77).

Survival

Overall survival from a systematic review of data from one randomised and 35 non-randomised retrospective studies (pooled data from 2617 patients) was 70% at one year, 45% at two years, 32% at three years and 17% at five years[279] (Table 77). Most of these studies used conventional (once daily) fractionation, although five studies used twice-daily fractionation. (Level 2++)

In the absence of randomised trials of radical radiotherapy versus supportive care alone, we obtained indirect evidence of effectiveness from consideration of the natural history of untreated NSCLC. In one study, none of 50 untreated patients with stage I/II NSCLC survived more than three years[282].

The survival figures for radiotherapy are poor in comparison to the five-year survival of patients who are treated with curative surgery alone. In our review (see chapter 6) we found that stage IA, IB, IIA and IIB patients had five year survival of 69, 52, 45 and 33% respectively, when treated surgically. However, confounding factors need to be taken into account when making comparisons between these two groups. A proportion of patients are upstaged during surgery as the true extent of the disease becomes apparent. Thus, surgical results are based on pathological staging and radiotherapy results are based on clinical staging, whereby a proportion of patients are likely to be 'under staged'. In addition, the patient groups are not equivalent. Most patients receiving radiotherapy alone were those not fit for surgery and had coexisting medical conditions and/or were in a frail condition. A direct comparison with surgical survival rates is therefore difficult to make.

Stage

The outcomes of treating patients of different stage are reported in a systematic review[279]. The review included thirty-five non-randomised retrospective studies. Weighted overall survival for studies including patients only with stage I NSCLC was 50% at two years and 19% at five years. For studies including patients with stage II or all stages, the weighted overall survival was 39% at two years and 14% at five years. The same systematic review[279] found some evidence, from studies that performed multi- or uni-variate analysis, that patients with smaller tumours have better survival at five years (T1 had better survival than T2 tumours). (Level 2++)

Radiotherapy dose and fractionation

One randomised controlled trial[283] compared the use of continuous hyperfractionated accelerated radiotherapy (CHART) (54Gy at 1.5Gy three times daily over 12 days) to conventional radiotherapy to 60Gy (at 2Gy per day over six weeks). Analysis of stage I and IIA patients showed that two year survival was 37% for CHART and 24% for conventional radiotherapy to 60Gy[284]. The four year survival was 18% for CHART and 14% for conventional radiotherapy[284]. The results demonstrate that CHART is superior to conventional radiotherapy to 60Gy for stage I and II NSCLC. (Level 1++).

The evidence also indicates, although not strongly, that higher doses are associated with improved outcome. The recent Cochrane systematic review[279] found better response rates and survival for subgroups of patients treated with higher radiation dose compared to those receiving a lower dose, although the reason for the choice of dose was rarely stated in these non-randomised trials (Level 2++). It is possible that less fit patients or those with more advanced disease may have received a lower dose.

Although most reported studies of once daily fractionation have used 2Gy fractions to total doses of 60Gy or greater, the fractionation most commonly used in the UK for stage I/II NSCLC is 55Gy in 20 fractions over 4 weeks. This is believed by most oncologists to be biologically equivalent to a dose of approximately 64Gy in 32 fractions over 6½ weeks.

Overall treatment time

A retrospective study of the effect of overall treatment time found that protracted treatment times were associated with significantly poorer ($p<0.0002$) two-year local progression free survival, for a group of N0 and N1[285] (Level 2+).

Mediastinal irradiation

The Cochrane review[279] found no clear evidence to support routine irradiation of the mediastinum. Studies of the stage I patients who had not received irradiation of the mediastinum found that isolated regional relapse was uncommon (0-3%). In addition, one study in the review did not find a significant effect on survival if the mediastinum had been irradiated in stage II patients[279](see Table 77)(Level 2++)

Performance Status

In the systematic review by Rowell and Williams[279] the majority of patients in the studies were of good performance status (WHO 0-1 or Karnofsky 70-100). Comparisons, in three studies with adequate data, showed that the median survival time was lower in patients with poor performance status. This was confirmed by multivariate analysis in two studies. One further study in the review found no difference in survival by performance status. Although there is little data on patients with poor performance staus and that this data is at times conflicting, overall, patients with poor performance status had a worse outcome. Overall, there is insufficient data on patients with PS 2 to support a recommendation for radical radiotherapy (Level 2++).

Weight Loss

Weight loss prior to treatment is associated with poorer outcome. Two studies within the systematic review[279] found survival was adversely affected by weight loss whilst one study reported that survival was unaffected (Level 2++).

Age

The evidence for the effect of age on the outcome after radical radiotherapy is conflicting. Most studies however, do not show an adverse effect of age[279] (Level 2++).

7.5.3 Morbidity and Quality of Life

Radiotherapy can cause pulmonary toxicity leading to early acute pneumonitis (occasionally fatal) or development of chronic pulmonary fibrosis. Oesophagitis is common when the mediastinum is included in the treatment volume. Patients receiving radiotherapy may also experience skin reactions, pericarditis and late oesophageal strictures. There is however a lack of documented evidence on treatment related morbidity and quality of life. Reporting of these outcomes was either poor and inconsistent, in studies included in the systematic review, or did not break the results down for stage I and II patients[279].

A cohort study of 46 stage I medically inoperable patients reported a gradual increase in dyspnoea and a significant deterioration of general symptoms including fatigue and appetite loss after radiotherapy[286] (Level 2+).

7.5.4 Patient Eligibility

The systematic review by Rowell and Williams[279] found variation between studies in the proportion of patients that declined surgery. These patients are likely to have less comorbidity and better performance status than those considered unfit for surgery, and therefore have better outcomes. This may be a source of the variability seen in the results of the trials in the review.

From the evidence presented above, we do not recommend radical radiotherapy for those with poor performance status (WHO ≥2). Weight loss is seen as a relative contra-indication. Age per se should not influence a decision to offer radical radiotherapy.

7.5.5 Conclusions

The systematic review by Rowell and Williams[279] collated the results of 35 non-randomised trials and found that there is a benefit in treating medically inoperable stage I and II NSCLC patients with radical radiotherapy (Level 2++). The review also found RCT evidence showing that continuous hyperfractionated accelerated radiotherapy (CHART) provides a better outcome than 60Gy conventionally fractionated[283], which was also confirmed in a later subgroup analysis of the stage I and II patients[284](Level 1++). The frequent attendance of patients receiving CHART may mean that hostel accommodation will need to be provided at the radiotherapy centre. Where CHART is not available, conventional radiotherapy to a dose of 64-66Gy in 32-33 fractions over 6½ weeks or 55Gy in 20 fractions over 4 weeks should be considered.

7.6 Treatment of Stage IIIA and IIIB Non Small Cell Lung Cancer patients

7.6.1 Introduction

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

Some of the studies included in this section include a small number of stage I and II patients. Although

the data for these patienets cannot be separated the numbers are small and the effect on the results is unlikely to be significant.

7.6.2 Effectiveness

We examined the effectiveness of radiotherapy alone in treating stage IIIA and IIIB NSCLC patients. We considered the use of conventional radiotherapy treatment, evidence for the optimal dose, the volume of chest to be irradiated and the effectiveness of alternative treatment regimens including hyperfractionation and continuous hyperfractionated accelerated radiotherapy (CHART).

We identified a systematic review[280] that included seven randomised controlled trials of over 100 patients[283,287-292]. We found no more recent studies with over 100 patients to update this review. The two-year survival for patients with stage IIIA and IIIB NSCLC treated with conventional radiotherapy (i.e. 5 fractions per week, 1.8-2Gy per day to a total dose of 60Gy or equivalent) ranges from 12.5% to 24% (Table 78) (Level 1+).

We identified no trials that compared the use of radiotherapy with no treatment or active supportive care. However, a systematic review that examined the natural history of NSCLC, found that two year survival ranged between 0-4% for untreated stage III disease[293]. Table 78 shows that two-year survival with radiotherapy alone appears range between 12.5% to 24%, suggesting that radiotherapy does provide a survival advantage over no treatment.

Stage of disease

Seven studies[294-300] (both retrospective and prospective), from a systematic review[280], provide evidence on comparative survival figures for stage IIIA versus stage IIIB NSCLC. Although stage IIIA and IIIB patients frequently receive the same radiotherapy treatment, Table 79 shows that in all but one of the studies stage IIIA patients had significantly better survival (Level 1+).

Outcomes following radical radiotherapy is associated more with disease bulk than stage[301]. In practice, this means that a small T4N0 cancer may have a better prognosis than more bulky earlier stage disease.

However, specific subsets of patients with stage IIIB may be excluded from radical radiotherapy both in trials and in routine clinical practice because of a higher incidence of distant metastasis and the need to irradiate a larger volume. The presence of supraclavicular and contralateral hilar (N3) nodal involvement is regarded by many as a contraindication to radical radiotherapy. Patients with pleural effusion, particularly if cytology positive, are also regarded as ineligible for radical radiotherapy.

Radiotherapy dose and fractionation

Evidence is scarce on the optimal dose for radiotherapy for stage IIIA and IIIB patients, or the effectiveness of radical versus palliative doses. One study, Perez et al.[302] compared doses of 40, 50 and 60Gy and found slightly better survival and local control at the higher dose at two years (Table 80) (Level 1+).

We examined the effectiveness of conventionally fractionated and hyperfractionated radiotherapy, but there are very few randomised studies that compare the two treatments. A systematic review that performed a meta-analysis of three studies did not find a statistically significant benefit in two year survival of one schedule over the other (OR 0.67 in favour of hyperfractionated radiotherapy, p=0.091)[303](Table 81) (Level 1+).

Cox et al.[304] examined doses between 60Gy conventionally fractionated and doses between 64.8Gy and 79.2Gy treating twice daily. They found no statistically significant difference to indicate a consistent survival advantage with increasing dose. However, they found 69.6Gy to be superior to 60Gy in stage III patients with good performance status and without weight loss. Higher doses offered no further improvements in survival (Table 81) (Level 1+).

A study by the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG)[288] observed better survival in the hyperfractionated arm of the study than in the conventional radiotherapy arm, although the difference was not statistically significant (Level 1++). Patients were only included if they had minimum weight loss and a Karnofsky performance status >70 (Table 81). A randomised study comparing the use of conventional radiotherapy (60Gy at 2Gy per day over six weeks) to CHART (54Gy at 1.5Gy three times daily over 12 days) in 563 patients found that CHART gave better local tumour control and survival[283] (Table 81). Two-year survival improved from 21% to 30% with CHART. Subgroup analysis indicated that the benefit from CHART was confined to the group with squamous histology (two-year survival improved from 20% to 33%) (Level 1++).

The CHARTWEL (CHART- Week-End Less) regimen has been designed to allow treatment to be carried out only during the week. Two-year local control rates were 37% and 55% in sequential groups treated with CHARTWEL 54Gy and 60Gy (without neoadjuvant chemotherapy)[305]; this compared favourably to the two year local control rate of 23% seen in the CHART arm of the CHART trial[283].

Overall treatment time

We investigated whether interruptions to a course of radiotherapy affected outcomes. A retrospective study (Table 82) found that longer overall treatment times were significantly (p<0.001) associated with poorer survival in a group consisting of 80% stage III patients[306] (Level 2+).

Mediastinal irradiation

There has been some debate whether to perform elective mediastinal irradiation. Any increase in treatment volume is likely to lead to an increase in the amount of normal tissue being irradiated, increasing morbidity. Although this is accepted as current practice in many parts of the world, we found no evidence in this area and therefore cannot support extending the treatment volume to include uninvolved lymph nodes. Despite this however, the mediastinum will frequently receive a significant dose when elective mediastinal irradiation has not been intentionally performed.

Performance status

We found little evidence on the relationship between performance status and outcome as many studies required good performance status (WHO PS 0-1) for study entry (e.g. Saunders 1999[283]; Saunders 2002[305], Sause 2000[288]). Two studies that performed a retrospective multivariate analysis of randomised controlled trials found that performance status was a major independent prognostic factor in patients with locally advanced NSCLC who are treated with radiotherapy[307,308] (Table 83) (Level 2+).

Weight Loss

A systematic review also found that evidence was inconsistent on whether weight loss was an independent prognostic factor[280]. Few studies included those with weight loss of >5%. We only found one study that performed univariate analysis on the effect of weight loss. The authors reported that weight loss >5% was not found to be a significant factor influencing overall survival[308] (Level 2+).

7.6.3 Morbidity and quality of life

Radiotherapy can cause pulmonary toxicity leading to early acute pneumonitis (occasionally fatal) or development of chronic pulmonary fibrosis. Oesophagitis is common when the mediastinum is included in the treatment volume. Skin reactions, pericarditis and late oesophageal strictures are also recorded.

We found only one study (Table 84) that examined quality of life before, during and after radical radiotherapy for stage III patients, although 12% of patients in this study had stage I or II disease.The study noted improvement in quality of life in 33% of patients and a worsening in 24%. However, a significant gradual decrease in the mean quality of life score was found over the 12 month follow up (p=0.02)[309] (Level 2+).

7.6.4 Patient Eligibility

Many stage IIIA and IIIB NSCLC patients will have combination treatment, but radiotherapy alone is useful for those patients of good performance who do not wish to have chemotherapy or those who may not be able to tolerate chemotherapy, for example if they have comorbid conditions.

From the evidence presented above, radical radiotherapy is not recommended for those with poor performance status (WHO ≥2). Weight loss is a relative contra-indication.

7.6.5 Conclusion

It is difficult to draw definitive conclusions about the effectiveness of using radiotherapy alone to treat stage IIIA and IIIB NSCLC because there is a lack of evidence comparing radiotherapy alone with best supportive care or with other treatment modalities. However, comparing the survival figures of stage III patients treated with radiotherapy alone to those from studies of the natural history of untreated NSCLC, it appears that the use of radical radiotherapy alone can provide some survival benefit. Although this section considers radical radiotherapy alone, the majority of patients considered sufficiently fit for radiotherapy will also receive chemotherapy (section 9.9).

The overall two year survival for stage IIIA and IIIB patients ranges between 12.5%-24% (Level 1+). Stage IIIB patients and those with poor performance status are less likely to do well treated with radiotherapy alone (Level 1+). There is no strong evidence about the optimal radiation dose but (as in section 7.5.5) there is evidence that CHART is more effective than conventional radiotherapy to 60Gy (Level 1++). Where CHART is not available, conventional radiotherapy to a dose of 64-66Gy in 32-33 fractions over 6½ weeks or 55Gy in 20 fractions over 4 weeks should be considered.

7.7 Economics of Radical Radiotherapy for Non Small Cell Lung Cancer

7.7.1 Introduction

For certain patient groups, radical radiotherapy offers advantages to patients in terms of improved life expectancy and quality of life. The disadvantages of this management strategy are the associated side effects and the cost of the resources (staff, equipment and consumables). These resources could potentially be put towards alternative beneficial uses, therefore it is important to assess whether the health gains are large enough to justify the cost.

7.7.2 CHART versus conventional radiotherapy

Coyle and Drummond[310] carried out a cost analysis alongside the multi-centre randomised controlled trial reported by Saunders et al[311]. The trial compared CHART with conventional radiotherapy to 60Gy.

Resource use and cost data were collected prospectively over three months for 284 patients in 10 UK trial centres. The patients had NSCLC stages I-III.

Table 85 shows the resource usage recorded and Table 86 the associated cost. CHART required more out-of-hours radiotherapy than conventional RT and patients spent more time in hospital, while patients receiving conventional RT spent more time travelling (costs have been inflated to 2002 prices using the Hospital and Community Health Services pay and prices index[312]). Radiotherapy was more costly in the CHART arm. Cost savings from reduced use of ambulances largely offset the increased inpatient costs associated with CHART. Overall, CHART cost an extra £900 per patient.

Coyle and Drummond[310] did not attempt to estimate the incremental cost-effectiveness of CHART, so for this guideline an approximate measure of cost-effectiveness was derived as follows. Table 87 shows the two year survival figures reported by Saunders et al[311]. We derived figures for life expectancy from the two year survival figures using the Declining Exponential Approximation of Life Expectancy (DEALE) method[313,314], which assumes a constant death rate in each arm. This gives an estimate of 0.4 life-years gained per patient at a cost of £2,100 per life-year gained.

The trial did not indicate substantial differences in quality of life between arms overall – some symptoms were worse in the CHART arm but by 6 weeks CHART patients were doing better. Assuming health-related quality of life (HRQL) over the remaining lifetime is on average 60% of full health (see appendix four) this would suggest an incremental cost-effectiveness of £3,500 per QALY, well below the £30,000 per QALY gained threshold. Table 88 shows a sensitivity analysis. Even when making fairly extreme assumptions (lower 95%CI for LY gained, upper 95%CI for cost and only 40% HRQL) the cost per QALY gained is still below £30,000.

Coyle and Drummond[310] suggest that the costs of CHART could be substantially reduced if more use was made of hostel accommodation instead of wards. Also, centres with slightly longer standard working hours might be able to reduce costs by carrying out more CHART within 'normal' working hours.

Subsequent to conducting this analysis, we identified a study that performed similar calculations. Wake et al[315] calculated a substantially higher figure £11,227 per LY gained. This figure is not accurate because a) the life-years gained was approximated by assuming it to be the difference in median survival and b) they assumed that the annual incremental cost would be four times the size of that observed in three months, whereas the time horizon was chosen in order to capture the vast majority of the cost differences. Wake et al considered other strategies, including combination therapy; hence this study is appraised in Chapter 9 on combination therapy for NSCLC.

7.7.3 Conformal radiotherapy

Conformal radiotherapy can potentially improve patient outcomes by better targeting of radiation to the malignant tissue. Hohenberg and Sedlmayer[316] compared, retrospectively, the costs of 3-D conformal radiotherapy and radiotherapy without the use of a multileaf collimator for patients with non-small cell lung cancer in three Austrian hospitals (results reported in English by Horwitz[317]). They found conformal radiotherapy to be more costly – see Table 89 (costs have been converted from Austrian Schillings using purchasing power parities). The increased costs were due to the need for:

- more expensive linear accelerator equipment;
- additional time for CT localisation & planning; and
- additional time for patient positioning and verification.

7.7.4 Economics conclusions and discussion

CHART appears to be more costly than conventional radical radiotherapy to 60Gy but relatively cost-effective. The evidence for this is relatively strong with both resource use and survival data coming from a multi-centre RCT set in the UK NHS. There is no direct evidence for lung cancer patients that either strategy is cost-effective compared with best supportive care (i.e. no radiotherapy); however, Glazebrook[318] and Barton et al[319] have found radiotherapy generally to be highly cost-effective. If we assume that conventional radical radiotherapy for lung cancer is cost-effective then it would appear that CHART is the strategy of choice in relevant patient groups (although there could be other fractionation strategies that are just as cost-effective but have not yet been evaluated). Implementation of CHART would require greater use of out-of-hours radiotherapy machines and bed usage. However, the number of patients that would require this treatment is not that great. The cost of CHART could be reduced if more CHART is performed during normal working hours and if hostel accommodation is used instead of ward beds. CHART is likely to be relatively more effective and cost-effective in patients at earlier stages of disease. Dale and Jones[320] use a radiobiological model to show that *in the long term* non-standard fractionation could actually reduce costs by preventing recurrence of disease.

A study showed that conformal radiotherapy is more costly than radiotherapy without multileaf collimation. Conformal radiotherapy could still potentially be cost-effective, if there are health gains, but as yet, there is no direct evidence of health improvements. Conformal radiotherapy has become the standard since this study was conducted.

7.8 Conclusion

Radical radiotherapy is indicated for stage I, II and III patients of good performance status (WHO 0-1) whose disease can be encompassed in a radiotherapy treatment volume without undue risk of normal tissue damage. Contra-indications to radical radiotherapy include pericardial effusions, cytologically positive pleural effusions and supraclavicular nodes. Contralateral hilar or contralateral mediastinal nodes are relative contra-indications for stage III NSCLC.

7.9 Recommendations

7.9.1 Clinical Practice Recommendations

Radical radiotherapy is indicated for patients with stage I, II or III NSCLC who have good performance status (WHO 0, 1) and whose disease can be encompassed in a radiotherapy treatment volume without undue risk of normal tissue damage. [D(GPP)]

All patients should undergo pulmonary function tests (including lung volumes and transfer factor) before having radical radiotherapy for NSCLC. [D(GPP)]

Patients who have poor lung function but are otherwise suitable for radical radiotherapy should still be offered radiotherapy, provided the volume of irradiated lung is small. [D(GPP)]

Patients with stage I or II NSCLC who are medically inoperable but suitable for radical radiotherapy should be offered the CHART regimen. [A]

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. [A]

If CHART is not available, conventionally fractionated radiotherapy to a dose of 64–66 Gy in 32–33 fractions over 6 ½ weeks or 55 Gy in 20 fractions over 4 weeks should be offered. [D(GPP)]

7.9.2 Research Recommendations

Research should be conducted into whether NSCLC patients with poor lung function have better survival, morbidity and quality of life when treated with radical radiotherapy alone compared to no treatment or treatment with chemotherapy or chemoradiotherapy

8 Chemotherapy for Non Small Cell Lung Cancer

8.1 Introduction

Stage IIIB or IV non-small cell lung cancer (NSCLC) is generally not considered to be curable, with five-year survival rates of less than 1%. However, chemotherapy can be useful in improving symptoms and quality of life in these patients. Chemotherapy also improves survival and although the increase is modest, it must be considered alongside the poor life expectancy in this group. The benefits must be carefully weighed against the risks of toxicity for the individual patient.

There is the possibility of treating patients with first, second and even third line systemic treatment, although many NSCLC patients treated with chemotherapy will only be suitable for first line treatment.

The Guideline Development Group decided to use the term 'active supportive care' (ASC) rather than 'best supportive care' (BSC) in this document to emphasise the nature of the care as an active process including other treatments such as radiotherapy. However, many trials use the term BSC and our evidence tables reflect this.

The development of this chapter included a review and update of the following technology appraisal. The appraisal is therefore now obsolete and has been replaced by this guideline.

Doxetaxel, paclitaxel, gemcitibine and vinorelbine for non-small-cell lung cancer. NICE Technology Appraisal No. 26 (2001).

8.2 The drugs included in this review

This review updates the Cochrane review[321] (2000) and the Health Technology Assessment (HTA) report[322] published in 2001, in addition to addressing other clinical questions. We therefore include data on the second generation drugs; cisplatin and carboplatin (platinums); ifosfamide, vinblastine, vindesine and mitomycin C. The HTA report examined four third generation chemotherapy drugs (docetaxel, paclitaxel, gemcitabine and vinorelbine) in the treatment of NSCLC. Since the HTA report was published docetaxel has been granted a licence to be used as first line therapy in the UK, and we have therefore looked for new evidence for its use in first and second line treatment.

Our review excludes new cytotoxic or biologically targeted agents, which were not licensed for use in the UK at the cut-off date for the literature search.

8.3 Methodology

Studies undertaken and completed after the publication of Detterbeck[323] and Health Technology Assessment 2001[322] by NICE were included.

The literature search identified a number of previous systematic reviews on chemotherapy for NSCLC. These included: Socinski et al[323], Health Technology Assessment[322,324], two Cochrane reviews[321,325] and Cancer Care Ontario Practice Guideline Initiative[326-329].

Additional studies were found by the literature search. The inclusion criteria for studies was as follows:

- All studies had to be randomised control trials in NSCLC
- Studies not covered by Detterbeck 2001 and the HTA report 2001
- Not covered by Cochrane 2000 and 2002 reviews

> Not covered by Cancer Care Ontario Practice Guideline Initiative 2001 & 2002.

The detail of the search strategy can be found in appendix six.

8.4 Patient Eligibility

In late stage NSCLC, chemotherapy offers the patient the possibility of symptom relief, improved disease control, better quality of life (QoL) and increased survival. However, not all patients with advanced disease (stage IIIB and IV) are fit enough to receive systemic treatment. In less fit patients, the risks of toxicity may outweigh the potential benefits of chemotherapy. In 2001 NICE estimated that between 1,320 and 5,280 lung cancer patients received chemotherapy each year[324], but the Royal College of Physicians[330] estimates that over 16,000 NSCLC patients a year are eligible for chemotherapy.

A recent systematic review[323] which summarised prognostic factors from 12,419 patients in ten trials of chemotherapy for NSCLC identified performance status (PS) to be the most important factor in the selection of patients for systemic treatment (Level 1+) (see appendix 2, Figure 4 for comparison of Karnofsky and WHO/ Zubrod performance status scales). Patients with PS WHO 0, 1 (or Karnofsky score of 80-100) are candidates for chemotherapy and patients with a performance status of WHO > 2 (or Karnofsky score of 10-50) should not be offered chemotherapy as there is no evidence that they will gain a palliative benefit or survival from such treatment (Level 1+). Selection of patients with PS WHO 2 or Karnofsky 60-70 for chemotherapy however, remains contentious. Although up to 20% of patients within some of the trials reviewed were PS 2, these patients have significantly lower survival rates and are likely to experience greater toxicity than patients who have a better PS (Level 1+)(See Table 90).

The extent (stage) of the disease is also important when considering patients for chemotherapy although the weight of this particular prognostic factor remains controversial[323].

The same systematic review[323] also reported that in some studies, male patients, those with metastases, those with increased lactate dehydrogenase levels (LDH), patients with >5% weight loss and patients >65 years of age were likely to demonstrate poorer survival having received chemotherapy (Level 1+).

8.5 Chemotherapy + Active Supportive Care (ASC) versus ASC

A systematic review undertaken by Cancer Care Ontario Practice Guideline Initiative[328] (whose evidence base included four meta-analyses and eight randomised trials) concluded that there is a modest survival benefit (ranging between 1.8 and 4.5 months) for platinum based chemotherapy plus ASC over ASC alone in the treatment of advanced NSCLC (Level 1+). The later randomised trials of single third generation drugs in their review also showed increases in median survival of 7-8 weeks[331] (Level 1+). This updated the HTA review[322,324] which had found evidence of gains in quality of life, compared to ASC, for the third generation drugs, when used in NSCLC patients with good performance status. Our search identified a further randomised trial[332]. The results are consistent with the earlier findings that platinum based chemotherapy increases median survival (by approximately 9 weeks)(Level 1+) see Table 91.

In their review, Socinski et al[323] observe that the rate of symptom relief appears to be higher than the objective response rate in all reported studies, suggesting that palliation can be achieved with tumour shrinkage that does not meet the standard criteria for objective response[323].

In the Cancer Care Ontario Practice Guideline Initiative review[328], the authors also noted that there was a distinct lack of quality of life data obtained using standardised scales in the randomised trials included. The authors concluded that, in terms of quality of life, there was generally an improvement of those patients treated with chemotherapy of any type in comparison to those treated with ASC (Level 1+). The more recent trial (Spiro et al, 2003[332]) found no difference in quality of life (Level 1+) see Table 91.

8.6 Second Generation versus Third Generation Regimens

Second generation chemotherapeutic agents include ifosfamide, vinblastine, vindesine, mitomycin C and platinums (carboplatin and cisplatin). The platinums have become commonly used in the treatment of lung cancer and are associated with side effects including nausea, vomiting and myelosuppression. Administration of antiemetics and IV fluids can reduce the incidence of some of these side effects and can make the administration of such agents more tolerable[333]. More recently, the third generation drugs (gemcitabine, paclitaxel, vinorelbine and docetaxel) have been shown to have significant activity against NSCLC, alone or in combination. This section will review the evidence comparing third generation drugs (either singly or in combination) versus a second generation drug (or second generation drugs in combination).

The HTA review included three suitable studies[334-336] and our literature search identified three further studies (reported in four papers) which randomised one group of patients to a regimen comprising second generation agents and one group to a third generation regimen [337-340]. In all the trials the platinum based regimens used cisplatin plus another second generation drug in comparison to a third generation drug. There was good homogeneity within the patient selection for the trials. In terms of clinical effectiveness, differences in one year survival rate and median survival did not reach statistical significance (Level 1+). Few trials reported toxicity in detail, see Table 92.

8.7 Carboplatin versus Cisplatin

Cisplatin was frequently used in the 1980s and 1990s for the treatment of both NSCLC and SCLC. Carboplatin, an analogue of cisplatin, has a more favourable toxicity profile and has been successfully substituted for cisplatin in specific situations. It is envisaged that carboplatin, which can be administered without the need for prehydration and may be used in patients with poorer renal function, may therefore allow a wider range of patients to be eligible for chemotherapy.

A recent systematic review[323] describes three trials which randomised one group of patients to a cisplatin containing regimen and one group to a regimen containing carboplatin[323] with the same additional chemotherapeutic agents. The NCC-AC search identified rour randomised trials to update this review[341-344]. (Few trials retrieved during the literature search randomised patients to either cisplatin or carboplatin based arm with the same additional agents administered to each group).

In these studies, no significant differences in response or survival were detected (Level 1+). One of the later randomised trials[343] found more frequent thrombocytopenia in the carboplatin arm and more nausea and vomiting in the cisplatin arm. (This trial was not powered to detect differences in response rates). Another of the recent trials[341] found similar numbers of grade 3 and 4 adverse events overall (40% for cisplatin, 41% for carboplatin). See Table 93. Therefore until further comparative data emerges, either carboplatin or cisplatin can be administered for NSCLC patients receiving platinum-containing regimens, taking account of their toxicities, efficacy and convenience.

8.8 Third generation chemotherapy treatment

8.8.1 Different combinations of third generation drugs + Platinums

We identified six recent randomised trials[341-343,345-347] plus one study[348] included in the HTA systematic review[322] assessing different combinations of third generation drugs with a platinum as first line treatment for advanced NSCLC.

The trials compared a range of regimens and although some combinations were superior within trials, the levels of outcomes obtained were not consistent across trials. Where similar combinations appear in different trials (albeit with different dosages) the range of response rates and survival across the trials is larger than that observed within trials (see Table 94). There is, therefore, no strong evidence that one regimen is superior over any other.

Higher response rates do not necessarily translate into improved survival in these trials. Toxicity analyses were

similarly complex, reflecting the known profiles of the agents' side effects. Details of specific endpoints are in Table 94. Two trials reported (non-clinical) quality of life[341,347] but did not detect differences that reached statistical significance.

The HTA report concluded that it was likely that the optimal treatment is a third generation drug (gemcitabine, paclitaxel or vinorelbine) in combination with a platinum based drug (cisplatin, carboplatin). The Guideline Development Group agreed with this, with the addition of docetaxel, and decided to make this a good practice point. However, there is insufficient evidence that any one particular combination is superior to another (Level 1+).

8.8.2 Three drugs versus two drugs combinations

Triplet chemotherapy regimens, either platinum or non-platinum based have been tested in phase I and II studies. However, it is difficult to compare effectiveness as different combinations of agents and different dosages are assessed in each trial. There are concerns about excessive toxicity that need addressing through phase III studies.

Our review is based on the relevant trials from the HTA review[334,336,349-352], a systematic review[323], and four recent randomised trials comparing three and two drug combinations[353-356] (See Table 95). There is no consistent evidence that either type of regimen is superior to the other. Where significant differences in response rates were detected these showed benefit of a platinum containing doublet over triplet therapy, and benefit of triplet therapy over a platinum sequential doublet[353] (Level 1+). Response rates are not necessarily indicative of differences in survival; quality of life, in a single trial, shows benefit of a platinum doublet. These observations will continue to be informed by later trials. Toxicity reflects the different agents' known side effects.

There is currently insufficient evidence that three drug combinations are superior, in terms of survival, than two-drug combinations, but there is some evidence that they are more toxic depending on the agents used.

8.8.3 Third generation drugs + Platinums vs. Third generation drugs + Non platinums

Before the advent of the third generation drugs for NSCLC, platinum based chemotherapy was the standard of care. We reviewed the evidence to assess the effectiveness of third generation drugs in combination, to replace the platinums. Comparisons of a platinum based regimen that includes one of the third generation drugs compared with third generation drug alone have yielded conflicting results. Our search identified two relevant trials[357,358] within the HTA review and six more recent randomised trials[337,342,355,359-361] (Table 96). Only two of the trials detected a significant difference in response between third generation agents with or without platinum in various combinations (Level 1+). None detected a difference in survival (Level 1+). Only two of the studies examined quality of life[359,360] neither detecting significant differences between the different regimens (Level 1+).

Toxicity reflected the agents' known profiles and is described in detail in Table 96.

8.9 Duration of therapy in advanced Non Small Cell Lung Cancer

The optimal duration of therapy in patients with advanced NSCLC has not yet been identified. Many patients with advanced NSCLC have co-morbidities which adversely affect their performance status and tolerance of chemotherapy. In recent phase III randomised trials of combination therapy, the typical median number of cisplatin or carboplatin based chemotherapy cycles delivered is three or four as any additional cycles result in cumulative toxicity experienced. There have been various strategies used to determine the number of chemotherapy cycles for advanced NSCLC: treat until progression; treat for two cycles beyond maximal response; or treat for a defined number of cycles- usually six to eight.

We identified two recent randomised trials assessing duration of treatment[362,363] (See Table 97). One of the later randomised trials[363] compared a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small cell lung cancer. In this trial, 230 patients were randomised to receive either four cycles of carboplatin and paclitaxel every 3 weeks (Arm A) or identical doses of carboplatin and paclitaxel every 3 weeks until progression (Arm B). In both arms, patients received weekly paclitaxel of 80mg/m^2 at progression. Patients in Arm B received between 0-15 cycles of chemotherapy, but the median number of cycles received in both groups was 4 because of disease progression or the patient's inability to tolerate further chemotherapy. In the second trial[362] 308 patients were randomised to receive either six or three cycles of mitomycin, vinblastine and cisplatin every 21 days. However, the median number of cycles administered was 4 and 3 respectively. There was no difference in tumour response or survival in either trial. Toxicity reflected the agents known profiles and is reported in Table 97.

The first trial[363] found no difference in quality of life between the two arms. The second trial[362] found quality of life improves for those randomised to receive three rather than four cycles.

The majority of patients within these trials to determine the optimum number of cycles of chemotherapy either did not have a major response to treatment or were unable to tolerate more than three or four cycles (Level 1+). As the trials were not able to answer the more specific question of whether patients who are responding to chemotherapy, and tolerating chemotherapy well, benefit from treatment beyond three to four cycles, the evidence on the duration of treatment remains inconclusive.

8.10 Dosage of chemotherapy treatment

We were not able to identify evidence that specifically examined this issue. A wide range of cisplatin doses have been used, but good comparative data are not currently available. There is a need for research to identify optimum dosage of chemotherapeutic agents.

8.11 Second-line chemotherapy in Non Small Cell Lung Cancer

Second-line chemotherapy has only recently been tested in randomised trials. The role of second-line treatment has been unclear because few patients have adequate performance status and survival is limited.

We identified a Cochrane review containing one randomised trial, comparing docetaxel with ASC[325], which was also included in the HTA review[322], and a further randomised trial[364] comparing docetaxel and paclitaxel for this group of patients (see Table 98).

The trial in the Cochrane review[325] and HTA review[322] randomised 204 non-small cell lung cancer patients to receive either docetaxel or active supportive care. The dose of docetaxel was reduced from 100 mg/m^2 to 75 mg/m^2 following an unacceptably high toxic death rate in the initial patients. The overall tumour response rate is 5.8% in the chemotherapy treated patients as compared to nil in the active supportive care group of patients[325] (Level 1+). The median survival was 4.6 months for patients given active supportive care when compared with 7 months for the chemotherapy group and 1 year survival was 19% in the active supportive care group and 29% in the chemotherapy group[325] (Level 1+). All quality of life parameters favoured the docetaxel arm, the differences in pain and fatigue experienced reached statistical significance[365]. The later trial, which compared docetaxel and paclitaxel for patients who had previously received platinum based chemotherapy and had a life expectancy of at least 12 weeks, reported median survival of 184 and 105 days respectively.

Toxicities occurred in the frequencies anticipated from agents' known profiles and are reported in Table 98.

8.12 Economics of chemotherapy for Non Small Cell Lung Cancer.

Chemotherapy can potentially improve survival, reduce symptoms, improve quality of life and lead to a reduction in healthcare costs (e.g. terminal care, radiotherapy costs). However these advantages have to be weighed against the additional costs of chemotherapy, which include the cost of drugs, supportive medications, administration and chemotherapy-related toxicity.

8.12.1 Chemotherapy versus Best Supportive Care 1st line

We identified and tabulated 10 economic evaluations[322,366-376] that compared chemotherapy with best supportive care. Four of the studies were

conducted in the UK and the rest were conducted in Canada (Table 99 and Table 100).

Maslove et al[366] carried out a retrospective cost analysis of 194 NSCLC patients from eight UK centres included in the Big Lung Trial [377]. The trial compared three courses of cisplatin-based chemotherapy plus best supportive care with best supportive care alone in patients with advanced disease. The costs were followed-up to death. The mean aggregate episode cost was significantly higher for chemotherapy patients compared to patients receiving BSC. However, the mean costs for all resources except those related to chemotherapy administration were not significantly different indicating that the resource impact of chemotherapy-related toxicity did not differ significantly between the two groups. The mean weekly cost was similar between the two patient groups suggesting that the additional costs for chemotherapy patients related to them having longer intervention episodes. Chemotherapy patients were 5.2 times more likely than BSC patients to be hospitalised during their episode ($p<0.001$) and had more out-patient attendances ($p=0.001$). Patients randomised to BSC alone were more likely to have had radiotherapy (odds ratio 0.51, $p=0.022$). The study did not report effectiveness, however Maslove (2001)[366], suggests that chemotherapy patients incur a cost of about £300 per extra week of survival, which is equivalent to £15,600 per LY gained.

Billingham et al[367] assessed the cost-effectiveness of mitomycin, ifosfamide and cisplatin plus palliative care versus palliative care. The study was a retrospective study of a subset of patients (116, South Birmingham) from the randomised MIC2 trial. The study, which followed-up costs to death, demonstrated that MIC increased survival by 2.4 months at an incremental cost of £2,924, which translates into an incremental cost-effectiveness ratio of £14,620 per LY gained (95% CI: £6168-£21,612). The MIC2 trial also reported that this survival gain was achieved without compromising patient's quality of life.

Clegg et al[322], for the Health Technology Assessment Report, developed three UK economic models to compare the cost-effectiveness of four chemotherapy regimens (paclitaxel, docetaxel, gemcitabine and vinorelbine, all with or without cisplatin) with BSC using a synthesis of relevant trial data and a number of different sources of resource use and cost data. Results here relate to the third modelling approach used (cost-effectiveness analysis versus BSC). The results and limitations of the first two models are outlined in Clegg et al[322]

Costs were followed-up to death. The regimens with the least incremental cost-effectiveness ratios versus BSC are vinorelbine, vinorelbine + cisplatin and gemcitabine. Gemcitabine + cisplatin and paclitaxel + cisplatin show reasonable cost-effectiveness. All these regimens retain their cost-effectiveness under a number of scenarios and assumptions tested in the sensitivity analysis. However, the single agents paclitaxel and docetaxel have relatively high cost-effectiveness ratios. The sensitivity analysis examined the effect of different scenarios on the cost-effectiveness results. It tested number of cycles, % patients not completing cycles, number of administrations, drug costs, reduced dose, cost of antiemetic drugs, BSC cost, use of mean survival rates rather than median, quality of life adjustment, outpatient administration and survival. The results were most sensitive to changes in survival. The quality of life adjustment used utility values derived by Berthelot et al[369]. The incremental cost per quality adjusted life years (QALYs) for those regimens that utility values were available for slightly increased cost-effectiveness in all cases except one. Clegg et al[322] also considered quantitative information on the relative quality of life impact of chemotherapy regimens and BSC. Their overall conclusions were that chemotherapy for NSCLC is cost-effective taking into account both survival and quality of life.

Lees et al[368] compared the cost-effectiveness of gemcitabine plus BSC versus BSC using the perspective of the UK NHS. The study used data collected in a RCT of 300 patients and assumed that gemcitabine was administered on an outpatient basis. The trial was designed to measure quality of life, not survival, and therefore the results are presented as a cost per progression-free survival where progression relates to time to radiotherapy. Costs were not followed-up to death. The study reported that gemcitabine + BSC was associated with an incremental cost per progression-free LY gained of £5,228 compared to BSC alone.

The remaining six studies were conducted in Canada. Four of these studies are based on the same economic model framework[369,370,372,374] and two are retrospective analyses of an old (1984) Canadian RCT [375,376] A wide range of regimens were considered. In terms of incremental cost-effectiveness versus BSC all estimates were below $20,000 (Canadian dollars) and in some cases chemotherapy was the dominant strategy (increased effectiveness at reduced costs). In terms of incremental QALYs, only two studies included a quality adjustment, and they presented very different results. Berthelot et al[369] found that quality adjusting LYs gained increased the cost-effectiveness ratio by about 50%, but regimens remained relatively cost-effective versus BSC (range: Vinblastine + cisplatin dominated BSC to paclitaxel (135) + cisplatin = $21,500 per QALY gained). However, Kennedy et al[375] found that BSC was the dominant strategy in terms of cost per QALY gained. This was mainly due to the divergence of utility values used for the studies. Kennedy et al 1995[375] used mean utility values of 0.34 for chemotherapy and 0.61 for BSC whereas Berthelot et al[369] used 0.52 to 0.63 for chemotherapy (depending on regimen) and 0.53 for BSC.

8.12.2 Chemotherapy versus chemotherapy 1st line

We identified and tabulated 18 economic evaluations that compared two or more chemotherapy regimens. Only one of the studies was conducted from the perspective of the UK NHS (Table 101 and Table 102).

> Three of the studies presented cost-effectiveness in terms of incremental cost per LY gained (Table 103):

Earle and Evans[378] used an economic model framework to evaluate the cost-effectiveness of paclitaxel + cisplatin versus etoposide + cisplatin. The incremental cost-effectiveness ratios ranged from $30,619 to $138,578 per LY gained depending on location of administration of paclitaxel (inpatient or outpatient) and the addition of a growth-colony stimulating factor (G-CSF). Evans[370], used the same economic model framework to assess the cost-effectiveness of vinorelbine with or without cisplatin versus etoposide + cisplatin and vinblastine + cisplatin. Again the cost-effectiveness ratios varied widely depending on the location of administration of vinorelbine and the addition of cisplatin to vinorelbine. The third study, Smith et al[379,380], used effectiveness data from a European RCT and applied US costs to estimate the cost-effectiveness of vinorelbine + cisplatin versus vindesine + cisplatin. The resulting incremental cost-effectiveness ratio was $15,500 per LY gained and $25,800 per QALY gained. Smith 1995 did not assess costs to death. It is not clear for the other two studies whether lifetime costs were assessed or not.

> Three of the studies also assessed cost-effectiveness, but used different effectiveness endpoints:

A UK study[368] evaluated the cost-effectiveness of gemcitabine + cisplatin compared to a number of other newer and older chemotherapy regimens. For all these comparisons data on effectiveness were derived from relevant RCTs and resource use and cost data were derived from a number of different sources. A number of assumptions with regard to resource use had to be made. The results suggest that gemcitabine + cisplatin is more costly with improved effectiveness compared to older chemotherapy regimens (etoposide + cisplatin, MIC, MVP) and is the dominant strategy (more effective, reduced costs) compared to other newer chemotherapy regimens (paclitaxel + cisplatin, paclitaxel + carboplatin, docetaxel + cisplatin, vinorelbine + cisplatin). It is unclear whether costs were followed-up to death.

Annemans et al[381], compared the cost per responder between paclitaxel + cisplatin and teniposide + cisplatin in four countries. The study found that the average cost-effectiveness ratios for the two groups were similar despite the high cost of chemotherapy drug cost in the paclitaxel arm. This was because the high drug cost was partly outweighed by lower hospitalisation costs for administration and lower chemotherapy-related toxicity costs. The study did not follow-up costs to death and assumed certain costs to be equal between the two groups.

The third study, Palmer and Brant[382], was a cost-effectiveness study of four cisplatin-based chemotherapy regimens (gemcitabine, vinorelbine, etoposide and mitomycin + ifosfamide). Average cost-effectiveness ratios (cost per tumour response)

were not statistically different between the four treatment groups. Gemcitabine + cisplatin had the most favourable cost-effective ratio. Costs were not followed up to death.

> The final 12 studies were cost-minimisation studies or cost analyses:

Ramsey et al[383] conducted a cost-minimisation analysis using data collected prospectively in a RCT of paclitaxel + carboplatin versus vinorelbine + cisplatin. There was no statistically significant difference in survival or cancer-related quality of life between the treatment arms. The mean lifetime cancer-related health care cost for the vinorelbine + cisplatin group was significantly lower than for the paclitaxel + carboplatin group ($40,292 versus $48,940, P=0.004). The mean difference was $8,648 (95% CI=$2,634 to $14,662). The majority of this difference was due to the higher cost of chemotherapy drugs in the paclitaxel arm. There were no notable differences in downstream costs. The chemotherapy drug cost and medical procedures cost was significantly higher in the paclitaxel arm (p=0.0003 and p<0.0001 respectively) and the chemotherapy administration costs were significantly higher in the vinorelbine arm (p<0.0001).

Rubio-Terres et al[384] conducted a cost-minimisation analysis of docetaxel+ cisplatin, paclitaxel + cisplatin and paclitaxel + carboplatin. Equivalent efficacy was demonstrated in a RCT. An economic model was constructed to estimate the treatment cost per patient over a median of 4 cycles (no follow-up of costs to death). The mean treatment cost for the docetaxel + cisplatin regimen was lower than that for the paclitaxel regimens. Statistical significance for the difference was not tested. The difference was mainly due to the lower cost of chemotherapy drugs in the docetaxel arm.

Chen et al[385], in a cost-minimisation analysis, also found that chemotherapy drug cost was responsible for the difference in treatment costs between paclitaxel + carboplatin and paclitaxel plus gemcitabine (maximum of 6 cycles, no follow-up of costs to death). Total treatment costs and chemotherapy drug costs were significantly higher for the paclitaxel + gemcitabine arm (p=0.034 and p=0.035 respectively).

Skowron et al[386], in a cost analysis, found that chemotherapy drug cost and in-patient administration cost constituted the highest cost components of chemotherapy in a retrospective cost analysis of 87 patients undergoing etoposide + cisplatin or vinorelbine + cisplatin or gemcitabine + cisplatin. No statistically significant difference was found in one year survival between the three groups. Chemotherapy cost was the highest cost component in the gemcitabine + cisplatin group and the cost of administration was the highest cost component in the other two treatment groups. However a number of important costs were not included in the study including a follow-up of costs to death and chemotherapy-related toxicity costs.

Khan et al[387], in a prospective cost-minimisation study comparing carboplatin and cisplatin (+/- other chemotherapy regimens) found that the cost per patient and cost per course was higher for carboplatin than for cisplatin (statistical significance not tested). This difference was predominantly due to the higher cost of carboplatin. Again, costs were not follow-up to death and some cost elements were excluded.

Vergnenegre et al[388], in a prospective study found that effectiveness, in terms of objective response rate, was similar between two chemotherapy treatment groups (mitomycin + vinorelbine + cisplatin versus mitomycin + vindesine + cisplatin). Mean cost per patient for 3 cycles of chemotherapy were also similar. Costs were not followed-up to death.

The five studies that are gemcitabine cost-minimisation studies are either authored or supported by the producer of gemcitabine. Four of the studies were economic models using efficacy data from relevant RCTs and supplemented by expert opinion[389-392]. Costs were not followed-up to death and critically a number of assumptions had to be made. It was assumed that gemcitabine would be administered on an outpatient basis and the cost of gemcitabine was either assumed or excluded from the analysis altogether. The fifth study[393] was a cost-minimisation study comparing gemcitabine + cisplatin versus etoposide + cisplatin. Efficacy and resource use data were collected prospectively in an RCT. No significant differences were found in terms of survival or mean cost per patient between the two treatment groups. Chemotherapy drug cost was significantly higher for gemcitabine + cisplatin (p>0.0001) and hospitalisation costs were higher (but not significantly) for etoposide + cisplatin. Follow-up of costs to death were not included.

Schiller et al[394] retrospectively identified costs for gemcitabine plus cisplatin (Gem/Cis) vs plus cisplatin (Vin/Cis) , paclitaxel plus cisplatin (Pac/Cis), paclitaxel plus carboplatin (Pac/Car), docetaxel plus cisplatin (Doc/Cis). The cost analysis was based on the results of two RCTs [342,351]. Cost of chemotherapy acquisition, drug administration, hospitalisations and medical resources were calculated from the perspectives of the national health services of five European countries. Gem/Cis was associated with a lower cost than other drug combinations.

8.12.3 Chemotherapy versus Best Supportive Care 2nd line

We identified two studies that assessed the cost-effectiveness of second line chemotherapy with single-agent docetaxel versus BSC.

Leigh et al[395] conducted a retrospective cost-effectiveness analysis using efficacy data from a RCT and resource use and cost data from one participating hospital in Canada (Table 104 and Table 105). Costs were followed-up to death. The incremental survival benefit of docetaxel versus BSC was 2 months (p=0.047) and the incremental cost per LY gained was $57,749 (Canadian dollars). For the sub-group of patients treated with the recommended dose of docetaxel (75 mg/m^2) the survival benefit was 4 months and the cost per LY gained was $31,776. Second line docetaxel costs an additional $10,600 per patient for an extra 4 months of life.

Clegg et al[322] (described above) using an economic model estimated the incremental cost-effectiveness of docetaxel to be £17,546 per LY gained compared to BSC (Table 100).

8.12.4 Supportive care treatment

Supportive care treatments administered alongside the chemotherapy regimen aim to reduce or eliminate the toxic side-effects of chemotherapy. These treatments can be costly and therefore it is important to assess their cost-effectiveness.

Supportive care treatments include antiemetics (control of chemotherapy-induced emesis), antimicrobials (control of chemotherapy-induced infection) and cytoprotective agents (protection of normal cells from chemotherapy-related toxicity). No economic evaluations were identified for any of these treatments in a pure NSCLC population.

Clegg et al[322] however, considered the effect antiemetics would have on the cost-effectiveness ratios of several chemotherapy regimens. The older antiemetic drugs (e.g. metoclopramide) have negligible costs and therefore would make little impact on cost-effectiveness, however the newer agents (e.g. ondansetron) are more effective but more expensive. In the Clegg et al[322] model adding antiemetics would slightly increase incremental cost-effectiveness ratios versus BSC. However, although they would increase drug costs, it is likely that they would also impact on efficacy (i.e. fewer patients discontinuing therapy, fewer dose reductions) and other costs (i.e. reduction in costs of managing chemotherapy-related toxicity).

8.12.5 Discussions

A number of important considerations need to be kept in mind when interpreting the results from these studies including:

> A number of different methods were used for capturing data and data analysis.

> The studies assessed a combination of different stages of disease.

> All the studies claimed to calculate direct medical costs, however, a number of different perspectives were used and some studies did not include all relevant costs.

> Length of follow-up varied between the studies. Only a proportion of studies assessed costs to death.

> Some studies made assumptions on the median number of cycles, doses used and method and location of administration. There is a great deal of uncertainty around these issues.

> The studies used a number of different effectiveness endpoints for the economic evaluation including LYs gained, QALYs, tumour response, progression-free LYs.

> The studies were conducted in a number of different countries and the results of an economic evaluation conducted in one country may not be generalisable to another country because of differences in clinical practice

Cost-effectiveness of first-line chemotherapy

Chemotherapy generally seems to improve survival at an additional cost relative to BSC. The cost per LY gained seems to be below £20,000 for most regimens that have been evaluated.

The evidence for this is from four economic evaluations set in the UK NHS, three of them using effectiveness data from a multicentre RCT and either prospectively or retrospectively collected data on patient-specific actual resource use.

None of the studies considered the addition of carboplatin rather than cisplatin. Carboplatin could be administered on an outpatient basis and therefore could be a lower cost, more cost-effective alternative, depending on relative drug prices and the costs of treating side effects. Cisplatin is given as an outpatient basis in some units, but its administration costs are likely to be greater because it has to be administered over a much longer period.

To properly assess the cost-effectiveness of chemotherapy, one needs to assess the effectiveness, not just in terms of improvements in survival but also in terms of quality of life (see below).

The choice of first-line chemotherapy regimen

The data suggest that newer regimens generally improve survival at additional cost relative to older regimens. Only one study was set in the UK and did not report cost per LY gained or QALYs.

There are only a limited number of studies that compare the relative cost-effectiveness of one of the newer regimens compared to another. Only one US study that followed-up costs to death reported a statistically significant difference in cost per patient (vinorelbine + cisplatin had significantly lower cost per patient than paclitaxel + carboplatin). The majority of the cost difference was due to the additional cost of chemotherapy. Since, drug acquisition costs in the UK are more favourable for vinorelbine; this would sugest that it could be cost-effective in the UK. However, these results might not strictly be applicable to the UK NHS, because, the patient groups may be dissimilar and the same intervention may have very different resource impacts in different health systems.

Hospitalisation (for administration of chemotherapy or for chemotherapy-related toxicity) as well as chemotherapy drug cost is driving the differences in the cost of drug regimens.

The differences in the estimated cost-effectiveness of different drug regimens are dependent, not just on the efficacy and toxicity of the drugs but also on the:

> Drug price (which can vary substantially, especially when drugs become subject to generic competition)

> Number of cycles/administrations assumed;

> Whether administration was on an outpatient or inpatient basis;

> Prevalence of dose reductions/cancellations.

> The HTA report did not consider differences between regimens in the cost of treating toxicity.

Second-line chemotherapy

Second-line chemotherapy generally seems to improve survival at an additional cost for appropriate patients. The evidence for this is relatively limited given that there have only been two studies (one Canadian and one UK).

There were no studies that assessed the incremental cost-effectiveness of supportive care treatments in an NSCLC population.

Quality of life issues

Quality of life is an important consideration in situations where treatment provides only modest survival gains. It is also an important consideration in treatments that may induce toxicity and therefore quality of life is likely to differ between chemotherapy regimens depending on their toxicity profile. However, only four of the economic evaluations made an attempt to quality adjust survival and from these it is unclear what effect adjusting survival gain with patient's quality of life would have on incremental cost-effectiveness ratios. For a person in perfect health £20,000 per LY gained would equal £20,000 per QALY gained. So for people in less than perfect health the cost per QALY gained would be expected to be higher, unless chemotherapy is actually improving the quality of life for these patients.

Berthelot et al[369], in their assessment of several chemotherapy regimens versus BSC, found that chemotherapy was either relatively cost-effective per QALY gained or dominant with the cost per QALY gained being about 50% higher than the cost per LY gained. Clegg et al[322] used Berthelot's utility values to quality adjust survival and found that the chemotherapy regimens remained relatively cost-effective compared to BSC. The costs per QALY gained were all slightly higher than the costs per LY gained in all but one case. However, another study[375] found BSC to be the dominant strategy. The only other study to assess utility values[379] compared three chemotherapy regimens not including BSC. The main reason for the difference in results relates to a divergence in utility values estimated by Kennedy. Kennedy used mean utility values of 0.34 for chemotherapy and 0.61 for BSC, Berthelot used 0.52 to 0.63 for chemotherapy (depending on regimen) and 0.53 for BSC and Smith 1995 used 0.60 for cisplatin-based regimens and 0.7 for single agent regimens. In each case utility values were derived from a number of oncologists so it is unclear why such a substantial divergence arose.

Clegg et al[322] also reviewed the quantitative information on quality of life and concluded that chemotherapy does not reduce overall quality of life and in some cases it may be improved relative to BSC as metastases that are not controlled are also associated with adverse symptoms that impact on a person's quality of life. Using Berthelot's utility scores the HTA report found chemotherapy regimens to be cost-effective relative to a threshold of £30,000 per QALY gained, ranging from £3,000 to £16,000 per QALY gained.

8.12.6 Conclusion on economics aspects of chemotherapy for Non Small Cell Lung Cancer

It is likely that chemotherapy as an adjunct to best supportive care for patients with NSCLC is cost-effective (value for money), however, estimates of cost-effectiveness are contingent on the estimated changes in overall health-related quality of life. More research is needed in this area. Chemotherapy drug regimens differ in terms of their effectiveness, cost and toxicity profiles, however the uncertainty around estimates means that it is not possible to rank different regimens in order of cost-effectiveness.

8.13 Conclusions

The conclusions from this section are that:

- Chemotherapy is likely to be cost-effective for patients with NSCLC. The cost-effectiveness would improve with regimens that can be administered on an outpatient basis and have lower toxicity. Cost-effectiveness might also improve when the drugs come off patent and face generic competition. (Level 1+).
- Patients with a better performance status respond better to chemotherapy (Level 1+).
- Chemotherapy involving platinum or third generation regimens increases survival and disease control compared to active supportive care (Level 1+). However, complete or partial response does not necessarily translate into improved survival or quality of life
- There is some evidence that Carboplatin and Cisplatin are similar in terms of response and improved survival; nevertheless they have contrasting toxicity profiles (Level 1+).
- There is insufficient evidence that any one particular combination of third generation drug plus platinum is superior to another
- There is insufficient evidence to determine whether regimens with two or three agents are superior
- There is currently insufficient evidence to determine whether third generation agents, alone or in combination, should be used with or without platinum
- There is insufficient evidence to identify the optimum duration of chemotherapy
- There is inadequate evidence to identify optimal dosages.

8.14 Recommendations

8.14.1 Clinical Practice Recommendations

Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100), to improve survival, disease control and quality of life. [A]

Chemotherapy for advanced NSCLC should be a combination of a single third generation drug (docetaxel, gemcitabine, paclitaxel or vinorelbine) plus a platinum drug. Either carboplatin or cisplatin may be administered, taking account of their toxicities, efficacy and convenience. [D(GPP)]

Patients who are unable to tolerate a platinum combination may be offered single-agent chemotherapy with a third-generation drug. [A]

Docetaxel monotherapy should be considered if second-line treatment is appropriate for patients with locally advanced or metastatic NSCLC in whom relapse has occurred after previous chemotherapy. [A]

8.14.2 Research Recommendations

Further research is needed into whether chemotherapy or active supportive care result in better symptom control, quality of life and survival for patients with advanced NSCLC of performance status 2.

Further trials should invesigate the optimum timing, combination, dosage and duration of chemotherapy for patients with NSCLC who are candidates for chemotherapy. These should include assessment of quality of life and survival.

9 Combination Treatment for Non Small Cell Lung Cancer

9.1 Introduction

Although NSCLC patients may benefit from treatment with surgery or radiotherapy alone, the cure rate remains disappointingly low. Data from other tumour types suggests that improved survival may be gained from combinations of these modalities.

Adjuvant treatment (chemotherapy or radiotherapy) is given after curative-intent surgery or radiotherapy, in an attempt to improve the cure rate. It has been shown to be effective in a number of other common solid tumours such as breast and colorectal cancer.

It is important to distinguish *neoadjuvant* treatment (usually chemotherapy) and *combined* chemoradiotherapy from *primary* chemotherapy. *Neoadjuvant* chemotherapy is given before planned curative-intent surgery or radiotherapy in patients with curable disease at presentation. *Combined* chemoradiotherapy is given to patients eligible for radical radiotherapy and the treatments are either given sequentially or concurrently. In both these settings, neoadjuvant and combined, the aim of adding chemotherapy is to improve the cure rate obtained with surgery or radiotherapy alone.

In contrast, *primary* chemotherapy is given to patients unsuitable for surgery or radical radiotherapy at presentation in the hope that downstaging their tumour might enable them to proceed to curative surgery or radical radiotherapy. The response rates and survival are much lower in this setting.

Induction chemotherapy is used as a general term to include neoadjuvant treatment and primary chemotherapy as defined above.

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 neoadjuvant 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. Operability or inoperability should refer to the decision based on resectability and all other factors for example lung function, that eventually determines whether a surgeon proceeds to operate or not.

One of the difficulties in reviewing studies of combination therapy is various methods are used for patient selection. While some studies have used surgical (pathological) staging with mediastinoscopy in addition to radiological (clinical) staging with CT, this is not applicable to all. Another issue relates to the substantial heterogeneity in clinical status and prognosis of patients.

In this chapter, 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. Treatments by surgery, radiotherapy or chemotherapy in isolation are dealt with separately in the previous chapters.

9.2 Techniques included in this review

We included the following combinations of treatment:

- preoperative chemotherapy
- postoperative chemotherapy
- preoperative radiotherapy
- postoperative radiotherapy
- postoperative chemoradiotherapy
- sequential and concurrent chemoradiotherapy

9.3 Methodology

In our initial search, we retrieved a number of systematic reviews published in 2001[396-398], in addition to a number of reviews from the Cochrane Database of Systematic Reviews[321,399] and a guideline[400]. The NCC-AC team undertook additional searches to update these reviews.

The search strategy is shown in appendix six.

9.4 Preoperative Chemotherapy

The role of preoperative chemotherapy has been examined in two categories of disease burden. Most studies have involved patients with stage IIIA and IIIB, while a few trials have considered stage I and II disease.

This section reviews preoperative chemotherapy for patients with stage I-III NSCLC as compared to surgery alone, and includes both neoadjuvant and primary chemotherapy. There was no available evidence on patient selection for treatment.

9.4.1 Effectiveness

A systematic review[396] reported tumour response to preoperative (primary) chemotherapy from six prospective phase II trials in patients with stage IIIA or IIIB NSCLC (Table 106). The review reported a non-weighted average effect size for radiological response rate of 64%, a disease progression of 4% and for histological complete response of 24% of patients[396] (Level 2++).

A recent guideline[400] reports survival outcomes for technically resectable stage IIIA NSCLC patients undergoing preoperative (primary) cisplatin-based chemotherapy with or without radiotherapy. The systematic review on which the guideline[400] is based, reports results from two full paper RCTs, which are reported together with an additional RCT retrieved in Table 107. The results of the guideline showed that preoperative chemotherapy significantly reduced mortality at 2 years compared with no chemotherapy in patients with stage IIIA disease (OR 0.18 (95% CI 0,06 to 0.51) (Level 2+). However, there are difficulties in interpretation of the two completed RCTs. For example, both studies included postoperative radiotherapy for some patients in both treatment arms, there were small numbers of patients in the treatment arms of the trials, stage IIIA is heterogeneous and different chemotherapy regimens and doses were used in the two trials.

The RCT[401] which updated this review in Table 107 included patients with stage IB - IIIA NSCLC and so, did not distinguish between the effects of adjuvant and neoadjuvant chemotherapy. The response rate to chemotherapy was 64%, but the trial reported no statistical difference in median, 3-year and 4-year survival between preoperative chemotherapy plus surgery and surgery alone. There was however a significant prolongation of disease-free survival in the chemotherapy group (13 months versus 27 months, p = 0.03) and a trend towards improved survival with preoperative chemotherapy, for the whole group showing a median survival of 37months (95% CI, 26.7 to 48.3) versus 26 months (95% CI, 19.8 to 33.6), where P=0.15. A subset analysis suggested a positive effect of preoperative chemotherapy on survival in stage I and II NSCLC patients (Level 1+).

9.4.2 Toxicity

A number of phase II studies have uniformly shown that the treatment is well tolerated and are reported in Table 108. One systematic review[396] of 17 phase II trials of induction chemotherapy showed that the non-weighted average mortality rate during induction treatment alone is 2% regardless of induction regimen. Furthermore, the non-weighted average treatment-related mortality occurring at any time during the induction, operative or postoperative recovery period is 4% (Level 2++). In terms of morbidity, grade 3 or 4 neutropenia (WHO scale) was the most common problem noted in the CCOPGI guideline[400] reporting 80% of patients developing severe neutropenia after the first course and four patients (15%) requiring hospitalisation for the treatment of neutropenic fever in one RCT reviewed (Level 1+)[400]. Other toxicities reported included nausea and vomiting (generally mild), diarrhoea, oesophagitis (rare in patients treated with chemotherapy alone), hypomagnesemia and alopecia (Level 1+). There is no definite evidence of a difference in surgical morbidity or mortality following chemotherapy compared to surgery alone, but further information is required to confirm the safety and efficacy of preoperative chemotherapy. For example, the additional RCT[401] retrieved reported higher postoperative mortality with chemotherapy (6.7% versus 4.5%) although this was not significant (p-0.37) (Table 108).

9.4.3 Conclusion

In conclusion, preoperative chemotherapy can produce complete radiological and pathological responses. There is no definite evidence so far that surgical morbidity and mortality are significantly increased however, a few stage I or II patients have been included in trials and although one large prospective study suggested a trend toward a greater survival benefit for this group, there is currently little evidence that preoperative chemotherapy prior to resection provides improves survival in early stage NSCLC.

Several studies have demonstrated an improvement in survival of stage IIIA patients treated with preoperative chemotherapy and surgery compared to surgery alone, with a median survival of about 3 years. However, at present the evidence base is not sufficient to recommend preoperative chemotherapy for these patients. The forthcoming results of the Medical Research Council (MRC) LU22 study may provide further useful data on the effects of preoperative (neoadjuvant) chemotherapy in the UK and continental practice.

9.5 Postoperative Chemotherapy

The use of postoperative chemotherapy is based on the premise that following resection of the lung cancer in early NSCLC recurrence can be both systemic as well as local.

9.5.1 Patient Eligibility

The majority of patients who survive surgery are fit for chemotherapy. One Cochrane systematic review was retrieved on eligibility for postoperative chemotherapy (Table 109). The review reported that age and gender did not seem to influence the results (the effect was homogenous). There were too few people with poor performance to reach valid conclusions regarding this variable.

9.5.2 Effectiveness

One systematic review on the effectiveness of postoperative chemotherapy was retrieved[321] (Table 110). Regimens including long-term alkylating agents and cisplatin-based regimens were considered separately. Two additional RCTs which used cisplatin-based regimens were retrieved.

The systematic review[321] reported from 5 trials (N=1250) that used long-term alkylating agents, all of which favoured surgery alone with a 15% higher risk of mortality (HR 1.15; 95%CI 1.04, 1.27, p=0.005) (Level 1+).

However, the review[321] also reported from 8 RCTs[402-409] that cisplatin-based regimens were associated with a 15% reduction in risk of death (HR 0.87; 95%CI, 0.74, 1.02, p=0.08) (Level 1+). We combined these results with the 2 additional RCTs[410,411] in a meta-analysis using the logarithm of the hazard ratio and its standard error calculated from the original reports. We found no evidence of significant heterogeneity among the studies and therefore a fixed effect model was used to combine the results.

The results of the meta-analysis (see appendix 5) gave a pooled estimate of 0.87 (95% CI 0.76 - 0.99) (p=0.048) in favour of postoperative chemotherapy (Level 1+).

9.5.3 Conclusion

In summary, recently accumulated data, shows that cisplatin-based adjuvant chemotherapy may produce a small but statistically significant survival benefit. The Guideline Development Group recommends postoperative chemotherapy should be discussed with patients who have had surgery, with particular attention to possible benefits and toxicity.

9.6 Preoperative Radiotherapy

It was thought at one time that preoperative radiotherapy would make resection of the primary tumour easier, as well as controlling occult residual disease. However, the area has not received much attention since the 1980s[396].

A systematic review [396] identified two large trials published in the 1970s but no subsequent additional randomised trials of pre-op radiotherapy involving at least 100 patients were retrieved (Table 111). These two trials recruited 331 and 568 operable patients who were randomised to either 40 or 50Gy of pre-op radiotherapy then surgery or surgery alone. The survival curves were almost identical, with 5-year survival rates of 7% and 14% for the preoperative radiotherapy, compared to 12% and 16% for surgery alone (no statistically significant difference) (Level 1+). There was no difference in the rate of complete resection or in the recurrence rate. The studies however, had some limitations. They relied on the staging and radiotherapy techniques available at the time. They also included 10% to 15% of patients with small cell lung cancer. Many of the patients may have had undiagnosed systemic disease because 40% - 50% of both arms died within 6 months.

In summary, we only identified two randomised trials, which do not suggest any benefit of routine preoperative radiotherapy.

9.7 Postoperative Radiotherapy

Postoperative radiotherapy has been examined with the hypothesis that cure rates should be improved by reducing local recurrence.

9.7.1 Complete resection

The patients included in this review are those with NSCLC that have undergone complete surgical resection of the primary tumour.

The Cancer Care Ontario Practice Guidelines Initiative have published evidence based guidance[412] for patients with completely resected stages II and IIIA NSCLC, which incorporates and updates a meta-analysis[413] by the Postoperative Radiotherapy Trialists Group (PORT). One additional RCT[414] was retrieved to update this evidence (Table 112). There were 2,000 patients in 12 trials. The results were very similar to the PORT meta-analysis, which found worse survival overall after postoperative radiotherapy and that the adverse effect of post operative radiotherapy was greater for patients with stage I/II N0-N1 disease and less obvious for stage III, N2 disease.

The CCOPGI review found significantly lower recurrence in the group randomised to postoperative radiation ($p<0.01$)[412]. Quality of life was not reported. Radiation related toxicity events were regarded as at an acceptable level. There were no treatment related deaths (Level 1+).

However, a number of criticisms can be made of studies included in the PORT meta-analysis. Seven of the nine studies included in the meta-analysis used ^{60}Co machines rather than linear accelerators (LINACs). This is likely to have implications in the accuracy of targeting the treatment volume and increasing the lung dose. In addition, the doses used were sometimes lower than would be used in modern treatment plans and thus potentially less effective. For these reasons the results of this meta-analysis for patients with stage III should be treated with some caution.

The additional RCT[414] retrieved reported more favourable results with the addition of radiotherapy in stage I NSCLC patients (Table 112). Statistically significant improved outcomes were reported for 5-year disease-free survival (71% versus 60% in control group ($p=0.039$)) and overall survival (67% versus 58% in control group ($p=0.048$)). There were no treatment related deaths reported (Level 1+).

In summary, despite these results from a recent RCT[414], the meta analyses have shown that there is still no strong evidence to recommend routine postoperative radiotherapy. However, for patients with stage III NSCLC, modern radiotherapy may possibly afford benefits in term of local control without the toxicity seen with earlier treatments; further randomised trials are need in this area.

9.7.2 Incomplete resection

Intuitively, postoperative radiotherapy where there has been incomplete resection of the primary tumour should be helpful in NSCLC patients. However, there is very little evidence in this area.

A systematic review[398,415], found only two studies[416,417] prior to 2000, each of which included around 30 patients with incomplete resection (Table 113). These two studies were not controlled, but reported encouraging five-year survival figures of 78% and 23% for N0 patients with positive resection margin. (Level 3) Our literature search uncovered no studies since 2000. Therefore, there is weak evidence that postoperative radiotherapy in patients with incompletely resected NSCLC may improve local control.

9.8 Postoperative Chemoradiotherapy

Postoperative chemoradiotherapy has been used in clinical trials for patients in with stage II and III NSCLC. It is envisaged that the addition of chemotherapy might enhance the effects of radiotherapy.

9.8.1 Effectiveness

A recent review[321] provides the best available evidence for the clinical effectiveness of postoperative chemoradiotherapy versus postoperative radiotherapy. One additional RCT[418] was retrieved. The results are presented in Table 114.

The review[321] of seven trials (807 patients in total) reported that the overall hazard ratio of 0.98 ($p=0.76$) was marginally in favour of chemoradiotherapy although the result was not statistically significant (Level 1+). However, it should be noted that the authors were not able to distinguish between those studies that included patients with complete resection only, incomplete resections only, and those that had a mixture of both. Keller et al[418] reported results from 488 stage II and IIIA patients who had undergone complete resection and were randomised to either postoperative radiotherapy or postoperative chemoradiotherapy. There was no statistically significant difference in median survival (38 months versus 39 months). There was a high incidence of side effects in the chemoradiotherapy arm, although the two arms had similar mortality (Level 1+).

In conclusion, there is not sufficient evidence at present to recommend the routine use of postoperative chemo radiotherapy.

9.9 Primary Chemoradiotherapy for inoperable Non Small Cell Lung Cancer

This section focuses on the use of combination of chemotherapy and radiotherapy for the treatment of stage IIIA, b NSCLC patients (although it is likely that a small proportion of patients within some of the trials had stage I or stage II disease). Chemoradiotherapy can be scheduled either concurrently or sequentially, usually involving chemotherapy first. This section discusses both of these techniques and compares the two approaches.

9.9.1 Patient Eligibility

One systematic review was retrieved which looked at patient eligibility for chemoradiotherapy[419,420]. The results of the systematic review are presented in Table 115.

Individual trials in the systematic review found that performance status was a major independent prognostic factor (see appendix 2, Figure 4 for comparison of Karnofsky and WHO/ Zubrod performance status scales). The review also found inconsistent evidence to identify weight loss as an independent prognostic factor[6] (Level1+).

9.9.2 Sequential Chemoradiotherapy

9.9.2.1 Effectiveness

Table 116 illustrates the retrieved results for effectiveness of non-cisplatin-based chemoradiotherapy (3 trials[292,421,422] , 431 patients). There were no significant differences in the objective response rates in the chemoradiotherapy arms when compared with radiotherapy alone (Level 1+). However, in patients treated with cisplatin based chemotherapy (7 trials[288,423-428] , 1857 patients) a trend toward better response rates was seen (Table 117) (Level1+).

Non-cisplatin based chemoradiotherapy does not improve survival compared with radiotherapy alone (Table 116). However, sequential cisplatin based chemoradiotherapy does (Table 117) (Level 1+). The rate of local control is not altered by use of sequential chemoradiotherapy (Level 1+).

9.9.2.2 Adverse effects

Treatment-related mortality with chemoradiotherapy is rare, averaging about 1% to 3% of all patients and does not appear to differ between treatment strategies Table 116 and Table 117 (Level 1+). Acute haematological toxicity is more common with chemoradiotherapy but is generally well tolerated. The toxicity rates vary depending on the chemotherapy agents and doses, but there is no clear difference based on treatment strategy in making comparisons across studies. Addition of chemotherapy to radiotherapy has not resulted in significantly increased toxicity compared with radiotherapy alone, with the exception of haematological toxicity, nausea and vomiting, which is variable depending on the agents used. Only one study[427] reported that there was more oesophagitis in the chemoradiotherapy arm. It is not known whether adding another treatment modality reduces the dose-intensity of the primary modality.

9.9.2.3 Quality of life

No quality of life data are available on sequential chemoradiotherapy.

9.9.2.4 Conclusion

These data suggest that sequential chemoradiation offers a survival advantage over radiotherapy alone for inoperable stage I to IIIB patients with NSCLC. However, the optimal dose and fractionation of the radiation remains under investigation.

9.9.3 Primary Concurrent Chemoradiotherapy for Inoperable Non Small Cell Lung Cancer

9.9.3.1 Identified evidence

When considering concurrent chemoradiotherapy, all interventions that had a planned overlap in treatment modalities were considered. A recent Cochrane review was retrieved[399]. There were no additional studies identified.

9.9.3.2 Effectiveness

A systematic review and meta-analysis of 14 RCTs, (2393 patients)[399] comparing concurrent chemoradiotherapy and radiotherapy alone reported a reduced risk of death at two-years (relative risk 0.93, p=0.01) and improved two-year locoregional progression-free survival (relative risk 0.84, p=0.03) and progression free survival at any site (relative risk 0.90, p=0.005) (Table 118) (Level 1+). The improvement of survival was more convincingly demonstrated in those receiving once daily radiotherapy or higher total doses of chemotherapy (Level 1+).

9.9.3.3 Adverse Effects

There were more adverse effects in the combination arm, especially oesophagitis. The incidence of treatment-related deaths (less than 1% overall), radiation pneumonitis, pulmonary fibrosis and late oesophageal damage were not increased by concurrent treatment. Anaemia of any grade was more common in the concurrent arm of the 3 trials in which this was reported. However, it should be emphasised that the RCTs included in this review only had limited adverse event reporting in terms of the incidence of late effects.

The NCC-AC did not find any evidence on quality of life.

9.9.4 Comparison of sequential versus concurrent chemoradiotherapy

A Cochrane review[399] compared concurrent and sequential chemoradiotherapy.

9.9.4.1 Effectiveness

A meta-analysis of three trials of concurrent versus sequential treatment was performed as part of the systematic review[399]. All three trials used cisplatin-based regimens and once daily radiotherapy to doses of 60-66Gy (Table 119). This indicated a significant improvement in two-year survival with concurrent as compared to sequential treatment (relative risk 0.86; 95% C.I. 0.78-0.95, p=0.003). Caution must be exercised in the interpretation of these data as these trials are as yet published only in abstract form.

9.9.4.2 Adverse effects

There were more deaths in the concurrent arms (approx 3% overall) but the difference did not reach statistical significance. Acute oesophagitis was more frequent in the concurrent arm. Again, there was limited adverse event reporting for example, for some aspects of toxicity, conclusions were based on only one or two of the three trials (Table 119) (Level 1+).

No evidence covering quality of life was found.

9.9.4.3 Conclusion

There is good evidence from a meta-analysis[399] that primary concurrent cisplatin-based chemoradiotherapy for inoperable stage III NSCLC increases survival compared to radiotherapy alone. However, this may be accompanied by an increased risk of adverse effects, particularly oesophagitis. (Level 1+). Treatment-related mortality is not increased but the effects on quality of life are unknown. It is unclear how this result relates to accelerated treatments such as CHART which is completed in 2 weeks. There is no clear evidence to recommend a particular chemotherapy regimen or frequency of administration.

From comparisons of sequential versus concurrent regimens for chemoradiotherapy, there is evidence of improved survival at two years with concurrent treatment, but this maybe at the expense of added toxicity. However the short follow-up in these studies means that the magnitude of benefit should still be regarded as uncertain. The limited conclusions regarding toxicity and the possible increase in treatment-related mortality mean that concurrent chemoradiotherapy cannot be recommended for routine use at the present time. As the three trials used conventionally fractionated radiotherapy to 60-66Gy, it is unclear how this related to alternative fractionation schedules, such as the 55Gy in 20 fraction regimen in widespread use in the UK or to CHART. (Level 1+).

For the present, the standard of care for patients with stage III NSCLC and good performance status (PS 0-1) is sequential chemoradiotherapy. Patients declining or considered fit enough for radiotherapy but not chemotherapy, may be offered radical radiotherapy alone, preferably CHART (see section 7).

There is insufficient evidence to recommend chemoradiotherapy for patients with stage I/II NSCLC, as very few (£5%) early stage patients were included in studies in the meta-analysis. The reasons for patients in this group being considered "medically inoperable" frequently mean that they would also be considered insufficiently fit to receive chemotherapy.

9.9.4.4 Future Considerations

Future research is needed to explore the potential of drugs other than cisplatin in concurrent regimens and to explore the optimal frequency of administration of cisplatin and other drugs. Quality of life data is essential for the complete evaluation of concurrent regimens. Trials investigating concurrent chemoradiotherapy with alternative fractionation schedules eg 55Gy in 20 fractions or CHART should be supported. Essential features of these trials would include detailed recording of the impact of quality of life and toxicity, particularly anaemia which may have a confounding effect.

Future developments in radiotherapy planning and treatment delivery may offset the added toxicity of concurrent chemoradiotherapy and still permit exploration of higher total radiotherapy doses.

9.10 Pancoast Tumours

Tumours arising in the apex of the chest with chest wall or brachial plexus invasion are known as Pancoast tumours. Over 90% of patients with Pancoast syndrome have non-small cell lung cancer[397]. The treatment of these tumours has been influenced by a report published in 1961 in which neo-adjuvant radiation was used in combination with surgery[397].

9.10.1 Patient Eligibility

One systematic review was retrieved which reported prognostic factors for combination radiotherapy and surgery for pancoast tumours specifically[397] (Table 115). The results reported that vertebral body invasion, subclavian artery invasion, rib involvement and N2, N3 node involvement and Horner's syndrome are poor prognostic factors (Level 3).

9.10.2 Effectiveness

One systematic review[397] was retrieved by the NCC-AC search that reported only survival-related outcomes from studies of combination treatment for Pancoast tumours (Table 121). Our search identified no additional evidence to update this review.

Radiotherapy and surgery results in a five-year survival of 27% (15%-40%). Five-year survival for completely resected patients is 34% (25-44%) (Level 3).

9.10.3 Conclusion

In conclusion, there is great variation in the survival figures for combination treatment for Pancoast tumours. There is an absence of randomised controlled trials of treatment policies in this condition. It is recommended that treatment be guided by stage and performance status as in other cases of NSCLC.

9.11 Economics of Combination Treatment for Non Small Cell Lung Cancer

The combined modality interventions in treatment of NSCLC are often associated with improved outcomes for some patients but increased overall cost, which necessitates the assessment of incremental cost-effectiveness[429].

The four economic analyses on combination treatment for NSCLC (including one abstract) were summarised in Table 122 and Table 123. The included studies compared standard radiotherapy alone with various forms of combined treatment.

Radiotherapy versus different non-conventional radiotherapy with/ without chemotherapy

The only UK study had evaluated the cost-effectiveness of different non-conventional radiotherapy regimens with or without chemotherapy, in comparison to standard radiotherapy[315]. The regimens under consideration were as follows:

1. Standard radiotherapy (60Gy in 30 fractions, 5 per week for 6 weeks).
2. Accelerated radiotherapy (the use of two or more fractions of standard fraction size daily to the same conventional total dose as standard radiotherapy. 60Gy in 30 fractions, 10 per week for 3 weeks).
3. Accelerated radiotherapy + chemotherapy (IV Carboplatin 70mg/m2/day on 1 to 5 days)
4. Hyperfractionated (nonaccelerated) radiotherapy (the use of two or more fractions daily of smaller than conventional fraction size)
5. Hyperfractionated radiotherapy + chemotherapy (cisplatin 20mg, fluorouracil 300mg, VP-16 50mg dys 1-5 and repeated at 4th week of radiotherapy. After radiotherapy, cisplatin 25mg, etoposide 120mg, ifosfamide 2g, uromitexan 3x400mg dy 1-3, all at 6x at 4wk intervals).
6. Split-course (splitting the total dose into at least two separate courses with an interruption of 10 to 14 days) + hyperfractionated radiotherapy +chemotherapy (cisplatin 30mg/m2 , days 1-3 and 28-30 and etoposide 100mg/m2 , days 1-3 and 28-30, or alternatively, cisplatin 60mg, adramycin 40 mg, for ac only + mitomycin 10mg or Epipodophyllotoxin etopside 100mg).
7. CHART (Continuous Hyperfractionated Accelerated Radiotherapy) (the use of many small fractions given over a reduced time. Total radiation is 54 Gy, 1.5Gy fractions-hyperfractionated and 3 fractions given per day for 12 days-accelerated)

The number of LYs gained from each intervention was obtained from seven different trials varying from 36 to 563 patients at various stages of NSCLC.

Among the seven different modalities, two procedures, split-course hyperfractionated radiotherapy with chemotherapy and CHART had a statistically significant survival advantage relative to standard radiotherapy. There was a gain of 1.05 life-years with the split-course hyperfractionated radiotherapy with chemotherapy and 0.27 LY gained with CHART relative to standard radiotherapy alone. The cost per LY gained was £2,311 for split-course hyperfractionated radiotherapy with chemotherapy and £11,227 for CHART, and these two modalities were determined to be cost-effective relative to their comparators (for our own estimate of the cost-effectiveness of CHART see Chapter 7 on radical radiotherapy alone for the treatment of NSCLC).

The literature search identified one abstract that presented the cost effectiveness of concurrent versus sequential chemotherapy and radiotherapy for locally advanced NSCLC patients [430]

The analysis was based on an RCT designed to compare:

> arm A: the induction treatment by platinum (120mg/m^2 day 1, 29 and 57) and vinorelbine (30mg/m^2/week, day 1 to day 78) followed by a thoracic radiation (66Gy); with

> arm B: thoracic radiation (66gy) with two concurrent chemotherapy cycles (platin 20mg/m^2 – etoposide 50mg/m^2, day 1 to 5) followed by two cycles (platinum-vinorelbine).

Direct hospital costs of chemotherapy, radiotherapy, side effects, follow-up, relapse treatments and terminal care until death were calculated. Concurrent chemoradiotherapy resulted in improved life expectancy with a lower cost.

Standard radiotherapy versus induction chemotherapy and radiotherapy

Dillman et al[424] aimed to find out whether chemotherapy before high-dose radiation therapy would have a beneficial effect compared with radiation alone for stage III NSCLC patients in the USA and Canada. The study was non-blinded randomised controlled trial. The duration of follow-up of the treatment cohort was three years.

Patients in the intervention group received cisplatin (100mg/m^2 ,days 1 and 29) and vinblastine (5mg/m^2 , days 1, 8, 15, 22 and 29) and then began radiotherapy on day 50 (60 Gy over a 6-week period). Patients in the control group received the same radiation therapy immediately. Direct costs of chemotherapy and radiotherapy were obtained from a private metropolitan hospital.

The results showed that induction chemotherapy with cisplatin and vinblastine before radiation significantly improved life expectancy (0.49 LY gained) and was found to be cost-effective ($7,143/LY gained).

Evans et al[431] evaluated the cost-effectiveness of the standard treatment of radiotherapy alone versus pre- and postoperative chemotherapy with and without postoperative radiotherapy, and chemotherapy and radiotherapy. LY gained for each type of combined treatments were obtained from retrospective data for stage IIIA patients and from randomised trials for stage IIIB patients.

In order to estimate costs, it was assumed that all patients received two cycles of preoperative mitomycin-vindecine-cisplatin (MVP) (mitomycin 8mg/ m^2 on day 1; vindesine 3mg/ m^2 on days 1, 8, and 22; and cisplatin 120mg/ m^2 on day 1-MVP). Patients who responded to the chemotherapy underwent thoracotomy for surgical resection followed by two further cycles of postoperative MVP for the first modality.

For the second regimen, it was assumed that all patients received three preoperative MVP and that 70% of those patients went on to surgery (complete resection). All patients who underwent surgery received two cycles postoperative MVP and postoperative mediastinal irradiation.

The third intervention for stage IIIB NSCLC patients involved two cycles of vinblastine-cisplatin and then radiotherapy (cisplatin 100mg/ m^2, on 1 and 29 and vinblastine 5mg/ m^2 on days 1, 8, 15, 22, and 29). Then, radiation was given on day 50, 60 Gy over a 6 week period.

All forms of combination therapies in this study improved life expectancy (1.26 LY gained for stage IIIA patients and 1.14 LY gained for stage IIIB patients) relative to radiotherapy alone. The cost per LY gained was Can$9,348 (£4,172) for pre- and postoperative chemotherapy, Can$14,958 (£6,674) for chemotherapy+ surgery +postoperative radiotherapy and Can$3,348 (£1,494) for chemotherapy + radiotherapy.

The sensitivity analysis reducing survival gains from each intervention by 25% and 50%. Although the cost-effectiveness ratio for all interventions increased, they stayed below the Can$20,000 cost effectiveness threshold adopted by this study, except for the second intervention with 50% reduced

survival gain. The second sensitivity analysis was conducted by increasing per diem rates by 10%, 20% and 30%. The impact of different costs of hospitalisation on the cost-effectiveness ratios for all interventions was quite modest. Hence, the cost-effectiveness estimates were robust.

9.11.1 Conclusions and Discussions

The cost-effectiveness studies showed, for specific forms of combination therapy, improvements in life expectancy, and a cost per LY gained that seems fairly low. However, we do not know the overall impact on quality of life associated with these therapies. If we were to assume that there was no overall difference in quality of life and that the average quality of life score is say 0.6 (see NSCLC chemotherapy chapter 8), then the cost per QALY gained would be below £30,000. Alternatively, if the quality of life actually improved with combination therapy, then these therapies are even more cost-effective.

Conversely, if the quality of life worsens with combination therapies due to toxicity, then the cost per QALY gained would be greater than those estimates presented and could exceed £30,000, in which case they are unlikely to be considered cost-effective.

A clearer conclusion can be drawn from the Vergnenegre study[430] since concurrent therapy was both less costly and more effective. However, since this study was reported from an abstract it is difficult to fully assess the validity and limitations of the results. Furthermore, as this was conducted overseas (in France), the resource implications observed may not be applicable to the UK NHS.

The reviewed studies were comparing only standard radiotherapy with other forms of combination therapies. Further studies are needed to compare different forms of combination therapies e.g. CHART + chemotherapy versus CHART.

9.12 Recommendations

9.12.1 Clinical Practice Recommendations

Patients with stage I, II or IIIA NSCLC who are suitable for resection should not be offered preoperative chemotherapy unless it is part of a clinical trial. [B]

Preoperative radiotherapy is not recommended for patients with NSCLC who are able to have surgery. [A]

Postoperative radiotherapy is not recommended for patients with NSCLC after complete resection. [A]

Postoperative radiotherapy should be considered after incomplete resection of the primary tumour for patients with NSCLC, with the aim of improving local control. [D]

Adjuvant chemotherapy should be offered to NSCLC patients who have had a complete resection, with discussion of the risks and benefits. [A]

Patients who are pathologically staged as II and III NSCLC following resection should not receive postoperative chemoradiotherapy unless it is within a clinical trial. [B]

Patients with stage III NSCLC who are not suitable for surgery but are eligible for radical radiotherapy should be offered sequential chemoradiotherapy. [A]

9.12.2 Research Recommendations

Research is needed to compare concurrent chemoradiotherapy with alternative fractionation schedules (such as 55 Gy in 20 fractions or CHART) with sequential chemoradiotherapy for patients with NSCLC. Outcomes measured should include detailed recording of the impact on quality of life and on toxicity.

Further large-scale prospective trials should be conducted into the effect on survival and quality of life of postoperative radiotherapy compared to surgery alone in the treatment of completely resected stage III NSCLC patients.

Prospective randomised controlled trials should be conducted into the effect on survival and quality of life of treatment with preoperative radiotherapy and chemotherapy in the treatment of patients with Pancoast tumours compared to surgery alone.

10 Endobronchial Treatment as Radical Treatment for Non Small Cell Lung Cancer

10.1 Introduction

In this chapter we examine the use of endobronchial techniques in the treatment of early stage non- small cell lung cancer (NSCLC). This section describes the use of these techniques as treatment with curative intent in patients who are unsuitable for treatment with other modalities. Most commonly this is due to comorbidity, particularly poor respiratory reserve. Endobronchial methods are also used commonly in palliative treatment and these will be discussed in the chapter 12 on palliative interventions and Supportive and Palliative Care.

The diagnosis and treatment of in situ carcinomas is outside the scope of this guideline, thus papers have been excluded if they only include patients with in situ carcinoma. However, many of the studies do include a proportion of patients with in situ carcinoma. This may have affected the survival figures measured as these patients are likely to have longer survival untreated than other patients.

10.2 Techniques included in this review

This chapter considers photodynamic therapy (PDT), brachytherapy, electrocautery, cryotherapy and Neodymium-Yttrium Aluminum Garnet (Nd-YAG) laser ablation. This review has looked at endobronchial therapies used for *curative intent* only.

10.3 Methodology

A systematic review by Cancer Care Ontario Practice Guidelines Initiative[432] was found which examined the use of photodynamic therapy in the treatment of early stage NSCLC.

The full search strategy can be found in appendix six.

10.4 Photodynamic Therapy

10.4.1 Technique

Photodynamic therapy (PDT) is based on the interaction of tumour- selective photo sensitizer (mainly porfimer sodium and haematoporphyrin derivative) and laser light of a particular wavelength (around 630nm for porfimer sodium).

There are many applications of the technique in cancer (particularly skin) and other areas. The majority of data in lung cancer is from patients deemed non-surgical candidates or as a palliative intervention. There has, however, been some work looking at treatment of early stage bronchoscopically accessible tumours with curative intent.

10.4.2 Quality and amount of evidence

A total of 49 papers were identified. This included 33 reviews, one RCT, 10 prospective cohort studies, two case series and three other papers. The majority of the papers pertained to use of PDT in late stage NSCLC for palliation. In total 41 papers were discarded for this reason, for non-systematic methods, or because the evidence had been included in a more recent paper or systematic review. Two systematic reviews were identified the most recent being that by the Cancer Care Ontario Practice Guidelines Initiative[432] on photodynamic therapy. Papers included in these reviews were mainly non-controlled observational studies. No randomised controlled trials were found.

10.4.3 Patient eligibility

Papers reporting on PDT for curative treatment included patients with early stage 0 and stage 1 disease. Patients generally were unsuitable for or

refused surgery. Papers looking at palliative treatment and assessment of technique were not included in this section. Two studies included a proportion of patients with in situ carcinoma.

10.4.4 Evidence of effectiveness

The systematic review by the Cancer Care Ontario Practice Guidelines Initiative[432] included evidence from 10 non-controlled observational studies and one summary paper. The results are presented in Table 124. A total of 444 patients were included in the trials. Overall, these methodologically weak studies found a 5 year survival ranging from 44-72% and a complete response rate ranging from 31-85%. Eight out of 10 studies reported toxicity and the most common adverse effect was photosensitivity, most commonly sunburn. The most serious adverse effects reported were respiratory failure and haemoptysis. (Level 3)

No data was found that compared PDT with other techniques, or no treatment.

10.4.5 Conclusions

PDT appears to be effective in managing small superficial squamous cell carcinoma. (Level 3) However, there is no evidence from randomised controlled trials and no comparisons with active supportive care or other treatment options. There is therefore insufficient evidence to recommend photodynamic therapy as a course of treatment in preference to other treatment options at the present time.

10.5 Brachytherapy

10.5.1 Technique

Brachytherapy is the use of a radioactive source within or near an endobronchial malignancy to deliver local irradiation. Iridium-192 is the most commonly used source. It is placed bronchoscopically through a catheter.

10.5.2 Quality and amount of evidence

A total of 51 papers were identified. This included 19 reviews, one RCT, 20 prospective cohort studies, five case series and six other papers. In total 49 papers were discarded for either covering palliative interventions rather than curative treatment, for non-systematic methods or because the evidence had been included in a more recent paper. Two non-controlled observational studies were included[433,434]. No randomised controlled trials were found.

10.5.3 Patient eligibility

Papers reporting on brachytherapy for curative treatment included patients with early stage 0 and stage 1 disease that were unsuitable for treatment with other modalities. Papers looking at palliative treatment and assessment of technique were not included in this section.

10.5.4 Evidence of effectiveness

The evidence is summarised in Table 125. Two non-controlled studies were found with low patient numbers[433,434]. Local control was found to be 75% at one year[434] and 85% at 2 years[433]. Two year survival was found to range from 58%[434] to 78%[433] (Level 3).There was no evidence that compared the use of brachytherapy to no treatment or to other treatment options for this patient group.

10.5.5 Conclusions

The two small non-controlled trials appear to show that treatment with brachytherapy can produce good response and survival results (Level 3), however this evidence is weakened by the low patient numbers involved. There was also no evidence that compared this treatment to other treatment options and therefore brachytherapy cannot be recommended as a first choice of treatment in early stage NSCLC patients.

10.6 Electrocautery

10.6.1 Technique

This technique uses high frequency electrical current, which produces heat from tissue resistance and then destroys tumour cells.

10.6.2 Quality and amount of evidence

A total of 20 papers were identified. This included 11 reviews, one RCT, four prospective cohort studies, one case series and three other papers. In total 18 papers were discarded for non-systematic methods or because the evidence had been included in a more recent paper. One non-controlled study was included in the review[435].

10.6.3 Patient eligibility

Papers reporting on electrocautery for curative treatment included patients with early stage 0 and stage 1 disease. Papers looking at palliative treatment and assessment of technique were not included in this section.

10.6.4 Evidence of effectiveness

There is very little evidence of its effectiveness as a curative therapy for lung cancer. Only one small study, by Van Boxem *et al*, with 13 patients[435] was found. The study found a complete response in 80% of lesions. (Level 3). Please see Table 126 for details.

10.6.5 Conclusions

There is very little evidence for the use of electrocautery in the treatment of early stage NSCLC for curative intent and the technique cannot at present be recommended in favour of alternative treatment modalities.

10.7 Cryotherapy

Cryotherapy involves destroying tissue by freezing. No studies on cryotherapy for curative treatment of invasive NSCLC were found from the literature search.

10.8 Nd YAG Laser ablation

We searched for studies on the use of a Nd YAG laser to cause direct thermal ablation bronchoscopically for attempted curative treatment. No evidence was found that examined the long term outcomes of patients treated this way. This technique has been more extensively used as a palliative intervention (see Chapter 12).

10.9 Economics of Endobronchial Therapy for Non Small Cell Lung Cancer

No studies met the criteria for inclusion. Studies were rejected which only included patients with in situ carcinoma. Other studies were rejected on the basis of relevance and quality.

10.10 Recommendations

10.10.1 Research Recommendations

Further randomised trials should be conducted on the effect on survival and quality of life of endobronchial techniques (photodynamic therapy, brachytherapy, cryotherapy, electrocautery, Nd-YAG laser ablation) used as curative treatment in patients with early-stage NSCLC not suitable for conventional treatment.

11 Treatment of Small Cell Lung Cancer

11.1 Introduction

Approximately 20% of all lung cancers are diagnosed as small cell lung cancer (SCLC). Around 40% of cases are classed as limited stage while the remainder are extensive stage[436] (see Staging chapter 5). Over the years, there have been different definitions of limited stage. Most now follow the IASLC definition of limited stage as disease confined to one hemi thorax (including pleural effusion) plus bilateral hilar or supraclavicular lymphadenopathy. Extensive disease is anything outside of these areas. While this may suggest that the two stages are distinct in terms of the type of treatment offered, there are subsets of patients with extensive disease who may benefit from the same treatment as limited disease. As survival is usually not affected by small differences in the degree of loco regional tumour involvement, selecting the most appropriate treatment is a matter of good or poor prognosis, instead of limited disease (LD) and extensive disease (ED) groups[436].

Evidence on the natural history of SCLC is only available from a small number of historical studies conducted prior to the availability of computed tomography. The results therefore, should be treated with caution as a number of patients considered to have limited stage disease may have been under-staged[436]. A recently published Cochrane review on chemotherapy versus best supportive care in SCLC patients with extensive disease[437] reports results from two trials by Kokron (1977 and 1982) in which patients received chemotherapy with symptomatic treatment (antibiotics and analgesics in the first study and infusion of Ringers solution 3 times/ week in the second study) (Table 128). The trials report that with symptomatic treatment only, survival of SCLC patients ranges between 56 and 93 days.

11.2 Treatment techniques included in this review

This review is confined to chemotherapy, chemo-radiotherapy (both thoracic radiotherapy and prophylactic cranial irradiation- PCI) and the addition of surgery to these treatments.

11.3 Methodology

SIGN reviewed the evidence included in this chapter. The methods are described in section 2.1.2. The search strategy can be found in appendix six.

11.4 Patient Eligibility

One systematic review was identified that examined factors affecting the prognosis of SCLC patients[438] (Table 127). Although such evidence can provide some tentative conclusions on the eligibility of patients for treatment, it does not clearly define how to select patients for treatment. Among the most significant factors consistently associated with poorer survival are poor performance status (WHO > or = 2, - see Appendix 2, Figure 4 for comparison of Karnofsky and WHO/ Zubrod performance status scales) and elevated lactate dehydrogenase levels (LDH) (Level 3). Other prognostic factors of moderate importance are the presence of extensive disease and being of the male sex. Multiple metastatic sites were also reported to be of moderate prognostic significance although too few studies included number of metastatic sites to be confident about this[438]. The significance of raised alkaline phosphate levels, low serum sodium and older age of patients is less well defined (Level 3).

In the UK, treatment decisions are not made on the basis of a single prognostic factor, such as disease

extent but on the number of adverse features. For example SCLC patients with 3-5 adverse features have a substantially worse prognosis than those with 0-2[439]. Prolonged survival is restricted to patients with 0-1 adverse features and these patients are offered more intensive treatments, whereas patients with multiple adverse features have minimal chance of prolonged survival and are offered less toxic treatments with palliative intent. It is important to explain to patients the rationale for recommending different treatments.

In conclusion, while patients with adverse prognostic features do not achieve the same degree of survival benefit as patients with a good performance status and/or normal LDH levels (Level 3), chemotherapy is likely to extend their life expectancy markedly (see 11.5), and these patients can gain excellent symptom palliation with treatment. However, the toxicity of treatment does appear to be higher in poor performance status patients, making patient selection for treatment a matter of clinical judgement.

11.5 Chemotherapy

As SCLC metastasises early, a systemic approach is appropriate for the majority of patients. Chemotherapy remains the mainstay of treating patients with SCLC and its effectiveness is well documented[436].

A recently published Cochrane review[437] on the effectiveness of chemotherapy for patients with extensive SCLC reported that the treatment prolongs survival in comparison with placebo in patients with advanced SCLC (Level 1++) (Table 128). For patients with poor prognosis, the risks and benefits are more finely balanced but the majority of patients will achieve subjective and objective responses, with an overall survival benefit (Level 1++). It can be inferred from the evidence discussed in 11.4 and in the following sections that for patients with limited SCLC, chemotherapy can also prolong survival and produce a response.

11.5.1 Single agent versus multiple agents

Although there are few randomised trials comparing combination and single agent chemotherapy, there is little doubt that combination therapy produces better results. One systematic review[436] including data from three randomised trials reports the evidence on single agent versus multiple agent regimens (Table 129). No additional RCTs were retrieved that update this review.

Lowenbraun et al[440] randomised 68 patients (a majority of whom had extensive disease) to single or combination therapy and reported a statistically significant difference in response rate (12% vs. 59% p< 0.005) and median survival time (18 weeks vs. 31 weeks, p= 0.01)[440] (Level 1+). Girling [441] found similar results from a randomised trial in SCLC patients with poor PS. Statistically significant results again favoured the combination chemotherapy treatment arm in terms of overall response (45 vs. 51%), median survival time (4 months vs. 6months) and 6-month survival (35% vs. 49%) (Level 1+). Souhami et al[442] also demonstrated that oral etoposide was inferior to intravenous combination chemotherapy in patients with poor performance status and extensive disease. Survival was significantly in favour of those receiving IV therapy (5.9 vs. 4.8 months; 1 year survival 19% vs. 10%, p=0.05) and all aspects of symptom control and quality of life (except acute nausea and vomiting) were the same or worse in the single drug (etoposide) arm of the trial.

We can conclude that results from the use of multi-agent chemotherapy yield better responses than use of single agent treatment (Level 1+).

11.5.2 Platinum versus non-platinum containing regimens

While the evidence for combination chemotherapy is clear, the most effective multiple agent chemotherapy regimen is still a matter of debate. Anthracycline-based regimens (e.g. doxorubicin, epirubicin) have often been preferred to platinum-based regimens because they are easier and cheaper to give in the outpatient setting.

Early studies suggested that such regimens were equipotent, but SIGN retrieved a meta-analysis[443]and a RCT[444] to update this evidence (Table 130). The meta-analysis[443] of cisplatin vs. non-cisplatin containing regimens retrieved 19 trials on 4054 lung cancer patients with both extensive and limited disease reported that the response rate for patients in the non-platinum based arm was 62%, while for those patients receiving cisplatin, it was increased to 69% (p<0.0001), with an odds ratio of 1.35 (95%CI 1.18-1.55), $p<10^{-5}$) (Level 1+). In terms of survival, the risk of death at 6 and 12 months for patients were lower in the platinum based arm; OR 0.87 (0.75-0.98, p=0.03) and OR 0.80 (0.69-0.93, p=0.002), respectively. While this meta-analysis however, included limited and extensive disease patients, it did not include studies of carboplatin, so these results cannot be extrapolated to treatment with carboplatin-based regimens. A single RCT [444] was published after the review was retrieved. Sundström et al[444] (2002) randomised 440 patients (approximately half of whom were patients with limited disease) to etoposide and cisplatin or epirubicin, cyclophosphamide and vincristine and concluded that overall the platinum regimen was statistically superior (p<0.0005) both in terms of 2-year survival (14% vs. 6%) and 5-year survival (5% vs. 2%) (Level 1++).

In conclusion, platinum based treatment is more effective for 1st line treatment of SCLC than non-platinum containing treatment regimens (Level 1+). It should also be noted that platinum combinations are associated with less mucosal toxicity, less myelosuppression and are easier to combine with radiotherapy than anthracycline-based regimens.

11.5.3 Cisplatin versus Carboplatin

A systematic review[438] compared the efficacy of carboplatin versus cisplatin (Table 131). Clinical practice currently resides with using cisplatin where survival is the primary aim and carboplatin where palliation is the primary aim. While the trials purport to show equivalence, they are either underpowered or the statistical significance of the difference is unclear (Level 1+).

11.5.4 Duration of treatment

There is evidence from a review reporting the results from several RCTs on the optimum number of cycles of chemotherapy for patients with limited disease SCLC, comparing 3 vs. 6, 4 vs. 8 and 5 or 6 vs. 12[445,446]. This evidence suggests that there is a small survival advantage for longer treatment but it is usually outweighed by the toxicity and burden of prolonged treatment (Level 1+). The compromise to quality of life that additional cycles of treatment can cause means that careful patient selection must take place before advocating more than four to six cycles of treatment. One RCT[447] which updates this review, reported that despite some encouraging results for maintenance therapy in extensive disease patients previously treated with etoposide, ifosfamide plus cisplatin, the significance of these results was not clear.

11.5.5 Dose Intensity

Dose intensity refers to the amount of drug delivered in a given period of time, which is usually standardised to body surface area (mg/m^2/day). It has been demonstrated that increasing the dose intensity results in improved outcomes in studies of some other 'chemo sensitive' cancers. There is a range of methods to achieve an increase in dose intensity. This review was restricted to increasing the dose or decreasing the interval of standard chemotherapy and excludes studies of high dose therapy with haemopoietic stem cell transplantation.

11.5.5.1 Standard Dose Intensity

A systematic review[436,438] was retrieved by SIGN reporting results of conventional methods of dose intensification for patients with limited and extensive disease (Table 133). One meta-analysis[448] within this review reported a retrospective analysis of the results of the intended dose of 60 studies, using a variety of different chemotherapeutic regimens and so, is of very limited value. No statistically significant results were found in relation to objective response, complete response or median survival time (Level 1+). Several more recent studies have prospectively evaluated the effects of increasing cytotoxic dose intensity in RCTs. An RCT[449] also within the review, evaluated and reported the effect of the *delivered* dose intensity in limited disease patients (300mg/m^2 cyclo days 1-4 and 100mg/m^2 cis) vs. 225 mg/m^2 cyclo days 1-4 and 80 mg/m^2 cisplatin, in conjunction with same doses of doxorubicin, etoposide and radiation in both arms) with more favourable results although, this study examined the effect of higher doses for the first treatment cycle only. At 6 months, the complete

response rate and the median duration of this response significantly favoured the dose-escalated arm. Overall survival was improved at 30 months and 2- year disease free survival was also superior, although there was increased toxicity within this arm (Level 1+). These results for increasing dose intensity are reflected in a later trial on patients with good prognostic factors[450]. None of the additional four phase three trials[451-454] on patients with extensive disease within the review[438] showed a survival advantage in the dose intensive arm and this arm often resulted in greater toxicity. An additional RCT[455], retrieved by the SIGN literature search, reported results of both limited and extensive stage patients. There was no significant difference in terms of survival, response and toxicity between the high-dose platinum arm compared to the carboplatin alone arm (Level 1+).

11.5.5.2 Dose Intensity with the Addition of Growth Factors

A systematic review[438] and four RCTs[456-459] were retrieved on the effectiveness of dose intensification with the addition of growth factors (Table 134). Several RCTs[460-462] within the review, with the exception of Steward et al[463] failed to demonstrate improved survival with more dose intensive support (Level 1+). Sculier et al[457] reported that there was no evidence that patient outcomes improved when patients were randomised to either standard chemotherapy with 6 courses of EVI (epirubicin 60 mg/m^2, vindesine 3 mg/m^2, ifosfamide 5 g/m^2) given on day 1 repeated every 3 weeks versus accelerated chemotherapy with EVI administered every 2 weeks and GM-CSF support versus accelerated chemotherapy with EVI and oral antibiotics (cotrimoxazole) (Level 1++). Mavroudis et al[456] randomised patients to either TEP (paclitaxel 175 mg/m^2 i.v. three-hour infusion on day 1, cisplatin 80 mg/m^2 i.v. on day 2 and etoposide 80 mg/m^2 i.v. on days 2-4 with G-CSF support (5 mcg/kg s.c. days 5-15) versus standard EP (cisplatin 80 mg/m^2 i.v. on day 1 and etoposide 120 mg/m^2 i.v. on days 1-3) in cycles every twenty-eight days but it was reported that TEP option was too toxic for routine use and the study was terminated early due to excessive toxicity and mortality in this arm. Thatcher et al[458], randomised patients to receive six cycles of ACE either every 3 weeks (control [C] group) or every 2 weeks with G-CSF (G group), standard dose of-intensity of ACE was increased by 50% in group G. The results concluded that increasing the dose-intensity of ACE with G-CSF support improved survival while maintaining acceptable toxicity. In the final trial retrieved[459]. patients were randomised to either standard CDE (cyclophosphamide 1,000 mg/m^2 and doxorubicin 45mg/m^2 on day 1 and etoposide 100mg/m^2 on days 1 to 3 every 3 weeks for 5 cycles) or intensified CDE (cyclophosphamide 1,250mg/m^2 and doxorubicin 55mg/m^2 on day 1, and etoposide 125mg/m^2 on days1 to 3 with G-CSF 5µg/Kg/d on days 4 to 13 every 2 weeks for 4 cycles). The authors reported that the dose intensity arm did not produce improved outcomes in SCLC patients.

Although some of these results seem encouraging, the evidence is neither clear nor sufficient to confidently recommend dose intensification. However, it is recognised that delays or dose reductions resulting in a lower cytotoxic dose intensity are likely to reduce the potential benefits of chemotherapy treatment.

11.5.6 Alternating versus sequential treatment strategies

Multi-drug regimens may be administered in two ways; either concurrently or alternately to maximise their potential for tumour eradication. The alternation of drugs acting through different ("non-cross resistant") mechanisms was postulated to reduce the opportunity for drug resistance to develop, and expected to improve outcomes [464]. This section will review the evidence for this in SCLC.

One systematic review retrieved by the SIGN literature review reported outcomes relating to the appropriate timing and delivery of chemotherapy (Table 135). The ten RCTs within the systematic review[436] analysed, together report that alternating chemotherapy regimens do not have a major effect on survival in limited stage patients (Level 1+). A sub-group analysis of the trials that used either CAV (Cyclophosphamide, Doxorubicin and Vincristine) or EP (Etoposide and Cisplatin) within the review produced mixed results (Table 135). While two of the trials, Fukuoka et al[465] and Feld et al[466], reported that improved response and survival rates were seen with the alternating regimens, only one of the trials reported that these reached statistical significance. Goodman et al[467] and Woll et al[462] on the other hand, reported that no difference in outcomes were seen in the alternating arm (Level 1+).

Although some differences in effectiveness were seen in the regimens used and the duration of treatment, there is insufficient evidence to recommend alternating chemotherapy (Level 1+).

11.5.7 Second Line Chemotherapy

It is generally believed that second line chemotherapy will only be of benefit to patients if a good response is achieved by first line treatment. In addition, the best results are obtained in patients who have at least 3 months between the best response achieved and progression[436].

A systematic review[438] was retrieved on the effectiveness of second line chemotherapy and no trials were retrieved to update this review. Gillenwater et al[438] reviewed a number of single and combination regimens and reported that the overall response rates range from 6-46% for single agents and 18-72 for combination regimens[436] (Table 136) (Level 1+). It should be noted that these response rates are at least as good as those for 1st line chemotherapy in advanced NSCLC.

In conclusion, the response rates and response duration that can be expected of second line treatment are generally poorer than those seen with 1st line treatment (Level 1+). As always, the burden of treatment on the patient should be considered when the magnitude of benefit is uncertain. Second line chemotherapy should be offered to patients who have achieved a response to first line treatment and discussed on an individual basis.

11.5.8 Conclusion

Chemotherapy is the initial treatment of choice for small cell lung cancer and can increase survival even in poor performance status patients. IV multi-drug regimens and regimens containing platinum are superior. Initial chemotherapy should comprise 4-6 cycles of treatment as maintenance therapy has not consistently been shown to improve overall survival.

Relapse of disease can be treated by chemotherapy but second line treatment response rates are poorer and the balance of benefit and toxicity should be discussed with the individual patient. Those who responded well to first line treatment and who had a disease free interval respond best.

11.6 Radiotherapy

Small cell lung cancer is a radiosensitive tumour and thus radiotherapy plays an important role in its treatment. Radiotherapy given as part of the initial treatment program has the potential to increase disease control in irradiated sites and as relapse may sometimes be limited to the chest or brain, there is also the potential for radiotherapy to improve survival. Here we consider consolidation thoracic irradiation and prophylactic cranial irradiation. Lower dose palliative radiotherapy given for the relief of symptoms is covered in chapter 12.

11.6.1 Thoracic irradiation

One recent systematic review[436] was retrieved on the effectiveness of thoracic radiotherapy. This review included seven randomised studies with over 100 limited disease patients (Table 137). While there is some heterogeneity in the results of these trials, they suggest a median survival benefit of approximately 1 month and a 6% improvement in 2-year survival with the addition of radiotherapy (chemotherapy alone: 13% vs. the addition of radiation: 19%) (Level 1+). In addition, a statistically significant improvement in local control was reported in all the studies although the manner in which each trial reported these results differed (Level 1+). Two earlier meta-analyses[468,469] that were not limited to RCTs randomising over 100 patients have supported these findings (Table 137). The meta-analysis of 13 RCTs by Pignon et al[469] showed that the addition of radiotherapy reduced the risk of death by 14% equivalent to a 5.4% increase in absolute 3-year survival. A similar improvement was shown in the meta-analysis of 11 studies by Warde and Payne [468] (Level 1+).

In terms of intrathoracic control, in a meta-analysis of nine RCTs, Warde and Payne[468] demonstrated an absolute improvement of 25% with the addition of radiotherapy, an improvement that was associated with a 1.2% absolute increase in the risk of treatment related mortality (Level 1+).

In a randomised study of thoracic irradiation in 210 patients with extensive stage SCLC achieving a complete response at distant sites and complete or partial response in the chest (mostly CT-based), the addition of thoracic irradiation increased 5-year survival from 3.7% to 9.1%[470].

The majority of RCTs from which evidence of the effectiveness of thoracic irradiation is derived were carried out in the 1970s and 1980s when the standard method of response assessment was the chest x-ray. Most patients were eligible for these studies if they were deemed to have had a complete response to chemotherapy. CT is now recognised as being vastly superior to assessment by chest x-ray alone and will identify variable amounts of disease not apparent on chest x-ray. Indeed some patients included in these studies of limited disease may have had more widespread disease, which would have been defined as extensive by CT.

The situation is further complicated by the variety of ways in which thoracic irradiation can be delivered. Options include giving thoracic irradiation following completion of chemotherapy or with the final cycle of chemotherapy (i.e. "late") or earlier in the treatment programme, commonly concurrently with the first or second cycle of chemotherapy ("early"). There is also uncertainty regarding the optimal dose and fractionation of radiotherapy.

Patients with limited disease require discussion with a clinical oncologist prior to commencement of chemotherapy to assess the feasibility of subsequent thoracic irradiation. Disease should not be so bulky as to result in an unacceptable high risk of lung damage. As poorer survival has been observed in patients with SCLC who have treatment interruptions during radiotherapy[471] or who smoke during radiotherapy[472], every effort should be made avoid these factors (see Table 139). Smoking during and after treatment is also discussed in chapter 13.

Patients with limited disease SCLC (and some with extensive disease SCLC) should therefore be considered for thoracic consolidation therapy if they have a CT based complete or a good partial response to chemotherapy.

11.6.1.1 Radiation dose and fractionation

A systematic review[436] retrieved only one RCT[473] that examined whether there is a dose response relationship for the addition of radiotherapy (Table 138) and one RCT comparing hyperfractionated with conventional radiotherapy[474] (Table 139).

Coy et al[473] randomised 168 patients who had either a complete response or partial response to chemotherapy to either 25Gy in 10 fractions over 2 weeks or 37.5Gy in 15 fractions over 3 weeks. Although there was no difference between the two arms in terms of complete response rate or overall survival, the higher dose arm did demonstrate an improvement in median local disease-free progression (11 months vs. 9 months, p=0.03) and in 2-year local disease-free progression survival (80% vs. 69%, p=0.03)[473] (Level 1+).

Turrisi et al[474] randomised 417 patients to receive either 45Gy of twice-daily radiation (1.5Gy fractions) over a period of 3 weeks or daily radiation over 5 weeks (in fractions of 1.8Gy) with concurrent cisplatin and etoposide (Table 140). While a statistically significant difference in survival was reported in favour of the more intensive (i.e. hyperfractionated) arm, it is not clear whether this was due either to a higher biologically effective dose in the hyperfractionated arm, or the hyperfractionation or scheduling itself[474]. The incidence of oesophagitis was also higher in the hyperfractionated arm.

A third RCT[475] randomised 262 patients receiving 3 cycles of etoposide plus cisplatin to either once daily thoracic radiation (50.4Gy in 28 fractions) or twice daily 48Gy on 32 fractions). The authors also reported that there was no improvement with twice daily irradtiation although it was not clear if the trial was powered to detect a difference.

While the optimal dose and fractionation of radiotherapy remains unclear, most clinical oncologists recommend a dose in the range of 40Gy/ 15 fractions over 3 weeks to 50Gy/ 25 fractions over 5 weeks. This dose has been used in an RCT of early versus late radiotherapy[476] see Table 138.

11.6.1.2 Timing and sequencing of chemotherapy and radiotherapy

The optimum timing in the delivery of radiotherapy and chemotherapy remains uncertain. A systematic review[436] included the results from five trials, in addition to two RCTs[477,478] retrieved with more recent data (Table 141).

A single trial of alternating chemoradiotherapy with sequential treatment showed no significant difference between arms[479]. The remaining trials compared early versus late radiotherapy using a range of radiotherapy doses and fractionation. In the "early" trials, radiotherapy was given concurrently with the first or second cycle of chemotherapy. In the remaining trial[480] radiotherapy was delivered prior to commencement of chemotherapy. "Late" radiotherapy was given concurrently with the fourth to sixth cycle of chemotherapy except in two trials when it was given following completion of chemotherapy[477,480]. Two trials indicated a benefit for early radiotherapy[476,481]. Two trials updated this review. While Skarlos et al[478] reported that the sample was small and there were no significant difference in findings, Takada et al[477] reported that while there were no significant difference in median survival or PFS, there was a trend in trend in favour of the concurrent arm.

Since conducting this review a recent Cochrane review[482] (unpublished at the time of writing) has found that there was no statistically significant difference between early and late radiotherapy and between concurrent and sequential chemoradiotherapy for SCLC. A conclusion cannot therefore be made specifying the optimal timing and sequencing of chemotherapy and radiotherapy for SCLC patients.

11.6.1.3 Conclusion

In limited stage SCLC, thoracic irradiation may therefore be given to patients concurrently with the first or second cycle of chemotherapy or to patients following completion of chemotherapy if there has been at least a good partial response within the thorax (Level 1++). While the optimal dose and fractionation of radiotherapy remains unclear, most clinical oncologists recommend a dose in the range of 40Gy/ 15 fractions over 3 weeks to 50Gy/ 25 fractions over 5 weeks.

For patients with extensive disease, thoracic irradiation may be considered following chemotherapy if there has been a complete response at distant sites and at least a good partial resonse within the thorax (Level 1+).

Radiotherapy should be delivered without interruption and patients should be actively encouraged to stop smoking prior to therapy.

11.6.2 Prophylactic Cranial Irradiation

The central nervous system is a recognised sanctuary site for micrometastases and cytotoxic drugs penetrate the blood-brain barrier poorly. Isolated brain metastases are a significant cause of failure in those who have had a complete response to initial therapy. Prophylactic cranial irradiation (PCI) attempts to eradicate microscopic disease in patients without symptoms of brain metastasis. The aim is to treat the group with highest risk of the brain being the sole site of metastasis, as they are the ones who could benefit from PCI. PCI is therefore usually considered for patients with limited disease who have had a complete or good partial response to primary treatment.

There is less evidence pertaining to the effectiveness of PCI in patients with extensive disease.

11.6.2.1 Effectiveness

Studies conducted during the 1970s and 1980s on the effectiveness of PCI provide limited data due to the lack of statistical power of the randomised data. In addition, these studies were based on patients with complete response judged by chest x-ray. A systematic review[483] was retrieved and there were no RCTs to update this evidence (Table 142). This meta-analysis of 987 patients randomised in 7 RCTs concluded that while PCI reduces the risk of brain metastasis by 54%, the risk of death is reduced by

16% (P=0.01) contributing to an increase in 3-year survival of 5.4% (20.7% vs. 15.3%) (Level 1++). The meta-analysis reported that there was no evidence of differential benefit with age or radiation dose, although there was a trend to lower rates of brain metastases with higher radiation doses. (Level 1++). In addition, the benefit of PCI appeared independent of disease extent, although only 14% of patients in the analysis had extensive disease and therefore the magnitude of benefit in patients with extensive disease should still be regarded as uncertain. There were no significant differences in neurocognitive function in an RCT[479] comparing PCI with no PCI. Although doses used in trials reported in the meta-analysis by Auperin[483] were most commonly 24-30Gy in 8-10 daily fractions, the regimen in most frequent use currently is 25Gy in 10 daily fractions. Further trials are examining the benefits of higher doses of PCI.

PCI is generally given following completion of chemotherapy and may be delivered at the same time as thoracic irradiation if this is also being given following chemotherapy. The meta-analysis by Auperin[483] also showed that PCI was more effective if commenced sooner (less than 4 months) rather than later after randomisation, indicating that PCI should not be unduly delayed following completion of chemotherapy (Level 1++).

11.6.2.2 Conclusions

In conclusion, limited disease SCLC patients should be considered for PCI if they have a CT based complete or a good partial response to primary treatment. Benefit is unclear for patients with extensive disease and the guideline development group recommended that these patients should be entered into clinical trials.

There is insufficient evidence to recommend a definite dose schedule.

11.7 Surgery for patients with SCLC

The majority of patients with SCLC present with systemic disease precluding surgery with curative intent. The role of surgery in SCLC is limited and to very specific groups of patients. Patients may undergo a surgical procedure and only on examination of the operative specimen the disease may appear to be SCLC or planned treatment may very occasionally be offered to patients with stage I SCLC usually after neo-adjuvant chemotherapy. Surgery has been used as a salvage treatment for those patients who have either relapsed or failed to respond to primary treatment involving chemotherapy and radiotherapy.

SIGN retrieved one RCT and three observational trials that reported results on the addition of chemotherapy to surgery. Lad et al[484] reports results from an RCT on the addition of surgical resection of the primary tumour following a complete or partial response to chemotherapy (see Table 143). As the authors point out, the 146 patients randomised were an unusually favourable population (82% of patients were PS 9+ on the Karnofsky scale, 92% had lost £ 10% body weight), this is reflected in the overall survival rate of 20% (Level 1++). Comparing the two treatment groups, pulmonary resection did not influence the pattern of relapse and survival actually favoured the non-surgical group by three months (Level 1++).

Table 143 shows three further observational studies[485-487]. Although the results of the trials reporting results on patients undergoing postoperative chemotherapy were favourable in terms of survival time, they were also conducted on small groups of atypical patients with less advanced disease (Level 2++).

In summary, there is insufficient evidence to recommend surgery for this group of patients.

11.8 Economics of the treatment of SCLC

Four studies were selected for tabulation (Table 144 and Table 145). Since the treatment of side-effects of chemotherapy is out of the scope of this guideline, we excluded studies on haematopoietic growth factors which were being used for treatment of chemotherapy side effects (reducing infections and neutropenic fever). Most of the remaining evidence was limited in terms of the treatments compared and was mainly concerned with chemotherapy.

11.8.1 Single agent / multiple agent Chemotherapy

Khan et al[387] conducted a cost analysis on the use of carboplatin versus cisplatin in treatment of patients with NSCLC, SCLC and ovarian cancer to determine which treatment has potential cost savings. The results showed that chemotherapy with cisplatin was less costly ($203) than carboplatin for limited and extensive stage of SCLC patients. Hospitalisation costs ($574± 1,197 with carboplatin, $475± 858 with cisplatin) and costs for chemotherapy agents ($7,280 ± 2,685 for carboplatin, 5,507 ± 3,725 for cisplatin) were higher with carboplatin treatment than treatment with cisplatin. Costs of growth factors ($992 ± 2,596 with carboplatin, $1,448 ± 3,266 for cisplatin) were higher for cisplatin. The results should be treated with caution due to high standard errors reported associated with each cost category and small number of patients in the study. The applicability of the results to the UK practice is uncertain: carboplatin is given as an outpatient basis in the UK and growth factors are not typically used.

The objective of Doyle et al's[488] study was to identify whether the use of etoposide phosphate with cisplatin due to its ease of administration resulted in cost-savings compared to etoposide with cisplatin. The analysis was based on clinical data obtained from a randomised controlled trial of cisplatin plus either etoposide phosphate or etoposide [489]. The use of etoposide phosphate saved $737 per patient. When the time savings of ease of administration of etoposide phosphate were added into the model, use of etoposide phosphate reduced the cost per patient by $2,897.

11.8.2 Alternating versus sequential chemotherapy treatment

A cost-effectiveness analysis on sequential versus alternating chemotherapy was conducted alongside a two year randomised controlled trial of cyclophosphamide, doxorubicin and vincristine alone or alternating with etoposide and cisplatin for the treatment of patients with extensive SCLC [490]. The use of alternating chemotherapy was associated with increased survival (0.13 years) and improved quality of life (0.10 QALY) with Can$450 (£190) additional cost. The additional cost per LY gained was Can$3,370 (£1,354) and cost per QALY gained was Can$4,500 (£1808) with alternating chemotherapy. The cost effectiveness of alternating chemotherapy was favourable when compared with standard chemotherapy. However, the clinical evidence did not show clear overall results in favour of alternating chemotherapy (see section 11.5.6).

11.8.3 Platinum versus non-platinum containing regimens: an original cost-effectiveness analysis

The literature search identified no economic studies that compared platinum based drugs regimens with non-platinum based drugs for SCLC. Therefore we conducted a simple cost-effectiveness analysis based on a well-conducted RCT as follows.

Sundstrom et al[444] reported a Norwegian RCT with five-year follow-up. The data were analysed separately for limited and extensive disease. The regimens compared were:

- Etoposide and cisplatin (EP) (up to 5 courses): Day 1 IV – etoposide 100mg/m^2 & cisplatin 75mg/m^2; Days 2&4 oral – etoposide 200mg/m^2
- Cyclophosphamide etoposide vincristine (CEV) (up to 5 courses): Day 1 IV – epirubicin 50mg/m^2, cyclophosphamide 1000 mg/m^2, vincristine 2 mg/m^2

Most patients had the full five cycles and the main reason for failure to complete was death. For patients with limited disease the trial reported significantly longer survival for EP. There was no significant between-arm difference in quality of life or in use of radiotherapy or prophylactic cranial irradiation.

Drug costs were taken from the British National Formulary[491] (assuming body surface area =1.8m^2) – see Table 146. The other assumptions are listed in Table 147.

Platinum-based drug regimens appear to be cost-effective for patients with both limited and extensive SCLC (compared with a threshold of £30,000 per QALY gained) – see Table 148 and Table 149. The sensitivity analysis (Table 150) suggests that the results for patients with limited disease are robust to

changes in the model parameters. The results for extensive disease would be much more sensitive due to the lack of significance in the treatment effect.

These results may be imprecise because actual hospital utilization was not measured. Also, although there were no significant differences in either radiotherapy or prophylactic cranial irradiation there may have been other differences not recorded by the trial, e.g. additional costs associated with treating side-effects, additional services during extended years of life or perhaps patient costs. The trial was not conducted on a UK population but there is no reason to assume that treatment effect would be markedly different.

11.8.4 Prophylactic Cranial Irradiation (PCI)

The clinical and cost-effectiveness of PCI was investigated using ten year retrospective data of patients with limited SCLC who had achieved a complete remission[492]. The mean overall survival improved by 13.5 months (11.2 months quality-adjusted) when PCI was used in conjunction with chemotherapy and radiotherapy. This strategy was cost-effective; the cost per LY gained was Can$840 (£350) and cost per QALY was Can$1,020 (£423). These results must be treated with caution because the improvement in survival from this small study (13.5 months) was much greater than the improvement implied by the Cochrane review (4 months using the DEALE method[313,314]). This would still be cost-effective compared with a cost per life-year threshold of say £20,000 as long as the incremental cost of PCI is below £6,000.

11.8.5 Conclusions and discussion

The economic evidence indicated that:

- platinum-based drug regimens can be cost-effective, especially for patients with limited disease
- cisplatin was found to be slightly less costly than carboplatin in one US study
- the use of PCI in conjunction with chemotherapy and radiotherapy appears to be cost-effective

The results should be interpreted cautiously because they were based on trials conducted outside the UK NHS. Hence treatment effects, resource outcomes and especially prices may not strictly be applicable. Furthermore, most of the studies did not report the clinical outcomes separately for the stage of disease.

11.9 Recommendations

11.9.1 Clinical Practice Recommendations

Patients with SCLC should be offered an assessment that includes evaluation of the major prognostic factors: performance status, serum lactate dehydrogenase, liver function tests, serum sodium, and stage. [D]

All patients with SCLC should be offered:

- **platinum-based chemotherapy [A]**
- **multidrug regimens, because they are more effective and have a lower toxicity than single-agent regimens. [A]**

Four to six cycles of chemotherapy should be offered to patients whose disease responds. Maintenance treatment is not recommended. [A]

Patients with limited-stage SCLC should be offered thoracic irradiation concurrently with the first or second cycle of chemotherapy or following completion of chemotherapy if there has been at least a good partial response within the thorax. For patients with extensive disease, thoracic irradiation should be considered following chemotherapy if there has been a complete response at distant sites and at least a good partial response within the thorax [A]

Patients undergoing consolidation thoracic irradiation should receive a dose in the range of 40 Gy in 15 fractions over 3 weeks to 50 Gy in 25 fractions over 5 weeks. [D(GPP)]

Patients with limited disease and complete or good partial response after primary treatment should be offered prophylactic cranial irradiation. [A]

Second-line chemotherapy should be offered to patients at relapse only if their disease responded to first-line chemotherapy. The benefits are less than those of first-line chemotherapy. [D(GPP)]

11.9.2 Research Recommendations

Clinical trials should be conducted to determine to benefit of prophylactic cranial irradiation compared to no prophylactic treatment in terms of survival and quality or life for patients with extensive disease SCLC and a complete response at distant metastatic sites and a complete or good partial response within the thorax after treatment.

12 Palliative Interventions and Supportive and Palliative Care

12.1 Introduction

This chapter focuses on palliative interventions and supportive and palliative care specifically for patients with lung cancer. This is a priority because most patients diagnosed with lung cancer have incurable disease and while effective treatment is often available, symptoms are often poorly evaluated and managed[493]. It is essential therefore, that the impact of lung cancer and its symptoms on the patient's psychological, social and physical state including activities of daily living are identified early and that patients are referred to the appropriate specialist for further assessment, if required. In this chapter we have reviewed the evidence on palliative interventions and palliative care specific to lung cancer patients. This chapter will also highlight supportive care services, including communication, in relation to patients with lung cancer which are important throughout the patient's journey.

12.1.1 Improving Supportive and Palliative Care for Adults with Cancer

The National Institute of Clinical Excellence (NICE) has recently published guidance and recommendations to improve supportive and palliative care for adults with cancer[494]. 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. It is based on the following principles of both supportive and palliative care:

Supportive care:

'...helps the patient 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 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.' [494]

It covers a range of issues relevant to people with cancer and their carers, including:

- self help and support
- user involvement
- information giving
- psychological support
- symptom control
- social support
- rehabilitation e.g. appliance officers, dietitians.
- complementary therapies
- spiritual support
- palliative care
- end-of-life and bereavement care.

Palliative care is:

'...the active holistic care of patients with advanced progressive illness. Management of pain and other symptoms and provision of psychological, social and spiritual support is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families. Many aspects of palliative care are also applicable earlier in the course of the illness in conjunction with other treatments.' [494]

Palliative care is based on the following principles:

- To provide relief from pain and other distressing symptoms
- Integrate the psychological and spiritual aspects of patient care
- Offer a support system to help patients to live as actively as possible until death and to help the family cope during the patent's illness and in their own bereavement
- Be applied early in the course of illness in conjunction with other therapes to prolong life (such as chemotherapy and radiotherapy), including investigations to better understand and manage distressing clinical complications

The professions involved in providing these services and aims, fall into 2 distinct categories:

- Those providing day-to-day care to patients and carers in the community or in hospitals.
- Those who specialize in palliative care (consultants in palliative medicine and clinical nurse specialists in palliative care for example), some of whom are accredited specialists.

Specialist palliative care teams require:

- palliative medicine consultants
- palliative care nurse specialists
- a team secretary/administrator

and a range of expertise provided by:

- physiotherapists
- occupational therapists
- dietitians
- pharmacists
- social workers
- chaplains/spiritual care givers
- professionals able to deliver psychological support as defined by the NICE guideline on Supportive and Palliative Care[494]

The Guideline Development Group strongly supports this guidance[494], in particular, the emphasis on:

- The responsibility of all professionals to provide high quality 'general' supportive and palliative care
- The need for a multidisciplinary approach
- The importance of good communication
- The timely involvement of specialist services when patients supportive and palliative care needs are not being met.

12.1.2 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 cava obstruction. Thoracic symptoms have been subdivided into management of dyspnoea (breathlessness), including malignant pleural effusion, non-obstructive airway symptoms (cough, haemoptysis, hoarseness and chest pain) and superior vena cava 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 Guideline Development Group to be of particular importance and the Group 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 palliative treatments, 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 cava obstruction, hypercalcaemia of malignancy). We have 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. Although we identified studies that review palliative interventions, surprisingly few include measures of quality of life.

The GDG are aware that the methodology followed has highlighted a lack of *specific* evidence relating to the management of many of the common symptoms experienced by patients with lung cancer. Subsequently this section may appear to ignore a number of approaches in common use, e.g. opioids for breathlessness. As a result the GDG would like to stress:

> this section can not be nor was intended to be a comprehensive or textbook account of the management of physical, psychological, other symptoms or problems encountered by patients with lung cancer

> that an absence of this level of evidence does not imply that nothing can be done to help

> the important role of the supportive and palliative care multidisciplinary team, in particular specialist palliative care teams in symptom control

The guideline development group felt they should highlight the importance of prompt referral and treatment for specialist palliative care services and made the following good practice point:

> Patients who may benefit from specialist palliative care services should be identified and referred without delay

12.2 Tools included in this review

Many techniques are included in this review, reflecting the diversity of symptoms, underlying causes and treatments available:

> Communication with patients with lung cancer

> Management of dyspnoea (breathlessness): bronchoscopy, laser treatment, photodynamic therapy, stents, treatments for breathlessness caused by malignant pleural effusion (pleural drainage, thoracentesis and pleurodesis by sclerotherapy agents), cryotherapy, brachytherapy, external beam radiotherapy and non-drug methods (e.g. psychosocial support, breathing control methods, coping strategies)

> Management of cough: palliative radiotherapy for cough and haemoptysis, antitussive therapy (opioids), treatment for cough caused by malignant pleural effusion (pleural drainage, thoracentesis and pleurodesis by sclerotherapy agents)

> Management of hoarseness: surgery

> Management of chest pain: palliative radiotherapy and treatment for chest pain caused by pleural disease

> Management of superior vena cava obstruction: chemotherapy or radiotherapy or both; stents, steroids

> Management of neurological symptoms (brain metastases): corticosteroids, whole brain radiotherapy, surgery and chemotherapy

> Management of pain caused by spinal cord compression: corticosteroids and radiotherapy; and surgery

> Management of pain caused by bone metastases

> Management of other symptoms (weight loss, loss of appetite, depression and difficulty with swallowing).

12.3 Methodology

The search for evidence of the effectiveness of palliative interventions was undertaken by NCC-AC and is in appendix six. The search for palliative care and communication was carried out by SIGN, and is in appendix six.

The search for the evidence referred to in this chapter was restricted to patients with lung cancer. The Guideline Development Group's collaborators, SIGN, found no research evidence assessing the effectiveness of different treatments for symptoms such as weight loss, loss of appetite, difficulty with swallowing and depression, specific to lung cancer patients but the GDG wanted to make good practice points as specific treatments are available for lung cancer patients which are detailed in section 12.13.

12.4 Communication

No evidence regarding the information needs of lung cancer patients specifically was retrieved by the SIGN literature search. In the light of recommendations from sources based on other patient groups however, the guideline development group wanted to make good practice points. The group also felt that communication was such an important issue that the recommendations made should appear early on in the guideline and as such, they can be found in the Access to Services chapter (3.6).

Government guidelines state that patients and their carers should be offered accurate, clear, full and prompt information that is culturally sensitive in both verbal and other means accessible to the patient, at every stage of the care pathway[495-498]. Good communication and adequate information can help reduce anger and anxiety, and improve patient confidence[499,500]. Information needs will vary depending on the particular patient, their age and individual knowledge base, carer, stage of disease, and performance status.

Information can be given in oral, audio taped, video taped, or written format, depending on patient preference, and availability of literature. The NHS Cancer Plan (2000)[495] states:

"All NHS Trusts and cancer Networks are being required to make high quality information available to all cancer patients. Information must be culturally sensitive and specific to local provision of services as well as information about the type of cancer and treatment option"

It is important for health care professionals not to assume what the patient knows, and to check out level and extent of knowledge. Facts may not always be remembered in the way they were given. Studies show that some patients only remember a tenth of what they were told during a consultation[495]. Effective communication between health care professionals across the primary/secondary interface is essential and should include:

> Patient problems

> What the patient was told

> What the patient understood (where possible)

> Management plan

> Involvement of other agencies

> That patients should not be given bad news by letter and only by phone in exceptional circumstances

The Nursing Contribution to Cancer Care (2002)[501] states that for site-specific cancers in a cancer unit or cancer centre, a clinical nurse specialist should be provided to support patients and carers.

12.4.1 Discussions at diagnosis:

Ideally the patient's partner or family member should be present, unless the patient specifically requests otherwise, in addition to a nurse or another healthcare professional. Information, both verbal and written (supported by any other format the patient prefers), should include, whenever possible, details of the stage of disease, treatment options

(including no treatment) and aims of treatment (which will include chances of cure and prognosis)[502,503] and information on supportive care e.g. diet. Patients should be given time to ask questions. The nurse (specialist nurse, when available) plays a vital role. For example, she/he provides support to the patient and relative(s) and can reiterate or clarify information.

12.4.2 Discussions regarding treatment options:

Patients may require clarification of treatment options, and time to consider these and to discuss with whomever they feel appropriate as well as further information in order to give informed consent.

12.4.3 Discussions regarding relapsed disease:

Patients should have the opportunity to be accompanied by a carer. Informing a patient of relapsed disease should be seen as breaking bad news, and approached as such. It is important that patients have the opportunity to ask questions, discuss treatment options and aims of treatment, which will include prognosis when desired by the patient and whenever possible. A realistic discussion of how the aims of a person's treatment can change and a re-evaluation of individual prognosis may be appropriate.

12.4.4 Discussions regarding end of life care:

This is a sensitive issue and may or may not involve the palliative care team. Patients should be given a choice about their end of life care and discussion about this issue should happen early in the course of their palliative treatment. Aims of treatment and care should be discussed with full involvement of the carer and other health care professionals as appropriate.

For more detailed recommendations regarding communication and provision of information, see the NICE Supportive and Palliative Care Guidance[497].

USEFUL LUNG CANCER PATIENT INFORMATION AND SUPPORT RESOURCES

There are many ways of finding out more about lung cancer. There are many booklets and internet sites available. Below are a few examples:

1. USEFUL INFORMATION BOOKLETS ON LUNG CANCER

The Roy Castle Lung Cancer Foundation
Freephone 0800 358 7200
Booklets –
" So You Have Just Been Told You Have Lung Cancer" (Personal thoughts from lung cancer patients and carers designed to address initial questions after diagnosis)
" Lung Cancer – Answering Your Questions" (A 50 page booklet answering most of the commonly asked questions relating to lung cancer)

Cancer BACUP
Freephone 0808 800 1234
Booklets –
" Understanding Cancer of the Lung" and other booklets on many aspects of cancer treatment and care, including Complimentary Therapies, Fatigue, Hair Loss and Diet.

British Lung Foundation
Leaflet –
" Living with Lung cancer. The facts (Nov 2002) This leaflet explains what lung cancer is, and provides information on diagnostic tests and treatment. Copy free with an SAE to the British lung foundation, 73-75 Goswell Road, London, EC1V 7ER. www.lunguk.org/index)

2. USEFUL BOOKLETS ON SYMPTOM CONTROL AND PALLIATIVE CARE

Cancer BACUP
Freephone 0808 800 1234
A number of booklets specifically for symptom control such as *" Controlling symptoms of cancer"* and *" Controlling pain"* and *" Dying with Cancer"* looking at practical and emotional issues that surround dying with cancer. Also, *" Coping at home- caring for someone with advanced cancer"* which is about services that can be accessed in the community. Also see the " Q&A" section that covers different questions on lung cancer. www.bacup.org.uk

3. USEFUL INFORMATION ON BREATHLESSNESS

Cancer BACUP
Freephone 0808 800 1234
Factsheet– " Management of Breathlessness" .

The Roy Castle Lung Cancer Foundation
Freephone 0800 358 7200
Booklet – *" A Practical Guide To Breathlessness"*; Video – " Take A Breather"

4. SOME USEFUL WEBSITES

It is difficult to monitor the quality of information on a website. If in doubt, patients should ask their nurse or doctor for further clarification on good quality websites that might be appropriate for their situation.

www.bacup.org.uk
www.nhsdirect.nhs.uk
www.alcase.org
www.macmillan.org.uk
www.roycastle.org
www.cancerresearchuk.org
www.patient.co.uk
www.mariecurie.org.uk
www.lungcanceronline.org
www.graylab.ac.uk
www.dipex.org

5. ADDITIONAL LUNG CANCER PATIENT SUPPORT

There are many different organisations which work with the NHS to provide support and information for lung cancer patients. Listed below are a few such organisations:

The Roy Castle Lung Cancer Foundation
Network of monthly Lung Cancer Patient Support Groups. Through its Information Line, provides contact details for local lung cancer nurses throughout the UK.
Freephone Helpline 0800 358 7200.

Benefit Enquiry Line
Provides information and advice about social security benefit entitlement
Freephone 0800 88 22 00

Cancer BACUP
Helps patients, their families and friends, to live with cancer. For information and support from cancer nurses, freephone 0808 800 1234.

Macmillan Cancer Relief
Services include Macmillan Nurses, doctors, cancer care and information units. Also, financial help for individuals, through patient grants.
Information Line 0845 601 6161.
The Macmillan CancerLine is open Mon-Fri 9am-6pm on 0808 8082020.

Marie Curie Cancer Care
Runs hospice centres throughout the UK, and a community nursing service to support cancer patients and their carers in their homes.
Telephone 0207 599 7777

The British Lung Foundation
Runs a network of Breathe Easy Patient Support Groups for patients with all types of lung disease.
Telephone 020 7688 5555

The NHS Smoking Helpline
Offers down to earth help and advice to people who want to stop smoking.
Freephone 0800 358 7200

12.5 Management of Dyspnoea (Breathlessness)

12.5.1 Introduction

Three-quarters of lung cancer patients experience dyspnoea at some time and this rises to around 90% in their last month of life[504]. It has a number of causes and is a distressing and sometimes life threatening symptom, the palliation of which can be of major benefit to the patient[505]. Each treatment is appropriate for a slightly different group of patients and is discussed independently. The effectiveness of non-drug interventions is assessed alongside medical treatments. The effectiveness of surgery is not reviewed as no evidence was retrieved.

Where malignant pleural effusion is the underlying cause it should be treated as described in section 12.5.6 below.

12.5.2 Physical De-bulking via the Rigid Bronchoscopy

Although rigid bronchoscopy (including the mechanical removal of the tumour) has been undertaken for several decades, there is relatively little published data reporting detailed outcomes. A single, recent systematic review[505] was retrieved, which described one case series of rigid bronchoscopy for lung cancer patients (see Table 151). Of the 56 patients, 62% were treated electively and 86% had mostly endoluminal tumours involving the trachea, carina, or main stem bronchi. The study reported a success rate of 91%, measured by both symptomatic assessment and bronchoscopy. The palliation of symptoms however, does depend on the location of the tumour. In patients with lobar obstruction for example, there was a 38% success rate compared with over 90% in patients with tracheal or main stem bronchial lesions (Level 3). Complications occurred in 20% of patients. The patient group was unusual in that 28% went on to have open surgical resection. Median survival of the remainder was six months (Level 3).

12.5.3 Laser Treatment

Historically the CO_2 laser was first used to treat airway lesions. This method suffers from a limited ability to coagulate bleeding and can only be transmitted in a straight line. Most of the published data involves the use of the Nd-YAG laser, which can be transmitted through a flexible or rigid bronchoscope.

Our search identified a single, recent systematic review[505] reporting four case series (which total more than 2,500 patients) achieving palliation of dyspnoea in 80% of patients (see Table 152). Success was influenced by the location of the tumour: 70-95% of patients with central lesions, 40-60% of patients with lobar obstruction and 57% of patients with complete occlusion of the airway (Level 3). Almost all patients had endoluminal tumours while patients with extrinsic compression were generally excluded. Symptom relief was measured using a combination of symptomatic assessment and bronchoscopy. This procedure was reported to have a mortality of 0.4%-3% and complications, including haemorrhage, in 3% of cases[505]. Between 50-60% of patients were retreated 3-4 months later; median survival was 6 months[505](Level 3).

12.5.4 Photodynamic Therapy

Photodynamic therapy (PDT) involves the administration of a photosensitiser, which is taken up by tumour cells. Subsequent exposure to light of a particular wavelength induces cell death. Light from PDT is reported to penetrate to a depth of 5-10mm, making tracheobronchial tumours well suited to this treatment. Routine bronchoscopic debridement typically follows treatment.

Our search identified two systematic reviews[505]; [506] and a recent case series. The first systematic review identified two case series meeting its inclusion criteria of having more than fifty patients[505]. The second review[506] incorporated 12 case series[506] with a total of 636 patients (see Table 153). One large study (175 patients) was included in both reviews. The first review found that photodynamic therapy temporarily palliated breathlessness in 60% of patients although palliation is much higher (80%) in patients with strictly endoluminal tumours (Level 3). There is a 4% one month mortality rate and 2% risk of major haemorrhage[505] (Level 3). The second review[506] reported skin photosensitivity (sunburn) in 5%-28%, haemoptysis in up to 18% in addition to

post-treatment cough, expectation of necrotic debris and dyspnoea which were noted by many authors. Nevertheless it concluded that almost all patients had relief of dyspnoea and cough along with an improvement in lung function. The recent study, a prospective case series of 40 patients, used PDT with hyperbaric oxygen and reported improved dyspnoea in all but one patient and improved haemoptysis in 10 of the 12 patients experiencing this[507] (Level 3).

12.5.5 Stents

A number of airway stents are available for the palliation of dyspnoea. These include silastic stents for the trachea or main stem bronchi, silastic Y stents for use at the carinal level and expandable metal stents that can be used in the trachea and the main bronchi. Stents are commonly used in patients with endoluminal obstruction and extrinsic compression.

Our search identified a recent systematic review (describing three case series) and a further two case series[508,509] (see Table 154). The systematic review[505] reported the success rate of endoluminal stents in three case series (413 patients) to be 90%. The majority of patients had central tumours and severe obstruction (Level 3). Stents placed at lobar level are often not as successful as those placed for central lesions[505]. The mortality of the procedure is reported as 0% to 7% with complications such as stent migration and mucus retention occurring in 10-20% of patients (Level 3).

These high levels of relief have also been observed in later case series of 34 and 14 patients with the most severe levels of breathlessness (for example as an emergency procedure)[160,508] (Table 154).

12.5.6 Pleural Effusion

Breathlessness due to pleural effusion may be relieved by needle aspiration or more completely by drainage with a tube left indwelling for a period of time. Recurrence in days or weeks is common, so symptomatic relief is usually temporary. Any symptomatic benefit gained may be extended by pleurodesis. Our review of the literature found no data on the use of pleural drainage or pleurodesis that was specific to lung cancer. However, we identified one guideline[510]and two systematic reviews[511,512] that examined pleural effusion in mixed populations (Table 155).

Recent guidelines by the British Thoracic Society[510]covered the management of malignant pleural effusions resulting from various primary tumours. Based on the evidence from their literature search and the experience of the expert group they found that chest tube drainage via an intercostal tube should be considered as the first line of treatment followed by chemical pleurodesis, for patients where a chest x-ray shows that there is complete lung re-expansion[510] (Level 1+). Our guideline development group considered that this result, based on a general population of patients with malignant pleural effusion, could be applied to lung cancer patients. However, lung cancer patients are more likely to have a collapsed or obstructed and therefore non-functioning lung and drainage of fluid may not lead to an improvement in breathlessness. The grade of the recommendation has therefore been extrapolated to a Grade B to reflect this.

A recent Cochrane systematic review[511] examined the results from 36 RCTs on pleurodesis and a systematic review by Tan et al[512] examined 227 papers (including 45 RCTs and 98 observational studies) on pleurodesis. The Cochrane review[511] concluded that there was evidence for three statements (Level 1++):

> A sclerosant instilled into the pleural space is more effective than placebo or tube drainage alone.

> Talc was associated with less recurrence than any other agent

> Thoracoscopic pleurodesis was more effective than bedside tube pleurodesis where talc was used

The systematic review by Tan et al[512] concluded similarly on these questions but was a more exhaustive review of the details of implementation and provides further details (Level 1+):

> Protracted tube drainage is not more effective than earlier tube removal.

> Rolling and tipping the patient does not confer advantage.

> Tube size is not important. Smaller tubes are as effective as larger ones

No data specific to lung cancer were found; most studies included a mixture of patients and did not break down the results by disease. Both reviews found that talc was the most effective agent. Again, the Guideline Development Group considered that it was reasonable to apply this finding to lung cancer patients although the recommendation would be downgraded to a grade B to reflect the fact that the target population of the studies was not specifically lung cancer patients.

12.5.7 Cryotherapy

Cryotherapy is the rapid freezing of tissue, which destroys tumour cells then debrided over several bronchoscopic procedures. Our search identified a recent systematic review[505] that described three case series (411 patients) (See Table 156). Palliation was 65-68%, with greater palliation in patients with central lesions compared to those with peripheral lesions (60% vs. 35% respectively). There is currently no data on the durability of results[505] (Level 3).

12.5.8 Brachytherapy

Brachytherapy is the delivery of radiation from an endobronchial source. A catheter is placed across the lesion, loaded with the appropriate radiation source, and this remains in place until the prescribed dose has been delivered.

Our search identified three RCTs[493,513,514] on the effectiveness of endobronchial brachytherapy alone (see Table 157), although one was underpowered to detect any differences in the treatments compared. Stout et al[493] randomised patients to either endobronchial brachytherapy or external radiotherapy and reported that both treatments produced good levels of symptomatic relief although they were better for external radiotherapy at the expense of more acute morbidity. While late side effects were similar, improved survival was recorded in the radiotherapy arm, which was statistically significant (Level 1+). One other trial was retrieved which combined endobronchial brachytherapy with radiotherapy. Langendijk et al[515] reported that the combination of techniques provides higher rates of

expansion of collapsed lung resulting in transient lower levels of dyspnoea and importantly, there is no significant increased risk of fatal haemoptysis .

12.5.9 External Beam Radiotherapy

External beam radiotherapy is the most common palliative treatment modality, received by between 20-30% of patients with lung cancer[516]. Our search identified two systematic reviews[516,517] and one RCT[518] (See Table 158). The first, a Cochrane systematic review[516] of ten randomised controlled trials compared different radiotherapy regimens (See Table 158). This found that symptoms improved under all regimens. There was no strong evidence that higher dosages gave greater palliation overall (lack of consistent reporting and assessment in the individual trials prohibit greater detail) although there was evidence of greater toxicity with higher doses. Recommended dosages are 10 Gy in one fraction or 16-17 Gy in 2 fractions although there is some evidence that higher doses produce a modest survival benefit in patients with good performance staus (Level 1++). The more recent review[517] did not identify any additional studies. A recent randomised controlled trial[518] of 230 patients comparing 10Gy in a single fraction or 20Gy in five fractions found similar levels of symptom relief (Level 1+).

12.5.10 Non-drug treatment

SIGN identified one recent UK RCT[519] assessing the effectiveness of a nurse-led clinic for the palliation of breathlessness that offered breathing control, activity pacing, relaxation techniques and psychosocial support (see Table 159). The weekly clinic was compared with best supportive care over an 8 week period. Performance status and symptoms universally deteriorated in the control group but were generally maintained in the intervention group. This was statistically significant for five of the11 outcome measures; breathlessness at best (Visual Analogue Scale (VAS) scale), performance status, depression (Hospital Anxiety and Depression (HAD) scale), physical symptoms (Rotterdam symptom checklist) and an activity subscale (Rotterdam symptom checklist). The research group considered the mechanism may be the emphasis on teaching more effective ways of coping with breathlessness and

the opportunity to talk about difficult feelings and concerns. Such non-drug approaches appear to be of benefit to patients with dyspnoea (Level 1+).

The Guideline Development Group considers that such non-drug treatments should be delivered by a multidisciplinary team, facilitated or co-ordinated by a professional with an interest in breathlessness and the necessary expertise in the techniques (e.g. nurse, physiotherapist, occupational therapist or other). Although it may be provided within a breathlessness clinic, patients should have access to such support wherever they are. In addition, there is scope to improve the efficacy of non-drug treatments and this is an area that requires further research.

12.5.11 Summary of management of dyspnoea

Comparison between the treatments is not straightforward because evidence is typically from non-randomised retrospective studies, outcomes are not measured systematically and many patients receive more than one type of intervention. Unfortunately a MRC randomised trial designed to answer this question failed to recruit sufficient patients[514]. The authors of the systematic review[505,520] that identified the most evidence on each intervention concluded that the acute mortality and morbidity for all the interventions for obstructive airway management are similar[505] (Level 3). Our search identified a single randomised trial comparing endobronchial brachytherapy with external radiation for the relief of breathlessness, cough and haemoptysis[493] (see Table 160). This found that both treatments relieved symptoms of cough, haemoptysis and breathlessness (59%, 85% and 78% for endobronchial brachytherapy, and 59%, 90% and 66% for external radiotherapy respectively). Median survival was higher with external radiotherapy (287 vs. 250 days). Interestingly, 28% of those receiving external radiotherapy went on to have endobronchial treatment (at a median 304 days) whereas 51% of those in the endobronchial group subsequently had external radiotherapy (at a median 125 days) (Level 1+).

In deciding the best course of treatment for a patient presenting with dyspnoea the authors of the recent systematic review[505] described above concluded the following issues should be considered (Level 4):

- Location of obstruction: trachea; main stem bronchus, bronchus intermedius; lobar, segmental
- Nature of obstruction: endoluminal, mixed, extrinsic
- Urgency
- Technical issues: ease for patient, durability of relief, availability of equipment and expertise, depth of penetration into tissue.

Whether or not the above interventions are undertaken, non-drug approaches appear to benefit patients with dyspnoea.

12.6 Management of Cough

Four in five lung cancer patients (79%) experience cough and a third (35%) experience haemoptysis[504,520].

12.6.1 Palliative radiotherapy for cough and haemoptysis

Our search identified a Cochrane systematic review (described above) and a later randomised controlled trial. The Cochrane systematic review[516](see section Table 158) reported the effectiveness of low dose radiotherapy in palliating a range of thoracic symptoms, including cough and haemoptysis (the outcomes for each symptom were combined in the results)(Level 1+). The first of the later RCTs (Table 158) found no difference in outcome with immediate treatment or delaying treatment until required for symptom relief for patients with previously untreated NSCLC that is locally too advanced for resection or radical radiotherapy with curative intent, minimal thoracic symptoms and no indication for immediate thoracic radiotherapy (Level 1+). The other RCT[518] favoured a fractionated regimen over a single dose (Level 1+).

12.6.2 Antitussive therapy for cough

Our search identified a systematic review on the management of cough[521] and a later double-blind, randomised controlled trial (see Table 161).

Each randomised, double-blind, placebo controlled trial within the systematic review had 79 patients and compared codeine and dextromethorphan to placebo. Both found cough reduced significantly (Level 1++). The later randomised controlled trial[522] of 140 lung cancer patients with a documented history of non-productive cough (at least 5 coughs per hour) compared the effectiveness of a non-opioid (although levodropropizine is not available in the UK) to an opioid antitussive (Level 1+). Cough severity scores (graded by both the patient and assessor) showed a significant decrease with treatment but no significant difference between the drugs. Opioid and non-opioid anti-tussives are effective in the treatment of cough (Level 1+). In UK clinical practice, generally codeine is used, and if ineffective, substituted for morphine.

12.6.3 Pleural drainage, thoracentesis and pleurodesis for malignant pleural effusion

Cough may also be a symptom of malignant pleural effusion. The effectiveness of treatment for this is discussed in section 12.5.6 above.

12.6.4 Summary of management of cough

Cough and haemoptysis (among a group of undifferentiated symptoms) are improved by palliative radiotherapy, both external and endoluminal. There is no strong evidence that higher doses of radiotherapy are associated with better or longer lasting palliation[516]. Cough is also reduced by opioid and non-opioid anti-tussives[521,522]. Cough caused by malignant pleural effusion can be treated as discussed in section 12.5.6.

12.7 Management of Hoarseness

About one in ten patients experience some hoarseness of their voice (11%)[504]. Our search identified only one, uncontrolled, trial of a surgical treatment (vocal cord medialisation for unilateral paralysis) which improved symptoms of hoarseness[523] (Level 3) (see Table 165). The Guideline Development Group observed hoarseness due to left recurrent laryngeal nerve involvement very rarely responds to external beam radiotherapy and recommends that cases should be referred to an ear nose and throat specialist for assessment.

12.8 Chest pain

A third of patients (37%) experience chest pain during their last 12 months of life, rising to approximately half during the last month[504]. Pain should be evaluated carefully in order to identify the underlying cause and provide the most appropriate treatment. Management includes explanation of the symptom to the patient (also addressing their concerns), treating the underlying cause when possible, (e.g. radiotherapy) non-drug and drug approaches. If pain is not progressively improving over a 1-2 week period (less if severe), advice should be obtained from specialists in palliative care or pain.

12.9 Superior Vena Cava Obstruction

12.9.1 Introduction

Superior Vena Cava Obstruction (SVCO) is due either to a tumour 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 1.7% of patients with NSCLC[524]. Traditional management of SVCO includes systemic corticosteroids (e.g. dexamethasone) and either radiotherapy (more commonly used for NSCLC) or chemotherapy (generally for SCLC). More recently, with the development of endovascular stenting, an expandable stent placed percutaneously in the SVC to relieve compression and restore blood flow, has been increasingly used. Our search identified a recent Cochrane systematic review[524] (see Table 162) on the treatment of SVCO by steroids, radiotherapy, chemotherapy and stents which drew on two randomised trials and 44 non-randomised studies, most of which were retrospective.

12.9.2 Chemotherapy and/ or Radiotherapy

The Cochrane review identified two relevant randomised trials. Based predominantly on non-randomised trials the review found that chemotherapy and/or radiotherapy relieved SVCO in 77% of patients with SCLC. Of those treated, 17% had a recurrence of SVCO. In NSCLC, chemotherapy and/or radiotherapy relieved SVCO in 60%, with 19% of those treated having a recurrence. In addition, the review noted that rates of relief of SVCO were very similar for chemotherapy and for radiotherapy in both cell types; 77% and 78% respectively for SCLC and 59% and 63% in NSCLC. Effectiveness was not clearly related to any particular radiotherapy fractionation schedule or chemotherapy regimen (Level 2++)

12.9.3 Stents

The Cochrane review[524] described fewer, smaller (15 patients or fewer) non-randomised studies of patients treated with stenting (Table 162). The review found that insertion of an SVC stent relieved SVCO in 95%, with 11% of patients developing recurrent SVCO. However, recanalisation was often achievable with a resulting long-term patency of 92%. The use of anticoagulation during and after insertion varied between studies, with most using heparin during placement, and some reporting use of warfarin following insertion. The systematic review could not conclude whether a particular policy of subsequent anticoagulation resulted in fewer stent thromboses, though morbidity following stent insertion was greater if thrombolytics were used (Level 2++).

12.9.4 Corticosteroids

Although corticosteroids are often used in high doses and short courses to treat SVCO along with radiotherapy, neither the Cochrane review[524] nor our search identified studies that examined the effectiveness of corticosteroids in SVCO.

12.9.5 Summary of the management of SVCO

Although largely based on retrospective and non-randomised studies the Cochrane review[524] concluded that chemotherapy and radiotherapy are effective in relieving SVCO and that stent insertion appears to provide relief in more patients more rapidly. The effectiveness of corticosteroids remains uncertain.

12.10 Management of Brain Metastases

12.10.1 Introduction

Brain metastases occur frequently in patients with lung cancer, especially SCLC, and have a profound effect on both quality of life and survival. Headaches (40%), motor deficits (36%), seizures (27%), disorientation (24%) and lethargy (16%) account for the vast majority of presenting symptoms[505]. Treatment is generally palliative, although occasionally it may be given with curative intent.

Aggressive treatment of the metastasis is by resection; treatments with a palliative intent include corticosteroids and whole brain radiotherapy (WBRT). Our search identified one systematic review[520] and two guidelines[525,526] relevant to this topic. Many of the studies of brain metastases involve patients with a variety of types of cancer, but lung cancer accounts for the majority (see Table 163).

12.10.2 Corticosteroids

Corticosteroids reduce symptoms caused by cerebral metastases (including headache, focal or generalised seizures and motor or sensory deficits) by reducing cerebral oedema. A recent systematic review[520] and a guideline[525] found corticosteroids palliate symptoms in the short term for most patients[525] although complications arise in approximately 30%[520] (longer term side effects were not reported). The median survival of patients with brain metastases is one or two months when treated with corticosteroids alone[520] (Level 3) (see Table 163).

12.10.3 Radiotherapy

Palliative whole brain radiotherapy (WBRT) may be offered to improve symptoms. Improvement in neurological symptoms can be seen in half of patients after 2 weeks and three-quarters after 4 weeks[505]. A recent systematic review examined seven randomised trials (4,104 evaluable patients)[505]. Dosage ranged between 12 Gy to 54 Gy, with between 1.6 and 6 Gy fractions. Many of the studies included some patients who had primary cancers at sites other than the lung. Median survival is approximately four months (range 2.5 to 5.3 months)[505] (Level 3) (See Table 163). Nevertheless, progressive brain disease remains the cause of death in approximately 40% of patients receiving WBRT[520]. A previous guideline states that corticosteroids and radiotherapy could be considered for headache due to cerebral metastases[526](Level 4).

12.10.4 Surgery

Resection of a solitary brain metastasis is currently sometimes considered for NSCLC patients who have undergone complete resection for the primary tumour and who have no other sites of metastases. Without treatment survival is very short[505].

Ten case series involving 565 patients were retrieved by a systematic review which reported median survival of 11 months (2 year survival 28%)[520]. Where a complete resection was achieved median survival increased to 20 months and two year survival increased to 41% (226 patients)[520] (see Table 163).

12.10.5 Chemotherapy

Although it has been assumed that chemotherapy drugs pass the blood-brain barrier poorly, a recent systematic review[520] commented that small scale series of NSCLC and SCLC patients had responses similar to those with tumours located elsewhere (Level 3). A previous guideline states that chemotherapy is effective at reducing pain caused by cerebral metastases in SCLC patients[525] (Level 4).

12.10.6 Summary of management of brain metastases

The results from a systematic review[520] and guidelines[525,526] indicate that corticosteroids and whole brain radiotherapy are effective in palliation of lung cancer patients with a single brain metastasis. There is some evidence that chemotherapy also reduces pain caused by cerebral metastasis[520,525].

12.11 Spinal Cord Compression

12.11.1 Introduction

Compression of the spinal cord, typically by metastatic epidural tumours, 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 [527]. Many types of cancer metastasise to the spinal column, but in relation to lung cancer the commonest cause is SCLC, with the majority of epidural metastases found in the thoracic region [528].

12.11.2 Corticosteroids, radiotherapy and surgery

Our search identified a systematic review[505] reporting one (underpowered) randomised controlled trial[529] and three case series[528,530,531] and two later case series[532,533] (see Table 164). The retrospective studies describe the combined outcomes of corticosteroids, radiotherapy and surgery. These include improved symptoms[533] and regaining (22%[528]) or retaining ambulatory status (Level 3). These studies concluded that any treatment of spinal cord compression should be initiated rapidly; treatment within 12 hours is associated with functional recovery[532]; conversely the studies observe a lack of recovery of functions of patients presenting with the severest symptoms (e.g. paraplegia)[528,530,533] (Level 3).

Although not based on analysis of prognostic factors the systematic review[505] suggests surgery should be considered in certain contexts: patients who have received previous irradiation to the area; patients who experience progressive neurological deterioration while receiving radiation; and for patients with symptomatic spinal instability or bone fragments causing compression[505] (Level 4).

12.11.3 Summary of management of spinal cord compression

Radiotherapy remains the mainstay of managing patients with spinal cord compression, with some evidence of its effectiveness in palliating pain and improving or at least preserving neurological function. Although there are no comparative studies surgery continues to be a largely supportive treatment in managing patients with specific symptoms (Level 3).

Patients with spinal cord compression should have treatment within 24 hours. Corticosteroids, radiotherapy and surgery where appropriate, should be administered. Patients with spinal cord compression should also have early referral to the physiotherapist and occupational therapist for assessment, treatment and rehabilitation. Referral to the occupational therapist should be made for wheelchair assessment, assessment of activities of daily living and home assessment (GPP).

12.12 Hypercalcaemia, Bone Pain and Pathological Fractures

As one of the most frequent sites of metastasis in lung cancer patients, bone metastases present either as painful lesions or as pathological fractures. An HTA report has been published on treatments for hypercalaemia[534]. Methods of treating bone metastases include radiotherapy, bisphosphonates and nerve blocks. After sifting and appraisal, there were no studies retrieved from our search to evaluate the effectiveness of these treatments that were confined to lung cancer patients only. A small number of RCTs on patients with a combination of primary sites however, did provide sufficient breakdown for lung cancer patients, although the results are extremely limited, both in terms of the numbers of patients and the outcomes reported, as they are sub-analysis of papers. To supplement this type of data, where appropriate, we extrapolated using the results of systematic reviews of RCTs of mixed primaries. Such reviews were primarily made up of patients with breast and prostate cancer and it is envisaged that bone metastases resulting from different primaries will respond in a similar way to interventions.

12.12.1 Radiotherapy

12.12.1.1 Effectiveness

Results on the effectiveness of radiotherapy on pain from bone metastasis were obtained from a Cochrane review[535] and an RCT[536], both of which reported results of cancer patients with a combination of primary sites (Table 166). Within the Cochrane review, radiotherapy was compared to an assumed rate of one in 100 patients having naturally resolving pain and the authors found that radiotherapy produced complete pain relief at one month in 25% of patients and at least 50% pain relief in 41% of patients at some time during the trial (Level 1++). In addition to these results, Salazar et al [536] reported that a total of 91% of patients responded to therapy, 45% achieving complete pain relief (Level 1+). In terms of adverse events, the Cochrane review[535] reported no obvious difference between the fractionation schedules in the incidence of nausea and vomiting, diarrhoea or pathological fractures although they acknowledged that the reporting of adverse effects was poor in the studies included (Level 1++).

12.12.1.2 Time to and Duration of Relief

The Cochrane review[535] also reported results on the time to pain relief. SIGN's literature review retrieved one additional RCT[536] which reported results on the time taken to maximum pain relief from three different radiotherapy treatment plans; A) 3Gy's fractions for 5 days, B) 2 fractions (6-8hrs apart) of 4Gy each in a single day, and C) 3Gy twice daily (6-8hrs apart) on two consecutive days (Table 167). The RCT reported that while the average time to any pain relief was three days, there was no statistical difference between any of the arms in terms of average time to maximum pain relief (range 6-9 days) or percentage of patients achieving net pain relief (Level 1+). The Cochrane review[535] reported that half of patients who achieved complete relief took more than 4 weeks and that median duration of relief was 12 weeks (Level 1++).

12.12.1.3 Single versus Multiple Fractions

The Cochrane review[535] and two RCTs[537,538] reported results on single vs. multiple radiotherapy fractions (Table 168). Steenland et al[538] examined the effectiveness of a single fraction of radiotherapy against a total dose of 24Gy given in six fractions of radiotherapy on almost 300 patients with lung cancer. The single dose arm produced favourable results, both in terms of complete response (28% vs. 19%) and percentage of patients with progression (55% vs. 46%) although the statistical significance of these results was not reported. In terms of the percentage of retreatments needed however, the arm of the trial undergoing multiple fractions of radiotherapy had many less (5% vs. 32%) although, again the significance of this result is not clear (Level 1+). The Cochrane review[535] and Sarkar et al[537,538] also reported that no difference was seen in terms of single fraction vs. multiple fractionation schedules (Level 1++) and so single fractions are appropriate in most circumstances.

12.12.2 Bisphosphonates

No RCTs were retrieved for lung cancer patients or which included a breakdown of results for lung cancer patients only. We identified two systematic reviews[539,540] on the effectiveness of bisphosphonates for the relief of pain and skeletal morbidity from bone metastases from a combination of primary sites. However, the GDG felt that such evidence could not be extrapolated to lung cancer patients[539,540]. The findings of Ross et al[539] suggested that benefit was apparent only after 6 months of treatment; this raises the question of their usefulness in patients with a shorter prognosis. The second review, Wong and Wiffen[540], reported that although there was some evidence for the effectiveness of bisphosphonates (Table 169), there was not enough to recommend them for first line treatment and their relative effectiveness for different neoplasms was inconclusive. Further research is required.

12.12.3 Conclusion

In conclusion, guidance exists (e.g. SIGN pain guidelines[526]) for standard treatments such as analgesics for the relief of symptoms from bone metastasis from all types of cancer which is not reviewed here. These standard treatments should be administered as first line treatment before more invasive treatment. If such interventions are insufficient, single fraction radiotherapy should be administered.

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

Other symptoms experienced by large numbers of patients that require palliative treatment and care include fatigue, weight loss, loss of appetite, difficulty with swallowing and depression. The Guideline Development Group's collaborators, SIGN, found no research evidence assessing the effectiveness of different treatments for these symptoms specific to lung cancer patients.

The Group recommends that for all symptoms there should be a multidisciplinary approach. This multidisciplinary group will include occupational therapists, physiotherapists and dieticians whose particular roles are outlined below. If the patient has unmet physical, psychological, social or spiritual needs despite this general palliative care approach, referral should be made to a specialist palliative care service, which will include access to counselling provision[494].

12.13.1 Occupational Therapists,Physiotherapists and Dieticians

The importance of a multidisciplinary approach in general and for rehabilitation in particular for patients with cancer has been highlighted in the NICE Supportive and Palliative Care Guidance[494].

Occupational therapists treat people with physical and mental health problems through the use of specific activities, to enable patients to reach their optimum level of function and independence in all aspects of their daily lives. Occupational therapists can assist with managing fatigue, breathlessness, pain, pressure care, weight loss, cognitive problems, bone metastases, anxiety, panic management and depression. Interventions such as energy conservation – emphasising the importance of planning, prioritising and pacing daily occupations – can have a beneficial effect on patients' self-esteem and well-being.

Physiotherapists treat physical conditions through specific treatment modalities such as electrotherapy, manipulation, tissue mobilisation, exercise, rehabilitation etc. Patients with lung cancer should be referred to a physiotherapist for advice on breathing techniques, positioning, life style changes, and relaxation and coping strategies. Exercise including progressive walking and stepping regimens to improve muscle strength as well as their exercise tolerance. Such exercise should be carefully prescribed within their disease limitations. One to one treatment also provides psychological support for the patient and the carer.

In addition to the above, the Guideline Group recognises the particular contribution that occupational therapists and physiotherapists make to patients with lung cancer and brain metastases or spinal cord compression, for example all aspects of rehabilitation including pressure care advice and management.

Dieticians provide specialist nutritional advice. Patients with lung cancer should have access to a registered dietician. Dieticians can advise on specific problems such as anorexia, weight loss, swallowing difficulties and fatigue.

12.14 Economics of Palliative Interventions

Two studies were selected for tabulation (Table 170 and Table 171). Four economic evaluations of chemotherapy versus best supportive care (BSC) are reported in Chapter 8 Chemotherapy for NSCLC[369,371,374,376].

Given that there is no evidence specifically for lung cancer patients in the treatment of malignant pleural effusion, evidence was sought regardless of cancer site and four economic analyses were selected for tabulation (Table 170 and Table 171).

12.14.1 Palliative Radiotherapy versus Best Supportive Care (BSC)

The objective of Coy et al[541] was to compare high dose palliative radiotherapy with BSC in terms of cost per LY gained and cost per QALY gained. Given that the study is comparing essentially palliative treatments, the use of un-adjusted life-years is clearly inadequate

High dose radiotherapy in addition to BSC resulted in slight improvements in survival (by 79 days) and QALY (by 0.15) that were statistically significant with an incremental cost of CAD$2,001 (£816) (clinical perspective) and CAD$ 2,652 (£1,081) (societal perspective) per patient. When the incremental costs and effectiveness (LY gained and QALY gained) were compared, the incremental cost-effectiveness ratio of radiotherapy + BSC over BSC alone was equal to CAD$ 12,836 (£5,235) per QALY gained from a clinical perspective. From a societal perspective the incremental cost-effectiveness ratio of radiotherapy + BSC over BSC was equal to CAD$17,012 (£6,938) per QALY gained.

The sensitivity analysis identified the best scenarios (upper bound of the approximate 95% confidence interval for LY/QALY gained, 80% of average cost) and the worst scenarios (the lower bound of the approximate 95% confidence interval for LY/QALY gained, 120% of average cost) for high dose palliative radiotherapy + BSC in comparison with BSC. The cost-effectiveness of high dose palliative radiotherapy + BSC over BSC ranged from £3,261 to £16,806 per QALY gained from the clinic perspective and, from £4,322 to £22,274 from the societal perspective.

According to the results of the analysis, the incremental cost-effectiveness ratio for high dose palliative radiotherapy combined with BSC lies below the threshold of £30,000/QALY gained, which is commonly used to select medical interventions. Hence, palliative radiotherapy combined with BSC was found to be a cost-effective strategy in comparison with BSC for advanced NSCLC. However, as the patients who received only BSC had already refused high dose radiotherapy, the potential for bias is high.

12.14.2 Nd-YAG Laser versus Bronchoscopic Electrocautery

Van Boxem[542] evaluated the costs and clinical outcomes of Nd-YAG laser versus electrocautery for palliation of patients with symptomatic tumour obstruction due to inoperable NSCLC. The rate of symptom improvement (dyspnoea relief), occurrence of complications, mean survival, and the length of hospital stay were observed as health outcomes. The perspective of the economic analysis was the health insurance company in the Netherlands.

It was observed that symptom improvements were achieved in about 70% of patients in both study groups and no treatment complication was recorded. The mean survival was 8.0± 2.5 months in the Nd-YAG laser group and 11.5± 3.5 months in the electrocautery group. The mean survival months were reported as LYs in Table 171.

The average costs of treatment per patient were £3,326 in the Nd-YAG laser group and £2,678 in electrocautery group. The cost difference was mainly due to longer hospital stay in the laser group (8.4 days) than in the electrocautery group (6.7 days); the number of treatment sessions was the same in each groups.

The comparison of costs of treatment per patient and LYs gained for both group showed that electrocautery was a dominant strategy. Life expectancy was slightly improved with electrocautery at lower cost.

12.14.3 Talc versus Bleomycin in the treatment of malignant pleural effusion

Zimmer et al[543] assessed the cost-effectiveness of talc slurry compared with bleomycin. No significant difference was found between the groups in terms of improvement in pain and dyspnoea scores (Table 171). There was a significant cost advantage with using talc to control symptomatic malignant pleural effusions. The cost of medication was $12.36 for talc and $955.83 for bleomycin treatment. The results of this study should be treated with some caution as it was restricted with small sample size and lack of detailed analysis on costs.

Diacon et al[544] result was similar to that of Zimmer et al. Their analysis included all relevant direct costs and effectiveness results were based on a randomised controlled trial. Thoracoscopic talc poudrage was a dominant strategy over bleomycin instillation with lower recurrence rate of effusion (13% vs. 41%) and lower costs (3,893 vs. 4,169 in Swiss francs).

The retrospective analysis of Read et al[545] found shorter length of stay associated with thoracoscopy with talc pleurodesis (4.6 ± 3.3 days) compared to the tube thoracostomy (13.9 ± 5.9 days).

Belani et al[546] found talc to be the most effective pleurodesis agent, however unlike the other studies it found talc to be more costly than bleomycin, mainly due to the need for operating theatre and anaesthesiology. The additional 15 symptom-free days associated with talc were at a cost of $308 per day.

All of the studies compared talc administered surgically with bleomycin administered by bedside thoracotomy. Hence it is not possible to separate the effects of the sclerosing agent from those pertaining to the type of procedure.

12.14.4 Chronic indwelling pleural catheter versus chest tube and sclerosis in the treatment of malignant pleural effusion

The management of malignant pleural effusions by indwelling pleural catheter was compared with chest tube and sclerosis [547]. When patients were treated with outpatient pleural catheter, the mean charge was lower ($3,391±$1,753) than the inpatient charges for patients treated with chest tube and sclerosis ($7,830±4,497) (p<0.001). The difference occurred due to seven days higher mean length of stay with the treatment of chest tube and sclerosis. There was no difference in survival between both treatment groups (see Table 171). However, if pleural catheter was placed in an inpatient basis, the charges would be higher ($11,188±7,964) than that for chest tube and sclerosis.

12.14.5 Conclusions and Discussions

The economic evidence found from the literature review for the management of malignant pleural effusions was not specific to lung cancer patients. No economic evidence based on the UK health system was found. Three economic analyses (two cost-effectiveness and one resource use) concluded that talc was a dominant strategy over bleomycin for the management of malignant pleural effusions and a fourth study indicated that talc was more costly but may be cost-effective. Outpatient pleural catheter could be cost-saving. However, this retrospective study measured hospital charges, which do not reflect the true costs.

The other reviewed studies were conducted in different health settings (Canada and the Netherlands) and these technologies may not be applicable to the UK NHS practice. They were restricted in their sample size. The studies were not randomised and patients were self-selecting, which may be a cause of bias. Further trials and economic evaluations are needed to compare different forms of palliative treatments of lung cancer patients that are more commonly available in UK healthcare context.

12.15 Recommendations

12.15.1 Clinical Practice 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'. [D(GPP)]

Patients who may benefit from specialist palliative care services should be identified and referred without delay. [D(GPP)]

External beam radiotherapy should be considered for the relief of breathlessness, cough, haemoptysis or chest pain. [A]

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

Debulking bronchoscopic procedures should be considered for the relief of distressing large-airway obstruction or bleeding due to an endobronchial tumour within a large airway. [D]

Patients with endobronchial symptoms that are not palliated by other means may be considered for endobronchial therapy. [D]

Patients with extrinsic compression may be considered for treatment with stents. [D]

Non-drug interventions based on psychosocial support, breathing control and coping strategies should be considered for patients with breathlessness. [A]

Non-drug interventions for breathlessness should be delivered by a multidisciplinary group, co-ordinated 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. [D(GPP)]

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

Patients who present with superior vena cava obstruction should be offered chemotherapy and radiotherapy according to the stage of disease and performance status. [A]

Stent insertion should be considered for the immediate relief of severe symptoms of superior vena caval obstruction or following failure of earlier treatment. [B]

Corticosteroids and radiotherapy should be considered for symptomatic treatment of cerebral metastases in lung cancer. [D]

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. [D(GPP)]

Pleural aspiration or drainage should be performed in an attempt to relieve the symptoms of a pleural effusion. [B]

Patients who benefit symptomatically from aspiration or drainage of fluid should be offered talc pleurodesis for longer-term benefit. [B]

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

Spinal cord compression is a medical emergency and immediate treatment (within 24 hours), with corticosteroids, radiotherapy and surgery where appropriate, is recommended. [D]

Patients with spinal cord compression should have an early referral to an oncology physiotherapist and an occupational therapist for assessment, treatment and rehabilitation. [D(GPP)]

12.15.2 Research Recommendations

The management of common symptoms such as cachexia, anorexia, fatigue and breathlessness experienced by patients with lung cancer needs further research. Specifically, research is required into clinically meaningful outcome measures for the treatment of the cachexia-anorexia syndrome. For example, does the level of physical activity as measured by an activity meter relate to performance status, quality of life and use of health and social care services?

Further research is required to determine the benefit of non-drug treatments for breathlessness, compared to no treatment or other drug based treatments, in terms of symptom relief and performance status for patients with lung cancer.

The effect of bisphosphonates in the relief of pain and skeletal morbidity from bone metastasis in lung cancer needs further research.

13 Service Organisation

13.1 Introduction

The most important change in the care of lung cancer patients in the last decade has been the development of integrated multi-disciplinary teams (MDTs) to facilitate their diagnosis and management (Calman-Hine Report[548]). Patients require a combination of a rapid diagnosis, empathetic handling and the confidence that their treatment is of a high quality. These objectives can be realised by optimising local service arrangements.

Before the Calman-Hine reforms, a regional randomised stratified analysis of the management pathways of 400 patients with an eventual diagnosis of lung cancer, found 80 such pathways[19]. More than 50% of patients did not present to hospital with a chest x-ray suspicious of lung cancer. There were substantial delays between diagnosis and treatment and many patients never saw a lung cancer specialist. This study illustrated that by utilising organised pathways, a better standard of care may be provided. The new pathways should ensure that all patients see a lung cancer specialist (usually a chest physician), that delays - especially to bronchoscopy, fine needle aspiration (FNA) or computerised tomography (CT) - are minimised and to ensure that all patients have a management plan as a result of input from a chest physician, a specialist nurse (including those from palliative care), a radiologist, medical and clinical oncologists and (usually) a surgeon. Such service changes have not been subject to randomised controlled trials and comparative studies pre and post reform are difficult. Although some evaluation may emerge, there is at present a professional consensus that patient care both organised around an MDT and consistent with the Manual of Cancer Service Standards[498], is superior to conventional non-specialised and fragmented care.

13.2 Issues examined in this review

These guidelines are concerned with evidence based, best practice recommendations for the diagnosis and treatment of lung cancer. The logistics of how to organise the service to best provide these interventions is outside of this document's remit. Details on service issues can be found in the Manual of Cancer Service Standards[498] and the NHS Cancer Plan[549]. There is however, some evidence reviewed in this chapter relating to specific organisational issues affecting the outcomes of patients with lung cancer. These are: the effects of using a multi-disciplinary team structure, one or two-stop clinics for the diagnosis of the disease, the involvement of specialist nursing staff in the care pathway and the effect of delays on treatment outcomes. We have also assessed the effectiveness of different follow up strategies.

13.3 Methodology

In this chapter, the NCC-AC and SIGN both carried out sections of the literature search and appraisal. The NCC-AC performed searches on rapid access clinics, specialist nurse support, multidisciplinary teams, timing of treatment and the patient perspective. SIGN carried out the search for follow-up. The search strategies can be found in appendix six.

The methodology used to appraise the papers was described earlier in section 2.1.2.

13.4 Multi- Disciplinary Teams (MDTs)

As input from many different professionals is required in the management of patients with lung cancer, MDT's are especially appropriate and can reduce delays caused by cross-referral between specialists. These teams may include, general physicians and nurses, chest physicians, palliative care physicians, clinical and medical oncologists, thoracic surgeons, geriatricians, cellular pathologists, radiologists, radiographers, occupational therapists, specialist nurses, physiotherapists, dieticians, pharmacists and clinical psychologists.

The importance of MDTs has been noted by a number of previous reports: the Calman- Hine report[548], Improving Outcomes in Lung Cancer (NHS Executive)[496], NHS Cancer Plan[549], Clinical Oncology Information Network guidelines[525], British Thoracic Society recommendations on organising care for lung cancer patients[550] and the American College of Chest Physicians[551] (Level 4). Expert opinion and formal consensus in the above reports suggests that:

> All patients with a likely diagnosis of lung cancer should be referred to a member of a lung cancer multi-disciplinary team (usually a chest physician).

> The care of all patients with a working diagnosis of lung cancer should be discussed at a lung cancer multi-disciplinary team meeting.

It is important that there is adequate administrative support for MDTs. We found no studies on the clinical or cost effectiveness of MDTs in lung cancer with regard to improvement of survival or quality of life.

13.5 Early Diagnosis Clinics

Patients with a putative diagnosis of lung cancer are often subject to multiple appointments and potentially considerable delays in the diagnostic pathway. An initial consultation in an outpatient clinic may result in separate appointments for a day-case bronchoscopy, a staging CT scan, a CT guided FNA, full pulmonary function tests, and then a separate clinic meeting to discuss the results. To overcome these problems, units have developed integrated diagnostic days. Patients are seen for the initial consultation and then may receive subsequent investigations (CT/ bronchoscopy/ FNA/ lung function tests) on either the same day (one stop clinic) or on a second day (two stop clinic).

We found no evidence on the effect of using a one-stop clinic approach in the treatment of lung cancer. The literature search retrieved one randomised pilot study on the use of two stop clinics. This study randomised 88 patients with suspicion of lung cancer to attend a two-stop clinic or to receive conventional care. The study found that the time from presentation to treatment was four weeks shorter (p=0.0025) in the two-stop clinic arm of the trial[552]. Although no significant difference was noted in survival it seems intuitive that faster treatment would lead to more patients being suitable for radical treatment and therefore improvement in survival. No significant difference was found in the overall quality of life between the two groups, but a survey of satisfaction found that patients in the two-stop clinic arm were more satisfied with the organisation of investigations (p=0.07) and their personal experience of care (p=0.09)[552](Level 1+). Please see Table 171 for details.

A survey of 61 lung cancer patients and carers carried out by the Roy Castle Lung Cancer Foundation and the National Collaborating Centre for Acute Care (see section 13.9.1 for details) found that one of the main opinions of the group was a desire for speedy access to services (Level 3).

We found no economic evidence in this area.

In conclusion, integrated One-stop or Two-stop clinics for the investigation of putative lung cancer patients are associated with a reduction in diagnostic delay and patient anxiety. They should be utilised where possible.

13.6 Specialist Nurse Support

We did not find any evidence on whether the involvement of specialist nurse support during diagnosis or treatment of patients with lung cancer had an effect on quality of life or survival. The British Thoracic Society (BTS) recommend that all cancer units should have a trained nurse who would see patients at or after diagnosis and then provide continuing support or establish a link with the general practitioner or community team[550] (Level 4). A survey of 61 lung cancer patients and carers carried out by the Roy Castle Lung Cancer Foundation and the National Collaborating Centre for Acute Care supports this recommendation. Respondants placed importance on having access to a lung cancer

support nurse throughout the treatment journey (see section 13.9.1 for details) (Level 3). No economic evidence was found in this area.

There is some evidence on the involvement of nursing support during follow up (see section 13.8).

The guideline development group supports the findings of the BTS report[550] and recommends that:

> All cancer units/centres should have one or more trained lung cancer nurse specialists to see patients before and after diagnosis, to provide continuing support, and to facilitate communication between the MDT, secondary care and the general practitioner and the community team. Their role includes the availability for patients to access advice and support whenever they need it

13.7 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[553]. Guidence on timing has also been issued by the Department of Health in the National Manual of Quality Measures for Cancer[554] and the Welsh Assembly Government in the All Wales minimum standards for lung cancer[555]. Patients should be treated within 31 days of the decision to treat and within 62 days of their urgent referral. In this section, we investigated the effect that delays in diagnosis or treatment might have on survival and quality of life.

The time for a tumour to double in size has been estimated from chest radiographs of solitary pulmonary nodules to be about 100 days for NSCLC and about 30 days for SCLC[32]. It seems intuitive that as the tumour grows, the chances of curative treatment or prolongation of survival would decrease. Although there is little definitive evidence in this area, some observational studies have reported that this is the case (Table 173).

13.7.1 Studies considered for the review

We found three studies that looked at delay before radiotherapy and three studies that looked at the delay before surgery. No studies had a breakdown of results showing the effect of the delay before chemotherapy. One study looked at the delay before treatment of any kind (radiotherapy, surgery or chemotherapy). Studies tended to use different start and end points of the time measured and few measured survival or quality of life.

13.7.2 Time before any treatment

One study that examined the influence of treatment delay on survival did not find a significant relationship using multivariate analysis[556]. This study looked at time from referral to treatment by radiotherapy, surgery or chemotherapy but did not examine delay in referral or patient delay, which may have an effect on survival (Level 3).

13.7.3 Time before radiotherapy

The study by O'Rourke and Edwards (2000)[557] found that whilst on the waiting list 21% of candidates for radical radiotherapy had significant disease progression which meant that the tumour could no longer be encompassed by the radiation port for radical treatment. The delay ranged from 18-131 days (median 54 days). Tumour growth ranged from 0-373% in this time although this was not significantly correlated with delay (Level 3). Another observational study noted that 95% of patients who were referred for continuous hyperfractionated accelerated radiotherapy were found not to be suitable for inclusion in an RCT which was being conducted[558]. The main reasons were poor general condition (37%), large tumour size (27%) or extrathoracic metastases (19%). The median delay between diagnosis and treatment was five weeks (range 3-9 weeks) (Level 3).

Patients not suitable for radical treatment, and not having symptoms demanding immediate treatment, were randomised in an RCT to receive immediate palliative radiotherapy or palliative radiotherapy delivered symptomatically[559]. No significant differences were found in symptom control, quality of life or survival (Level 1+).

A systematic review that reported observational results mostly from breast cancer and head and neck cancer studies found that delays in treatment were associated with higher five year local recurrence rates[560]. Although they found very few studies on lung cancer, the results may be applicable (Level 3).

13.7.4 Time before surgery

Only one study looked at the influence of the delay until surgery on survival on 1082 patients[561]. No significant relationship was found although 34 patients were excluded because their surgery was >154 days after diagnosis (Level 3).

Two studies examined whether patients found to be at later stages of the disease had experienced longer delays. One found that there was no significant relationship[562] and the other found that stage III and IV patients had experienced significantly longer delays[563] (Level 3).

13.7.5 Summary of impact of waiting times for treatment

The disagreement in the results for all treatment modalities may well be due to the heterogeneity in the definitions of 'delay' which studies have used. Delay can arise for many reasons including delay in referral, patient delay and hospital delay. These different delays have not been fully addressed by the past studies in this area for lung cancer. Due to the high incidence of distant metastases compared with other cancers, it may be difficult to identify the impact of waiting times on reduced local control and subsequent outcomes. This is an area where future research would be useful.

Although there is a lack of consistent clinical evidence, in terms of patient preferences and reduction of anxiety at a difficult time it is important to reduce the time taken as much as possible. Patient views are discussed in further detail in the next section.

No economic evidence was found in this area.

The guideline development group concluded that:

> Patients with lung cancer suitable for radical treatment, chemotherapy or requiring radiotherapy or ablative treatment for relief of symptoms, should be treated without undue delay, according to Welsh Assembly Government and Department of Health recommendations (within 31 days of the decision to treat and within 62 days of their urgent referral)[554,555]

> Patients who cannot be offered curative treatment, can be either observed until symptoms arise and then treated with palliative radiotherapy or treated with palliative radiotherapy immediately.

Further research is necessary to determine:

> The impact of the time between first symptom (or first detection if asymptomatic) and treatment, on survival and quality of life of lung cancer patients.

13.8 Follow Up

This section refers to the surveillance of patients in remission after treatment. SIGN carried out a search for literature on strategies for following up patients (see chapter 2).

No systematic reviews were found but one randomised controlled trial[564] on nurse led follow up, and one cohort study[565] on smoking cessation were identified and are discussed below. The search identified no evidence on specific follow up strategies after different types of treatment (surgical, radiotherapy, chemotherapy or palliative), or whether certain routine tests should be performed. However the guideline development group decided to make some good practice points where no high quality evidence was retrieved.

13.8.1 General follow-up issues

Follow-up Plan

The guideline development group wished to make a good practice point that after finishing radical treatment, a personal follow-up plan should be discussed and agreed with patients, following discussion with all healthcare professionals involved in the patient's care. GPs should also be informed of the plan.

Smoking Cessation

No randomised controlled trials were identified on the effect of smoking cessation on the outcomes of treatment. The literature search did identify one cohort study[565] that examined the difference in outcomes of patients who were and were not smoking within one month of their surgery (see Table 174). Those patients who were still smoking within 1 month of the operation were 2.7 times more likely to have major pulmonary events 95% CI 1.18 to 6.17 p=0.018 (Level 2++). An additional cohort study, Nakagawa et al[566] reported on the impact that smoking status had on the incidence of postoperative pulmonary complications (PPC's) after pulmonary surgery. The authors reported that the cessation of smoking preoperatively has a positive impact on the incidence of PPC's. Patients who had ceased smoking for more than 5 weeks experienced a decrease in PPC's although it is unclear if this was statistically significant (level 2+). However, there is no data on the effect of smoking cessation on any other outcome measures such as survival or quality of life after surgery. Evidence on the effect on smoking during radiotherapy treatment for SCLC is discussed in chapter 11.

One consensus report recommended that patients should stop smoking because there is a higher risk of a second primary cancer in patients who remain active smokers after treatment for a first primary lung cancer[567] (Level 4).

The guideline development group decided to recommend that patients with lung cancer, and particularly those with a better prognosis should be encouraged to stop smoking and should be given information on the NHS stop smoking services. Any encouragement of cessation of smoking should be sensitively approached.

Nurse led follow-up

One randomised controlled trial was identified on nurse led follow up[564]. This trial recruited patients thought to have a life expectancy of greater than three months after primary treatment. One group of patients was randomised to nurse led follow up of outpatients, while the other group received conventional medical follow up (see Table 175).

Although there was no significant difference in survival or overall quality of life score, the nurse led follow up was associated with less severe dyspnoea at 3 months (p=0.03), better scores for emotional functioning at 12 months(p=0.03) and less peripheral neuropathy at 12 months (p=0.05) (Level 1++).

After completion of their treatment, patients with an expectation of life greater than three months should have access to protocol controlled nurse led follow up as an option.

13.8.2 Follow up after Surgery

No studies were retreieved that looked specifically at survival and quality of life outcomes for routine follow up after surgery. However, the guideline development group felt it was reasonable to follow up patients for six months after surgery to check for postoperative complications. A recent consensus statement[567] on follow up suggested that follow up should take place at a frequency suitable to measure the adverse effects of the treatment and recommended that patients receive a chest x-ray at the follow up visit (Level 4).

The consensus statement[567] went on to recommend that, after the initial visit, patients should be followed up every three months for the first two years, and then every six months up to five years (Level 4). There is no evidence that follow up beyond five years is beneficial.

There is debate about the merits of using a symptom led follow up strategy (where imaging is only performed for patients with new symptoms or signs) as opposed to having regular appointments with patients. Evidence in this area is conflicting. Three cohort studies were identified[568-570] in the NCC-AC economics search, that examined survival after regular or symptom related follow up (see Table 176 and Table 177). Two studies found no significant difference in survival[568,570] and one found better survival in those patients followed up regularly[569]. (Level 2+). Quality of life was not measured by any of the studies and no overall conclusion can be made about the best strategy for follow up.

13.8.3 Follow up after Radical Radiotherapy

A recent consensus document[567] found that the interval between end of treatment and follow up should be related to anticipated toxicity from the treatment (Level 4). The search identified no further evidence relating to follow up after radical radiotherapy. The guideline development group considered that it was good practice for these patients to be followed up routinely, with thoracic imaging, for nine months after the completion of treatment in order to treat any pneumonitis as appropriate, identify the need for further radiotherapy and the prognosis.

There is no evidence that follow up beyond five years is beneficial for this group of patients. Six monthly follow up with radiographs in well patients essentially offers a form of screening for new lesions – particularly likely if patients continue to smoke. However, there appears to be no evidence that a policy of regular review is better than symptom-led review.

13.8.4 Follow up after Palliative Radiotherapy or Chemotherapy

No evidence on the use of follow up after palliative radiotherapy or chemotherapy was found. The guideline development group considered that is was good practice to follow up patients routinely one month after the end of treatment. The examination should include chest x-ray, if clinically indicated. A recent consensus document[567] also suggested that the interval between end of treatment and follow up should be related to anticipated toxicity from the treatment. They also went on to suggest that a chest x-ray should be carried out and that follow up visits should continue every 1-2 months for the first six months (Level 4).

The GDG also wanted to make the following research recommendation:

> For patients who have had attempted curative treatment and have completed their initial follow up, trials should examine the duration of follow up and whether regular routine follow up is better than symptom led follow up in terms of survival, symptom control and quality of life.

13.8.5 Economics of Follow-up after curative surgery

Five studies were selected for tabulation that analyzed follow-up of NSCLC patients who had undergone curative resection. There was no evidence on follow-up after other treatment modalities, e.g. chemotherapy, radiotherapy, combination or palliative treatment.

The literature review showed that there is diversity of follow-up after complete resection for lung cancer. See Table 176 and Table 177 for the definition of each follow-up protocol used and details of the studies.

Routine follow-up versus symptom-related follow-up

Three studies assessed the cost effectiveness of regular follow-up of patients who underwent resection for NSCLC using retrospective data[568-570].

Egermann et al.[568] analysed 10-year retrospective data for 563 NSCLC patients who had operated with curative intent. It was assumed that follow-up could provide a chance for a second curative treatment. Therefore the life-years (LYs) gained was calculated for those patients (n=23) who underwent further operation with curative intent during the follow-up period. The improvement in life expectancy of those patients was low and not significant (0.05 LYs gained). They added the costs of re-operations of the patients into the costs of follow-up procedures. The cost effectiveness of regular follow-up was SF90,000 (£39,000) which was above the upper limit of acceptable cost-effectiveness (£30,000). Hence, the regular follow-up was not cost-effective.

Westeel et al.[569] produced contrary results, through the analysis of 14-year retrospective data for the similar group of patients in France. The median-disease free survival (19 months) for the whole study population was assessed and costs were calculated for this period. Regular follow-up improved life expectancy (0.11 LYs gained) and was found to be cost-effective ($16,154)[569].

Younes et al.[570] carried out a cost-effectiveness analysis on strict versus symptom related follow-up. No significant improvement in survival was obtained with strict follow-up. Symptom related follow-up was less costly than strict follow-up. Hence, symptom related strategy was cost-saving.

Non-intensive versus intensive follow-up

Virgo et al.[571] identified specific follow-up strategies from the literature. By using Medicare hospital charges, they estimated the cost for a single patient with lung cancer followed up for five years. They assumed that there was no improvement in life expectancy with intensive follow-up. They concluded that non-intensive follow-up was cost-saving.

Nurse-led telephone follow-up versus outpatient follow-up

The only study conducted in the UK was Moore et al.'s analysis that aimed to assess the costs and effectiveness of nurse-led follow- up versus conventional follow-up of patients with lung cancer who had completed their initial treatment[564]. According to the results of the randomised controlled trial, there was no significant difference between the two groups in terms of the overall quality of life, median survival time and cost per patient. However, patients' satisfaction was higher with nurse-led follow-up. In addition, the intervention group had significantly fewer medical consultations with a doctor (p=0.004) at 3 months, fewer radiographs taken at 3 months (p=0.04) and 6 months (p=0.03). It was concluded than nurse-led follow-up led to cost-savings and higher patient satisfaction.

Discussion and Limitations of Economic studies

The literature indicates that routine follow-up of patients after curative surgery for NSCLC adds to overall health service costs. The studies found that follow-up was associated only with small improvements in life expectancy. They differed substantially in terms of the estimated cost-effectiveness of follow-up (£16,000-£30,000). These differences were caused by the approach taken for the assessment of the clinical effectiveness and costs of the follow-up in each study.

Egermann et al [568] and Westeel et al[569] both estimated from their respective cohorts that about 4% of patients benefited from follow-up by being diagnosed with an operable new lesion. The crucial difference between the studies was the assumption about the life-years gained that would be attributable to the diagnosis of new cancer during follow-up.

Egermann et al [568] estimated a gain of 9 months by comparing the life expectancy of those who had a second resection with those who didn't. This could be an under-estimate because patients that did have a second re-section probably would have had a lower than average life expectancy in the absence of the second resection. However, their overall estimate of effectiveness might be an under-estimate because included were the patients who were identified due to symptoms rather than the follow-up procedures.

Westeels et al[569] estimated a gain of 3 years because all seven patients were alive 3 years after their recurrence – again this is a biased estimate of the true incremental gain in life expectancy. This does seem to be an over-estimate, as it is the same as the estimated life-expectancy of patients after their *first* resection[142] and also it doesn't subtract the life expectancy that they would have had if they had not had a second re-section. In addition to apparently under-estimating the effectiveness of follow-up, they clearly under-estimate the costs substantially by not including the cost of the additional re-sections (a crucial omission).

It is not possible to conclude on the cost-effectiveness of follow-up of NSCLC patients after curative surgery because there are no precise estimates of the improvement in life expectancy associated with second re-section in asymptomatic patients. However, the evidence presented overall does not point to routine follow-up being cost-effective, as the only study to show it to be cost-effective clearly under-estimated the incremental cost-effectiveness ratio. Of course cost, effectiveness and cost-effectiveness are dependent on the nature of the follow-up protocol and few follow-up protocols have been evaluated.

One UK study[564] based on a randomised controlled trial concluded that nurse-led follow-up by telephone was cost saving without affecting the quality of life or survival of patients when compared with conventional outpatient follow-up. This might be a more cost-effective option that outpatient follow-up.

There is diversity of follow-up after complete resection of lung cancer. The ideal surveillance has not been defined. Future research based on randomised controlled trials is needed to compare the effectiveness and cost-effectiveness of different follow-up strategies. The studies examined follow-up of lung cancer patients only after resection. There was no evidence on follow-up after chemotherapy, radiotherapy, combination therapy or palliative care.

13.9 The Patient's Perspective

The 1995 Department of Health publication, A Policy Framework for Commissioning Cancer Services[548], recommended that services be 'patient centred'. This document paved the way for cancer patient involvement in service provision.

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)*[572] and in Wales, *Signposts - A Practical Guide to Public and Patient Involvement in Wales (2001)*[573]. 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.

Though 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 5% surviving five years[3], 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 Cancer Relief Macmillan's CancerVOICES) 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.

13.9.1 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[574]

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 (Level 3).

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)[549] 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.

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[575] (Level 3). They have also been less satisfied, than other people with cancer, with the care received[576] (Level 3). A national needs assessment of lung cancer patients and carers, undertaken on behalf of Macmillan Cancer Relief, identified a myriad of deficiencies in the organisation of care delivery and in areas of information and support[20].

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.

13.9.2 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[577] (Level 3). 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)[22], 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*[548]. 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 guideline development group 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.

13.10 Recommendations

13.10.1 Clinical Practice Recommendations

All patients with a likely diagnosis of lung cancer should be referred to a member of a lung cancer MDT (usually a chest physician). [D]

The care of all patients with a working diagnosis of lung cancer should be discussed at a lung cancer MDT meeting. [D]

Early diagnosis clinics 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. [A]

All cancer units/centres should have one or more trained lung cancer 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. [D]

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). [D]

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. [A]

When patients finish their treatment a personal follow-up plan should be discussed and agreed with them after discussion with the professionals involved in the patient's care. GPs should be informed of the plan. [D(GPP)]

After completion of their treatment, patients with an expectation of life of more than 3 months should have access to protocol-controlled, nurse-led follow-up. [A]

Patients who have had attempted curative surgery for NSCLC, or radical radiotherapy should be followed up routinely by a member of the MDT for up to 9 months to check for post-treatment complications. Thoracic imaging should be part of the review. [D]

For patients who have had attempted curative surgery for NSCLC, any routine follow-up should not extend beyond 5 years. [D]

Patients who have had palliative radiotherapy or chemotherapy should be followed up routinely at 1 month after completion of treatment. A chest X-ray should be part of the review if clinically indicated. [D]

Patients with lung cancer – in particular those with a better prognosis – should be encouraged to stop smoking. [D]

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. [D(GPP)]

13.10.2 Research Recommendations

For patients who have had attempted curative treatment and have completed their initial follow up, trials should examine the duration of follow-up and whether regular routine follow-up is better than symptom-led follow-up in terms of survival, symptom control and quality of life.

The impact of the time between first symptom (or first detection if asymptomatic) and the treatment of lung cancer on patients' survival and quality of life should be investigated.

14 Priority Areas for Audit

A national cancer dataset has been developed by the NHS Information Authority in collaboration with clinicians and the Department of Health. A data subset for lung cancer has been derived by the Intercollegiate Lung Cancer Group to support the National Lung Cancer Data Project (LUCADA), a national ongoing audit programme for lung cancer. The guideline development group notes that many of the recommendations within the complete guideline are auditable through this dataset. All English Cancer Networks are being encouraged to take part in this programme which began its national roll-out in July 2004. A copy of this dataset and further details of the LUCADA project can be found at:
http://www.nhsia.nhs.uk/ncasp/pages/audit_topics/cancer.asp?om=m1#lung
or:
http://www.rcplondon.ac.uk/college/ceeu/ceeu_lung_home.htm

The audit criteria highlighted below are based on the recommendations selected as key priorities for implementation. Only two of these highlighted criteria fall within the LUCADA dataset. We have specified audit criteria, exceptions and definitions of terms for those recommendations that are not included LUCADA.

Recommendation	Criterion	Definition of terms
All patients diagnosed with lung cancer should be offered information, both verbal and written, on all aspects of their diagnosis, treatment and care. This information should be tailored to the individual requirements of the patient and audio and videotaped formats should also be considered.	Percentage of patients diagnosed with lung cancer that are offered information, both verbal and written, on all aspects of their diagnosis, treatment and care. This information should be tailored to the individual requirements of the patient and audio and videotaped formats should also be considered.	
Urgent referral for a chest X-ray should be offered when a patient presents with: > haemoptysis, or > any of the following unexplained or persistent (that is, lasting more than 3 weeks) symptoms or signs: – cough – chest/shoulder pain – dyspnoea – weight loss – chest signs – hoarseness – finger clubbing – features suggestive of metastasis from a lung cancer (for example in brain, bone, liver or skin) – ervical/supraclavicular lymphadenopathy	Percentage of patients that present to a GP with the following symptoms and signs who are offered an urgent referral for a chest X-ray: > haemoptysis, or > any of the following unexplained or persistent (that is, lasting more than 3 weeks) symptoms or signs: – cough – chest/shoulder pain – dyspnoea – weight loss – chest signs – hoarseness – finger clubbing – features suggestive of metastasis from a lung cancer (for example in brain, bone, liver or skin) – ervical/supraclavicular lymphadenopathy	
If a chest x-ray or chest CT suggests lung cancer (including pleural effusion and slowly resolving consolidation), patients should be offered an urgent referral to a member of the lung cancer multidisciplinary team (MDT) usually a chest physician.	Percentage of patients with a chest x-ray or chest CT suggestive of lung cancer (including pleural effusion and slowly resolving consolidation) that are offered an urgent referral to a member of the lung cancer multidisciplinary team, usually a chest physician.	Rapid – rapid enough to ensure time to diagnosis and treatment standards are achieved
Every cancer network should have a system of rapid access to FDG-PET scanning for eligible patients.	Percentage of eligible patients within the cancer network that have a FDG-PET scan.	

Recommendation	Criterion	Definition of terms
Patients with stage I or II NSCLC who are medically inoperable, but suitable for radical radiotherapy should be offered the continuous hyperfractionated accelerated radiotherapy (CHART) regimen.	Percentage of medically inoperable patients with stage I or II NSCLC who are suitable for radical radiotherapy who are treated using the continuous hyperfractionated accelerated radiotherapy (CHART) regimen.	
Chemotherapy should be offered to patients with stages III and IV NSCLC and good performance status (WHO 0, 1 or a Karnofsky score of 80–100) to improve survival, disease control and quality of life.	This is covered by the LUCADA dataset.	
Non-drug interventions for breathlessness should be delivered by a multidisciplinary group, co-ordinated 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 within a breathlessness clinic, patients should have access to it in all care settings.	Percentage of patients with lung cancer that experience breathlessness who have access to support from a multidisciplinary group with an interest in breathlessness and expertise in non-drug interventions (for example, a nurse, physiotherapist or occupational therapist).	
The care of all patients with a working diagnosis of lung cancer should be discussed at a lung cancer MDT meeting.	This is covered by the LUCADA dataset.	
Early diagnosis clinics 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.	Percentage of patients with putative lung cancer who are seen in an early diagnosis clinic.	
All cancer units/centres should have one or more trained lung cancer 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.	Percentage of patients seen by a trained lung cancer nurse specialist before and after diagnosis, who provides continuing support, facilitates communication between the secondary care team (including the MDT), the GP, the community team and the patient, and helps patients to access advice and support whenever they need it.	

15 Bibliography

1. Office for National Statistics (2003) Mortality statistics cause. Review of the Registrar General on deaths by cause, sex and age, in England and Wales, 2002. London: Office for National Statistics.
2. Quinn, M., Babb, P., Brock, A., Kirby, L., and Jones, J. (2001) Cancer trends in England and Wales 1950-1999. Studies on medical and population subjects No. 66. London: The Stationary Office.
3. Office for National Statistics (2001) Cancer survival, England 1993-2000. London: Office for National Statistics.
4. Welsh Cancer Intelligence & Surveillance Unit (2003) Cancer Survival in Wales, 1989-1998. Cardiff: Welsh Cancer Intelligence & Surveillance Unit.
5. Department of Health (2002) NHS performance indicators: February 2002. London: Department of Health.
6. Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG. Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician. Philadelphia: W.B.Saunders Company, 2001.
7. Haward RA, Forman D. The health care epidemiology of lung cancer. In: Muers MF, MacBeth F, Wells FC, Miles A, eds. *The effective management of lung cancer*, 1, 2001. pp 1-15. London: Aesculapius Medical Press.
8. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004, **328**(7455):1519.
9. Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ* 2000, **321**(7257):323-9.
10. Alberg AJ,.Samet JM. Epidemiology of lung cancer. *Chest* 2003, **123**(1 Suppl):21S-49S.
11. Froggatt, P. (1988) Fourth report of the independent scientific committee on smoking and health. London: The Stationary Office.
12. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. *BMJ* 1997, **315**(7114):980-8.
13. Hughes JM, Weill H. Asbestos and man-made fibers. In: Samet JM, ed. *Epidemiology of lung cancer*, 8, 1994. pp 185-205. New York: Marcel Dekker, Inc.
14. Darby S, Hill D, Doll R. Radon: a likely carcinogen at all exposures. *Annals of Oncology* 2001, **12**(10):1341-51.
15. NHS Executive (1998) Guidance on commissioning cancer services improving outcomes in lung cancer - the research evidence. London: NHS Executive.
16. National Institute for Clinical Excellence (2001) Information for national collaborating centres and guideline development groups. London: National Institute for Clinical Excellence.
17. Oxford Centre for Evidence-based Medicine Levels of evidence http://www.cebm.net/ [accessed 21-1-2003].

18. NHS Centre for Reviews and Dissemination (2001) Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews.

19. Melling PP, Hatfield AC, Muers MF, Peake MD, Storer CJ, Round CE *et al.* Lung cancer referral patterns in the former Yorkshire region of the UK. *British Journal of Cancer* 2002, **86**(1):36-42.

20. Krishnasamy, M. and Wilkie, E. (1999) Lung cancer: patients', families' and professionals' perceptions of health care need. A national needs assessment study. London: Macmillan Practice Development Unit.

21. Koyi H, Hillerdal G, Branden E. Patient's and doctors' delays in the diagnosis of chest tumors. *Lung Cancer* 2002, **35**(1):53-7.

22. Commission for Health Improvement (CHI) and Audit Commission (2001) National Service Framework Assessments No.1 NHS cancer care in England and Wales. London: Commission for Health Improvement (CHI).

23. Baird J. Raising the public profile of lung cancer—report of a National Lung Cancer Awareness campaign in the UK. *Lung Cancer* 2003, **42**(1):119-23.

24. Beckles MA, Spiro SG, Colice GL, Rudd RM. Initial evaluation of the patient with lung cancer: Symptoms, signs, laboratory tests, and paraneoplastic syndromes. *Chest* 2003, **123**(1 Suppl):97S-104S.

25. Department of Health (2000) Referral guidelines for suspected cancer. London: Department of Health.

26. Schreiber G,.McCrory DC. Performance characteristics of different modalities for diagnosis of suspected lung cancer: Summary of published evidence. *Chest* 2003, **123**(1 Suppl):115S-28S.

27. Rivera MP, Detterbeck F, Mehta AC. Diagnosis of lung cancer: The guidelines. *Chest* 2003, **123**(1 Suppl):129S-36S.

28. Detterbeck FC, Rivera M. Clinical presentation and diagnosis. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 4, 2001. pp 45-72. Philedelphia: W.B.Saunders Company.

29. National Radiological Protection Board Patient dose information http://www.nrpb.org/radiation_topics/medical/ted_equivalent.htm [accessed 3-5-2004].

30. Siegelman SS, Khouri NF, Leo FP, Fishman EK, Braverman RM, Zerhouni EA. Solitary pulmonary nodules: CT assessment. *Radiology* 1986, **160**(2):307-12.

31. Seemann MD, Seemann O, Luboldt W, Bonel H, Sittek H, Dienemann H *et al.* Differentiation of malignant from benign solitary pulmonary lesions using chest radiography, spiral CT and HRCT. *Lung Cancer* 2000, **29**(2):105-24.

32. Geddes DM. The natural history of lung cancer: a review based on rates of tumour growth. *British Journal of Diseases of the Chest* 1979, **73**(1):1-17.

33. Yankelevitz DF, Gupta R, Zhao B, Henschke CI. Small pulmonary nodules: evaluation with repeat CT—preliminary experience. *Radiology* 1999, **212**(2):561-6.

34. Yankelevitz DF, Reeves AP, Kostis WJ, Zhao B, Henschke CI. Small pulmonary nodules: volumetrically determined growth rates based on CT evaluation. *Radiology* 2000, **217**(1):251-6.

35. Swensen SJ, Brown LR, Colby TV, Weaver AL. Pulmonary nodules: CT evaluation of enhancement with iodinated contrast material. *Radiology* 1995, **194**(2):393-8.

36. Yamashita K, Matsunobe S, Tsuda T, Nemoto T, Matsumoto K, Miki H *et al.* Solitary pulmonary nodule: preliminary study of evaluation with incremental dynamic CT. *Radiology* 1995, **194**(2):399-405.

37. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA* 2001, **285**(7):914-24.

38. Dunagan D, Chin R, Jr., McCain T, Case L, Harkness B, Oaks T *et al.* Staging by positron emission tomography predicts survival in patients with non-small cell lung cancer. *Chest* 2001, **119**(2):333-9.

39. Hain SF, Curran KM, Beggs AD, Fogelman I, O'Doherty MJ, Maisey MN. FDG-PET as a "metabolic biopsy" tool in thoracic lesions with indeterminate biopsy. *European Journal of Nuclear Medicine* 2001, **28**(9):1336-40.

40. Hickeson M, Yun M, Matthies A, Zhuang H, Adam L-E, Lacorte L *et al.* Use of a corrected standardized uptake value based on the lesion size on CT permits accurate characterization of lung nodules on FDG-PET. *European Journal of Nuclear Medicine* 2002, **29**(12):1639-47.

41. Imdahl A, Jenkner S, Brink I, Nitzsche E, Stoelben E, Moser E *et al.* Validation of FDG positron emission tomography for differentiation of unknown pulmonary lesions. *European Journal of Cardio-Thoracic Surgery* 2001, **20**(2):324-9.

42. Keith CJ, Miles KA, Griffiths MR, Wong D, Pitman AG, Hicks RJ. Solitary pulmonary nodules: Accuracy and cost-effectiveness of sodium iodide FDG-PET using Australian data. *European Journal of Nuclear Medicine* 2002, **29**(8):1016-23.

43. Lee J, Aronchick JM, Alavi A. Accuracy of F-18 fluorodeoxyglucose positron emission tomography for the evaluation of malignancy in patients presenting with new lung abnormalities: a retrospective review. *Chest* 2001, **120**(6):1791-7.

44. Marom EM, Sarvis S, Herndon JE, Patz EF, Jr. T1 lung cancers: sensitivity of diagnosis with fluorodeoxyglucose PET. *Radiology* 2002, **223**(2):453-9.

45. Matthies A, Hickeson M, Cuchiara A, Alavi A. Dual time point 18F-FDG PET for the evaluation of pulmonary nodules. *Journal of Nuclear Medicine* 2002, **43**(7):871-5.

46. Pitman AG, Hicks RJ, Kalff V, Binns DS, Ware RE, McKenzie AF *et al.* Positron emission tomography in pulmonary masses where tissue diagnosis is unhelpful or not possible. *Medical Journal of Australia* 2001, **175**(6):303-7.

47. Pitman AG, Hicks RJ, Binns DS, Ware RE, Kalff V, McKenzie AF *et al.* Performance of sodium iodide based (18)F-fluorodeoxyglucose positron emission tomography in the characterization of indeterminate pulmonary nodules or masses. *British Journal of Radiology* 2002, **75**(890):114-21.

48. Sasaki M, Kuwabara Y, Yoshida T, Nakagawa M, Koga H, Hayashi K *et al.* Comparison of MET-PET and FDG-PET for differentiation between benign lesions and malignant tumors of the lung. *Annals of Nuclear Medicine* 2001, **15**(5):425-31.

49. Willkomm P, Bangard M, Guhlke S, Sartor J, Bender H, Gallkowski U *et al.* Comparison of [18F]FDG-PET and I-3[123I]-iodo-a-methyl tyrosine (I(1-123 IMT)-SPECT in primary lung cancer. *Annals of Nuclear Medicine* 2002, **16**(7):503-6.

50. Herder GJ, van Tinteren H, Comans EF, Hoekstra OS, Teule GJ, Postmus PE *et al.* Prospective use of serial questionnaires to evaluate the therapeutic efficacy of 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in suspected lung cancer. *Thorax* 2003, **58**(1):47-51.

51. Blum J, Handmaker H, Lister-James J, Rinne N. A multicenter trial with a somatostatin analog (99m)Tc depreotide in the evaluation of solitary pulmonary nodules. *Chest* 2000, **117**(5):1232-8.

52. Grewal RK, Dadparvar S, Yu JQ, Babaria CJ, Cavanaugh T, Sherman M *et al.* Efficacy of Tc-99m depreotide scintigraphy in the evaluation of solitary pulmonary nodules. *Cancer Journal* 2002, **8**(5):400-4.

53. Agusti C, Xaubet A, Monton C, Sole M, Soler N, Carrion M *et al.* Induced sputum in the diagnosis of peripheral lung cancer not visible endoscopically. *Respiratory Medicine* 2001, **95**(10):822-8.

54. Honeybourne D, Babb J, Bowie P, Brewin A, Fraise A, Garrard C *et al.* British Thoracic Society guidelines on diagnostic flexible bronchoscopy. *Thorax* 2001, **56**(Suppl 1):i1-i21.

55. Xie HB, Cornwell R, Grossman JE, Hoerl HD, Kurtycz DF. Bronchoscopy-guided transtracheal and transbronchial fine-needle aspiration biopsy: a 5-year institutional review of 111 cases. *Diagnostic Cytopathology* 2002, **27**(5):276-81.

56. Hashmi SN, Mubarik A, Qureshi AH, Saeed W, Ijaz A. Role of endobronchial biopsy in the diagnosis of lung diseases. *Journal of the College of Physicians & Surgeons Pakistan* 2002, **12**(10):628-30.

57. Laroche C, Fairbairn I, Moss H, Pepke-Zaba J, Sharples L, Flower C *et al*. Role of computed tomographic scanning of the thorax prior to bronchoscopy in the investigation of suspected lung cancer. *Thorax* 2000, **55**(5):359-63.

58. Bungay HK, Pal CR, Davies CW, Davies RJ, Gleeson FV. An evaluation of computed tomography as an aid to diagnosis in patients undergoing bronchoscopy for suspected bronchial carcinoma. *Clinical Radiology* 2000, **55**(7):554-60.

59. Dahlstrom JE, Langdale-Smith GM, James DT. Fine needle aspiration cytology of pulmonary lesions: a reliable diagnostic test. *Pathology* 2001, **33**(1):13-6.

60. Yamagami T, Iida S, Kato T, Tanaka O, Nishimura T. Combining fine-needle aspiration and core biopsy under CT fluoroscopy guidance: A better way to treat patients with lung nodules? *American Journal of Roentgenology* 2003, **180**(3):811-5.

61. Yamagami T, Iida S, Kato T, Tanaka O, Toda S, Kato D *et al*. Usefulness of new automated cutting needle for tissue-core biopsy of lung nodules under CT fluoroscopic guidance. *Chest* 2003, **124**(1):147-54.

62. Yu LS, Deheinzelin D, Younes RN, Chojniak R. Computed tomography-guided cutting needle biopsy of pulmonary lesions. *Revista do Hospital Das Clinicas; Faculdade de Medicina da Universidade de Sao Paulo* 2002, **57**(1):15-8.

63. Dennie CJ, Matzinger FR, Marriner JR, Maziak DE. Transthoracic needle biopsy of the lung: results of early discharge in 506 outpatients. *Radiology* 2001, **219**(1):247-51.

64. Manhire A, Charig M, Clelland C, Gleeson F, Miller R, Moss H *et al*. Guidelines for radiologically guided lung biopsy. *Thorax* 2003, **58**(11):920-36.

65. McNeill TM,.Chamberlain JM. Diagnostic anterior mediastinotomy. *Annals of Thoracic Surgery* 1966, **2**(4):532-9.

66. Olak J. Parasternal mediastinotomy (Chamberlain procedure). *Chest Surgery Clinics of North America* 1996, **6**(1):31-40.

67. Best LA, Munichor M, Ben Shakhar M, Lemer J, Lichtig C, Peleg H. The contribution of anterior mediastinotomy in the diagnosis and evaluation of diseases of the mediastinum and lung. *Annals of Thoracic Surgery* 1987, **43**(1):78-81.

68. Swanson SJ, Jaklitsch MT, Mentzer SJ, Bueno R, Lukanich JM, Sugarbaker DJ. Management of the solitary pulmonary nodule: role of thoracoscopy in diagnosis and therapy. *Chest* 1999, **116**(6 Suppl):523S-4S.

69. Mitruka S, Landreneau RJ, Mack MJ, Fetterman LS, Gammie J, Bartley S *et al*. Diagnosing the indeterminate pulmonary nodule: percutaneous biopsy versus thoracoscopy. *Surgery* 1995, **118**(4):676-84.

70. Mack MJ, Hazelrigg SR, Landreneau RJ, Acuff TE. Thoracoscopy for the diagnosis of the indeterminate solitary pulmonary nodule. *Annals of Thoracic Surgery* 1993, **56**(4):825-30.

71. Cardillo G, Regal M, Sera F, Di Martino M, Carbone L, Facciolo F *et al*. Videothoracoscopic management of the solitary pulmonary nodule: a single-institution study on 429 cases. *Annals of Thoracic Surgery* 2003, **75**(5):1607-12.

72. Allen MS, Deschamps C, Lee RE, Trastek VF, Daly RC, Pairolero PC. Video-assisted thoracoscopic stapled wedge excision for indeterminate pulmonary nodules. *Journal of Thoracic and Cardiovascular Surgery* 1993, **106**(6):1048-52.

73. Hsu CP, Hanke I, Douglas JM, Jr. Diagnostic video-assisted thoracoscopic procedures. *Annals of Surgery* 1995, **222**(5):626-31.

74. Comber LA, Keith CJ, Griffiths M, Miles KA. Solitary pulmonary nodules: Impact of quantitative contrast-enhanced CT on the cost-effectiveness of FDG-PET. *Clinical Radiology* 2003, **58**(9):706-11.

75. Dietlein M, Weber K, Gandjour A, Moka D, Theissen P, Lauterbach KW *et al*. Cost-effectiveness of FDG-PET for the management of solitary pulmonary nodules: a decision analysis based on cost reimbursement in Germany. *European Journal of Nuclear Medicine* 2000, **27**(10):1441-56.

76. Elixhauser A, Reker DM, Gillespie KN, Fletcher J, Wolinsky FD. A comparison of in-house and regionalized computerized tomography scanning: clinical impact and cost. *Health Services Research* 1990, **25**(1 Pt 2):177-96.

77. Gambhir SS, Shepherd JE, Shah BD, Hart E, Hoh CK, Valk PE *et al*. Analytical decision model for the cost-effective management of solitary pulmonary nodules. *Journal of Clinical Oncology* 1998, **16**(6):2113-25.

78. Gambhir SS, Shephard JE, Handmaker H, et a. Analysis of the cost-effectiveness of a somatostatin analog-Tc99m-depreotide (Neotect) in the scintigraphic evaluation of solitary pulmonary nodules (SPN). *Journal of Nuclear Medicine* 1999, **40**:57P.

79. Gould MK, Sanders GD, Barnett PG, Rydzak CE, Maclean CC, McClellan MB *et al*. Cost-effectiveness of alternative management strategies for patients with solitary pulmonary nodules. *Annals of Internal Medicine* 2003, **138**(9):724-35.

80. Govert JA, Kopita JM, Matchar D, Kussin PS, Samuelson WM. Cost-effectiveness of collecting routine cytologic specimens during fiberoptic bronchoscopy for endoscopically visible lung tumor. *Chest* 1996, **109**(2):451-6.

81. Institute of Clinical PET (1994) Clinical application and economic implications of PET in the assessment of solitary pulmonary nodules: a retrospective study. Foothill Ranch, California: Institute of Clinical PET.

82. Kosuda S, Ichihara K, Watanabe M, Kobayashi H, Kusano S. Decision-tree sensitivity analysis for cost-effectiveness of chest 2-fluoro-2-D-[(18)F]fluorodeoxyglucose positron emission tomography in patients with pulmonary nodules (non-small cell lung carcinoma) in Japan. *Chest* 2000, **117**(2):346-53.

83. Kosuda S, Ichihara K, Watanabe M, Kobayashi H, Kusano S. Decision-tree sensitivity analysis for cost-effectiveness of whole-body FDG PET in the management of patients with non-small-cell lung carcinoma in Japan. *Annals of Nuclear Medicine* 2002, **16**(4):263-71.

84. Miles KA. An approach to demonstrating cost-effectiveness of diagnostic imaging modalities in Australia illustrated by positron emission tomography. *Australasian Radiology* 2001, **45**(1):9-18.

85. Osada H, Kojima K, Tsukada H, Nakajima Y, Imamura K, Matsumoto J. Cost-effectiveness associated with the diagnosis and staging of non-small-cell lung cancer. *Japanese Journal of Thoracic & Cardiovascular Surgery* 2001, **49**(1):1-10.

86. Raab SS, Hornberger J, Raffin T. The importance of sputum cytology in the diagnosis of lung cancer: a cost-effectiveness analysis. *Chest* 1997, **112**(4):937-45.

87. Raab SS,.Hornberger J. The effect of a patient's risk-taking attitude on the cost effectiveness of testing strategies in the evaluation of pulmonary lesions. *Chest* 1997, **111**(6):1583-90.

88. Shepherd JE. Cost effectiveness analysis for the role of FDG-PET in lung carcinoma [Abstract]. *Journal of Nuclear Medicine* 1999, **40**:56.

89. Valk PE, Pounds TR, Tesar RD, Hopkins DM, Haseman MK. Cost-effectiveness of PET imaging in clinical oncology. *Nuclear Medicine & Biology* 1996, **23**(6):737-43.

90. Detterbeck FC, Jones DR, Parker LA. Intrathoracic staging. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 5, 2001. pp 73-93. Philadelphia: W.B.Saunders Company.

91. Webb WR, Gatsonis C, Zerhouni EA, Heelan RT, Glazer GM, Francis IR *et al.* CT and MR imaging in staging non-small cell bronchogenic carcinoma: report of the Radiologic Diagnostic Oncology Group. *Radiology* 1991, **178**(3):705-13.

92. Heelan RT, Demas BE, Caravelli JF, Martini N, Bains MS, McCormack PM *et al.* Superior sulcus tumors: CT and MR Imaging. *Radiology* 1989, **170**(3 I):637-41.

93. Maskell NA,.Butland RJ. BTS guidelines for the investigation of a unilateral pleural effusion in adults. *Thorax* 2003, **58**(Suppl 2):ii8-17.

94. Dales RE, Stark RM, Raman S. Computed tomography to stage lung cancer. Approaching a controversy using meta-analysis. *American Review of Respiratory Disease* 1990, **141**(5 Pt 1):1096-101.

95. Toloza EM, Harpole L, McCrory DC. Noninvasive staging of non-small cell lung cancer a review of the current evidence. *Chest* 2003, **123**(1 Suppl):137S-46S.

96. Reed CE, Harpole DH, Posther KE, Woolson SL, Downey RJ, Meyers BF *et al.* 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. *Journal of Thoracic and Cardiovascular Surgery* 2003, **126**(6):1943-51.

97. Gonzalez-Stawinski GV, Lemaire A, Merchant F, O'Halloran E, Coleman RE, Harpole DH *et al.* A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 2003, **126**(6):1900-5.

98. Fritscher-Ravens A, Davidson BL, Hauber HP, Bohuslavizki KH, Bobrowski C, Lund C *et al.* Endoscopic ultrasound, positron emission tomography, and computerized tomography for lung cancer. *American Journal of Respiratory & Critical Care Medicine* 2003, **168**(11):1293-7.

99. 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.

100. Scottish Intercollegiate Guidelines Network and Scottish Cancer Therapy Network (1998) Management of lung cancer - a national clinical guideline recommended for use in Scotland by the Scottish Intercollegiate Guidelines Network. Edinburgh: Scottish Intercollegiate Guidelines Network.

101. Graeter TP, Hellwig D, Hoffman K, Ukena D, Kirsch C-M, Schaefers H-J. Mediastinal lymph node staging in suspected lung cancer: comparison of positron emission tomography with F-18-Fluorodeoxyglucose and mediastinoscopy. *Annals of Thoracic Surgery* 2003, **75**(1):231-6.

102. Laudanski J, Kozlowski M, spacing a, Chyczewski L. The preoperative study of mediastinal lymph nodes metastasis in lung cancer by endoscopic ultrasonography (EUS) and helical computed tomography (CT). *Lung Cancer* 2001, **34**(Suppl 2):S123-S126.

103. Toloza EM, Harpole L, Detterbeck F, McCrory DC. Invasive staging of non-small cell lung cancer: A review of the current evidence. *Chest* 2003, **123**(1 Suppl):157S-66S.

104. Fultz PJ, Feins RH, Strang JG, Wandtke JC, Johnstone DW, Watson TJ *et al.* Detection and diagnosis of nonpalpable supraclavicular lymph nodes in lung cancer at CT and US. *Radiology* 2002, **222**(1):245-51.

105. Detterbeck FC, Jones DR, Molina PL. Extrathoracic staging. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 6, 2001. pp 94-110. Philadelphia: W.B.Saunders Company.

106. DeGrendele H, Belani CP, Naumann R, White C. Fluorodeoxyglucose positron emission tomography as a staging and prognostic tool in non-small-cell lung cancer. *Clinical Lung Cancer* 2003, **4**(4):213-6.

107. Ferrigno D,.Buccheri G. Cranial computed tomography as a part of the initial staging procedures for patients with non-small-cell lung cancer. *Chest* 1994, **106**(4):1025-9.

108. Kormas P, Bradshaw JR, Jeyasingham K. Preoperative computed tomography of the brain in non-small cell bronchogenic carcinoma. *Thorax* 1992, **47**(2):106-8.

109. Marom EM, McAdams HP, Erasmus JJ, Goodman PC, Culhane DK, Coleman RE *et al.* Staging non-small cell lung cancer with whole-body PET. *Radiology* 1999, **212**(3):803-9.

110. Ingemann JL, Hirsch FR, Peters K, Jensen F, Thomsen C. Diagnosis of abominal metastases in small cell carcinoma of the lung: A prospective study of computer tomography and ultrasonography. *Lung Cancer* 1992, **8**(1):37-46.

111. Mulshine JL, Makuch RW, Johnston-Early A. Diagnosis and significance of liver metastases in small cell carcinoma of the lung. *Journal of Clinical Oncology* 1984, **2**(7):733-41.

112. Erasmus JJ, Patz EF, Jr., McAdams HP, Murray JG, Herndon J, Coleman RE *et al.* Evaluation of adrenal masses in patients with bronchogenic carcinoma using 18F-fluorodeoxy-glucose positron emission tomography. *American Journal of Roentgenology* 1997, **168**(5):1357-62.

113. Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. *Journal of Nuclear Medicine* 1996, **37**(6):943-8.

114. Porte H, Roumilhac D, Eraldi L, Cordonnier C, Puech P, Wurtz A. The role of mediastinoscopy in the diagnosis of mediastinal lymphadenopathy. *European Journal of Cardio-Thoracic Surgery* 1998, **13**(2):196-9.

115. Ettinghausen SE,.Burt ME. Prospective evaluation of unilateral adrenal masses in patients with operable non-small-cell lung cancer. *Journal of Clinical Oncology* 1991, **9**(8):1462-6.

116. Burt M, Heelan RT, Coit D, McCormack PM, Bains MS, Martini N *et al.* Prospective evaluation of unilateral adrenal masses in patients with operable non-small-cell lung cancer: Impact of magnetic resonance imaging. *Journal of Thoracic and Cardiovascular Surgery* 1994, **107**(2):584-9.

117. Porte HL, Ernst OJ, Delebecq T, Metois D, Lemaitre LG, Wurtz AJ. Is computed tomography guided biopsy still necessary for the diagnosis of adrenal masses in patients with resectable non-small-cell lung cancer? *European Journal of Cardio-Thoracic Surgery* 1999, **15**(5):597-601.

118. Schwartz LH, Ginsberg MS, Burt ME, Brown KT, Getrajdman GI, Panicek DM. MRI as an alternative to CT-guided biopsy of adrenal masses in patients with lung cancer. *Annals of Thoracic Surgery* 1998, **65**(1):193-7.

119. Bury T, Dowlati A, Paulus P, Corhay JL, Benoit T, Kayembe JM *et al.* Evaluation of the solitary pulmonary nodule by positron emission tomography imaging. *European Respiratory Journal* 1996, **9**(3):410-4.

120. Hsia TC, Shen YY, Yen RF, Kao CH, Changlai SP. Comparing whole body 18F-2-deoxyglucose positron emission tomography and technetium-99m methylene diophosphate bone scan to detect bone metastases in patients with non-small cell lung cancer. *Neoplasma* 2002, **49**(4):267-71.

121. Hochstenbag MM, Snoep G, Cobben NA, Schols AM, Thunnissen FB, Wouters EF *et al.* Detection of bone marrow metastases in small cell lung cancer. Comparison of magnetic resonance imaging with standard methods. *European Journal of Cancer* 1996, **32A**(5):779-82.

122. van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA *et al.* Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 2002, **359**(9315):1388-93.

123. MacManus MR, Hicks R, Fisher R, Rischin D, Michael M, Wirth A *et al.* FDG-PET-detected extracranial metastasis in patients with non-small cell lung cancer undergoing staging for surgery or radical radiotherapy—survival correlates with metastatic disease burden. *Acta Oncologica* 2003, **42**(1):48-54.

124. Dizendorf EV, Baumert BG, von Schulthess GK, Lutolf UM, Steinert HC. Impact of whole-body 18F-FDG PET on staging and managing patients for radiation therapy. *Journal of Nuclear Medicine* 2003, **44**(1):24-9.

125. Erdi YE, Rosenzweig K, Erdi AK, Macapinlac HA, Hu Y-C, Braban LE *et al*. Radiotherapy treatment planning for patients with non-small cell lung cancer using positron emission tomography (PET). *Radiotherapy and Oncology* 2002, **62**(1):51-60.

126. MacManus MP, Hicks RJ, Ball DL, Ciavarella F, Binns D, Hogg A *et al*. Imaging with F-18 FDG PET is superior to Tl-201 SPECT in the staging of non-small cell lung cancer for radical radiation therapy. *Australasian Radiology* 2001, **45**(4):483-90.

127. Mah K, Caldwell CB, Ung YC, Danjoux CE, Balogh JM, Ganguli SN *et al*. The impact of (18)FDG-PET on target and critical organs in CT-based treatment planning of patients with poorly defined non-small-cell lung carcinoma: a prospective study. *International Journal of Radiation Oncology, Biology, Physics* 2002, **52**(2):339-50.

128. Richardson GE, Venzon DJ, Edison M, Brown M, Frame JN, Ihde DC *et al*. Application of an algorithm for staging small-cell lung cancer can save one third of the initial evaluation costs. *Archives of Internal Medicine* 1993, **153**(3):329-37.

129. Black WC, Armstrong P, Daniel TM. Cost effectiveness of chest CT in T1N0M0 lung cancer. *Radiology* 1988, **167**(2):373-8.

130. Bonadies J, D'Agostino RS, Ruskis AF, Ponn RB. Outpatient mediastinoscopy. *Journal of Thoracic and Cardiovascular Surgery* 1993, **106**(4):686-8.

131. Canadian Lung Oncology Group. Investigation for mediastinal disease in patients with apparently operable lung cancer. *Annals of Thoracic Surgery* 1995, **60**(5):1382-9.

132. Colice GL, Birkmeyer JD, Black WC, Littenberg B, Silvestri G. Cost-effectiveness of head CT in patients with lung cancer without clinical evidence of metastases. *Chest* 1995, **108**(5):1264-71.

133. Crocket JA, Wong EY, Lien DC, Nguyen KG, Chaput MR, McNamee C. Cost effectiveness of transbronchial needle aspiration. *Canadian Respiratory Journal* 1999, **6**(4):332-5.

134. Eddy RJ. Cost-effectiveness of CT scanning compared with mediastinoscopy in the preoperative staging of lung cancer. *Canadian Association of Radiologists Journal* 1989, **40**(4):189-93.

135. Esnaola NF, Lazarides SN, Mentzer SJ, Kuntz KM. Outcomes and cost-effectiveness of alternative staging strategies for non-small-cell lung cancer. *Journal of Clinical Oncology* 2002, **20**(1):263-73.

136. Guyatt GH, Bethune DCG, Deslauriers J, Inculet RI, Lefcoe MS, Winton TL *et al*. Investigating extrathoracic metastatic disease in patients with apparently operable lung cancer. The Canadian Lung Oncology Group. *Annals of Thoracic Surgery* 2001, **71**(2):425-33.

137. Houston GA, Sanders JA, Little DD, Griffith JE, Clericuzio C, Balducci L. Staging of lung cancer. A cost-effectiveness analysis. *American Journal of Clinical Oncology* 1985, **8**(3):224-30.

138. Jelinek JS, Redmond J, III, Perry JJ, Burrell LM, Benedikt RA, Geyer CA *et al*. Small cell lung cancer: staging with MR imaging. *Radiology* 1990, **177**(3):837-42.

139. Mayr NA, Yuh WT, Muhonen MG, Fisher DJ, Nguyen HD, Ehrhardt JC *et al*. Cost-effectiveness of high-dose MR contrast studies in the evaluation of brain metastases. *AJNR American Journal of Neuroradiology* 1994, **15**(6):1053-61.

140. Remer EM, Obuchowski N, Ellis JD, Rice TW, Adelstein DJ, Baker ME. Adrenal mass evaluation in patients with lung carcinoma: a cost-effectiveness analysis. *American Journal of Roentgenology* 2000, **174**(4):1033-9.

141. Tanaka K, Kubota K, Kodama T, Nagai K, Nishiwaki Y. Extrathoracic staging is not necessary for non-small-cell lung cancer with clinical stage T1-2 N0. *Annals of Thoracic Surgery* 1999, **68**(3):1039-42.

142. Dietlein M, Weber K, Gandjour A, Moka D, Theissen P, Lauterbach KW *et al*. Cost-effectiveness of FDG-PET for the management of potentially operable non-small cell lung cancer: priority for a PET-based strategy after nodal-negative CT results. *European Journal of Nuclear Medicine* 2000, **27**(11):1598-609.

143. Gambhir SS, Hoh CK, Phelps ME, Madar I, Maddahi J. 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* 1996, **37**(9):1428-36.

144. Scott WJ, Shepherd J, Gambhir SS. Cost-effectiveness of FDG-PET for staging non-small cell lung cancer: a decision analysis. *Annals of Thoracic Surgery* 1998, **66**(6):1876-83.

145. Verboom P, van Tinteren H, Hoekstra OS, Smit EF, Van den Bergh JHAM, Schreurs AJM *et al*. Cost-effectiveness of FDG-PET in staging non-small cell lung cancer: The PLUS study. *European Journal of Nuclear Medicine & Molecular Imaging* 2003, **30**(11):-1449.

146. von Schulthess GK, Steinert HC, Dummer R, Weder W. Cost-effectiveness of whole-body PET imaging in non-small cell lung cancer and malignant melanoma. *Academic Radiology* 1998, **5**(Suppl 2):S300-S302.

147. Hetzel M, Arslandemir C, Konig H-H, Buck AK, Nussle K, Glatting G *et al*. F-18 NaF PET for Detection of Bone Metastases in Lung Cancer: Accuracy, Cost-Effectiveness, and Impact on Patient Management. *Journal of Bone & Mineral Research* 2003, **18**(12):2206-14.

148. Harewood GC, Wiersema MJ, Edell ES, Liebow M. Cost-minimization analysis of alternative diagnostic approaches in a modeled patient with non-small cell lung cancer and subcarinal lymphadenopathy. *Mayo Clinic Proceedings* 2002, **77**(2):155-64.

149. Detterbeck FC, Egan TM. Surgery for stage II non-small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 12, 2001. pp 191-7. Philadelphia: W.B.Saunders.

150. Detterbeck FC, Jones DR. Surgery for stage IIIB non-small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 20, 2001. pp 283-9. Philadelphia: W.B.Saunders.

151. Detterbeck FC, Jones DR. Surgical treatment of stage IIIA(N2) non-small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 17, 2001. pp 244-56. Philadelphia: W.B.Saunders.

152. Jones DR, Detterbeck FC. Surgery for stage I non-small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 11, 2001. pp 177-90. Philedelphia: W.B.Saunders Company.

153. British Thoracic Society.,.Society of Cardiothoracic Surgeons of Great Britain and Ireland. BTS guidelines on the selection of patients with lung cancer for surgery. *Thorax* 2001, **56**(2):89-108.

154. Kiser AC, Detterbeck FC. General aspects of surgical treatment. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : an evidence-based guide for the practicing clinician*, 8, 2001. pp 133-47. Philadelphia: W.B.Saunders.

155. Nagasaki F, Flehinger BJ, Martini N. Complications of surgery in the treatment of carcinoma of the lung. *Chest* 1982, **82**(1):25-9.

156. Ginsberg RJ, Hill LD, Eagan RT, Thomas P, Mountain CF, Deslauriers J *et al*. Modern thirty-day operative mortality for surgical resections in lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 1983, **86**(5):654-8.

157. Deslauriers J, Ginsberg RJ, Piantadosi S, Fournier B. Prospective assessment of 30-day operative morbidity for surgical resections in lung cancer. *Chest* 1994, **106**(6 Suppl):329S-30S.

158. Whittle J, Steinberg EP, Anderson GF, Herbert R. Use of Medicare claims data to evaluate outcomes in elderly patients undergoing lung resection for lung cancer. *Chest* 1991, **100**(3):729-34.

159. Thomas P, Piraux M, Jacques LF, Gregoire J, Bedard P, Deslauriers J. Clinical patterns and trends of outcome of elderly patients with bronchogenic carcinoma. *European Journal of Cardio-Thoracic Surgery* 1998, **13**(3):266-74.

160. von Knorring J, Lepantalo M, Lindgren L, Lindfors O. Cardiac arrhythmias and myocardial ischemia after thoracotomy for lung cancer. *Annals of Thoracic Surgery* 1992, **53**(4):642-7.

161. Romano PS,.Mark DH. Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. *Chest* 1992, **101**(5):1332-7.

162. Deslauriers J, Ginsberg RJ, Dubois P, Beaulieu M, Goldberg M, Piraux M. Current operative morbidity associated with elective surgical resection for lung cancer. *Canadian Journal of Surgery* 1989, **32**(5):335-9.

163. Martini N, Bains MS, Burt ME, Zakowski MF, McCormack P, Rusch VW *et al.* Incidence of local recurrence and second primary tumors in resected stage I lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 1995, **109**(1):120-9.

164. Wada H, Tanaka F, Yanagihara K, Ariyasu T, Fukuse T, Yokomise H *et al.* Time trends and survival after operations for primary lung cancer from 1976 through 1990. *Journal of Thoracic and Cardiovascular Surgery* 1996, **112**(2):349-55.

165. Damhuis RAM,.Schutte PR. Resection rates and postoperative mortality in 7,899 patients with lung cancer. *European Respiratory Journal* 1996, **9**(1):7-10.

166. Duque JL, Ramos G, Castrodeza J, Cerezal J, Castanedo M, Yuste MG *et al.* Early complications in surgical treatment of lung cancer: a prospective, multicenter study. Grupo Cooperativo de Carcinoma Broncogenico de la Sociedad Espanola de Neumologia y Cirugia Toracica. *Annals of Thoracic Surgery* 1997, **63**(4):944-50.

167. Silvestri GA, Handy J, Lackland D, Corley E, Reed CE. Specialists achieve better outcomes than generalists for lung cancer surgery. *Chest* 1998, **114**(3):675-80.

168. Wada H, Nakamura T, Nakamoto K, Maeda M, Watanabe Y. Thirty-day operative mortality for thoracotomy in lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 1998, **115**(1):70-3.

169. Harpole DH, Jr., DeCamp MM, Jr., Daley J, Hur K, Oprian CA, Henderson WG *et al.* Prognostic models of thirty-day mortality and morbidity after major pulmonary resection. *Journal of Thoracic and Cardiovascular Surgery* 1999, **117**(5):969-79.

170. van Rens MT, de la Riviere AB, Elbers HR, Van Den Bosch JM. Prognostic assessment of 2,361 patients who underwent pulmonary resection for non-small cell lung cancer, stage I, II, and IIIA. *Chest* 2000, **117**(2):374-9.

171. Battafarano RJ, Piccirillo JF, Meyers BF, Hsu H-S, Guthrie TJ, Cooper JD *et al.* Impact of comorbidity on survival after surgical resection in patients with stage I non-small cell lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 2002, **123**(2):280-7.

172. Bernard A, Ferrand L, Hagry O, Benoit L, Cheynel N, Favre J-P. Identification of prognostic factors determining risk groups for lung resection. *Annals of Thoracic Surgery* 2000, **70**(4):1161-7.

173. Licker M, Spiliopoulos A, Freya J-G, De Perrot M, Chevalley C, Tschopp J-M. Management and outcome of patients undergoing thoracic surgery in a regional chest medical centre. *European Journal of Anaesthesiology* 2001, **18**(8):540-7.

174. Van Meerbeeck JP, Damhuis RA, Vos de Wael ML. High postoperative risk after pneumonectomy in elderly patients with right-sided lung cancer. *European Respiratory Journal* 2002, **19**(1):141-5.

175. Weinmann M, Jeremic B, Toomes H, Friedel G, Bamberg M. Treatment of lung cancer in the elderly. Part I: Non-small cell lung cancer. *Lung Cancer* 2003, **39**(3):233-53.

176. Wahi R, McMurtrey MJ, DeCaro LF, Mountain CF, Ali MK, Smith TL *et al.* Determinants of perioperative morbidity and mortality after pneumonectomy. *Annals of Thoracic Surgery* 1989, **48**(1):33-7.

177. Patel RL, Townsend ER, Fountain SW. Elective pneumonectomy: factors associated with morbidity and operative mortality. *Annals of Thoracic Surgery* 1992, **54**(1):84-8.

178. Miller DL, McManus KG, Allen MS, Ilstrup DM, Deschamps C, Trastek VF *et al.* Results of surgical resection in patients with N2 non-small cell lung cancer. *Annals of Thoracic Surgery* 1994, **57**(5):1095-101.

179. Harpole DH, Jr., Herndon JE, Young WG, Jr., Wolfe WG, Sabiston DC, Jr. Stage I nonsmall cell lung cancer. A multivariate analysis of treatment methods and patterns of recurrence. *Cancer* 1995, **76**(5):787-96.

180. Ferguson MK, Reeder LB, Mick R. Optimizing selection of patients for major lung resection. *Journal of Thoracic and Cardiovascular Surgery* 1995, **109**(2):275-81.

181. Knott-Craig CJ, Howell CE, Parsons BD, Paulsen SM, Brown BR, Elkins RC. Improved results in the management of surgical candidates with lung cancer. *Annals of Thoracic Surgery* 1997, **63**(5):1405-9.

182. Yano T, Yokoyama H, Fukuyama Y, Takai E, Mizutani K, Ichinose Y. The current status of postoperative complications and risk factors after a pulmonary resection for primary lung cancer. A multivariate analysis. *European Journal of Cardio-Thoracic Surgery* 1997, **11**(3):445-9.

183. Sok M, Dragas AZ, Erzen J, Jerman J. Sources of pathogens causing pleuropulmonary infections after lung cancer resection. *European Journal of Cardio-Thoracic Surgery* 2002, **22**(1):23-7.

184. Watanabe Y. Substaging of stage I—a commentary. *Lung Cancer* 2003, **42**(1):59-61.

185. Smythe WR. Treatment of stage I and II non-small-cell lung cancer. *Cancer Control* 2001, **8**(4):318-25.

186. Smythe WR. Treatment of stage I non-small cell lung carcinoma. *Chest* 2003, **123**(1 Suppl):181S-7S.

187. Adebonojo SA, Bowser AN, Moritz DM, Corcoran PC. Impact of revised stage classification of lung cancer on survival a military experience. *Chest* 1999, **115**(6):1507-13.

188. Inoue K, Sato M, Fujimura S, Sakurada A, Takahashi S, Usuda K *et al.* Prognostic assessment of 1310 patients with non-small-cell lung cancer who underwent complete resection from 1980 to 1993. *Journal of Thoracic and Cardiovascular Surgery* 1998, **116**(3):407-11.

189. Pastorino U, Andreola S, Tagliabue E, Pezzella F, Incarbone M, Sozzi G *et al.* Immunocytochemical markers in stage I lung cancer: relevance to prognosis. *Journal of Clinical Oncology* 1997, **15**(8):2858-65.

190. Mountain CF,.Dresler CM. Regional lymph node classification for lung cancer staging. *Chest* 1997, **111**(6):1718-23.

191. Kotlyarov EV,.Rukosuyev AA. Long-term results and patterns of disease recurrence after radical operations for lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 1991, **102**(1):24-8.

192. Read RC, Schaefer R, North N, Walls R. Diameter, cell type, and survival in stage I primary non-small-cell lung cancer. *Archives of Surgery* 1988, **123**(4):446-9.

193. Naruke T, Goya T, Tsuchiya R, Suemasu K. Prognosis and survival in resected lung carcinoma based on the new international staging system. *Journal of Thoracic and Cardiovascular Surgery* 1988, **96**(3):440-7.

194. Pairolero PC, Williams DE, Bergstralh EJ, Piehler JM, Bernatz PE, Payne WS. Postsurgical stage I bronchogenic carcinoma: morbid implications of recurrent disease. *Annals of Thoracic Surgery* 1984, **38**(4):331-8.

195. Williams DE, Pairolero PC, Davis CS, Bernatz PE, Payne WS, Taylor WF *et al.* Survival of patients surgically treated for stage I lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 1981, **82**(1):70-6.

196. Myrdal G, Lambe M, Gustafsson G, Nilsson K, Stahle E. Survival in primary lung cancer potentially cured by operation: influence of tumor stage and clinical characteristics. *Annals of Thoracic Surgery* 2003, **75**(2):356-63.

197. Suzuki K, Nagai K, Yoshida J, Moriyama E, Nishimura M, Takahashi K *et al.* Prognostic factors in clinical stage I non-small cell lung cancer. *Annals of Thoracic Surgery* 1999, **67**(4):927-32.

198. Churchill ED, Sweet RH, Sutter L. The surgical management of carcinoma in the lung a study of cases treated at the Massachussetts General Hospital from 1930-50. *Journal of Thoracic and Cardiovascular Surgery* 1950, **20**:349-65.

199. Ramsey HE, Cahan WG, Beattie EJ, Humphrey C. The importance of radical lobectomy in lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 1969, **58**(2):225-30.

200. Errett LE, Wilson J, Chiu RC, Munro DD. Wedge resection as an alternative procedure for peripheral bronchogenic carcinoma in poor-risk patients. *Journal of Thoracic and Cardiovascular Surgery* 1985, **90**(5):656-61.

201. Kodama K, Doi O, Higashiyama M, Yokouchi H. Intentional limited resection for selected patients with T1 N0 M0 non- small-cell lung cancer: A single-institution study. *Journal of Thoracic and Cardiovascular Surgery* 1997, **114**(3):347-53.

202. Yoshikawa K, Tsubota N, Kodama K, Ayabe H, Taki T, Mori T. Prospective study of extended segmentectomy for small lung tumors: the final report. *Annals of Thoracic Surgery* 2002, **73**(4):1055-8.

203. Okada M, Yoshikawa K, Hatta T, Tsubota N. Is segmentectomy with lymph node assessment an alternative to lobectomy for non-small cell lung cancer of 2 cm or smaller? *Annals of Thoracic Surgery* 2001, **71**(3):956-60.

204. Ginsberg RJ, Rubinstein LV, Benfield JR. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. *Annals of Thoracic Surgery* 1995, **60**(3):615-23.

205. Jensik RJ. The extent of resection for localized lung cancer: segmental resection. In: Kittle CF, ed. *Current controversies in thoracic surgery*, 1986. pp 175-82. Philadelphia: WB Saunders.

206. Warren WH,.Faber LP. Segmentectomy versus lobectomy in patients with stage I pulmonary carcinoma. Five-year survival and patterns of intrathoracic recurrence. *Journal of Thoracic and Cardiovascular Surgery* 1994, **107**(4):1087-93.

207. Kutschera W. Segment resection for lung cancer. *Thoracic & Cardiovascular Surgeon* 1984, **32**(2):102-4.

208. Landreneau RJ, Sugarbaker DJ, Mack MJ, Hazelrigg SR, Luketich JD, Fetterman L *et al.* Wedge resection versus lobectomy for stage I (T1 N0 M0) non-small-cell lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 1997, **113**(4):691-8.

209. Strauss. Extent of surgical resection influences survival in stage Ia NSCLC. *Proceedings of the American Society of Clinical Oncology* 1998, **17**:42-6.

210. Miller JI,.Hatcher CR, Jr. Limited resection of bronchogenic carcinoma in the patient with marked impairment of pulmonary function. *Annals of Thoracic Surgery* 1987, **44**(4):340-3.

211. Pastorino U, Valente M, Bedini V, Infante M, Tavecchio L, Ravasi G. Limited resection for Stage I lung cancer. *European Journal of Surgical Oncology* 1991, **17**(1):42-6.

212. Kohman LJ, Meyer JA, Ikins PM, Oates RP. Random versus predictable risks of mortality after thoracotomy for lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 1986, **91**(4):551-4.

213. Kadri MA,.Dussek JE. Survival and prognosis following resection of primary non small cell bronchogenic carcinoma. *European Journal of Cardio-Thoracic Surgery* 1991, **5**(3):132-6.

214. Busch E, Verazin G, Antkowiak JG, Driscoll D, Takita H. Pulmonary complications in patients undergoing thoracotomy for lung carcinoma. *Chest* 1994, **105**(3):760-6.

215. Deneffe G, Lacquet LM, Verbeken E, Vermaut G. Surgical treatment of bronchogenic carcinoma: a retrospective study of 720 thoracotomies. *Annals of Thoracic Surgery* 1988, **45**(4):380-3.

216. Izbicki JR, Knoefel WT, Passlick B, Habekost M, Karg O, Thetter O. Risk analysis and long-term survival in patients undergoing extended resection of locally advanced lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 1995, **110**(2):386-95.

217. Izbicki JR, Thetter O, Habekost M, Karg O, Passlick B, Kubuschok B *et al.* Radical systematic mediastinal lymphadenectomy in non-small cell lung cancer: A randomized controlled trial. *British Journal of Surgery* 1994, **81**(2):229-35.

218. Izbicki JR, Passlick B, Karg O, Bloechle C, Pantel K, Knoefel WT *et al.* Impact of radical systematic mediastinal lymphadenectomy on tumor staging in lung cancer. *Annals of Thoracic Surgery* 1995, **59**(1):209-14.

219. Izbicki JR, Passlick B, Pantel K, Pichlmeier U, Hosch SB, Karg O *et al.* Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. *Annals of Surgery* 1998, **227**(1):138-44.

220. 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**(3):290-4.

221. Passlick B, Kubuschock B, Sienel W, Thetter O, Pantel K, Izbicki JR. Mediastinal lymphadenectomy in non-small cell lung cancer: effectiveness in patients with or without nodal micrometastases - results of a preliminary study. *European Journal of Cardio-Thoracic Surgery* 2002, **21**(3):520-6.

222. Wu Y, Huang ZF, Wang SY, Yang XN, Ou W. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer* 2002, **36**(1):1-6.

223. Yim AP, Izzat MB, Liu HP, Ma CC. Thoracoscopic major lung resections: an Asian perspective. *Seminars in Thoracic and Cardiovascular Surgery* 1998, **10**(4):326-31.

224. McKenna RJ, Jr., Fischel RJ, Wolf R, Wurnig P. Video-assisted thoracic surgery (VATS) lobectomy for bronchogenic carcinoma. *Seminars in Thoracic and Cardiovascular Surgery* 1998, **10**(4):321-5.

225. Lewis RJ,.Caccavale RJ. Video-assisted thoracic surgical non-rib spreading simultaneously stapled lobectomy (VATS(n)SSL). *Seminars in Thoracic and Cardiovascular Surgery* 1998, **10**(4):332-9.

226. Roviaro G, Varoli F, Vergani C, Maciocco M. Video-assisted thoracoscopic surgery (VATS) major pulmonary resections: the Italian experience. *Seminars in Thoracic and Cardiovascular Surgery* 1998, **10**(4):313-20.

227. Walker WS. Video-assisted thoracic surgery (VATS) lobectomy: the Edinburgh experience. *Seminars in Thoracic and Cardiovascular Surgery* 1998, **10**(4):291-9.

228. Kaseda S, Aoki T, Hangai N. Video-assisted thoracic surgery (VATS) lobectomy: the Japanese experience. *Seminars in Thoracic and Cardiovascular Surgery* 1998, **10**(4):300-4.

229. Brown WT. Video-assisted thoracic surgery: the Miami experience. *Seminars in Thoracic and Cardiovascular Surgery* 1998, **10**(4):305-12.

230. Gharagozloo F, Tempesta B, Margolis M, Alexander EP. Video-assisted thoracic surgery lobectomy for stage I lung cancer. *Annals of Thoracic Surgery* 2003, **76**(4):1009-14.

231. Thomas JR,.von Gunten CF. Clinical management of dyspnoea. *Lancet Oncology* 2002, **3**(4):223-8.

232. Kirby TJ, Mack MJ, Landreneau RJ, Rice TW. Lobectomy—video-assisted thoracic surgery versus muscle-sparing thoracotomy. A randomized trial. *Journal of Thoracic and Cardiovascular Surgery* 1995, **109**(5):997-1001.

233. Giudicelli R, Thomas P, Lonjon T, Ragni J, Morati N, Ottomani R *et al.* Video-assisted minithoracotomy versus muscle-sparing thoracotomy for performing lobectomy. *Annals of Thoracic Surgery* 1994, **58**(3):712-7.

234. Kaseda S, Aoki T, Hangai N, Shimizu K. Better pulmonary function and prognosis with video-assisted thoracic surgery than with thoracotomy. *Annals of Thoracic Surgery* 2000, **70**(5):1644-6.

235. Scott WJ, Howington J, Movsas B. Treatment of stage II non-small cell lung cancer. *Chest* 2003, **123**(1 Suppl):188S-201S.

236. Bulzebruck H, Bopp R, Drings P, Bauer E, Krysa S, Probst G *et al.* New aspects in the staging of lung cancer. Prospective validation of the International Union Against Cancer TNM classification. *Cancer* 1992, **70**(5):1102-10.

237. Jie C, Wever AM, Huysmans HA, Franken HC, Wever-Hess J, Hermans J. Time trends and survival in patients presented for surgery with non-small-cell lung cancer 1969-1985. *European Journal of Cardio-Thoracic Surgery* 1990, **4**(12):653-7.

238. Maggi G, Casadio C, Mancuso M, Oliaro A, Cianci R, Ruffini E. Resection and radical lymphadenectomy for lung cancer: prognostic significance of lymphatic metastases. *International Surgery* 1990, **75**(1):17-21.

239. Martini N, Burt ME, Bains MS, McCormack PM, Rusch VW, Ginsberg RJ. Survival after resection of stage II non-small cell lung cancer. *Annals of Thoracic Surgery* 1992, **54**(3):460-5.

240. Mountain CF, Lukeman JM, Hammar SP, Chamberlain DW, Coulson WF, Page DL *et al.* Lung cancer classification: the relationship of disease extent and cell type to survival in a clinical trials population. *Journal of Surgical Oncology* 1987, **35**(3):147-56.

241. Naruke T, Tsuchiya R, Kondo H, Asamura H, Nakayama H. Implications of staging in lung cancer. *Chest* 1997, **112**(4 Suppl):242S-8S.

242. van Velzen E, Snijder RJ, Brutel DLR, Elbers HR, Van Den Bosch JM. Lymph node type as a prognostic factor for survival in T2 N1 M0 non-small cell lung carcinoma. *Annals of Thoracic Surgery* 1997, **63**(5):1436-40.

243. Jassem J, Skokowski J, Dziadziuszko R, Jassem E, Szymanowska A, Rzyman W *et al.* Results of surgical treatment of non-small cell lung cancer: validation of the new postoperative pathologic TNM classification. *Journal of Thoracic and Cardiovascular Surgery* 2000, **119**(6):1141-6.

244. Ferguson MK,.Lehman AG. Sleeve lobectomy or pneumonectomy: optimal management strategy using decision analysis techniques. *Annals of Thoracic Surgery* 2003, **76**(6):1782-8.

245. Martin-Ucar AE, Chaudhuri N, Edwards JG, Waller DA. Can pneumonectomy for non-small cell lung cancer be avoided? An audit of parenchymal sparing lung surgery. *European Journal of Cardio-Thoracic Surgery* 2002, **21**(4):601-5.

246. Detterbeck FC, Kiser AC. T3 non-small cell lung cancer (stage IIB-IIIA). In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 15, 2001. pp 223-32. Philadelphia: W.B.Saunders.

247. Downey RJ, Martini N, Rusch VW, Bains MS, Korst RJ, Ginsberg RJ. Extent of chest wall invasion and survival in patients with lung cancer. *Annals of Thoracic Surgery* 1999, **68**(1):188-93.

248. Okada M, Tsubota N, Yoshimura M, Miyamoto Y, Matsuoka H. How should interlobar pleural invasion be classified? Prognosis of resected T3 non-small cell lung cancer. *Annals of Thoracic Surgery* 1999, **68**(6):2049-52.

249. Trastek VF, Pairolero PC, Piehler JM, Weiland LH, O'Brien PC, Payne WS *et al.* En bloc (non-chest wall) resection for bronchogenic carcinoma with parietal fixation. Factors affecting survival. *Journal of Thoracic and Cardiovascular Surgery* 1984, **87**(3):352-8.

250. Piehler JM, Pairolero PC, Weiland LH, Offord KP, Payne WS, Bernatz PE. Bronchogenic carcinoma with chest wall invasion: factors affecting survival following en bloc resection. *Annals of Thoracic Surgery* 1982, **34**(6):684-91.

251. Mountain CF. Expanded possibilities for surgical treatment of lung cancer. Survival in stage IIIa disease. *Chest* 1990, **97**(5):1045-51.

252. Harpole DH, Jr., Healey EA, DeCamp MM, Jr., Mentzer SJ, Strauss GM, Sugarbaker DJ. Chest wall invasive non-small cell lung cancer: patterns of failure and implications for a revised staging system. *Annals of Surgical Oncology* 1996, **3**(3):261-9.

253. Allen MS, Mathisen DJ, Grillo HC, Wain JC, Moncure AC, Hilgenberg AD. Bronchogenic carcinoma with chest wall invasion. *Annals of Thoracic Surgery* 1991, **51**(6):948-51.

254. Ricci C, Rendina EA, Venuta F. En bloc resection for T3 bronchogenic carcinoma with chest wall invasion. *European Journal of Cardio-Thoracic Surgery* 1987, **1**(1):23-8.

255. Paone JF, Spees EK, Newton CG, Lillemoe KD, Kieffer RF, Gadacz TR. An appraisal of en bloc resection of peripheral bronchogenic carcinoma involving the thoracic wall. *Chest* 1982, **81**(2):203-7.

256. Patterson GA, Ilves R, Ginsberg RJ, Cooper JD, Todd TR, Pearson FG. The value of adjuvant radiotherapy in pulmonary and chest wall resection for bronchogenic carcinoma. *Annals of Thoracic Surgery* 1982, **34**(6):692-7.

257. Lopez L, Lopez PJ, Varela A, Baamonde C, Socas L, Salvatierra A *et al.* Surgical treatment of stage III non-small cell bronchogenic carcinoma involving the chest wall. *Scandinavian Journal of Thoracic & Cardiovascular Surgery* 1992, **26**(2):129-33.

258. Ratto GB, Piacenza G, Frola C, Musante F, Serrano I, Giua R *et al.* Chest wall involvement by lung cancer: computed tomographic detection and results of operation. *Annals of Thoracic Surgery* 1991, **51**(2):182-8.

259. Casillas M, Paris F, Tarrazona V, Padilla J, Paniagua M, Galan G. Surgical treatment of lung carcinoma involving the chest wall. *European Journal of Cardio-Thoracic Surgery* 1989, **3**(5):425-9.

260. van Velzen E, de la Riviere AB, Elbers HJ, Lammers JW, Van Den Bosch JM. Type of lymph node involvement and survival in pathologic N1 stage III non-small cell lung carcinoma. *Annals of Thoracic Surgery* 1999, **67**(4):903-7.

261. Albertucci M, DeMeester TR, Rothberg M, Hagen JA, Santoscoy R, Smyrk TC. Surgery and the management of peripheral lung tumors adherent to the parietal pleura. *Journal of Thoracic and Cardiovascular Surgery* 1992, **103**(1):8-12.

262. Shah SS,.Goldstraw P. Combined pulmonary and thoracic wall resection for stage III lung cancer. *Thorax* 1995, **50**(7):782-4.

263. McCaughan BC, Martini N, Bains MS, McCormack PM. Chest wall invasion in carcinoma of the lung. Therapeutic and prognostic implications. *Journal of Thoracic and Cardiovascular Surgery* 1985, **89**(6):836-41.

264. Magdeleinat P, Alifano M, Benbrahem C, Spaggiari L, Porrello C, Puyo P *et al.* Surgical treatment of lung cancer invading the chest wall: results and prognostic factors. *Annals of Thoracic Surgery* 2001, **71**(4):1094-9.

265. Burt ME, Pomerantz AH, Bains MS, McCormack PM, Kaiser LR, Hilaris BS *et al.* Results of surgical treatment of stage III lung cancer invading the mediastinum. *Surgical Clinics of North America* 1987, **67**(5):987-1000.

266. Robinson LA, Wagner JH, Ruckdeschel JC. Treatment of stage IIIA non-small cell lung cancer. *Chest* 2003, **123**(1 Suppl):202S-20S.

267. Ruckdeschel JC. Combined modality therapy of non-small cell lung cancer. *Seminars in Oncology* 1997, **24**(4):429-39.

268. Garland L, Robinson LA, Wagner H. Evaluation and management of patients with stage IIIA (N2) non-small-cell lung cancer. *Chest Surgery Clinics of North America* 2001, **11**(1):69-100.

269. Sugi K, Kaneda Y, Nawata K, Fujita N, Ueda K, Nawata S *et al.* Cost analysis for thoracoscopy: thoracoscopic wedge resection and lobectomy. *Surgery Today* 1998, **28**(1):41-5.

270. Liu HP. Cost containing strategies in video-assisted thoracic surgery. *Asian Journal of Surgery* 1999, **22**(1):56-61.

271. Liu HP, Wu YC, Liu YH, Hsieh MJ, Cheng KS, Chu JJ *et al.* Cost-effective approach of video-assisted thoracic surgery: 7 years experience. *Changgeng Yi Xue Za Zhi* 2000, **23**(7):405-12.

272. Lewis RJ, Caccavale RJ, Sisler GE, Bocage JP, O'Brien K, Warner S. Is video-assisted thoracic surgery cost effective? *New Jersey Medicine* 1996, **93**(12):35-41.

273. Nakajima J, Takamoto S, Kohno T, Ohtsuka T. Costs of videothoracoscopic surgery versus open resection for patients with of lung carcinoma. *Cancer* 2000, **89**(11 Suppl):2497-501.

274. Patton MD,.Schaerf R. Thoracotomy, critical pathway, and clinical outcomes. *Cancer Practice* 1995, **3**(5):286-94.

275. Wright CD, Wain JC, Grillo HC, Moncure AC, Macaluso SM, Mathisen DJ. Pulmonary lobectomy patient care pathway: a model to control cost and maintain quality. *Annals of Thoracic Surgery* 1997, **64**(2):299-302.

276. Zehr KJ, Dawson PB, Yang SC, Heitmiller RF. Standardized clinical care pathways for major thoracic cases reduce hospital costs. *Annals of Thoracic Surgery* 1998, **66**(3):914-9.

277. Abratt RP. Modeling tumor and treated lung volume influences in the irradiation of non-small-cell lung cancer patients. *International Journal of Radiation Oncology, Biology, Physics* 2001, **49**(2):481-5.

278. Rodrigues G, Lock M, D'Souza D, Yu E, van Dyk J. Prediction of radiation pneumonitis by dose-volume histogram parameters in lung cancer - a systematic review. *Radiotherapy and Oncology* 2004, **71**(2):127-38.

279. Rowell NP,.Williams CJ. Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable). *Cochrane Database of Systematic Reviews* 2001, **Issue 2**:Art No.: CD002935.

280. Clark JA, Rosenman JG, Detterbeck FC. Radiotherapy alone for stage IIIA,B non-small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 18, 2001. pp 257-66. Philadelphia: W.B.Saunders.

281. Firat S, Bousamra M, Gore E, Byhardt RW. Comorbidity and KPS are independent prognostic factors in stage I non-small-cell lung cancer. *International Journal of Radiation Oncology, Biology, Physics* 2002, **52**(4):1047-57.

282. Vrdoljak E, Mise K, Sapunar D, Rozga A, Marusic M. Survival analysis of untreated patients with non-small-cell lung cancer. *Chest* 1994, **106**(6):1797-800.

283. Saunders M, Dische S, Barrett A, Harvey A, Griffiths G, Palmar M. Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial. CHART Steering committee. *Radiotherapy and Oncology* 1999, **52**(2):137-48.

284. Bentzen SM, Saunders MI, Dische S, Parmar MK. Updated data for CHART in NSCLC: further analyses. *Radiotherapy and Oncology* 2000, **55**(1):86-7.

285. Koukourakis M, Hlouverakis G, Kosma L, Skarlatos J, Damilakis J, Giatromanolaki A *et al.* The impact of overall treatment time on the results of radiotherapy for nonsmall cell lung carcinoma. *International Journal of Radiation Oncology, Biology, Physics* 1996, **34**(2):315-22.

286. Langendijk JA, Aaronson NK, de Jong JM, ten Velde GP, Muller MJ, Slotman BJ *et al.* Quality of life after curative radiotherapy in Stage I non-small-cell lung cancer. *International Journal of Radiation Oncology, Biology, Physics* 2002, **53**(4):847-53.

287. Le Chevalier T, Arriagada R, Quoix E, Ruffie P, Martin M, Tarayre M *et al.* Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. *Journal of the National Cancer Institute* 1991, **83**(6):417-23.

288. Sause W, Kolesar P, Taylor S IV, Johnson D, Livingston R, Komaki R *et al.* Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest* 2000, **117**(2):358-64.

289. Perez CA, Bauer M, Emami BN, Byhardt R, Brady LW, Doggett RL *et al.* Thoracic irradiation with or without levamisole (NSC #177023) in unresectable non-small cell carcinoma of the lung: a phase III randomized trial of the RTOG. *International Journal of Radiation Oncology, Biology, Physics* 1988, **15**(6):1337-46.

290. Simpson JR, Bauer M, Perez CA, Wasserman TH, Emami B, Doggett RL *et al.* Radiation therapy alone or combined with misonidazole in the treatment of locally advanced non-oat cell lung cancer: report of an RTOG prospective randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 1989, **16**(6):1483-91.

291. Blanke C, Ansari R, Mantravadi R, Gonin R, Tokars R, Fisher W *et al.* Phase III trial of thoracic irradiation with or without cisplatin for locally advanced unresectable non-small-cell lung cancer: a Hoosier Oncology Group protocol. *Journal of Clinical Oncology* 1995, **13**(6):1425-9.

292. Johnson DH, Einhorn LH, Bartolucci A, Birch R, Omura G, Perez CA *et al.* Thoracic radiotherapy does not prolong survival in patients with locally advanced, unresectable non-small cell lung cancer. *Annals of Internal Medicine* 1990, **113**(1):33-8.

293. Rivera MP, Detterbeck FC, Loomis DP. Epidemiology and classification of lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 3, 2001. pp 25-44. Philadelphia: W.B.Saunders.

294. Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Perez CA. N2 (clinical) non-small cell carcinoma of the lung: prospective trials of radiation therapy with total doses 60 Gy by the Radiation Therapy Oncology Group. *International Journal of Radiation Oncology, Biology, Physics* 1991, **20**(1):7-12.

295. Curran WJ, Jr.,.Stafford PM. Lack of apparent difference in outcome between clinically staged IIIA and IIIB non-small-cell lung cancer treated with radiation therapy. *Journal of Clinical Oncology* 1990, **8**(3):409-15.

296. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Hyperfractionated radiation therapy with or without concurrent low-dose daily carboplatin/etoposide for stage III non-small-cell lung cancer: a randomized study. *Journal of Clinical Oncology* 1996, **14**(4):1065-70.

297. Kreisman H, Lisbona A, Olson L, Propert KJ, Modeas C, Dillman RO *et al.* Effect of radiologic stage III substage on nonsurgical therapy of non-small cell lung cancer. *Cancer* 1993, **72**(5):1588-96.

298. Reinfuss M, yszewski J, Kowalska T, Rzepecki W, ek D. Palliative radiotherapy in asymptomatic patients with locally advanced, unresectable, non-small cell lung cancer. *Strahlentherapie und Onkologie* 1993, **169**(12):709-15.

299. Rosenthal SA, Curran WJ, Jr., Herbert SH, Hughes EN, Sandler HM, Stafford PM *et al.* Clinical stage II non-small cell lung cancer treated with radiation therapy alone. The significance of clinically staged ipsilateral hilar adenopathy (N1 disease). *Cancer* 1992, **70**(10):2410-7.

300. Wurschmidt F, Bunemann H, Bunemann C, Beck-Bornholdt HP, Heilmann HP. Inoperable non-small cell lung cancer: a retrospective analysis of 427 patients treated with high-dose radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 1994, **28**(3):583-8.

301. Etiz D, Marks LB, Zhou SM, Bentel GC, Clough R, Hernando ML *et al.* Influence of tumor volume on survival in patients irradiated for non-small-cell lung cancer. *International Journal of Radiation Oncology, Biology, Physics* 2002, **53**(4):835-46.

302. Perez CA, Pajak TF, Rubin P, Simpson JR, Mohiuddin M, Brady LW *et al.* Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987, **59**(11):1874-81.

303. Lung Cancer Disease Site Group and Cancer Care Ontario Practice Guidelines Initiative (2000) Altered fractionation of radical radiation therapy in the management of unresectable non-small cell lung cancer. Ontario: Cancer Care Ontario Practice Guidelines Initiative.

304. Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Pajak TF. A randomized phase I/II trial of hyperfractionated radiation therapy with total doses of 60.0 Gy to 79.2 Gy: possible survival benefit with greater than or equal to 69.6 Gy in favorable patients with Radiation Therapy Oncology Group stage III non-small-cell lung carcinoma: report of Radiation Therapy Oncology Group 83-11. *Journal of Clinical Oncology* 1990, **8**(9):1543-55.

305. Saunders MI, Rojas A, Lyn BE, Wilson E, Phillips H. Dose-escalation with CHARTWEL (continuous hyperfractionated accelerated radiotherapy week-end less) combined with neo-adjuvant chemotherapy in the treatment of locally advanced non-small cell lung cancer. *Clinical Oncology* 2002, **14**(5):352-60.

306. Chen M, Jiang GL, Fu XL, Wang LJ, Qian H, Chen GY *et al.* The impact of overall treatment time on outcomes in radiation therapy for non-small cell lung cancer. *Lung Cancer* 2000, **28**(1):11-9.

307. Scott C, Sause WT, Byhardt R, Marcial V, Pajak TF, Herskovic A *et al.* Recursive partitioning analysis of 1592 patients on four Radiation Therapy Oncology Group studies in inoperable non-small cell lung cancer. *Lung Cancer* 1997, **17**(Suppl 1):S59-S74.

308. Firat S, Byhardt RW, Gore E. Comorbidity and Karnofksy performance score are independent prognostic factors in stage III non-small-cell lung cancer: An institutional analysis of patients treated on four RTOG studies. *International Journal of Radiation Oncology, Biology, Physics* 2002, **54**(2):357-64.

309. Langendijk JA, Aaronson NK, de Jong JM, ten Velde GP, Muller MJ, Lamers RJ *et al.* Prospective study on quality of life before and after radical radiotherapy in non-small-cell lung cancer. *Journal of Clinical Oncology* 2001, **19**(8):2123-33.

310. Coyle D,.Drummond MF. Costs of conventional radical radiotherapy versus continuous hyperfractionated accelerated radiotherapy (CHART) in the treatment of patients with head and neck cancer or carcinoma of the bronchus. Medical Research Council CHART Steering Committee. *Clinical Oncology (Royal College of Radiologists)* 1997, **9**(5):313-21.

311. Saunders MI, Dische S, Barrett A, Parmar MK, Harvey A, Gibson D. Randomised multicentre trials of CHART vs conventional radiotherapy in head and neck and non-small-cell lung cancer: an interim report. CHART Steering Committee. *British Journal of Cancer* 1996, **73**(12):1455-62.

312. Netten, A. and Curtis, L. (2002) Unit costs of health and social care. Canterbury: Personal Social Services Research Unit, University of Kent and Canterbury.

313. Beck JR, Pauker SG, Gottlieb JE, Klein K, Kassirer JP. A convenient approximation of life expectancy (the "DEALE"). II. Use in medical decision-making. *American Journal of Medicine* 1982, **73**(6):889-97.

314. Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the "DEALE"). I. Validation of the method. *American Journal of Medicine* 1982, **73**(6):883-8.

315. Wake, B. L., Taylor, R. S., and Sandercock, J. (2002) Hyperfractionated/ accelerated radiotherapy regimens for the treatment of non-small cell lung cancer. A systematic review of clinical and cost-effectiveness. Birmingham: University of Birmingham, Department of Public Health and Epidemiology.

316. Hohenberg G,.Sedlmayer F. Costs of standard and conformal photon radiotherapy in Austria. *Strahlentherapie und Onkologie* 1999, **175**(Suppl 2):99-101.

317. Horwitz EM. Three-dimensional conformal radiation therapy: what are the costs and benefits? *Surgical Oncology Clinics of North America* 2000, **9**(3):455-67.

318. Glazebrook GA. Radiation therapy: a long term cost benefit analysis in a North American region. *Clinical Oncology (Royal College of Radiologists)* 1992, **4**(5):302-5.

319. Barton MB, Gebski V, Manderson C, Langlands AO. Radiation therapy: are we getting value for money? *Clinical Oncology (Royal College of Radiologists)* 1995, **7**(5):287-92.

320. Dale RG,.Jones B. Radiobiologically based assessments of the net costs of fractionated radiotherapy. *International Journal of Radiation Oncology, Biology, Physics* 1996, **36**(3):739-46.

321. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy for non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2000, **Issue 2**:Art No.: CD002139.

322. Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer. *Health Technology Assessment (Winchester, England)* 2001, **5**(32):1-195.

323. Socinski MA. Chemotherapy for stage IV non-small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 22, 2001. pp 307-25. Philadelphia: W.B.Saunders.

324. National Institute of Clinical Excellence (2001) Guidance on the use of docetaxel, paclitaxel, gemcitabine and vinorelbine for the treatment of non-small cell lung cancer. London: National Institute of Clinical Excellence.

325. Bonfill X, Serra C, Sacristan M, Nogue M, Losa F, Montesinos J. Second-line chemotherapy for non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2000, **Issue 4**:Art No.: CD002804.

326. Lung Cancer Disease Site Group and Cancer Care Ontario Practice Guidelines Initiative (2001) The role of single-agent Docetaxel (Taxotere) as a second-line treatment for advanced non-small cell lung cancer. Ontario: Cancer Care Ontario Practice Guideline Initiative.

327. Lung Cancer Disease Site Group and Cancer Care Ontario Practice Guidelines Initiative (2001) Use of Vinorelbine in non-small cell lung cancer. Ontario: Cancer Care Ontario Practice Guideline Initiative.

328. Lung Cancer Disease Site Group and Cancer Care Ontario Practice Guidelines Initiative (2002) Chemotherapy in stage IV (metastatic) non-small cell lung cancer. Ontario: Cancer Care Ontario Practice Guidelines Initiative.

329. Lung Cancer Disease Site Group and Cancer Care Ontario Practice Guidelines Initiative (2002) Use of Gemcitabine in non-small cell lung cancer. Ontario: Cancer Care Ontario Practice Guidelines Initiative.

330. Royal College of Physicians of London (2000) The cancer patient's physician: recommendations for the development of medical oncology in England and Wales. London: Royal College of Physicians of London.

331. Lopez PG, Stewart DJ, Newman TE, Evans WK. Chemotherapy in stage IV (metastatic) non-small-cell lung cancer. Provincial Lung Disease Site Group. *Cancer Prevention and Control* 1997, **1**(1):18-27.

332. Spiro SG, Rudd RM, Souhami RL, Brown J, Fairlamb DJ, Gower NH *et al.* Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life. *Thorax* 2004, **59**(10):828-36.

333. Stinchcombe TE, Socinski MA. General aspects of chemotherapy. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practising clinician*, 10, 2001. pp 162-73. Philedelphia: W.B.Saunders Company.

334. Bokkel Huinink WW, Bergman B, Chemaissani A, Dornoff W, Drings P, Kellokumpu-Lehtinen PL *et al.* Single-agent gemcitabine: An active and better tolerated alternative to standard cisplatin-based chemotherapy in locally advanced or metastatic non-small cell lung cancer. *Lung Cancer* 1999, **26**(2):85-94.

335. Le Chevalier T, Brisgand D, Douillard JY, Pujol JL, Alberola V, Monnier A *et al.* Randomized study of vinorelbine and cisplatin versus vindesine and cisplatin versus vinorelbine alone in advanced non-small-cell lung cancer: results of a European multicenter trial including 612 patients. *Journal of Clinical Oncology* 1994, **12**(2):360-7.

336. Perng RP, Chen YM, Ming-Liu J, Tsai CM, Lin WC, Yang KY *et al.* Gemcitabine versus the combination of cisplatin and etoposide in patients with inoperable non-small-cell lung cancer in a phase II randomized study. *Journal of Clinical Oncology* 1997, **15**(5):2097-102.

337. Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M *et al.* Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicentre trial. *Lancet* 2001, **357**(9267):1478-84.

338. Giaccone G,.European Organization for Research and Treatment of Cancer Group. Early results of a randomized phase III trial of platinum-containing doublets versus a nonplatinum doublet in the treatment of advanced non-small cell lung cancer: European Organization for Research and Treatment of Cancer 08975. *Seminars in Oncology* 2002, **29**(3 Suppl 9):47-9.

339. Vansteenkiste J, Vandebroek J, Nackaerts K, Dooms C, Galdermans D, Bosquee L *et al.* Influence of cisplatin-use, age, performance status and duration of chemotherapy on symptom control in advanced non-small cell lung cancer: Detailed symptom analysis of a randomised study comparing cisplatin-vindesine to gemcitabine. *Lung Cancer* 2003, **40**(2):191-9.

340. Vansteenkiste JF, Vandebroek JE, Nackaerts KL, Weynants P, Valcke YJ, Verresen DA *et al.* Clinical-benefit response in advanced non-small-cell lung cancer: A multicentre prospective randomised phase III study of single agent gemcitabine versus cisplatin-vindesine. *Annals of Oncology* 2001, **12**(9):1221-30.

341. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E *et al.* Randomized, Multinational, Phase III Study of Docetaxel Plus Platinum Combinations Versus Vinorelbine Plus Cisplatin for Advanced Non-Small-Cell Lung Cancer: The TAX 326 Study Group. *Journal of Clinical Oncology* 2003, **21**(16):3016-24.

342. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J *et al.* Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *New England Journal of Medicine* 2002, **346**(2):92-8.

343. Zatloukal P, Petruzelka L, Zemanova M, Kolek V, Skrickova J, Pesek M *et al.* Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. *Lung Cancer* 2003, **41**(3):321-31.

344. Rosell R, Gatzemeier U, Betticher DC, Keppler U, Macha HN, Pirker R *et al.* Phase III randomised trial comparing paclitaxel/ carboplatin with paclitaxel/ cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. *Annals of Oncology* 2002, **13**(10):1539-49.

345. Belani CP, Barstis J, Perry MC, La Rocca RV, Nattam SR, Rinaldi D *et al.* Multicenter, Randomized Trial for Stage IIIB or IV Non–Small-Cell Lung Cancer Using Weekly Paclitaxel and Carboplatin Followed by Maintenance Weekly Paclitaxel or Observation. *Journal of Clinical Oncology* 2003, **21**(15):2933-9.

346. Comella P,.Southern Italy Cooperative Oncology Group. Phase III trial of cisplatin/gemcitabine with or without vinorelbine or paclitaxel in advanced non-small cell lung cancer. *Seminars in Oncology* 2001, **28**(2 Suppl 7):7-10.

347. Scagliotti GV, de Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S *et al.* Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *Journal of Clinical Oncology* 2002, **20**(21):4285-91.

348. Bonomi PD. Novel treatment approaches for non-small cell lung cancer. *Lung Cancer* 2000, **29**(Suppl 2):129.

349. Baldini E, Tibaldi C, Ardizzoni A, Salvati F, Antilli A, Portalone L *et al.* Cisplatin-vindesine-mitomycin (MVP) vs cisplatin-ifosfamide-vinorelbine (PIN) vs carboplatin-vinorelbine (CaN) in patients with advanced non-small-cell lung cancer (NSCLC): a FONICAP randomized phase II study. Italian Lung Cancer Task Force (FONICAP). *British Journal of Cancer* 1998, **77**(12):2367-70.

350. Colleoni M, Vicario G, Pancheri F, Sgarbossa G, Nelli P, Manente P. A randomized phase II trial of cisplatinum plus mitomycin-C plus vinorelbine and carboplatin plus vinorelbine in advanced non-small cell lung cancer. *International Journal of Oncology* 1997, **10**(3):619-22.

351. Comella P, Frasci G, Panza N, Manzione L, De Cataldis G, Cioffi R *et al.* Randomized trial comparing cisplatin, gemcitabine, and vinorelbine with either cisplatin and gemcitabine or cisplatin and vinorelbine in advanced non-small-cell lung cancer: interim analysis of a phase III trial of the Southern Italy Cooperative Oncology Group. *Journal of Clinical Oncology* 2000, **18**(7):1451-7.

352. Crino L, Scagliotti GV, Ricci S, de Marinis F, Rinaldi M, Gridelli C *et al.* Gemcitabine and cisplatin versus mitomycin, ifosfamide, and cisplatin in advanced non-small-cell lung cancer: A randomized phase III study of the Italian Lung Cancer Project. *Journal of Clinical Oncology* 1999, **17**(11):3522-30.

353. Alberola V, Camps C, Provencio M, Isla D, Rosell R, Vadell C *et al.* Cisplatin Plus Gemcitabine Versus a Cisplatin-Based Triplet Versus Nonplatinum Sequential Doublets in Advanced Non-Small-Cell Lung Cancer: A Spanish Lung Cancer Group Phase III Randomized Trial. *Journal of Clinical Oncology* 2003, **21**(17):3207-13.

354. Danson S, Middleton MR, O'Byrne KJ, Clemons M, Ranson M, Hassan J *et al.* Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. *Cancer* 2003, **98**(3):542-53.

355. Greco FA, Gray JR, Jr., Thompson DS, Burris HA, III, Erland JB, Barton JH, Jr. *et al.* Prospective randomized study of four novel chemotherapy regimens in patients with advanced nonsmall cell lung carcinoma: a minnie pearl cancer research network trial. *Cancer* 2002, **95**(6):1279-85.

356. Rudd, R. M., Gower, N. H., Spiro, S. G., Eisen, T., Harper, P. G., Littler, J., Hatton, M., Johnson, P. W. M., Martin, W. M. C., Rankin, E. M., James, L. E., Gregory, W., Qian, W., and Lee, S. M. Gemcitabine plus Carboplatin versus Mitomycin, Ifosfamide and Cisplatin in Patients with Stage IIIB or IV Non-Small Cell Lung Cancer: A Phase III Randomised Study of the London Lung Cancer Group. [unpublished data] 2004.

357. Depierre A, Chastang C, Quoix E, Lebeau B, Blanchon F, Paillot N *et al.* Vinorelbine versus vinorelbine plus cisplatin in advanced non-small cell lung cancer: a randomized trial. *Annals of Oncology* 1994, **5**(1):37-42.

358. Lorusso V, Pezzella G, Catino AM, Guida M, Scoditti S, Lorenzo R *et al.* Results of a clinical multicentric randomized phase II study of non-small cell lung cancer treated with vinorelbine-cisplatin versus vinorelbine alone. *International Journal of Oncology* 1995, **6**(1):65-8.

359. Gridelli C, Gallo C, Shepherd FA, Illiano A, Piantedosi F, Robbiati SF *et al.* Gemcitabine Plus Vinorelbine Compared With Cisplatin Plus Vinorelbine or Cisplatin Plus Gemcitabine for Advanced Non-Small-Cell Lung Cancer: A Phase III Trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group. *Journal of Clinical Oncology* 2003, **21**(16):3025-34.

360. Smit EF, Van Meerbeeck JP, Lianes P, Debruyne C, Legrand C, Schramel F *et al.* Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group—EORTC 08975. *Journal of Clinical Oncology* 2003, **21**(21):3909-17.

361. Kosmidis P, Mylonakis N, Nicolaides C, Kalophonos C, Samantas E, Boukovinas J *et al.* Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small-cell lung cancer: a phase III randomized trial. *Journal of Clinical Oncology* 2002, **20**(17):3578-85.

362. Smith IE, O'Brien ME, Talbot DC, Nicolson MC, Mansi JL, Hickish TF *et al.* Duration of chemotherapy in advanced non-small-cell lung cancer: a randomized trial of three versus six courses of mitomycin, vinblastine, and cisplatin. *Journal of Clinical Oncology* 2001, **19**(5):1336-43.

363. Socinski MA, Schell MJ, Peterman A, Bakri K, Yates S, Gitten R *et al.* Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. *Journal of Clinical Oncology* 2002, **20**(5):1335-43.

364. Esteban E, Gonzalez dS, Fernandez Y, Corral N, Fra J, Muniz I *et al.* Prospective randomised phase II study of docetaxel versus paclitaxel administered weekly in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *Annals of Oncology* 2003, **14**(11):1640-7.

365. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M *et al.* Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *Journal of Clinical Oncology* 2000, **18**(10):2095-103.

366. Maslove, L., McInnes, F., Chaplin, S., Posnett, J., West, P., and West, M. Analysis of the additional costs of chemotherapy for patients with advanced non-small cell lung cancer. [unpublished data] 2001.

367. Billingham LJ, Bathers S, Burton A, Bryan S, Cullen MH. Patterns, costs and cost-effectiveness of care in a trial of chemotherapy for advanced non-small cell lung cancer. *Lung Cancer* 2002, **37**(2):219-25.

368. Lees M, Aristides M, Maniadakis N, McKendrick J, Botwood N, Stephenson D. Economic evaluation of gemcitabine alone and in combination with cisplatin in the treatment of nonsmall cell lung cancer. *Pharmacoeconomics* 2002, **20**(5):325-37.

369. Berthelot JM, Will BP, Evans WK, Coyle D, Earle CC, Bordeleau L. Decision framework for chemotherapeutic interventions for metastatic non-small-cell lung cancer. *Journal of the National Cancer Institute* 2000, **92**(16):1321-9.

370. Evans WK. Cost-effectiveness of vinorelbine alone or vinorelbine plus cisplatin for stage IV NSCLC. *Oncology (Huntington)* 1998, **12**(3 Suppl 4):18-26.

371. Evans WK,.Le Chevalier T. The cost-effectiveness of navelbine alone or in combination with cisplatin in comparison to other chemotherapy regimens and best supportive care in stage IV non-small cell lung cancer. *European Journal of Cancer* 1996, **32A**(13):2249-55.

372. Evans WK. Cost-effectiveness of gemcitabine in stage IV non-small cell lung cancer: an estimate using the Population Health Model lung cancer module. *Seminars in Oncology* 1997, **24**(2 Suppl 7):S7-56-S7-63.

373. Evans WK. An estimate of the cost effectiveness of gemcitabine in stage IV non-small cell lung cancer. *Seminars in Oncology* 1996, **23**(5 Suppl 10):82-9.

374. Earle CC,.Evans WK. A comparison of the costs of paclitaxel and best supportive care in stage IV non-small-cell lung cancer. *Cancer Prevention and Control* 1997, **1**(4):282-8.

375. Kennedy W, Reinharz D, Tessier G, Contandriopoulos AP, Trabut I, Champagne F *et al.* Cost utility of chemotherapy and best supportive care in non-small cell lung cancer. *Pharmacoeconomics* 1995, **8**(4):316-23.

376. Jaakkimainen L, Goodwin PJ, Pater J, Warde P, Murray N, Rapp E. Counting the costs of chemotherapy in a National Cancer Institute of Canada randomized trial in nonsmall-cell lung cancer. *Journal of Clinical Oncology* 1990, **8**(8):1301-9.

377. Brown JM, Thorpe H, Napp V, Stephens RJ, Gower NH, Fairlamb DJ *et al.* The Big Lung Trial Quality of Life Study: Determining the effect of cisplatin-based chemotherapy for supportive care patients with non-small cell lung cancer (NSCLC). *Proceedings of the American Society of Clinical Oncology* 2003, 2533.

378. Earle CC,.Evans WK. Cost-effectivenes of paclitaxel plus cisplatin in advanced non-small-cell lung cancer. *British Journal of Cancer* 1999, **80**(5-6):815-20.

379. Smith TJ, Hillner BE, Neighbors DM, McSorley PA, Le Chevalier T. Economic evaluation of a randomized clinical trial comparing vinorelbine, vinorelbine plus cisplatin, and vindesine plus cisplatin for non-small-cell lung cancer. *Journal of Clinical Oncology* 1995, **13**(9):2166-73.

380. Hillner BE,.Smith TJ. Cost-effectiveness analysis of three regimens using vinorelbine (Navelbine) for non-small cell lung cancer. *Seminars in Oncology* 1996, **23**(2 Suppl 5):25-30.

381. Annemans L, Giaccone G, Vergnenegre A. The cost-effectiveness of paclitaxel (Taxol) + cisplatin is similar to that of teniposide + cisplatin in advanced non-small cell lung cancer: a multicountry analysis. *Anti-Cancer Drugs* 1999, **10**(6):605-15.

382. Palmer AJ,.Brandt A. The cost-effectiveness of four cisplatin-containing chemotherapy regimens in the treatment of stages III B and IV non-small cell lung cancer: an Italian perspective. *Monaldi Archives for Chest Disease* 1996, **51**(4):279-88.

383. Ramsey SD, Moinpour CM, Lovato LC, Crowley JJ, Grevstad P, Presant CA *et al.* Economic analysis of vinorelbine plus cisplatin versus paclitaxel plus carboplatin for advanced non-small-cell lung cancer. *Journal of the National Cancer Institute* 2002, **94**(4):291-7.

384. Rubio-Terres C, Tisaire JL, Kobina S, Moyano A. Cost-minimisation analysis of three regimens of chemotherapy (docetaxel-cisplatin, paclitaxel-cisplatin, paclitaxel-carboplatin) for advanced non-small-cell lung cancer. *Lung Cancer* 2002, **35**(1):81-9.

385. Chen YM, Perng RP, Lee YC, Shih JF, Lee CS, Tsai CM *et al.* Paclitaxel plus carboplatin, compared with paclitaxel plus gemcitabine, shows similar efficacy while more cost-effective: a randomized phase II study of combination chemotherapy against inoperable non-small-cell lung cancer previously untreated. *Annals of Oncology* 2002, **13**(1):108-15.

386. Skowron A, Krzakowski M, Brandys J, Madrzak J, Ramlau R, Zukowska H *et al.* Cost analysis of chemotherapy in advanced non-small cell lung cancer. *Nowotwory* 2001, **51**(6):565-9.

387. Khan ZM, Rascati KL, Koeller JM. Economic analysis of carboplatin versus cisplatin in lung and ovarian cancer. *Pharmacoeconomics* 1999, **16**(1):43-57.

388. Vergnenegre A, Perol M, Pham E. Cost analysis of hospital treatment—two chemotherapic regimens for non-surgical non-small cell lung cancer. GFPC (Groupe Francais Pneumo Cancerologie). *Lung Cancer* 1996, **14**(1):31-44.

389. Copley-Merriman C, Martin C, Johnson N, Sacristan JA, Drings PA, Bosanquet N. Economic value of gemcitabine in non-small cell lung cancer. *Seminars in Oncology* 1996, **23**(5 Suppl 10):90-8.

390. Copley-Merriman C, Corral J, King K, Whiteside R, Voi M, Dorr FA *et al.* Economic value of gemcitabine compared to cisplatin and etoposide in non-small cell lung cancer. *Lung Cancer* 1996, **14**(1):45-61.

391. Koch P, Johnson N, van Schaik J, Andersen S, Blatter J, Bosanquet N *et al.* Gemcitabine: clinical and economic impact in inoperable non-small cell lung cancer. *Anti-Cancer Drugs* 1995, **6**(Suppl 6):49-54.

392. Tennvall GR,.Fernberg JO. Economic evaluation of gemcitabine single agent therapy compared with standard treatment in stage IIIB and IV non-small cell lung cancer. *Medical Oncology* 1998, **15**(2):129-36.

393. Sacristan JA, Kennedy-Martin T, Rosell R, Cardenal F, Anton A, Lomas M *et al.* Economic evaluation in a randomized phase III clinical trial comparing gemcitabine/cisplatin and etoposide/cisplatin in non-small cell lung cancer. *Lung Cancer* 2000, **28**(2):97-107.

394. Schiller J, Tilden D, Aristides M, Lees M, Kielhorn A, Maniadakis N *et al.* Retrospective cost analysis of gemcitabine in combination with cisplatin in non-small cell lung cancer compared to other combination therapies in Europe. *Lung Cancer* 2004, **43**(1):101-12.

395. Leighl NB, Shepherd FA, Kwong R, Burkes RL, Feld R, Goodwin PJ. Economic analysis of the TAX 317 trial: docetaxel versus best supportive care as second-line therapy of advanced non-small-cell lung cancer. *Journal of Clinical Oncology* 2002, **20**(5):1344-52.

396. Detterbeck FC, Socinski MA. Induction therapy and surgery for I-IIIA, B non-small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 19, 2001. pp 267-82. Philadelphia: W.B.Saunders.

397. Detterbeck FC, Jones DR, Rosenman JG. Pancoast tumors. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 16, 2001. pp 233-43. Philadelphia: W.B.Saunders.

398. Socinski MA, Detterbeck FC, Rosenman JG. Adjuvant therapy of resected non-small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 14, 2001. pp 206-19. Philadelphia: W.B.Saunders.

399. Rowell NP,.O'Rourke NP. Synchronous chemoradiotherapy in non-small cell lung cancer (Cochrane review in progress). *Cochrane Database of Systematic Reviews* 2004, **Issue 1**:Art No.: CD002140.

400. Lung Cancer Disease Site Group and Cancer Care Ontario Practice Guidelines Initiative (2002) Use of preoperative chemotherapy with or without postoperative radiotherapy in technically resectable stage IIIA non-small cell lung cancer. Ontario: Cancer Care Ontario Practice Guideline Initiative.

401. Depierre A, Milleron B, Moro-Sibilot D, Chevret S, Quoix E, Lebeau B *et al.* Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *Journal of Clinical Oncology* 2002, **20**(1):247-53.

402. Sawamura K, Mori T, Doi O, Yasumitsu T, Kawahara O, Kuwabara M *et al.* A prospective randomized controlled study of the postoperative adjuvant therapy for non-small cell lung cancer [Abstract]. *Lung Cancer* 1988, **4**:A166.

403. Feld R, Rubinstein L, Thomas PA. Adjuvant chemotherapy with cyclophosphamide, doxorubicin, and cisplatin in patients with completely resected stage I non-small-cell lung cancer. The Lung Cancer Study Group. *J Natl Cancer Inst* 1993, **85**(4):299-306.

404. Kimura H, Yamaguchi Y, Fujisawa T, Baba M, Shiba M. A randomized controlled study of postoperative adjuvant chemoimmunotherapy of resected non-small cell lung cancer with IL2 and LAK cells [abstract]. *Lung Cancer* 1991, **7**(Suppl 1):133.

405. Lung Cancer Study Group. A clinical trial in patients with stage II and III completely resected non-small cell cancer of the lung comparing chemotherapy (CAP) versus no therapy following surgery. [unpublished data] 2004.

406. Niiranen A, Niitamo-Korhonen S, Kouri M, Assendelft A, Mattson K, Pyrhonen S. Adjuvant chemotherapy after radical surgery for non-small-cell lung cancer: a randomized study. *J Clin Oncol* 1992, **10**(12):1927-32.

407. Ohta M, Tsuchiya R, Shimoyama M, Sawamura K, Mori T, Miyazawa N *et al.* Adjuvant chemotherapy for completely resected stage III non-small-cell lung cancer. Results of a randomized prospective study. The Japan Clinical Oncology Group. *J Thorac Cardiovasc Surg* 1993, **106**(4):703-8.

408. Study Group for Adjuvant Chemotherapy for Lung Cancer. A randomised controlled trial of postoperative adjuvant chemotherapy in non-small cell lung cancer. *Hai-gan* 1992, **32**:481-6.

409. Wada H, Hitomi S, Teramatsu T. Adjuvant chemotherapy after complete resection in non-small-cell lung cancer. West Japan Study Group for Lung Cancer Surgery. *J Clin Oncol* 1996, **14**(4):1048-54.

410. Waller D, Peake MD, Stephens RJ, Gower NH, Milroy R, Parmar MK *et al.* Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. *Eur J Cardiothorac Surg* 2004, **26**(1):173-82.

411. Mineo TC, Ambrogi V, Corsaro V, Roselli M. Postoperative adjuvant therapy for stage IB non-small-cell lung cancer. *European Journal of Cardio-Thoracic Surgery* 2001, **20**(2):378-84.

412. Lung Cancer Disease Site Group and Cancer Care Ontario Practice Guidelines Initiative (2002) Postoperative adjuvant radiation therapy in stage II or IIIA completely resected non-small cell lung cancer. Ontario: Cancer Care Ontario Practice Guidelines Initiative.

413. PORT Meta-analysis Trialists Group. Postoperative radiotherapy for non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2003, **Issue 1**:Art No.: CD002142.

414. Trodella L, Granone P, Valente S, Valentini V, Balducci M, Mantini G *et al.* Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. *Radiotherapy and Oncology* 2002, **62**(1):11-9.

415. Socinski MA. The current status of adjuvant chemotherapy for resected non-small cell lung cancer. *Seminars in Oncology* 1999, **26**(5 Suppl 15):27-33.

416. The Lung Cancer Study Group. The benefit of adjuvant treatment for resected locally advanced non-small-cell lung cancer. *Journal of Clinical Oncology* 1988, **6**(1):9-17.

417. Emami B, Kaiser L, Simpson J, Shapiro S, Roper C, Lockett MA. Postoperative radiation therapy in non-small cell lung cancer. *American Journal of Clinical Oncology* 1997, **20**(5):441-8.

418. Keller SM, Adak S, Wagner H, Herskovic A, Komaki R, Brooks BJ *et al.* A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. *New England Journal of Medicine* 2000, **343**(17):1217-22.

419. Hensing TA, Detterbeck F, Socinski MA. The role of induction therapy in the management of resectable non-small cell lung cancer. *Cancer Control* 2000, **7**(1):45-55.

420. Hensing TA, Halle JS, Socinski MA. Chemoradiotherapy for stage IIIA, B non-small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 21, 2001. pp 291-303. Philadelphia: W.B.Saunders.

421. Trovo MG, Minatel E, Veronesi A. Combined radiotherapy and chemotherapy versus radiotherapy alone in locallu advanced epidermoid bronchogenic carcinoma: a randomized study. *Cancer* 1990, **65**:400-4.

422. Morton RF, Jett JR, McGinnis WL. Thoracic radiation therapy alone compared with combined chemoradiotherapy for locally unresectable non-small cell lung cancer: a randomized study, phase III trial. *Annals of Internal Medicine* 1991, **115**:681-6.

423. Mattson K, Holsti LR, Holsti P, Jakobsson M, Kajanti M, Liippo K *et al.* Inoperable non-small cell lung cancer: radiation with or without chemotherapy. *European Journal of Cancer and Clinical Oncology* 1988, **24**(3):477-82.

424. Dillman RO, Seagren SL, Propert KJ, Guerra J, Eaton WL, Perry MC *et al.* A randomised trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *New England Journal of Medicine* 1990, **323**(14):940-5.

425. Miller TP, Crowley JJ, Mira J. A randomized trial of chemotherapy and radiotherapy for stage III non-small cell lung cancer. *Cancer Therapeutics* 1998, **1**:229-36.

426. Kim TE,.Murren JR. Therapy for stage IIIB and stage IV non-small cell lung cancer. *Clinics in Chest Medicine* 2002, **23**(1):209-24.

427. Sharma S, Sharma R, Bhowmik KT. Sequential chemoradiotherapy versus radiotherapy in the management of locally advanced non-small-cell lung cancer. *Advances in Therapy* 2003, **20**(1):14-9.

428. Fairlamb, D. J, Milroy, R., Gower, N. H., Brown, J., Maslove, L., Napp, V., Parmar, M. K. B., Peake, M. D., Rudd, R. M., Souhami, R. L., Spiro, S. G., Stephens, R. J., Thorpe, H., Waller, D., and West, P. Chemotherapy for patients with non-small cell lung cancer: the radical radiotherapy setting of the Big Lung Trial. [unpublished data] 2003.

429. Evans WK. The cost and cost-effectiveness of treating non-small-cell lung cancer. *Oncology Spectrums* 2002, **3**(1):35-41.

430. Vergnenegre A, Combescure C, Fournel P, Bayle S, Gimenez C, Souquet P-J *et al.* Cost-analysis of a phase III trial comparing a concurrent versus a sequential chemo-radiotherapy (CT-RT) for locally advaneced non small cell lung cancer (NSCLC) [abstract]. *Lung Cancer* 2003, **41**(Suppl 2):S6.

431. Evans WK, Will BP, Berthelot JM, Earle CC. Cost of combined modality interventions for stage III non-small-cell lung cancer. *Journal of Clinical Oncology* 1997, **15**(9):3038-48.

432. Lung Cancer Disease Site Group and Cancer Care Ontario Practice Guidelines Initiative (2002) The role of photodynamic therapy (PDT) in patients with non-small cell lung cancer. Ontario: Cancer Care Ontario Practice Guidelines Initiative.

433. Marsiglia H, Baldeyrou P, Lartigau E, Briot E, Haie-Meder C, Le Chevalier T *et al.* High-dose-rate brachytherapy as sole modality for early-stage endobronchial carcinoma. *International Journal of Radiation Oncology, Biology, Physics* 2000, **47**(3):665-72.

434. Perol M, Caliandro R, Pommier P, Malet C, Montbarbon X, Carrie C *et al.* Curative irradiation of limited endobronchial carcinomas with high-dose rate brachytherapy: Results of a pilot study. *Chest* 1997, **111**(5):1417-23.

435. van Boxem TJ, Venmans BJ, Schramel FM, van Mourik JC, Golding RP, Postmus PE *et al.* Radiographically occult lung cancer treated with fibreoptic bronchoscopic electrocautery: a pilot study of a simple and inexpensive technique. *European Respiratory Journal* 1998, **11**(1):169-72.

436. Morris DE, Socinski MA, Detterbeck FC. Limited stage small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 24, 2001. pp 341-59. Philadelphia: W.B.Saunders Company.

437. Agra Y, Pelayo M, Sacristan M, Sacristan A, Serra C, Bonfill X. Chemotherapy versus best supportive care for extensive small cell lung cancer. *Cochrane Database of Systematic Reviews* 2003, **Issue 4**:Art No.: CD001990.

438. Gillenwater HH, Socinski MA. Extensive stage small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, **25**, 2001. pp 360-75. Philadelphia: W.B.Saunders Company.

439. Cerny T, Blair V, Anderson H, Bramwell V, Thatcher N. Pretreatment prognostic factors and scoring system in 407 small-cell lung cancer patients. *International Journal of Cancer* 1987, **39**(2):146-9.

440. Lowenbraun S, Bartolucci A, Smalley RV. The superiority of combination chemotherapy over single agent chemotherapy in small cell lung carcinoma. *Cancer* 1979, **44**:406-13.

441. Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. *Lancet* 1996, **348**(9027):563-6.

442. Souhami RL, Spiro SG, Rudd RM, Ruiz de Elvira MC, James LE, Gower NH *et al.* Five-day oral etoposide treatment for advanced small-cell lung cancer: randomized comparison with intravenous chemotherapy. *Journal of the National Cancer Institute* 1997, **89**(8):577-80.

443. Pujol JL, Carestia, Daures JP. Is there a case for cisplatin in the treatment of small-cell lung cancer: a meta-analysis of randomized trials of a cisplatin-containing regimen versus a regimen without this alkylating agent. *British Journal of Cancer* 2000, **83**(1):8-15.

444. Sundstrom S, Bremnes RM, Kaasa S, Aasebo U, Hatlevoll R, Dahle R *et al.* Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *Journal of Clinical Oncology* 2002, **20**(24):4665-72.

445. Sculier JP, Berghmans T, Vermylen P, Ninane V. Topics in thoracic oncology. *Revue Medicale de Bruxelles* 1997, **18**(4):204-8.

446. Sculier JP, Berghmans T, Castaigne C, Luce S, Sotiriou C, Vermylen P *et al.* Maintenance chemotherapy for small cell lung cancer: a critical review of the literature. *Lung Cancer* 1998, **19**(2):141-51.

447. Hanna NH, Sandier AB, Loehrer PJ, Sr., Ansari R, Jung SH, Lane K *et al.* Maintenance daily oral etoposide versus no further therapy following induction chemotherapy with etoposide plus ifosfamide plus cisplatin in extensive small-cell lung cancer: a Hoosier Oncology Group randomized study. *Annals of Oncology* 2002, **13**(1):95-102.

448. Klasa RJ, Murray N, Coldman AJ. Dose-intensity meta-analysis of chemotherapy regimens in small-cell carcinoma of the lung. *Journal of Clinical Oncology* 1991, **9**:499-508.

449. Arriagada R, Le Chevalier T, Pignon JP. Initial chemotherapeutic doses and surbibal in patients with limited small-cell lung cancer. *New England Journal of Medicine* 1993, **329**:1848-52.

450. Masutani M, Ochi Y, Kadota A, Akusawa H, Kisohara A, Takahashi N *et al.* Dose-intensive weekly alternating chemotherapy for patients with small cell lung cancer: randomized trial, can it improve survival of patients with good prognostic factors? *Oncol Rep* 2000, **7**(2):305-10.

451. Figueredo AT, Hryniuk WM, Strautmanis I. Co-trimoxazole prophylaxis during high-dose chemotherapy of small-cell lung cancer. *Journal of Clinical Oncology* 1985, **3**:54-64.

452. Ihde DC, Mulshine JL, Kramer BS. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *Journal of Clinical Oncology* 1994, **12**:2022-34.

453. Johnson DH, Einhorn LH, Birch R. A randomized comparison of high-dose versus conventional-dose cyclophosphamide, doxorubicin, and vincristine for extensive-stage small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *Journal of Clinical Oncology* 1987, **5**:1731-8.

454. Souhami RL, Rudd R, Ruiz de Elvira MC. Randomized trial comparing weekly versus 3-week chemotherapy in small-cell lung cancer: a Cancer Research Campaign trial. *Journal of Clinical Oncology* 1994, **12**:1806-13.

455. Hirsch FR, Oterlind K, Jeppesen N, Dombernowsky P, Ingeberg S, Grundtvig Sorensen P *et al.* Superiority of high-dose platinum (cisplatin and carboplatin) compared to carboplatin alone in combination chemotherapy for small-cell lung carcinoma: A prospective randomised trial of 280 consecutive patients. *Annals of Oncology* 2001, **12**:647-53.

456. Mavroudis D, Papadakis E, Veslemes M, Tsiafaki X, Stavrakakis J, Kouroussis C *et al.* A multicenter randomized clinical trial comparing paclitaxel-cisplatin- etoposide versus cisplatin-etoposide as first-line treatment in patients with small-cell lung cancer. *Annals of Oncology* 2001, **12**:463-70.

457. Sculier JP, Paesmans M, Lecomte J, Van Cutsem O, Lafitte JJ, Berghmans T *et al.* A three-arm phase III randomised trial assessing, in patients with extensive-disease small-cell lung cancer, accelerated chemotherapy with support of haematological growth factor or oral antibiotics. *British Journal of Cancer* 2001, **85**(10):1444-51.

458. Thatcher N, Girling DJ, Hopwood P, Sambrook RJ, Qian W, Stephens RJ. Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: results of a British Medical Research Council Multicenter Randomized Trial. Medical Research Council Lung Cancer Working Party. *Journal of Clinical Oncology* 2000, **18**(2):395-404.

459. Ardizzoni A, Tjan-Heijnen VC, Postmus PE, Buchholz E, Biesma B, Karnicka-Mlodkowska H *et al.* Standard versus intensified chemotherapy with granulocyte colony-stimulating factor support in small-cell lung cancer: a prospective European Organization for Research and Treatment of Cancer-Lung Cancer Group Phase III Trial-08923. *Journal of Clinical Oncology* 2002, **20**(19):3947-55.

460. Furuse K, Fukuoka M, Nishiwaki Y. Phase III study of intensive weekly chemotherapy with recombinant human granulocyte colony-stimulating factor versus standard chemotherapy in extensive-disease small-cell lung cancer. The Japan Clinical Oncology Group. *Journal of Clinical Oncology* 1998, **16**:2126-32.

461. Pujol J-L, Douillard J-Y, Riviere A. Dose-intensity of a four-drug chemotherapy regimen with or without recombinant human granulocyte-macrophage colony-stimulating factor in extensive-stage small-cell lung cancer: a multicenter randomized phase III study. *Journal of Clinical Oncology* 1997, **15**:2082-9.

462. Woll PJ, Hodgetts J, Lomax L. Can cytotoxic dose-intensity be increased by using granulocyte colony-stimulating factor? A randomized controlled trial of lenograstim in small-cell lung cancer. *Journal of Clinical Oncology* 1995, **13**:652-9.

463. Steward WP, von Pawal J, Gatzemeier U. Effects of granulocyte-macrophage colony-stimulating factor and dose intensification of V-ICE chemotherapy in small-cell lung cancer: a prospective randomized study of 300 patients. *Journal of Clinical Oncology* 1998, **16**:642-50.

464. Goldie JH,.Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treatment Reports* 1979, **63**(11-12):1727-33.

465. Fukuoka M, Furuse K, Saijo N. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. *Journal of the National Cancer Institute* 1991, **83**:855-61.

466. Feld R, Evans WK, Coy P, Hodson I, MacDonald AS, Osoba D *et al.* Canadian multicenter randomized trial comparing sequential and alternating administration of two non-cross-resistant chemotherapy combinations in patients with limited small-cell carcinoma of the lung. *Journal of Clinical Oncology* 1987, **5**(9):1401-9.

467. Goodman GE, Crowley JJ, Blasko JC. Treatment of limited small-cell lung cancer with etoposide and cisplatin alternating with vincristine, doxorubicin, and cyclophosphamide versus concurrent etoposide, vincristine, doxorubicin, and cyclophosphamide and chest radiotherapy. *Journal of Clinical Oncology* 1990, **8**:39-47.

468. Warde P,.Payne D. Does thoracic irradiation improve survival and local control in limited-stage small cell carcinoma of the lung? A meta-analysis. *Journal of Clinical Oncology* 1992, **10**:890-5.

469. Pignon JP, Arriagada R, Ihde DC. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *New England Journal of Medicine* 1992, **327**:1618-24.

470. Jeremic B, Shibamoto Y, Nikolic N, Milicic B, Milisavljevic S, Dagovic A *et al.* Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. *Journal of Clinical Oncology* 1999, **17**(7):2092-9.

471. Videtic GM, Fung K, Tomiak AT, Stitt LW, Dar AR, Truong PT *et al.* Using treatment interruptions to palliate the toxicity from concurrent chemoradiation for limited small cell lung cancer decreases survival and disease control. *Lung Cancer* 2001, **33**(2-3):249-58.

472. Videtic GM, Stitt LW, Dar AR, Kocha WI, Tomiak AT, Truong PT *et al.* Continued cigarette smoking by patients receiving concurrent chemoradiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. *Journal of Clinical Oncology* 2003, **21**(8):1544-9.

473. Coy P, Hodson I, Rosenman J. The effect of dose of thoracic irradiation on recurrence in patients with limited stage small cell lung cancer, initial results of a Canadian multicenter randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 1988, **14**:219-26.

474. Turrisi AT, III, Kim K, Blum R, Sause WT, Livingston RB, Komaki R *et al.* Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *New England Journal of Medicine* 1999, **340**(4):265-71.

475. Bonner JA, Sloan JA, Shanahan TG, Brooks BJ, Marks RS, Krook JE *et al.* Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma. *Journal of Clinical Oncology* 1999, **17**(9):2681-91.

476. Murray N, Coy P, Pater JL, Hodson I, Arnold A, Zee BC *et al.* Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. *Journal of Clinical Oncology* 1993, **11**(2):336-44.

477. Takada M, Fukuoka M, Kawahara M, Sugiura T, Yokoyama A, Yokota S *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *Journal of Clinical Oncology* 2002, **20**(14):3054-60.

478. Skarlos DV, Samantas E, Briassoulis E, Panoussaki E, Pavlidis N, Kalofonos HP *et al.* Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG). *Annals of Oncology* 2001, **12**(9):1231-8.

479. Gregor A, Cull A, Stephens RJ. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *European Journal of Cancer* 1997, **33**(11):1717-9.

480. Work E, Nielsen OS, Bentzen SM, Fode K, Palshof T. Randomized study of initial versus late chest irradiation combined with chemotherapy in limited-stage small-cell lung cancer. Aarhus Lung Cancer Group. *Journal of Clinical Oncology* 1997, **15**(9):3030-7.

481. Jeremic B, Shibamoto Y, Acimovic L, Milisavljevic S. Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer: a randomized study. *Journal of Clinical Oncology* 1997, **15**(3):893-900.

482. Pijls-Johannesma MCG, De Ruysscher DKM, Rutten I, Vansteenkiste JF, Lambin P. Early versus late chest radiography for limited stage small cell lung cancer (Protocol for a Cochrane review). *Cochrane Database of Systematic Reviews* 2004, **Issue 2**:Art No.: CD004700.

483. Auperin A, Arriagada R, Pignon JP, Le Pechoux C, Gregor A, Stephens RJ *et al.* Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *New England Journal of Medicine* 1999, **341**(7):476-84.

484. Lad T, Piantadosi S, Thomas P, Payne D, Ruckdeschel J, Giaccone G. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. *Chest* 1994, **106**(6 Suppl):320S-3S.

485. Davis S, Crino L, Tonato M, Darwish S, Pelicci PG, Grignani F. A prospective analysis of chemotherapy following surgical resection of clinical stage I-II small-cell lung cancer. *American Journal of Clinical Oncology* 1993, **16**(2):93-5.

486. Fujimori K, Yokoyama A, Kurita Y, Terashima M. A pilot phase 2 study of surgical treatment after induction chemotherapy for resectable stage I to IIIA small cell lung cancer. *Chest* 1997, **111**(4):1089-93.

487. Shepherd FA, Ginsberg RJ, Patterson GA, Evans WK, Feld R. A prospective study of adjuvant surgical resection after chemotherapy for limited small cell lung cancer. A University of Toronto Lung Oncology Group study. *Journal of Thoracic and Cardiovascular Surgery* 1989, **97**(2):177-86.

488. Doyle JJ, Dezii CM, Sadana A. A pharmacoeconomic evaluation of cisplatin in combination with either etoposide or etoposide phosphate in small cell lung cancer. *Seminars in Oncology* 1996, **23**(6 Suppl 13):51-60.

489. Hainsworth JD, Levitan N, Wampler GL. Phase II randomized study of cisplatin plus etoposide phosphate or etoposide in the treatment of small cell lung cancer. *Journal of Clinical Oncology* 2004, **12**:1436-41.

490. Goodwin PJ, Feld R, Evans WK, Pater J. Cost-effectiveness of cancer chemotherapy: an economic evaluation of a randomized trial in small-cell lung cancer. *Journal of Clinical Oncology* 1988, **6**(10):1537-47.

491. Joint Formulary Committee. British National Formulary . London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003.

492. Tai TH, Yu E, Dickof P, Beck G, Tonita J, Ago T *et al.* Prophylactic cranial irradiation revisited: cost-effectiveness and quality of life in small-cell lung cancer. *International Journal of Radiation Oncology, Biology, Physics* 2002, **52**(1):68-74.

493. Stout R, Barber P, Burt P, Hopwood P, Swindell R, Hodgetts J *et al.* Clinical and quality of life outcomes in the first United Kingdom randomized trial of endobronchial brachytherapy (intraluminal radiotherapy) vs. external beam radiotherapy in the palliative treatment of inoperable non-small cell lung cancer. *Radiotherapy and Oncology* 2000, **56**(3):323-7.

494. National Institute for Clinical Excellence (2004) Guidance on cancer services. Improving supportive and palliative care for adults with cancer - the manual. London: National Institute for Clincal Excellence.

495. NHS Executive (2000) Cancer Information Strategy. London: NHS Executive.

496. NHS Executive (1998) Guidance on commissioning cancer services improving outcomes in lung cancer - the manual. London: NHS Executive.

497. National Institute for Clinical Excellence (2004) Guidance on cancer services. Improving supportive and palliative care for adults with cancer - executive summary. London: National Institute for Clinical Excellence.

498. Department of Health (2004) Manual of cancer services standards. London: NHS Executive.

499. Grahn G,.Danielson M. Coping with the cancer experience. II. Evaluating an education and support programme for cancer patients and their significant others. *European Journal of Cancer Care* 1996, **5**(3):182-7.

500. Sell L, Devlin B, Bourke SJ, Munro NC, Corris PA, Gibson GJ. Communicating the diagnosis of lung cancer. *Respiratory Medicine* 1993, **87**(1):61-3.

501. Department of Health (2000) The nursing contribution to cancer care: a strategic programme of action in support of the national cancer programme. London: Department of Health.

502. Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer: results from a large study in UK cancer centres. *British Journal of Cancer* 2001, **84**(1):48-51.

503. Fallowfield L, Lipkin M, Hall A. Teaching senior oncologists communication skills: results from phase I of a comprehensive longitudinal program in the United Kingdom. *Journal of Clinical Oncology* 1998, **16**(5):1961-8.

504. Muers MF,.Round CE. Palliation of symptoms in non-small cell lung cancer: a study by the Yorkshire Regional Cancer Organisation Thoracic Group. *Thorax* 1993, **48**(4):339-43.

505. Detterbeck FC, Jones DR, Morris DE. Palliative treatment of lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 29, 2001. pp 419-36. Philadelphia: W.B.Saunders.

506. Moghissi K,.Dixon K. Is bronchoscopic photodynamic therapy a therapeutic option in lung cancer? *European Respiratory Journal* 2003, **22**(3):535-41.

507. Tomaselli F, Maier A, Pinter H, Stranzl H, Smolle-Juttner FM. Photodynamic therapy enhanced by hyperbaric oxygen in acute endoluminal palliation of malignant bronchial stenosis (clinical pilot study in 40 patients). *European Journal of Cardio-Thoracic Surgery* 2001, **19**(5):549-54.

508. Miyazawa T, Yamakido M, Ikeda S, Furukawa K, Takiguchi Y, Tada H *et al.* Implantation of Ultraflex nitinol stents in malignant tracheobronchial stenoses. *Chest* 2000, **118**(4):959-65.

509. Vonk-Noordegraaf A, Postmus PE, Sutedja TG. Tracheobronchial stenting in the terminal care of cancer patients with central airways obstruction. *Chest* 2001, **120**(6):1811-4.

510. Antunes G, Neville E, Duffy J, Ali N. BTS guidelines for the management of malignant pleural effusions. *Thorax* 2003, **58**(Suppl 2):ii29-ii38.

511. Shaw P,.Agarwal R. Pleurodesis for malignant pleural effusions. *Cochrane Database of Systematic Reviews* 2004, **Issue 1**:Art No.: CD002916.

512. Tan, C., Swift, S., Sedrakyan, A., Browne, E., and Treasure, T. A systematic review of the management of malignant pleural effusions. [unpublished data] 2004.

513. Langendijk H, de Jong J, Tjwa M, Muller M, ten Velde G, Aaronson N *et al.* External irradiation versus external irradiation plus endobronchial brachytherapy in inoperable non-small cell lung cancer: a prospective randomized study. *Radiotherapy and Oncology* 2001, **58**(3):257-68.

514. Moghissi K, Bond MG, Sambrook RJ, Stephens RJ, Hopwood P, Girling DJ. Treatment of endotracheal or endobronchial obstruction by non-small cell lung cancer: lack of patients in an MRC randomized trial leaves key questions unanswered. Medical Research Council Lung Cancer Working Party. *Clinical Oncology (Royal College of Radiologists)* 1999, **11**(3):179-83.

515. Langendijk JA, Tjwa MK, de Jong JM, ten Velde GP, Wouters EF. Massive haemoptysis after radiotherapy in inoperable non-small cell lung carcinoma: is endobronchial brachytherapy really a risk factor? *Radiotherapy and Oncology* 1998, **49**(2):175-83.

516. MacBeth F, Toy E, Coles B, Melville A, Eastwood A. Palliative radiotherapy regimens for non-small cell lung cancer. *Cochrane Database of Systematic Reviews* 2001, **Issue 4**:Art No.: CD002143.

517. Sirzen F, Kjellen E, Sorenson S, Cavallin-Stahl E. A systematic overview of radiation therapy effects in non-small cell lung cancer. *Acta Oncologica* 2003, **42**(5-6):493-515.

518. Bezjak A, Dixon P, Brundage M, Tu DS, Palmer MJ, Blood P *et al.* Randomized phase III trial of single versus fractionated thoracic radiation in the palliation of patients with lung cancer (NCIC CTG SC.15). *International Journal of Radiation Oncology, Biology, Physics* 2002, **54**(3):719-28.

519. Bredin M, Corner J, Krishnasamy M, Plant H, Bailey C, A'Hern R. Multicentre randomised controlled trial of nursing intervention for breathlessness in patients with lung cancer. *BMJ* 1999, **318**(7188):901-4.

520. Detterbeck FC, Bleiweis MS, Ewend MG. Surgical treatment of Stage IV non-small cell lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. *Diagnosis and treatment of lung cancer : An evidence-based guide for the practicing clinician*, 23, 2001. pp 326-38. Philadelphia: W.B.Saunders.

521. Irwin RS, Boulet LP, Cloutier MM, Fuller R, Gold PM, Hoffstein V *et al.* Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. *Chest* 1998, **114**(2 Suppl):133S-81S.

522. Luporini G, Barni S, Marchi E, Daffonchio L. Efficacy and safety of levodropropizine and dihydrocodeine on nonproductive cough in primary and metastatic lung cancer. *European Respiratory Journal* 1998, **12**(1):97-101.

523. Kraus DH, Ali MK, Ginsberg RJ, Hughes CJ, Orlikoff RF, Rusch VW *et al.* Vocal cord medialization for unilateral paralysis associated with intrathoracic malignancies. *Journal of Thoracic and Cardiovascular Surgery* 1996, **111**(2):334-41.

524. Rowell NP,.Gleeson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus. *Cochrane Database of Systematic Reviews* 2001, **Issue 4**:Art No.: CD001316.

525. Royal College of Radiologists,.Clinical Oncology Information Network (COIN). Guidelines on the non-surgical management of lung cancer : a document for local expert groups in the United Kingdom preparing lung cancer management policy documents. *Clinical Oncology* 1999, **11**(1):S1-S53.

526. SIGN (2000) Control of pain in patients with cancer: a national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network.

527. Gilbert RW, Kim JH, Posner JB. Epidural spinal cord compression from metastatic tumor: diagnosis and treatment. *Annals of Neurology* 1978, **3**(1):40-51.

528. Bach F, Agerlin N, Sorensen JB, Rasmussen TB, Dombernowsky P, Sorensen PS *et al.* Metastatic spinal cord compression secondary to lung cancer. *Journal of Clinical Oncology* 1992, **10**(11):1781-7.

529. Young RF, Post EM, King GA. Treatment of spinal epidural metastases. Randomized prospective comparison of laminectomy and radiotherapy. *Journal of Neurosurgery* 1980, **53**(6):741-8.

530. Pedersen AG, Bach F, Melgaard B. Frequency, diagnosis, and prognosis of spinal cord compression in small cell bronchogenic carcinoma. A review of 817 consecutive patients. *Cancer* 1985, **55**(8):1818-22.

531. Sundaresan N, Bains M, McCormack P. Surgical treatment of spinal cord compression in patients with lung cancer. *Neurosurgery* 1985, **16**(3):350-6.

532. Zaidat OO,.Ruff RL. Treatment of spinal epidural metastasis improves patient survival and functional state. *Neurology* 2002, **58**(9):1360-6.

533. Hoskin PJ, Grover A, Bhana R. Metastatic spinal cord compression: radiotherapy outcome and dose fractionation. *Radiotherapy and Oncology* 2003, **68**(2):175-80.

534. Ross JR, Saunders Y, Demonds PM, Patel S, Wonderling D, Normand C *et al.* A systematic review of the role of biphosphonates in metastatic disease. *Health Technology Assessment* 2004, **8**(4).

535. McQuay HJ, Collins SL, Carroll D, Moore RA. Radiotherapy for the palliation of painful bone metastases. *Cochrane Database of Systematic Reviews* 1999, **Issue 3**:Art No.: CD001793.

536. Salazar OM, Sandhu T, da Motta NW, Escutia MA, Lanzos-Gonzales E, Mouelle-Sone A *et al.* Fractionated half-body irradiation (HBI) for the rapid palliation of widespread, symptomatic, metastatic bone disease: a randomized Phase III trial of the International Atomic Energy Agency (IAEA). *International Journal of Radiation Oncology, Biology, Physics* 2001, **50**(3):765-75.

537. Sarkar SK, Sarkar S, Pahari B, Majumdar D. Multiple and single fraction palliative radiotherapy in bone secondaries - A prospective study. *Indian Journal of Radiology & Imaging* 2002, **12**(2):281-4.

538. Steenland E, Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J *et al.* The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiotherapy and Oncology* 1999, **52**(2):101-9.

539. Ross JR, Saunders Y, Edmonds PM, Patel S, Broadley KE, Johnston SRD. Systematic review of role of bisphosphonates on skeletal morbidity in metastatic cancer. *BMJ* 2003, **327**.

540. Wong R,.Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database of Systematic Reviews* 2002, **Issue 2**:Art No.: CD002068.

541. Coy P, Schaafsma J, Schofield JA. The cost-effectiveness and cost-utility of high-dose palliative radiotherapy for advanced non-small-cell lung cancer. *International Journal of Radiation Oncology, Biology, Physics* 2000, **48**(4):1025-33.

542. van Boxem T, Muller M, Venmans B, Postmus P, Sutedja T. Nd-YAG laser vs bronchoscopic electrocautery for palliation of symptomatic airway obstruction. *Chest* 1999, **116**(4):1108-12.

543. Zimmer PW, Hill M, Casey K, Harvey E, Low DE. Prospective randomized trial of talc slurry vs bleomycin in pleurodesis for symptomatic malignant pleural effusions. *Chest* 1997, **112**(2):430-4.

544. Diacon AH, Wyser C, Bolliger CT, Tamm M, Pless M, Perruchoud AP *et al.* Prospective randomized comparison of thoracoscopic talc poudrage under local anesthesia versus bleomycin instillation for pleurodesis in malignant pleural effusions. *American Journal of Respiratory & Critical Care Medicine* 2000, **162**(4 Pt 1):1445-9.

545. Read CA, Wohlrab JL, Szwed TW, Anderson ED. Thoracoscopy with talc pleurodesis shortens hospitalization. *Journal of Bronchology* 2002, **9**(4):281-5.

546. Belani CP, Einarson TR, Arikian SR, Doyle J. Cost-effectiveness analysis of pleurodesis in the management of malignant pleural effusion. *Journal of Oncology Management* 2004, **4**:24-34.

547. Putnam JB, Jr., Walsh GL, Swisher SG, Roth JA, Suell DM, Vaporciyan AA *et al.* Outpatient management of malignant pleural effusion by a chronic indwelling pleural catheter. *Annals of Thoracic Surgery* 2000, **69**(2):369-75.

548. Department of Health (1995) A policy framework for commissioning cancer services: a report by the expert advisory group on cancer to the chief medical officers of England and Wales. London: Department of Health.

549. Department of Health (2000) The NHS cancer plan. London: Department of Health.

550. The Lung Cancer Working Party of the British Thoracic Society Standards of Care Committee. BTS recommendations to respiratory physicians for organising the care of patients with lung cancer. *Thorax* 1998, **53**(Suppl 1):S1-S8.

551. Alberts WM, Bepler G, Hazelton T, Ruckdeschel JC, Williams Jr JH. Practice organization. *Chest* 2003, **123**(1 Suppl):332S-7S.

552. Murray PV, O'Brien MER, Sayer R, Cooke N, Knowles G, Miller AC *et al.* The pathway study: results of a pilot feasibility study in patients suspected of having lung carcinoma investigated in a conventional chest clinic compared to a centralised two-stop pathway. *Lung Cancer* 2003, **42**:283-90.

553. Royal College of Physicians of London and Royal College of Radiologists (1993) Reducing delays in cancer treatment. some targets . London: Roayal College of Physicians of London.

554. Department of Health National manual of quality measures for cancer peer review 2004 http://www.dh.gov.uk [accessed 25-5-0004].

555. Cancer Services Co-ordinating Group (CSCG) Lung cancer services: all Wales minimum standards 2000 http://www.wales.gov.uk/subihealth/content/cscg/lung-e.pdf [accessed 23-7-2003].

556. Bozcuk H,.Martin C. Does treatment delay affect survival in non-small cell lung cancer? A retrospective analysis from a single UK centre. *Lung Cancer* 2001, **34**(2):243-52.

557. O'Rourke N,.Edwards R. Lung cancer treatment waiting times and tumour growth. *Clinical Oncology* 2000, **12**(3):141-4.

558. Dische S, Gibson D, Parmar M, Saunders MI. Time course from first symptom to treatment in patients with non-small cell lung cancer referred for radiotherapy: a report by the CHART Steering Committee. *Thorax* 1996, **51**(12):1262-5.

559. Falk SJ, Girling DJ, White RJ, Hopwood P, Harvey A, Qian W *et al.* Immediate versus delayed palliative thoracic radiotherapy in patients with unresectable locally advanced non-small cell lung cancer and minimal thoracic symptoms: randomised controlled trial. *BMJ* 2002, **325**:465-8.

560. Huang J, Barbera L, Brouwers M, Browman G, Mackillop WJ. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. *Journal of Clinical Oncology* 2003, **21**(3):555-63.

561. Aragoneses FG, Moreno N, Leon P, Fontan EG, Folque E. Influence of delays on survival in the surgical treatment of bronchogenic carcinoma. *Lung Cancer* 2002, **36**(1):59-63.

562. Billing JS,.Wells FC. Delays in the diagnosis and surgical treatment of lung cancer. *Thorax* 1996, **51**(9):903-6.

563. Christensen ED, Harvald T, Jendresen M, Aggestrup S, Petterson G. The impact of delayed diagnosis of lung cancer on the stage at the time of operation. *European Journal of Cardio-Thoracic Surgery* 1997, **12**(6):880-4.

564. Moore S, Corner J, Haviland J, Wells M, Salmon E, Normand C *et al.* Nurse led follow up and conventional medical follow up in management of patients with lung cancer: randomised trial. *BMJ* 2002, **325**(7373):1145-7.

565. Vaporciyan AA, Merriman KW, Ece F, Roth JA, Smythe WR, Swisher SG *et al.* Incidence of major pulmonary morbidity after pneumonectomy: association with timing of smoking cessation. *Annals of Thoracic Surgery* 2002, **73**(2):420-5.

566. Nakagawa M, Tanaka H, Tsukuma H, Kishi Y. Relationship between the duration of the preoperative smoke-free period and the incidence of postoperative pulmonary complications after pulmonary surgery. *Chest* 2001, **120**(3):705-10.

567. Saunders M, Sculier JP, Ball D, Capello M, Furuse K, Goldstraw P *et al.* Consensus: the follow-up of the treated patient. *Lung Cancer* 2003, **42**(Suppl 1): S17-S19.

568. Egermann U, Jaeggi K, Habicht JM, Perruchoud AP, Dalquen P, Soler M. Regular follow-up after curative resection of nonsmall cell lung cancer: a real benefit for patients? *European Respiratory Journal* 2002, **19**(3):464-8.

569. Westeel V, Choma D, Clement F, Woronoff-Lemsi MC, Pugin JF, Dubiez A *et al.* Relevance of an intensive postoperative follow-up after surgery for non-small cell lung cancer. *Annals of Thoracic Surgery* 2000, **70**(4):1185-90.

570. Younes RN, Gross JL, Deheinzelin D. Follow-up in lung cancer: how often and for what purpose? *Chest* 1999, **115**(6):1494-9.

571. Virgo KS, Naunheim KS, McKirgan LW, Kissling ME, Lin JC, Johnson FE. Cost of patient follow-up after potentially curative lung cancer treatment. *Journal of Thoracic and Cardiovascular Surgery* 1996, **112**(2):356-63.

572. Department of Health (2001) Involving patients and the public in healthcare: a discussion document. London: Department of Health.

573. National Assembly for Wales (2001) Signposts - a practical guide to public and patient involvement in Wales. Cardiff: National Assembly for Wales/ OPM.

574. Department of Health (2002) National surveys of NHS patients Cancer national overview 1999/2000. NHS cancer plan: a baseline survey. London: Department of Health.

575. Houts PS, Yasko JM, Kahn SB, Schelzel GW, Marconi KM. Unmet psychological, social, and economic needs of persons with cancer in Pennsylvania. *Cancer* 1986, **58**(10):2355-61.

576. Fakhoury WK, McCarthy M, Addington-Hall J. The effects of the clinical characteristics of dying cancer patients on informal caregivers' satisfaction with palliative care. *Palliative Medicine* 1997, **11**(2):107-15.

577. Crawford MJ, Rutter D, Manley C, Weaver T, Bhui K, Fulop N *et al.* Systematic review of involving patients in the planning and development of health care. *BMJ* 2002, **325**(7375):1263.

578. van Tinteren H, Hoekstra O, Smit E, van den Bergh J, Schreurs A, Stallaert R *et al.* Randomized controlled trial (RCT) to evaluate the cost-effectiveness of positron emission tomography (PET) added to convential diagnosis in non-small cell lung cancer (NSCLC) [Abstract]. *Proceedings of the American Society of Clinical Oncology* 2000,1885.

579. Massard G, Moog R, Wihlm JM, Kessler R, Dabbagh A, Lesage A *et al.* Bronchogenic cancer in the elderly: Operative risk and long-term prognosis. *Thoracic & Cardiovascular Surgeon* 1996, **44**(1):40-5.

580. Kruger M, Uschinsky K, Hassler K, Engelmann C, Lacquet L, Grodzki T *et al.* Postoperative complications after bronchoplastic procedures in the treatment of bronchial malignancies. *European Journal of Cardio-Thoracic Surgery* 1998, **14**(1):46-53.

581. Liu G-J, Zhang H, Fu T, Wang K-Z. Risk factors associated with morbidity and operative mortality of pneumonectomy. *Chinese Journal of Cancer Research* 2001, **13**(3):217-20.

582. Suzuki K, Nagai K, Yoshida J, Ohmatsu H, Takahashi K, Nishimura M *et al.* Video-assisted thoracoscopic surgery for small indeterminate pulmonary nodules: indications for preoperative marking. *Chest* 1999, **115**(2):563-8.

583. Thomas P,.Rubinstein L. Cancer recurrence after resection: T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Annals of Thoracic Surgery* 1990, **49**(2):242-6.

584. Fergusson RJ, Gregor A. Developing lung cancer services - the impact of modernisation of the NHS. In: Muers M, Thatcher N, Wells F, Miles A, eds. *The effective management of lung cancer*, 10, 2003. pp 113-8. London: Aesculapius Medical Press.

585. Toy E, MacBeth F, Coles B, Melville A, Eastwood A. Palliative thoracic radiotherapy for non-small-cell lung cancer: a systematic review. *American Journal of Clinical Oncology* 2003, **26**(2):112-20.

586. Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: mediastinal staging in the 1990s—meta-analytic comparison of PET and CT. *Radiology* 1999, **213**(2):530-6.

587. Shon IH, O'Doherty MJ, Maisey MN. Positron emission tomography in lung cancer. *Seminars in Nuclear Medicine* 2002, **32**(4):240-71.

588. Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koeter GH *et al.* Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *New England Journal of Medicine* 2000, **343**(4):254-61.

589. MacManus MP, Hicks RJ, Matthews JP, Hogg A, McKenzie AF, Wirth A *et al.* High rate of detection of unsuspected distant metastases by pet in apparent stage III non-small-cell lung cancer: implications for radical radiation therapy. *International Journal of Radiation Oncology, Biology, Physics* 2001, **50**(2):287-93.

590. Perez CA, Stanley K, Grundy G, Hanson W, Rubin P, Kramer S *et al.* Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung: report by the Radiation Therapy Oncology Group. *Cancer* 1982, **50**(6):1091-9.

591. Earle CC, Chapman RH, Baker CS, Bell CM, Stone PW, Sandberg EA *et al.* Systematic overview of cost-utility assessments in oncology. *Journal of Clinical Oncology* 2000, **18**(18):3302-17.

592. Papatheofanis FJ. Utility evaluations for Markov states of lung cancer for PET-based disease management. *Quarterly Journal of Nuclear Medicine* 2000, **44**(2):186-90.

593. Cykert S,.Phifer N. Surgical decisions for early stage, non-small cell lung cancer: which racially sensitive perceptions of cancer are likely to explain racial variation in surgery? *Medical Decision Making* 2003, **23**(2):167-76.

594. NHS Executive (2003) NHS Reference costs 2002. London: NHS Executive.

595. West P, Maslove L, Gower N, Stephens RJ. Estimating the financial cost of supportive care plus cisplatin-based chemotherapy compared with supportive care alone in the treatment of patients with advanced non-small cell lung cancer (NSCLC) using data from the Big Lung Trial (BLT) [abstract]. *Lung Cancer* 2003, **41**(Suppl 2):S7.

596. Wolstenholme JL,.Whynes DK. The hospital costs of treating lung cancer in the United Kingdom. *British Journal of Cancer* 1999, **80**(1-2):215-8.

Appendices 1-8 are provided in a separate document (CD-ROM attached)