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SIGN 137 • Management of lung cancer

A national clinical guideline

February 2014

Evidence

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS 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, *or* RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, 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 or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
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^{+}
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

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Scottish Intercollegiate Guidelines Network

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Contents

1 Introduction

1.1 THE NEED FOR A GUIDELINE

Lung cancer is the second most common cancer in Scotland after non-melanoma skin cancer.[1] There are approximately 4,800 new cases and 4,000 deaths each year.[1] Eighty nine per cent of cases occur in patients over 60 years.[1] Incidence is higher, and survival is poorer, in people of lower socioeconomic status.[1]

A number of risk factors for lung cancer have been identified, but the overwhelmingly dominant one is exposure to tobacco smoke, with about 90% of patients being smokers or ex-smokers.[2] Consequently, measures aimed at controlling tobacco use offer the best prospect for reducing the risk of, and mortality from, the disease. Reductions in the prevalence of smoking over the last 40 years have prevented an estimated 1.6 million premature deaths in the United Kingdom, many of these from lung cancer.[3] Although the ideal must be to discourage people from taking up smoking in the first place, evidence suggests that the benefits of giving up smoking before middle age are substantial in terms of reducing the risk of lung cancer.[4, 5] Even after lung cancer has been diagnosed, the prognosis may be improved for some patients if they stop smoking (*see section 3*). ASH Scotland and NHS Health Scotland have published joint, evidence based guidelines on smoking cessation.[6]

1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 80. The key questions on which the update is based are listed in Annex 1.

Where sections were not updated, text and recommendations are reproduced verbatim from SIGN 80. The original supporting evidence was not re-appraised by the current guideline development group. Sections that have been updated from SIGN 80 are flagged with the following symbol: **Revised**

1.1.2 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

2	Key recommendations	New
3	Smoking	Minor update
4	Diagnostic investigations	Minor update to 4.2.3 PET-CT scanning New sections: 4.6 Pleural aspiration cytology, 4.7 Advanced bronchoscopic techniques, and 4.10 Applicability of cytology samples for optimal assessment
5	Staging investigations	Minor updates to 5.1 Introduction, and 5.4.3 FDG-PET scanning and detection of distant metastases Major updates to 5.3.4 PET scanning of mediastinal nodes, and 5.4.7 Adrenal gland metastases New sections: 5.3.5 Neck ultrasonography fine needle aspiration, and 5.3.6 Endoscopic sampling of the mediastinal lymph nodes
6	Surgery	Minor updates to 6.1 Introduction, 6.1.1 Influence of surgical experience/practice, 6.2.2 Reduction of surgical morbidity and mortality, and 6.2.3 Video-assisted thorascopic surgery (stage I) Major update to 6.2.4 Mediastinal lymph node management of patients with NSCLC
7	Radiotherapy	Minor update to 7.4.2 Radiotherapy in patients with isolated brain metastases New sections: 7.1.3 Stereotatic radiotherapy, 7.1.4 Intensity modulated radiotherapy, 7.2 Radical radiotherapy in patients with NSCLC, and 7.6 Prophylactic cranial irradiation in patients with extensive disease SCLC.
8	Systemic anticancer therapy	Major updates to 8.2 First-line therapy for patients with stage IIIB and IV NSCLC, and 8.5 Postoperative systemic anticancer therapy New sections: 8.1 Molecular testing of predictive biomarkers in NSCLC 8.3 Maintenance therapy, and 8.4 Second line therapy
9	Combined modalities	Major update to 9.2 Concurrent chemoradiotherapy in patients with NSCLC
10	Palliative interventions	Minor update to 10.1 Management of malignant pleural effusion New sections: 10.2 Management of endobronchial obstructions, and 10.4.1 Bisphosphonates
11	Supportive and palliative care	No revision
12	Multidisciplinary teams, follow up and communication	No revision
13	Provision of information	Completely revised
14	Implementing the guideline	Completely revised

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

The guideline covers all aspects of the management of patients with small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and provides information for discussion with patients and carers.

The guideline does not address other thoracic malignant disease such as mesothelioma, carcinoma in situ or secondary cancers that have spread to the lungs. Strategies for primary prevention or screening are also outwith the remit of the guideline. The guideline does not address the public health issues associated with smoking. Further information is available in a report from the NHS Health Development Agency.[7]

1.2.2 TARGET USERS OF THE GUIDELINE

The guideline is intended for use by chest physicians, surgeons, radiologists, pathologists, medical and clinical oncologists, pharmacists, public health practitioners, nurses, general practitioners, palliative care teams, allied health professionals, patients and carers.

1.3 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.3.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off label' use.

Medicines may be prescribed off label in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off label' use of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[8]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".[8]

The General Medical Council (GMC) recommends that when prescribing a medicine off-label, doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists).
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources.
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice.
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the the summary of product characteristics (SPC).[9] The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[10]

1.3.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Care Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice relevant to this guideline is summarised in the section 14.4.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

2.1 SMOKING

B **Advise patients to stop smoking as soon as the diagnosis of lung cancer is suspected and explain the benefits of doing so.**

2.2 STAGING INVESTIGATIONS

B **Histological confirmation of mediastinal nodes should be considered if nodes are > 10mm in short axis on CT or nodes are positive on PET-CT.**

A **Endoscopic assessment of the mediastinal lymph nodes with EBUS-FNA with or without EUS-FNA should be offered to patients with suspected lung cancer prior to mediastinoscopy.**

2.3 SURGERY

D **Patients with stage I and II NSCLC should be considered for curative surgery whenever possible.**

2.4 RADIOTHERAPY

B **Patients with NSCLC stage I and II who are medically inoperable or who do not consent to surgery should be offered radical radiotherapy.**

2.5 SYSTEMIC ANTICANCER THERAPY

A **First line single agent tyrosine kinase inhibitors should be offered to patients with advanced NSCLC who have a sensitising *EGFR* mutation. Adding combination systemic anticancer therapy to a TKI confers no benefit and should not be used.**

2.6 SUPPORTIVE AND PALLIATIVE CARE

B **All patients with lung cancer should have access to a specialist palliative care team.**

2.7 MULTIDISCIPLINARY TEAMS

D **All patients with a diagnosis of lung cancer should have their treatment and management planned and directed by a multidisciplinary team.**

3 Smoking

Revised Although patients who smoke may believe that quitting is futile following a cancer diagnosis, there are proven benefits for smoking cessation for the cohort of patients in whom treatment results in prolonged survival. Stopping smoking can cut the relative risk of death by 45% (95% confidence interval (CI), 0.38 to 0.79).[11,12,13] This is due to a reduced likelihood of cancer recurrence or progression rather than reduction in cardiopulmonary death.[12] Continued smoking following a cancer diagnosis may:[11,12,14] **2++ 2+**

- reduce survival time
- increase the risk of a recurrence, or a secondary primary tumour
- reduce treatment efficacy
- affect quality of life
- exacerbate and prolong treatment-induced complications such as mucositis, dry mouth, loss of taste and voice, impaired pulmonary function, wound healing, and tissue and bone necrosis.

In patients being considered for surgery there is evidence that preoperative smoking cessation has the potential to reduce:[12,15,16] **2++ 3**

- postoperative pulmonary complications
- length of stay in specialised units and overall stay in hospital
- demand on resources.

The timing of smoking cessation relative to resection does not significantly affect postoperative complications or pulmonary function test results one year later and should not be a reason to delay surgical resection.[17] The NICE guideline on the diagnosis and management of lung cancer also concluded that potentially curative surgery should not be delayed to allow patients to stop smoking.[18] **2- 4**

Discussing smoking cessation, particularly around the time of initial presentation, provides a powerful window of opportunity, as patients and their families and carers are often receptive at this time to consider cessation. Without additional treatment support, 95% of those who try to give up smoking will be smoking again within six months.[19] Effective pharmacological therapies and behavioural approaches exist to help smokers quit, ranging from brief opportunistic interventions to more intense programmes provided by local specialist cessation services.[6] **4**

Cancer patients, and particularly those with lung cancer, can suffer from weight loss, anorexia, breathlessness, and cough. The benefits of smoking cessation often include increased appetite, improved sense of smell and taste, weight gain, less sputum production, and an increase in oxygen intake and energy.[13,20,21] **4**

B **Advise patients to stop smoking as soon as the diagnosis of lung cancer is suspected and explain the benefits of doing so.**

B **Inform patients that smoking increases the risk of pulmonary complications.**

D **Do not postpone surgery for lung cancer to allow patients to stop smoking.**

See section 13.2 for sources of support for people who would like to stop smoking.

4 Diagnostic investigations

4.1 INTRODUCTION

Lung cancer is frequently suggested from chest X-ray findings: for example a solitary pulmonary nodule, pulmonary or hilar mass, poorly resolving pneumonia or pleural effusion. Histological or cytological confirmation of the diagnosis is desirable, though not always possible, and can be achieved by a variety of methods: image guided percutaneous biopsy, bronchoscopy, mediastinoscopy or thoracoscopy. Tissue diagnosis should be followed by subtyping of the cancer according to the current WHO classification.[22] It may not be possible to use this classification fully if biopsy specimens or cytology samples are small. The simple diagnostic dichotomy of SCLC or NSCLC is insufficient for planning further management and more recent recommended diagnostic approaches should be followed.[23] The management of patients with an incomplete diagnosis should be discussed by the multidisciplinary team.

No evidence was identified supporting the use of blood tests, for example tumour markers, in the diagnosis of lung cancer.

Sometimes in patients of poor performance status *(see Annex 4)* with major comorbidity, it is neither safe nor necessary to pursue invasive investigations to secure a tissue diagnosis. Clinicians must act sensibly, sensitively and with compassion in such circumstances and proceed to non-surgical treatment or palliative care, usually after discussion in the multidisciplinary team setting. Similarly, where patients do not wish to be investigated, their preferences must be respected; refusal to undergo invasive investigation should not prejudice continuing care.

Although diagnostic and staging investigations are mentioned separately in this guideline, it may be possible to obtain the diagnosis and staging in a single procedure. This practice has the potential to reduce the number of investigations required and the time to definitive treatment. Cases must be considered individually, based on the clinical and pathological information required for a management plan. If a single sampled site, presumed to represent metastatic malignancy, returns no evidence of tumour or insufficient material for adequate pathological assessment, including molecular studies, a repeat procedure needs to be considered.

4.2 IMAGING

4.2.1 CHEST X-RAY

Patients with lung cancer can present with a normal or abnormal chest X-ray.[24] Referral to the respiratory team is required if risk factors and symptoms raise the possibility of cancer even if the chest X-ray is normal. Patients with lung cancer often have obstructive features (37%) and pleural effusions (22%).[24] 3

D **A chest X-ray should be performed on all patients being investigated for the possibility of lung cancer.**

✓ Further investigation is recommended in patients with clinically suspected lung cancer even if the chest X-ray is normal.

4.2.2 CT SCANNING

The role of contrast enhanced computed tomography (CT) scanning of the chest and abdomen in the diagnosis of lung cancer has been investigated in studies of the differential diagnosis of a solitary pulmonary nodule, where cases were reported by two independent experienced radiologists.[25-27] This does not necessarily reflect typical practice. 3

In a randomised controlled trial (RCT) designed to evaluate the impact of an early CT on management choices, 171 patients had their CT scans reviewed before fibre optic bronchoscopy (FOB), allowing the cancellation or a change to an alternative invasive procedure if appropriate. The trial included patients with distal collapse and visible tumours larger than 5 cm. Patients with peripheral lesions were excluded. CT scanning at an early stage in the patient's journey allowed selection of the most appropriate investigation for confirmation of diagnosis and stage.[28] The generalisability of these conclusions is not clear, given the patient selection criteria. **1+**

Results from CT scanning are subject to variation caused by different scanning techniques, but suggest that CT scanning of the chest and abdomen has a high sensitivity (89–100%) but a relatively low specificity (56–63%) and a poor negative predictive value (60–100%). This may be improved by serial scans.[27] **3**

These results suggest that CT scanning alone should not be used to confirm a diagnosis of lung cancer and that histological and cytological confirmation of the diagnosis will be required in most cases.

The same scan is often used for both diagnostic and staging purposes *(see section 5.2.1)*.

B **Contrast enhanced CT scanning of the chest and abdomen is recommended in all patients with suspected lung cancer, regardless of chest X-ray results.**

D **A tissue diagnosis should not be inferred from CT appearances alone.**

D **Contrast enhanced CT scanning of the chest and abdomen should be performed prior to further diagnostic investigations, including bronchoscopy, and the results used to guide the investigation that is most likely to provide both a diagnosis and stage the disease to the highest level.**

4.2.3 PET-CT SCANNING

Revised Fluorodeoxyglucose (FDG) positron emission tomography (PET or PET-CT) scanning has been investigated as a diagnostic tool in the differential diagnosis of lung cancer and benign lesions presenting in the lung as a solitary nodule. It is a noninvasive whole body staging test for lung cancer (*see section 5*). Early studies used PET alone, which has now been superseded by PET-CT.

A meta-analysis, a systematic review and 12 diagnostic studies were identified.[29-42] The meta-analysis suggests that FDG PET scanning has a diagnostic sensitivity of 96% and a specificity of 78% but there is considerable variation within the studies included.[29] **2+**

FDG PET-CT may be less reliable in detecting a small lung nodule (<1 cm) due to its inherent spatial resolution.

C **FDG PET-CT scanning may be used to investigate patients presenting with solitary lung lesions but histological/cytological confirmation of results will still be required.**

4.3 BRONCHOSCOPY

The value of bronchoscopy depends on the location of the primary tumour. Peripheral tumours in subsegmental bronchi may not be visible.

The evidence base for the role of bronchoscopy in both central and peripheral tumours comes from two large systematic reviews.[43,44] **2++**

4.3.1 CENTRAL TUMOURS

Flexible bronchoscopy has good diagnostic sensitivity (83–88%) for central lesions.[43,44] Sampling using multiple techniques gives the highest diagnostic yield. As a single procedure, bronchial biopsy is the most reliable. Table 1 shows the variation in sensitivity for each method. **2++**

Table 1: Percentage diagnostic sensitivity in central tumours

Technique	% Sensitivity	
	Detterbeck[43]	Schreiber[44]
Biopsy	83	74
Brushings	64	59
Washings	48	48
All three modalities	83	88

B **Patients with central lesions who are otherwise fit should undergo flexible bronchoscopy in order to establish a histological or cytological diagnosis.**

B **Visible tumours should be sampled using more than one technique to optimise sensitivity.**

4.3.2 PERIPHERAL TUMOURS

Flexible bronchoscopy has a lower diagnostic sensitivity for peripheral lesions compared with central lesions *(see Tables 1 and 2)*. Although fluoroscopy may improve the diagnostic yield of bronchoscopy in sampling peripheral lesions, results still compare poorly with percutaneous fine needle aspiration (FNA) biopsy *(see section 4.4)*.[43,44] **2++**

Table 2: Percentage diagnostic sensitivity in peripheral tumours

Technique	% Sensitivity	
	Detterbeck[43]	Schreiber[44]
Biopsy	60	46
Brushings	48	52
Washings	37	43
All three modalities	66	69

B **Bronchoscopy may provide a diagnosis for peripheral lesions, although percutaneous FNA biopsy is the preferred approach.**

4.4 PERCUTANEOUS FNA BIOPSY

Percutaneous FNA biopsy is a highly sensitive technique for diagnosing lung cancer (sensitivity of 88–92%).[44,45] Fine needle aspirations can be done as blind percutaneous biopsy or guided by fluoroscopy, ultrasound, CT or magnetic resonance imaging (MRI). Larger cutting needles can also be used to obtain biopsy cores of intact tissue for histology. Sensitivity is greater for peripheral lung lesions than fibre optic bronchoscopy.[45] There is a high false negative rate (25%) resulting in limited ability to confirm a benign diagnosis. This may be improved by using core biopsies for histology rather than aspirates for cytology.[45] Potential complications include bleeding and pneumothorax (chest drain 10%, haemoptysis 3%, mortality 0.04%). **2++**

B **Percutaneous FNA biopsy should be considered as the preferred diagnostic technique in patients with peripheral lesions.**

4.5 SPUTUM CYTOLOGY

There is a wide variation (10–97%) in the sensitivity of sputum cytology in the diagnosis of lung cancer.[31,44,46] High sensitivity is only achieved by the use of specific and carefully controlled protocols for sample collection. In routine practice the diagnostic yield appears to be at the lower end of the range, suggesting that this technique is best reserved for cases with large central lesions where bronchoscopy or other diagnostic tests are contraindicated. **3**

D **Sputum cytology should only be used in patients with large central lesions, where bronchoscopy or other diagnostic tests are deemed unsafe.**

4.6 PLEURAL ASPIRATION CYTOLOGY

Revised Since cytological examination of aspirated effusion fluid may provide a cytological diagnosis, it should be performed, rather than fluid being discarded. When cytological examination fails to confirm malignancy, both radiologically guided biopsy procedures and thoracoscopic biopsy are equally effective with similar diagnostic yields (87.5–94.1%).[47] **1+**

4.7 ADVANCED BRONCHOSCOPIC TECHNIQUES

4.7.1 PERIPHERAL LUNG LESIONS

Revised Systematic reviews of traditional fibre optic bronchoscopy indicate a diagnostic sensitivity of 69–94% for the diagnosis of lung cancer with CT guided percutaneous core biopsy or FNA having a sensitivity of 86–94%, specificity of 41–100% and an overall diagnostic accuracy of 83–93%.[18,44,48] **2++ 2+**

The evidence for X-ray guidance to improve bronchoscopic yield is mixed, with one study showing no significant increase in diagnostic yield using X-ray guidance (71% *v* 76%)[49] while another report has suggested higher yields may be obtained (sensitivity 92%, and overall accuracy 90%).[50] Computed tomography virtual bronchoscopic navigation in conjunction with both endobronchial ultrasound (EBUS) and fluoroscopy increased diagnostic yield to 80% from 67% in the control group.[51] The most significant increase was seen in relation to small tumours (<20 mm) where the yield was increased from 56% to 76%.[51] **1++ 2+**

An RCT concluded that EBUS did not increase diagnostic yield for peripheral lesions compared with traditional bronchoscopy,[52] but other studies utilising radial ultrasound probes have shown better results. A meta-analysis of 16 systematic reviews evaluating radial probe EBUS indicated a point sensitivity of 0.73, specificity of 1.0, positive predictive value (PPV) of 26.84 and negative predictive value (NPV) of 0.28 although the authors commented on a very wide range of results.[53] **1++ 2++**

Electromagnetic guidance systems to aid bronchoscopy have shown a diagnostic sensitivity of 60%, specificity of 91%, PPV of 95%, NPV of 42% and overall accuracy of 67%.[18] Electromagnetic guidance used in conjunction with EBUS had a higher diagnostic yield (88%) compared to EBUS alone (69%).[54] **1++**

Advanced bronchoscopic techniques may have a role in obtaining diagnostic material from primary tumours in some patients but there is insufficient evidence that it provides a higher diagnostic yield than traditional image guided approaches and fibre optic bronchoscopy.

B **The use of advanced bronchoscopic techniques should be considered in patients with tumours where sampling with traditional approaches has failed to provide suitable diagnostic material.**

4.7.2 CENTRAL LUNG LESIONS

Studies of EBUS to visualise and sample centrally placed lesions which are not visible bronchoscopically have reported diagnostic sensitivities of 82–94%.[55] **2++**

4.8 VIDEO-ASSISTED THORACOSCOPY

Video-assisted thoracoscopic surgery (VATS) provides a highly sensitive (97–100%) method of obtaining histological and cytological material for confirmation of the diagnosis of lung cancer in patients with pleural effusions or peripheral lesions where this has not been possible to achieve by other less invasive means. It is also a sensitive method of obtaining material intraoperatively prior to definitive resection.[56,57] It has a low complication rate (0.8% open conversion rate). **3**

D **Thoracoscopy should be considered for patients with pleural effusions or peripheral lesions where less invasive means have not achieved histological and cytological confirmation of diagnosis.**

4.9 ANTERIOR MEDIASTINOTOMY/MEDIASTINOSCOPY

Anterior mediastinotomy/mediastinoscopy may be used to establish a tissue diagnosis in selected patients presenting with mediastinal or hilar masses where this has not been achieved by other less invasive means.[58] **3**

✓ Anterior mediastinotomy/mediastinoscopy should be considered in patients with lung cancer presenting with hilar and mediastinal masses where histological or cytological confirmation has not been achieved by less invasive means.

4.10 APPLICABILITY OF CYTOLOGICAL SAMPLES FOR OPTIMAL ASSESSMENT

Revised

Diagnostic cytology specimens show a high level of diagnostic concordance with matched histology samples in the differentiation of small cell lung cancer from non-small cell lung cancers.[59] A moderate to high degree of concordance with histology can also be achieved for subclassification of NSCLC (88% in one study and 96% in another).[60,61] Some of these studies had selected populations and did not reflect a typical clinical situation. Such high levels of diagnostic accuracy, based upon morphology without the use of additional immunohistochemistry have not been found in other studies.[62-64] These studies examined the role of immunohistochemistry in the subclassification of NSCLC and using a varying panel of antibodies showed that the unclassified rate could be reduced from 36% to 14-23%. It is important that cytological material is appropriately processed to permit further histological analysis. **2^{++}** **2^{+}** **2^{-}**

A number of studies to detect mutations demonstrated that molecular diagnostic tests can be successfully performed on a range of cytological sample types.[61,65-69] The criteria for inclusion of specimens as 'adequate' for testing is variable and reported success rate for testing ranges from 77% to 98% with no clear consensus.[61,68] One study demonstrated 100% concordance, in 20 cases, between results from a molecular diagnostic test for mutations in epidermal growth factor receptor (*EGFR*) gene carried out on cytological samples, although these data are likely to be subject to some publication bias.[67] **2^{+}** **2^{-}**

B **Cytology samples can be used to provide material suitable for both NSCLC subtyping and some molecular analysis, provided the samples are appropriately handled and processed.**

4.11 GOOD PRACTICE IN PATHOLOGICAL REPORTING

Immunohistochemistry (IHC) should be used in all cases of NSCLC which cannot be subtyped on morphological grounds (NSCLC-NOS), where suitable material is available, to predict likely NSCLC subtype and reduce overall NSCLC-NOS rates. In biopsy samples, an NOS rate of under 10% is achievable.[70] For cytology samples there are less data and specimens are more variable in their suitability for additional testing although a similar NOS rate may be seen as a reasonable target.

3

✓ The first priority in reporting histology and cytology specimens is to establish a diagnosis. Primary malignancies should then be classified as SCLC or NSCLC. NSCLC tumours should be subtyped where possible.

✓ All histology and cytology specimens should be reported by a consultant pathologist, who is a member of the Royal College of Pathologists continuous professional development (CPD) programme, who participates in relevant external quality assurance (EQA) schemes and works in a pathology laboratory with clinical pathology accreditation (CPA).

✓ Every effort should be made, during the diagnostic phase, to preserve tumour material for molecular biomarker analysis.

✓ Tissue from biopsies and resection specimens should be archived in the pathology department in a manner consistent with current legislation on consent and stored in line with the recommendations of the Royal College of Pathologists. The material should be available for review if required for the further management of the patient and for audit, teaching and research, as permitted by appropriate consent.

5 Staging investigations

5.1 INTRODUCTION

Revised

Staging is the assessment of the extent of disease and is performed for prognostic and therapeutic purposes. Ideally, diagnosis and staging should be obtained through a single procedure. Lung cancer is staged using the 7th edition of the TNM staging system, which covers staging for NSLC and SCLC *(see Annex 2)*.[71] The system has two major components: the anatomical extent of the disease (TNM; tumour, nodes, metastases) and the cell type.[71] Clinical staging (c) relies on information obtained from imaging studies and biopsies. Pathological staging (p) is determined following surgical resection.

Accurate staging also allows more valid comparisons of outcomes to be made across hospitals and managed clinical networks.

The imaging tools most commonly used to stage lung cancer are CT, MRI, ultrasound (US), and PET-CT. Minimally invasive EBUS and endoscopic US (EUS), and invasive procedures such as mediastinoscopy and anterior mediastinotomy are common staging procedures for pathology.

The reliability of each of these tests, and the implications for the interpretation of results, is determined from the false negative (FN) and the false positive (FP) rates *(see Annex 3)*.

5.2 T STAGE IN NON-SMALL CELL LUNG CANCER

Radiographic differentiation of T1 and T2 disease does not significantly alter the choice of therapy. It is much more important to be able to predict T3 and T4 involvement if surgical resection is being considered.

5.2.1 CT SCANNING

In Western countries a staging contrast-enhanced CT of the thorax and upper abdomen is the standard method for assessing operability in lung cancer patients. The reliability of CT in predicting T3 or T4 disease is poor.[72] CT is equally poor at predicting chest wall invasion and mediastinal involvement.[72]

2++

B **Patients with suspected T3 or T4 disease who are otherwise fit for surgery should not be denied surgical exploration on the basis of a CT scan alone.**

5.2.2 MRI SCANNING

With the exception of superior sulcus tumours, MRI confers no benefit over CT in the assessment of patients with chest wall and mediastinal involvement.[73-77] Looking specifically at mediastinal invasion, particularly invasion of blood vessels, some studies have shown MRI to be more beneficial than CT.[77]

2++

B **MRI is not recommended in the routine assessment of the T stage except in patients with superior sulcus tumours. It may be of value in selected patients with suspected mediastinal invasion.**

5.2.3 THORACOSCOPY

Thoracoscopy may be beneficial in correctly determining the T stage in patients with T3 or T4 disease when less invasive methods have been inconclusive.[78] The role of thoracoscopy in pleural staging (M1a) is covered in section 5.4.2.

2+

C **Thoracoscopy may be considered for more accurate determination of the T stage in patients with suspected mediastinal or chest wall invasion when less invasive techniques have been inconclusive.**

5.3 N STAGE IN NON-SMALL CELL LUNG CANCER

The most important aspect of intrathoracic staging is accurate determination of nodal involvement. CT and MRI scans rely on lymph node size to predict malignant involvement. A 10 mm node size is the usual cut-off, having an average sensitivity and specificity of 75% and 76% respectively.[79]

5.3.1 HILAR NODES (N1)

The reliability of CT, MRI and thoracoscopy in staging N1 nodes is poor.[78,80-82] This may be a concern if radical radiotherapy is being considered and the primary tumour is distant from the hilum. **2++**

5.3.2 CT SCANNING OF MEDIASTINAL NODES (N2/3)

For all categories of patients with lung cancer, the reliability of CT in the assessment of mediastinal nodes is poor with average false positive and negative rates of 45% and 13% respectively.[83] The false negative rate is higher with central tumours and adenocarcinomas (22% and 19%). **2++**

B **A positive CT scan result for mediastinal lymphadenopathy** (>10 mm in short axis diameter) **indicates the need for pathological sampling of the enlarged nodes** (with the exception of extensive infiltrating disease) **if clinically indicated.**

5.3.3 MRI SCANNING OF MEDIASTINAL NODES (N2/3)

Conventional MRI is not superior to CT in the assessment of mediastinal nodes.[73,74,77,84,85] **2++**

B **MRI has no role in the routine staging of mediastinal lymphadenopathy.**

5.3.4 PET SCANNING OF MEDIASTINAL NODES (N2/3)

Revised FDG PET-CT is more accurate than CT in detecting mediastinal nodal metastases in patients with NSCLC.[86] The false negative rate of FDG PET in mediastinal nodes of 10 mm in short axis diameter on CT was very low (5%).[87] **2+**

The false negative rate of FDG PET in mediastinal nodes >15 mm in short axis diameter on CT was relatively high (21%).[87] These patients should have mediastinal nodal sampling before radical surgery, unless FDG PET-CT reveals distant metastases. FDG PET-CT staging may be limited by the pathology type, metabolic activity and location of the primary tumour, and status of the hilar nodes. Mediastinal nodal sampling may be considered in patients with central tumours, low FDG uptake in the primary tumour, PET positive N1 node, or enlarged nodes on CT.[88, 89] **2+ 4**

The specificity of FDG PET in mediastinal nodal staging is approximately 80%.[90] Given a relatively high false positive rate, FDG PET positive mediastinal nodes should be confirmed with nodal sampling, if this will alter management.[90] **2+**

B **All patients with NSCLC who are being considered for radical treatment should have a staging FDG PET-CT scan before treatment.**

B **Patients with a negative FDG PET-CT scan result of mediastinal nodes of 10 mm or less in short axis on CT scanning could proceed to radical treatment.**

B **Histological confirmation of mediastinal nodes should be considered if nodes are >10 mm in short axis diameter on CT or nodes are positive on PET-CT scanning.**

5.3.5 NECK ULTRASONOGRAPHY FINE NEEDLE ASPIRATION

Revised Accurate detection of supraclavicular nodal metastasis (N3) is a crucial factor in the prognosis and management of patients with NSCLC. Supraclavicular nodes may be identified on clinical examination, or in the staging CT or PET-CT. Accurate staging can be achieved by neck ultrasound fine needle aspiration which is relatively quick, does not involve radiation, and can guide nodal sampling for pathological diagnosis as well as staging (pN3).[91-93] **3**

D **Neck ultrasound fine needle aspiration should be considered for a pathological diagnosis and staging in the case of a positive supraclavicular node on clinical examination, by CT or PET-CT scanning.**

5.3.6 ENDOSCOPIC SAMPLING OF THE MEDIASTINAL LYMPH NODES

Revised Assessing the mediastinum with endobronchial ultrasound fine needle aspiration (EBUS-FNA) and endoscopic ultrasound (EUS-FNA) offers a diagnosis and nodal staging in a single step and is a less invasive technique than surgical staging alone.[94] The technique is associated with a low risk of complicatons and less need for general anaesthesia. The use of these techniques readily allows for repeat sampling of the mediastinum which is simpler than repeat mediastinoscopy.[95] **1++ 2++**

A **Endoscopic assessment of the mediastinal lymph nodes with EBUS-FNA with or without EUS-FNA should be offered to patients with suspected lung cancer prior to mediastinoscopy.**

5.4 M STAGE IN NON-SMALL CELL LUNG CANCER

Approximately 40% of patients with NSCLC present with distant metastases and of these around 90% have clinical symptoms.[96,97] The most common sites of metastases are brain, bone, liver, adrenal glands and lung.

5.4.1 CLINICAL EVALUATION

The most important part of staging for distant metastases is the clinical evaluation taking account of the patient's history (especially if there has been weight loss), complemented by physical examination along with haematological and biochemical tests. Imaging techniques are most useful when correlated with the findings of a clinical evaluation. Occult distant metastases are present in 15–30% of patients with clinical stage III disease.[98] **2+**

C **Patients with clinical stage I or II disease on the basis of a CT scan of the chest and abdomen, PET-CT and a negative clinical evaluation do not require further investigation to look for extrathoracic metastases.**

5.4.2 PLEURAL EFFUSION

Spread of lung cancer to the pleural space with the development of an effusion indicates M1a disease. Pleural aspiration is essential for accurate staging in patients with a pleural effusion. A pleural biopsy should be undertaken in patients with negative fluid cytology.[79] Some patients may require VATS biopsy to confirm pleural malignancy as aspiration and pleural biopsy alone may be insufficient. **2+**

D

- **In patients being considered for active therapy, pleural effusion should be investigated with pleural aspiration and/or pleural biopsy using image guided or thoracoscopic biopsy.**
- **The presence of malignant cells is required to categorise the lesion as M1a.**

✓ Thoracoscopy should be considered if aspiration and image-guided pleural biopsy are negative.

5.4.3 FDG PET-CT SCANNING AND DETECTION OF DISTANT METASTASES

Revised FDG PET-CT has been shown to identify unsuspected metastases in 10 –15% of patients with NSCLC. When the scan is positive the lesion should be biopsied or followed up.[90,99-102] **2+**

In one retrospective study the rate of FDG PET detected distant metastasis increases with disease stage prior to PET: 7.5% in stage I, 18% in stage II and 24% in stage III.[103] **3**

FDG PET-CT allows more accurate classification of the stage of the disease, and reduces unnecessary surgical procedures.[99,100] This suggests that it would be of most benefit in patients with NSCLC who are candidates for surgery or radical radiotherapy. One of the main limitations of PET scanning is that high glucose metabolism in the brain and kidney makes evaluation of metastases at these sites difficult and unreliable. **2+**

C **All patients with NSCLC who are being considered for radical treatment should have a staging PET-CT scan to detect occult distant metastases.**

5.4.4 BRAIN METASTASES

Contrast-enhanced CT is the most commonly used imaging method to detect brain metastases and is as reliable as non-contrast-enhanced MRI.[104-111] Contrast-enhanced MRI will detect more metastases than contrast-enhanced CT but does not detect metastases in a greater number of patients. CT of the head is not warranted in asymptomatic patients initially staged as clinical stage I-II.[105,106] In patients with N2 disease who are still being considered for curative treatment, a CT scan of the head is warranted.[105] **2+**

C **Contrast-enhanced head CT or MRI in asymptomatic patients with clinical stage I-II disease is not recommended.**

✓ Contrast-enhanced head CT or MRI is warranted in patients with N2 disease who are being considered for curative treatment.

5.4.5 BONE METASTASES

Bone scanning with Tc-99m has a high false positive rate. Compared to conventional isotope bone scanning, FDG PET-CT is more specific and sensitive.[18] If a PET scan is not indicated and symptoms of bone metastases are present a Tc-99m nuclear bone scan may be helpful. A positive bone scan should be confirmed by additional studies (eg X-ray, MRI, biopsy). **2++**

B **A positive nuclear bone scan in patients with otherwise potentially curable disease should be confirmed by other studies** (eg plain X-rays, MRI or biopsy)**.**

5.4.6 LIVER METASTASES

Liver metastases are found in approximately 2% of asymptomatic patients initially staged as clinical stage I-III on the basis of a chest CT.[112] Benign hepatic lesions are common in the general population and the presence of a liver abnormality >10 mm in an asymptomatic patient with lung cancer requires further characterisation by US, contrast enhanced CT, FDG PET-CT, or MRI.[90,102,113-115] Definitive confirmation of a suspected liver metastasis is best accomplished by needle biopsy which has a diagnostic accuracy of 90%.[116] Complications are rare (1–2%) and consist mainly of haemorrhage.[117] **2+ 4**

C
- **US, contrast enhanced CT, FDG PET-CT or MRI can be used to characterise most benign focal hepatic abnormalities >10 mm.**
- **A definitive confirmation of a liver metastasis can only be made by needle biopsy.**
- **The management of patients with lesions too small to characterise by imaging and not amenable to biopsy is best guided by an estimation of the chance of metastatic disease given the clinical stage and symptoms.**

5.4.7 ADRENAL GLAND METASTASES

Incidental adrenal masses are seen in approximately 0.6% of all abdominal CTs. Seventy per cent to 95% of these in the general population will be benign non-functioning adenomas.[118,119] In clinical stage I-III patients the frequency of adrenal enlargement is similar to the normal population, although approximately half of patients will have metastases on biopsy.[120] **2++**

The incidence of adrenal enlargement in patients with lung cancer increases with higher stage disease. Adrenal glands less than 2 cm have a 10% chance of being malignant increasing to 75% for glands more than 4 cm.[121-123] 2++

An adrenal adenoma can be reliably diagnosed by chemical shift MRI, unenhanced CT and delayed contrast-enhanced CT, making these suitable techniques for excluding metastases.[121,122] Percutaneous needle biopsy has an overall complication rate of 8–9% with 3–4% having major complications (eg pneumothorax or significant haemorrhage).[124] At less than 5%, FDG PET scanning appears to have the lowest false positive and false negative rates for adrenal metastases.[121] 2++

Revised In a meta-analysis FDG PET-CT was found to be highly sensitive (97%) and specific (91%) in differentiating malignant from benign adrenal disease, although studies were highly heterogeneous.[125] FDG PET-CT interpretation criteria varied but there was no significant difference in their accuracy. Several primary studies also showed high sensitivity and specificity of FDG PET-CT for adrenal staging in patients with lung cancers.[126,127] No trials of head-to-head comparison of PET-CT, MRI and ultrasound were identified. 2++

Unenhanced CT density Houndsfield units (HU) <10 and low FDG uptake has high specificity for benign adenoma.[125] High FDG activity in an adrenal mass has high specificity for metastasis although there were variations in FDG PET-CT interpretation criteria (visual analysis, standardised uptake value (SUV), SUV ratio etc).[125,127-129] The American College of Chest Physicians guidelines proposed evaluation with CT and MR criteria, additional imaging including PET, and in inconclusive cases, pathology confirmation by percutaneous biopsy or adrenalectomy.[88] EUS-FNA has also been shown to be effective in adrenal staging especially of the left adrenal gland.[130,131] 2++ 3 4

B **A negative FDG PET-CT reliably excludes adrenal metastases.**

B **In patients with PET-CT positive adrenal lesions pathology, confirmation may be considered unless there is overwhelming clinical and imaging evidence of widespread metastatic disease.**

D **In patients with indeterminate adrenal lesions on FDG PET-CT further assessment with adrenal specific CT or MRI criteria may be considered. If noninvasive imaging findings are indeterminate, adrenal sampling such as EUS-FNA, percutaneous biopsy or adrenalectomy may be considered.**

5.4.8 LUNG METASTASES

Small pulmonary lesions are frequently seen in addition to the primary tumour on chest CT. These lesions are usually benign.[132,133] 2+

C **Patients with small pulmonary nodules should not be denied a curative approach without a definitive diagnosis** (by biopsy, FNA or wedge resection)**.**

5.5 SMALL CELL LUNG CANCER

The TNM system is used to stage SCLC.[71]

Clinical evaluation can identify most patients who either have extensive disease or who are unsuitable for thoracic radiotherapy. Patients who are felt to be at high risk of having distant metastases and who are being considered for contrast enhanced intensive treatment should undergo further staging investigations in a sequential manner.[134] 2++

A pragmatic strategy is to stage patients by clinical evaluation and contrast enhanced CT of the chest and abdomen and only proceed to further investigations if clinically indicated.

B **Investigation for distant metastases is recommended when intensive treatment is being considered for patients with SCLC who are considered to be at high risk of having distant metastases.**

✓ Patients with SCLC should be staged by clinical evaluation and contrast enhanced CT of the chest and abdomen. If the CT does not demonstrate extensive disease and the clinical examination is negative, management should proceed on the assumption of limited stage disease.

6 Surgery

6.1 INTRODUCTION

Revised Surgery is the mainstay of curative treatment for patients with NSCLC. Surgical resection rates in Scotland and Britain are lower than in other countries in the western world. At present the Scottish resection rate of 11% compares unfavourably with rates of 17% throughout the rest of Europe and 21% in North America. Any increase in resection rates should be achieved without decreasing patient safety or significantly increasing unnecessary thoracotomies.[135]

The potential effects of smoking cessation on surgical outcome are described in section 3.

Past studies have stated a cut-off of 40% for the post operative predictive (ppo) forced expiratory volume (FEV_1) and carbon monoxide transfer factor (TLCO) for surgery. Many of these studies had small sample sizes.[136] To increase resection rates it may be necessary to look at patients with ppo FEV_1 and TLCO of less than 30%. It may also be important to consider patients with poor FEV1s preoperatively, such as patients considered for lung reduction surgery.[137] These patients would represent a select group and would need careful preoperative assessment which may involve perfusion scanning and pulmonary artery pressure measurement.[136] 3 4

Patients who perform well at the six minute walk or shuttle test, but have ppo FEV_1 or TLCO less than 30% have also been associated with good surgical outcomes. Surgery may be possible as a sub-lobar resection and VATS surgery may make surgery feasible in some patients.[138] 3

Patients with lung cancer present as a very heterogeneous group and all management decisions, including suitability for surgery, should be tailored on the basis of a multidisciplinary team meeting. The thoracic surgeon is a key member of the multidisciplinary team.

6.1.1 INFLUENCE OF SURGICAL EXPERIENCE/PRACTICE

Revised The link between an individual surgeon's operative mortality and case volume is unclear.[139,140] Larger units offer significant advantages in terms of practice outcomes, training and resource availability.[141,142] Video-assisted thoracoscopic surgery should be performed by a well trained thoracic surgeon with extensive open experience in a recognised VATS unit.[143] 3

6.2 NON-SMALL CELL LUNG CANCER

6.2.1 RADICAL SURGERY (STAGE I AND II)

Three retrospective studies,[144-146] two prospective studies[147,148] and nine case series[149-157] covering 8,037 patients were identified. No indication of the operation type (eg lobectomy or pneumonectomy) or performance status data was given in the studies. Radical surgery confers a five-year survival of 54–80% for patients with stage Ia lung cancer and 38–65% for patients with stage Ib lung cancer. Surgery gives the highest chance of cure for patients with stage I and II NSCLC. 3

D **Patients with stage I and II NSCLC should be considered for curative surgery whenever possible.**

6.2.2 REDUCTION OF SURGICAL MORBIDITY AND MORTALITY

Revised Several observational studies comparing 30-day postoperative mortality for different surgical interventions (eg sub-lobar resection, lobectomy and pneumonectomy) were identified.[140,144,158-161] Patient characteristics varied considerably across the different studies and none of the studies described performance status and how this affects the choice of operation. Limiting the scope of the operation lowers mortality at 30 days; wedge resection has the lowest mortality rate, followed by lobectomy, then pneumonectomy. Lobectomy is preferred to sub-lobar resection and segmentectomy is superior to wedge resection on the basis of a reduced recurrence rate,[162] except in patients who are of marginal fitness. Sleeve lobectomy is a preferable option to pneumonectomy where clearance can be achieved with a bronchoplastic procedure. 3

Six observational studies were identified that report on the 30-day mortality rate for inoperable lesions at thoracotomy.[163-168] A significant mortality is associated with thoracotomies which do not progress to lung resection. **3**

D **Lung resection should be as limited as possible without compromising cancer clearance. Lobectomy remains the procedure of choice for fit patients.**

D **Every effort should be made to avoid a thoracotomy that does not progress to a lung resection.**

6.2.3 VIDEO-ASSISTED THORACOSCOPIC SURGERY (STAGE I)

Revised Video-assisted thoracoscopic surgery in patients with stage I NSCLC is associated with a lower incidence of complications, less disturbance to the immune response, and a shorter hospital stay compared to open thoracotomy.[169-172] Survival rates at two and five years are comparable.[171-173] Patients over the age of 70 also had fewer complications following VATS (28% *v* 45%, p=0.04), shorter hospital stay (five days, range 2–20 *v* six days, range 2–27, p<0.001) and comparable survival rates.[174] All evidence identified related to stage I disease rather than later stages. **2++** **1+** **2+**

VATS is comparable to open surgery for systematic node dissection in terms of numbers of nodes dissected, operative mortality, morbidity and recurrence.[175]

B **Video-assisted thoracoscopic surgical resection may be offered to patients with clinical stage I NSCLC lung cancer.**

6.2.4 MEDIASTINAL LYMPH NODE MANAGEMENT OF PATIENTS WITH NSCLC

Revised Accurate staging of lymph node involvement in the mediastinum is vital for patients undergoing active treatment (*see sections 5.1 and 5.3*). The options for mediastinal lymph node management are:

Discretionary nodal sampling - enlarged or otherwise suspect nodes seen at surgery are taken for histological examination.

Systematic node dissection - samples are taken from each accessible mediastinal lymph node station for histological examination.

Radical mediastinal lymphadenectomy - all nodes in each accessible lymph node station are removed, often together with any associated connective tissue and fat.

Discretionary nodal sampling leads to reduced survival rates compared to the other two options.[176,177] Little evidence was identified to determine whether systematic lymph node dissection or radical mediastinal lymphadenectomy was the best lymph node strategy at surgical resection. Extensive nodal sampling/ adenectomy improves the accuracy of staging but it is unclear whether or not radical mediastinal lymphadenectomy improves overall survival, and this technique may add to operative time and increase postoperative morbidity.[178-180] **2+**

Mediastinal lymph node management should be in accordance with the International Association for the Study of Lung Cancer guidelines.[181]

B **Systematic nodal dissection should be undertaken for lymph node management at resection. Simple nodal sampling is not adequate and radical mediastinal lymphadenectomy is not necessary.**

6.2.5 RESECTION IN PATIENTS WITH STAGE IIIA NSCLC

A number of retrospective case series with relatively small numbers (30–100 cases) have been published describing the clinical outcomes achieved following surgery in selected patients with stage IIIA disease.[182] Patients were managed using a multimodality approach that included preoperative systemic anticancer therapy (SACT) and occasionally radiotherapy. Most studies suggested a survival benefit with a systemic anticancer therapy plus surgical resection protocol, compared with contemporary non-surgical management.

Patients who are suitable for surgery should have early (single station intracapsular lymph node) disease as determined by mediastinoscopy, the ability to tolerate induction treatment, evidence of response to this treatment and the fitness to subsequently tolerate major surgery. It is likely that few patients will meet these criteria.

✓ Patients with proven early N2 NSCLC may be considered for surgery as part of multimodality treatment. All of these cases must be discussed at the multidisciplinary team meeting.

6.3 SMALL CELL LUNG CANCER

6.3.1 EFFECTIVENESS OF SURGERY

In general, routine surgery for limited stage SCLC is not recommended. An RCT examining the role of surgery in patients who had responded to five cycles of cyclophosphamide, doxorubicin and vincristine (CAV) systemic therapy failed to show any benefit for the surgical arm.[183] **1++**

No RCTs were identified comparing adjuvant surgery to systemic anticancer therapy and radiotherapy alone. Retrospective trials indicate a combination of primary surgery and adjuvant systemic anticancer therapy and thoracic and cranial irradiation improves survival,[184-186] but further research is required before strong conclusions can be drawn.

There are two specific situations in which surgery may be beneficial:

1. Patients with clinical stage T1-2 N0 SCLC should be evaluated for potential surgical resection. They should be investigated thoroughly with CT chest and abdomen, radionuclide bone scan, CT brain and bone marrow biopsies. On confirmation of localised disease, surgery should be considered. Case series examining systemic anticancer therapy following resection of early stage SCLC suggest that adjuvant systemic anticancer therapy may confer a survival advantage.[187-190] **3**
2. Occasionally a peripheral mass with no preoperative histology is found to be SCLC following resection. This tends to occur in patients at an early stage of the disease, who have operable cancer according to the standard criteria for NSCLC. Adjuvant systemic anticancer therapy may confer a survival advantage.[187-189]

A **Routine surgery for limited disease SCLC is not recommended.**

D **Patients with early stage SCLC may be considered for resection following extensive staging investigation.**

✓ Adjuvant systemic anticancer therapy should be considered following resection of early stage SCLC.

6.4 GOOD PRACTICE IN LUNG CANCER SURGERY

✓ Lung cancer surgery should be practised in high volume thoracic surgery centres by surgeons trained in thoracic surgery who undertake this surgery as a major component of their clinical commitment.

✓ The thoracic surgery unit should have appropriate specialist support available pre- and postoperatively, including chest physicians, anaesthetists, radiologists, specialist nurses and pathologists with an interest in pulmonary diseases.

✓ Thoracic surgery centres should:

- have a thoracic high dependency unit with dedicated staff and adequate monitoring facilities
- have ready access to intensive care support
- be efficiently linked to oncology specialties and geographically distant referring physicians.

✓ Treatment plans should be formulated following case review in fully serviced multidisciplinary team meetings.

✓ Lung cancer resection specimens should be reported by pathologists with reference to the WHO classification of lung and pleural tumours and the Royal College of Pathologists' minimum dataset for lung cancer histopathology reports.[22,191]

7 Radiotherapy

7.1 NON-SMALL CELL LUNG CANCER

7.1.1 RADICAL RADIOTHERAPY (STAGE I AND II)

A Cochrane review and a systematic review identified 44 retrospective case series including a total of 3,683 patients treated with regimens of radiotherapy with doses of more than 50 Gy in 25 fractions or its radiobiological equivalent.[192,193] The studies are difficult to compare because of unknown variation in entry criteria or pre-treatment prognostic criteria. Study results are inconsistent, with three and five year survival rates ranging from 0–55%. It is not clear whether the inconsistencies are due to variations in patient selection, treatment techniques or completeness of follow up. **2++**

The evidence does suggest that radical radiotherapy is effective in prolonging survival in patients with NSCLC stage I and II who are medically inoperable or refuse surgery.

One RCT has shown that continuous hyperfractionated accelerated radiation therapy (CHART) is more effective than 60 Gy over six weeks in patients with disease stage I to III.[194] **1++**

B **Patients with NSCLC stage I and II who are medically inoperable or who do not consent to surgery should be offered radical radiotherapy.**

7.1.2 HYPERFRACTIONATED AND/OR ACCELERATED RADIOTHERAPY (STAGE III)

A meta-analysis and two RCTs were identified[195,196] that suggest a survival benefit for accelerated and hyperfractionated radical radiation therapy compared with conventional radiotherapy.[197,196,197] No benefit was observed for hyperfractionated radical radiation therapy of standard time length over conventional radiotherapy. **1+**

A **Patients having radical radiotherapy should be given CHART** (54 Gy in 36 fractions over 12 days) **in preference to 60 Gy in 30 fractions over six weeks.**

7.1.3 STEREOTACTIC RADIOTHERAPY

Revised In patients with stage I peripheral lung cancer who are deemed unsuitable for surgery, observational evidence suggests that stereotactic ablative radiotherapy (SABR) in three to five fractions can produce local control rates in excess of 80%, which is comparable to surgery.[198] Larger or more centrally located tumours require more fractionated radiotherapy. **2+**

SABR is well tolerated by patients and requires fewer visits than standard radiotherapy (RT).[198] **2+**

SABR is a technically demanding treatment and ideally all centres should have 4-dimensional CT scans for planning, image guided radiation therapy and appropriate treatment planning algorithms, and be involved in external audit and quality assurance programmes.

B **Patients with early-stage peripheral lung cancers who are not suitable for surgery should be considered for stereotactic ablative radiotherapy.**

7.1.4 INTENSITY MODULATED RADIOTHERAPY

Revised A systematic review identified insufficient evidence to determine the efficacy of intensity modulated radiotherapy compared to conventional conformal radiotherapy.[199] **2++**

7.2 RADICAL RADIOTHERAPY IN PATIENTS WITH NSCLC

Revised There is a paucity of RCT data on reducing radiation-related morbidity, either by altering the radiation technique or by adding in other agents to treatment regimes. In many chemoradiotherapy trials pulmonary function limits are set for exclusion criteria. Safe lower limits of respiratory function (FEV_1 or TLCO) for radical radiotherapy have not been established.[136] **4**

Meta-analysis of retrospective studies of radical radiotherapy in patients with stage I and stage II NSCLC who are not fit for surgery showed overall survival varied from 50–93% at one year and 0–42% at five years. The presence of weight loss or comorbidity adversely affected survival.[192] **2++**

The NICE guideline on the diagnosis and treatment of lung cancer considered the assessment of fitness for treatment with curative intent based on mortality and morbidity in postoperative dyspnoea and quality of life, with the following recommendations:[18] **4**

D **A clinical oncologist specialising in lung oncology should determine suitability for radical radiotherapy, taking into account performance status and comorbidities.**

D **Perform spirometry in all patients being considered for treatment with curative intent. Measure TLCO if breathlessness is disproportionate or there is other lung pathology.**

7.3 PALLIATIVE THORACIC RADIOTHERAPY IN PATIENTS WITH SYMPTOMATIC, LOCALLY ADVANCED LUNG CANCER

No RCTs comparing palliative thoracic radiotherapy with active symptom control or systemic anticancer therapy in patients with chest symptoms were identified.

In RCTs comparing different radiotherapy regimens, the majority of patients with locally advanced lung cancer obtain symptomatic benefit from palliative radiotherapy. Chest pain improves in 50–88%, haemoptysis in 73–98%, cough in 52–72%, and dyspnoea in 32–37% of patients. Palliative thoracic radiotherapy was effective in improving local chest symptoms for the majority of patients with NSCLC for at least half of their remaining life.[200-202] **1+**

There is no evidence that longer, more fractionated regimens of palliative thoracic radiotherapy give better or more durable symptom control than lower dose regimens of one or two fractions. Higher dose regimens of palliative thoracic radiotherapy result in increased toxicity, especially radiation oesophagitis. There is evidence that patients with good performance status live longer after more fractionated higher dose regimens of palliative thoracic radiotherapy, such as 39 Gy in 13 fractions.[200-202] **1+**

No RCTs specifically including patients with SCLC were identified, resulting in uncertainty regarding the effectiveness of palliative radiotherapy for this group of patients.

A **Patients with thoracic symptoms and good performance status not suitable for radical radiotherapy should be considered for more fractionated, higher dose regimens of palliative radiotherapy, such as 39 Gy in 13 fractions.**

A **Patients with thoracic symptoms and poor performance status not suitable for radical radiotherapy should receive palliative radiotherapy.**

✓ Patients with SCLC should be considered for palliative thoracic radiotherapy if they have significant chest symptoms and other treatments have been ineffective or are considered inappropriate.

7.4 RADIOTHERAPY IN PATIENTS WITH SCLC AND NSCLC BRAIN METASTASES

7.4.1 WHOLE BRAIN IRRADIATION

No randomised evidence was identified to determine the relative benefits of whole brain radiotherapy versus focal radiotherapy versus surgery in patients with NSCLC with three or fewer brain metastases.

For patients with brain metastases, 20 Gy in five fractions is as effective as more prolonged regimens.[203] For patients with a good prognosis, 30 Gy in 10 fractions is more effective in terms of survival than 12 Gy in two fractions.[204] Both the absolute survival benefit and impact on quality of life from radiotherapy in patients with brain metastases remains an area of ongoing research. **1+**

7.4.2 RADIOTHERAPY IN PATIENTS WITH ISOLATED BRAIN METASTASES

Revised Two RCTs exploring the role of radiotherapy and surgery in the treatment of single metastases to the brain demonstrate a survival benefit for surgical resection of solitary brain metastases followed by whole brain radiotherapy compared to whole brain radiotherapy alone, in patients who have controlled extracranial disease.[205, 206] **1+**

A recent study examining the effect of adjuvant whole brain radiotherapy following radiosurgery or resection showed no survival advantage but a reduction in intracranial relapses.[207] **1+**

B **Patients with single brain metastases should be offered resection followed by adjuvant radiotherapy.**

7.5 PROPHYLACTIC CRANIAL IRRADIATION IN PATIENTS WITH SCLC AND LIMITED DISEASE

In studies of patients in remission following systemic anti-cancer therapy who were randomised between no further treatment or prophylactic cranial irradiation (PCI), those patients receiving radiotherapy were found to have a reduction in brain metastases (relative risk (RR) 0.46, 95% CI 0.38 to 0.57) with improved overall survival (RR 0.84, 95% CI 0.73 to 0.97). [208,209] **1++**

A **Prophylactic cranial irradiation should be offered to patients with limited disease SCLC achieving remission after systemic anticancer therapy.**

7.6 PROPHYLACTIC CRANIAL IRRADIATION IN SCLC PATIENTS WITH EXTENSIVE DISEASE

Revised Patients with extensive disease who respond to initial SACT gain additional survival benefit from treatment with PCI.[210-212] PCI leads to a reduction in the rate of brain metastasis (RR 0.46, 95% CI 0.38 to 0.57) and a 16% reduction in mortality, even after adjustment for extent of initial disease.[210] PCI is, however, associated with an increase in adverse effects, longer duration of hair loss and fatigue, and a small but negative impact on functioning scales.[212] **1+**

A **Prophylactic cranial irradiation should be offered to patients with extensive stage small cell lung cancer who have demonstrated a response to systemic anticancer therapy. Patients should be informed of the potential prolongation of treatment-related side effects** (hair loss and fatigue) **as well as decreased functioning scales to allow informed treatment decisions to be made.**

7.7 PALLIATIVE RADIOTHERAPY IN PATIENTS WITH SYMPTOMATIC METASTASES

Many patients with lung cancer develop symptomatic metastases that can be treated using radiotherapy.

A systematic review and one RCT on palliative radiotherapy for bone metastases were identified.[213,214] The RCTs were not restricted to patients with lung cancer, although a significant proportion of the patients did have lung cancer. The systematic review identified 11 trials involving 3,435 patients. There was no difference in overall or complete pain response rates between single fraction (usually 8 Gy) or multifraction radiotherapy, although patients treated with a single fraction had a significantly higher re-treatment rate and were at greater risk of developing a pathological fracture (3.0% *v* 1.6%). The remaining RCT is an interim analysis of single fraction versus multifraction radiotherapy in treating neuropathic bone pain and suggests radiotherapy may have a positive role to play in treating such pain. **1+**

No RCTs investigating the role of radiotherapy on skin metastases were identified.

A **Patients with lung cancer and symptomatic bone metastases should be treated with a single 8 Gy fraction of palliative radiotherapy.**

✓ Patients with symptomatic skin metastases should be considered for palliative radiotherapy with single fractions of 8 Gy.

8 Systemic anticancer therapy

8.1 MOLECULAR TESTING OF PREDICTIVE BIOMARKERS IN PATIENTS WITH NSCLC

Revised Molecular analysis and stratification of lung cancer is rapidly becoming a standard of care for the selection of patients for specific targeted therapy. The performance of these tests is largely determined by clinical demand and the availability of the therapeutic agent(s) selected with each particular biomarker test. These tests are, in general, performed on pathologically validated tumour tissue following diagnosis and subtyping by standard morphology and, as required, immunohistochemistry.

This is a rapidly evolving area. Currently *EGFR* mutation testing is recommended, as proposed in various guidelines, since EGFR tyrosine kinase inhibitors are accepted for restricted use in Scotland (see section 14.4).[136,215-219] Other molecular abnormalities which may be tested for include anaplastic lymphoma kinase (*ALK*) gene rearrangement, v-raf murine sarcoma viral oncogene homolog B gene (*BRAF)* mutation and Kirsten rat sarcoma proto-oncogene (*KRAS*) mutation. Drugs targeting these mutations are at various stages of development. **4**

To support the expanding need for more detailed pathological information from lung cancer samples, it is essential that adequate tumour tissue is made available. The vast majority of cases are diagnosed solely on small biopsy or cytology samples, so tissue availability is very limited. Every effort should be made, within the constraints of patient safety, to maximize tumour yield from any invasive diagnostic procedure. The pathologist should also conserve as much material as possible, in anticipation of molecular pathology testing, by the judicious use of material for initial diagnosis and tumour subtyping. This will be greatly assisted by the provision of full clinical details accompanying samples submitted for pathological diagnosis.

8.2 FIRST LINE THERAPY FOR PATIENTS WITH STAGE IIIB AND IV NSCLC

Revised Results from a meta-analysis and systematic review demonstrate the benefit of SACT for patients with advanced non-small cell lung cancer (absolute improvement in survival of 9% at 12 months versus control).[220] **1++**

Four randomised trials of single agent SACT (gemcitabine, paclitaxel, docetaxel and vinorelbine) versus best supportive care (including radiotherapy) in patients with advanced NSCLC reveal a trend to improved quality of life with increased survival in three of the four studies.[221-224] No particular combination of these agents in regimens with platinum has been shown to be more effective.[225] **1+**

Standard treatment is in four cycles, and exceptionally six cycles.[226,227] Continuing beyond four cycles may increase progression-free survival but at the expense of an increase in toxicity and worse quality of life without any significant gain in survival.[226, 227] **1++** **1+**

In patients who have advanced disease and a performance status <2 at the time of diagnosis of NSCLC, first line treatment should be offered according to histology. Patients with non-squamous histology demonstrated a superior survival when treated with cisplatin and pemetrexed compared with cisplatin and gemcitabine (hazard ratio (HR) 0.84, 95% CI 0.74 to 0.96, p=0.011). Patients with squamous histology do not benefit from pemetrexed/platinum combination.[228, 229] **1+**

In patients with adenocarcinoma, overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine (n=847; 12.6 *v* 10.9 months).[228] **1+**

EGFR tyrosine kinase inhibitors (TKIs) are effective as first line treatment of advanced NSCLC in patients with sensitising *EGFR* mutations. The optimum treatment is orally delivered single agent therapy. TKIs significantly increased progression-free survival (PFS) (HR 0.45, 95% CI 0.36 to 0.58, P<0.0001) over SACT.[230] In a European trial, the median PFS was 9.4 months in the erlotinib (TKI) group and 5.2 months in the doublet SACT group, (HR 0.42, 95% CI 0.27 to 0.64), p<0.0001.[231] **1+**

Randomised evidence does not support the use of SACT in combination with a TKI in any patient group.[231,232] 1++

A **First line single agent tyrosine kinase inhibitors should be offered to patients with advanced NSCLC who have a sensitising *EGFR* mutation. Adding combination systemic anticancer therapy to a TKI confers no benefit and should not be used.**

A **Patients who have advanced disease, are performance status 0-1, have predominantly non-squamous NSCLC and are *EGFR* mutation negative should be offered combination systemic anticancer therapy with cisplatin and pemetrexed.**

A **All other patients with NSCLC should be offered combination systemic anticancer therapy with cisplatin/carboplatin and a third generation agent** (docetaxel, gemcitabine, paclitaxel or vinorelbine)**.**

A **Platinum doublet systemic anticancer therapy should be given in four cycles; it is not recommended that treatment extends beyond six cycles.**

8.3 MAINTENANCE THERAPY

Revised A multi-centre, randomised, double blind placebo-controlled study comparing pemetrexed plus best supportive care (BSC) with placebo plus BSC in patients with advanced NSCLC who had not progressed after four cycles of platinum based SACT reported that the median PFS was significantly longer in the pemetrexed than the placebo group; 4.3 versus 2.6 months (HR 0.50, 95% CI 0.42 to 0.61). Overall survival was 13.4 months versus 10.6 months (HR 0.79, 95% CI 0.65 to 0.95). In the non-squamous subgroup (481/663, 73%) PFS was also significantly longer for pemetrexed than placebo; 4.5 versus 2.6 months (HR 0.44, 95% CI 0.36 to 0.55).[233] 1+

Erlotinib maintenance treatment provided a statistically significant increase in progression-free survival and overall survival in patients treated with standard first line platinum based SACT, both in the whole study population and in a post hoc analysis in patients with stable disease. In the whole study population the changes in these outcomes were considered to be of modest size. Median PFS was statistically significantly longer in the erlotinib group compared with placebo group, 12.3 weeks versus 11.1 weeks (HR 0.71, 95% CI 0.62 to 0.82), with a similar HR in patients with EGFR IHC-positive tumours, representing around 70% of the patient population (0.69, 95% CI 0.58 to 0.82).[234] 1+

Both RCTs were included in a systematic review that concluded that maintenance therapy (same agent or switch) improves PFS and overall survival in patients without tumour progression post induction platinum-based SACT but that good quality of life data are needed due to the toxicity potential.[235] 1+

Neither erlotinib nor pemetrexed are recommended by the SMC for use within NHSScotland for maintenance treatment in patients with locally advanced or metastatic NSCLC (*see section 14.4*).

8.4 SECOND LINE THERAPY

Revised In patients who are performance status ≤2 at the time of progression of their advanced NSCLC, second line treatment with single agent docetaxel, erlotinib or pemetrexed improve survival rates compared to best supportive care.[236] 1+

Second line docetaxel improved time to progression, survival and quality of life. Patient's opioid requirements and weight loss were reduced with docetaxel compared to best supportive care only. This was clearest in the patients who received 100 mg/m^2 rather than 75 mg/m^2 every three weeks, however the higher dose was associated with more overall toxicity, and is not recommended as standard.[237, 238] 1+

Weekly docetaxel is not recommended over three-weekly due to increased toxicity.[239] 1+

Randomised evidence does not support the use of combination SACT as second line treatment for patients with advanced NSCLC based on an increase in toxicity without any gain in survival.[240] 1++

Second line erlotinib improves overall survival compared to best supportive care in patients with NSCLC. Median survival was improved with moderate toxicity. The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group (p<0.001); the median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, respectively (HR 0.61, adjusted for stratification categories; p<0.001). Overall survival was 6.7 months and 4.7 months, respectively (HR 0.70; p<0.001) in favour of erlotinib.[236, 241] 1++

Compared with single agent docetaxel, treatment with pemetrexed resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects in the second-line treatment of patients with advanced predominantly non-squamous cell NSCLC.[241] 1++

A **Second line systemic anticancer therapy with single agent docetaxel or erlotinib should be considered for patients with performance status 0-2 recurrent NSCLC who have been previously treated with first line SACT for advanced disease.**

A **Second line systemic anticancer therapy with pemetrexed should be considered for patients with advanced non-squamous cell NSCLC who have been previously treated with first line SACT for advanced disease.**

8.5 POSTOPERATIVE SYSTEMIC ANTICANCER THERAPY

Revised

Postoperative SACT in patients with completely resected stage II to IIIa NSCLC confers an overall survival advantage of around 4% at five years (HR 0.86, 95% CI 0.8 to 0.92).[242] The benefit appears to diminish with longer follow up, possibly due to an increase in non-cancer deaths in those treated with SACT.[243] Different SACT regimens were used in the trials but most contained platinum. No particular SACT regimen appears better than any other. 1+

The benefit of adjuvant SACT in patients with stage I disease is less certain. There appears to be no benefit in patients with stage Ia disease but there may be benefit in those with tumours >4 cm.[244] Further trials are required in this group. 1+

There appears to be a correlation between an effect from SACT and better performance status, but very few patients with PS ≥2 were included in the trials.[242] 1++

No other subgroup defined by sex, age or histology benefits more or less from adjuvant SACT.[242] 1++

A **Patients with good performance status** (PS 0-1) **who have completely resected NSCLC** (stage II to IIIa) **should be offered platinum based postoperative systemic anticancer therapy.**

✓ The risks and benefits of postoperative systemic anticancer therapy should be discussed with each patient.

8.6 SYSTEMIC ANTICANCER THERAPY FOR PATIENTS WITH SCLC

Limited disease SCLC

The role of SACT in the treatment of patients with limited disease SCLC has been discussed in previous evidence based guidelines.[245, 246] Both symptom control and median survival are increased with combination, as opposed to single agent, SACT, with objective response rates around 90%, but even with optimal combination therapy *(see section 9)*, two year survival is only around 25% in the UK.[247] There are no studies of SACT versus best supportive care as SACT has been the standard first line therapy in SCLC since the 1970s.

Extensive disease SCLC

Patients with extensive disease SCLC are not curable and, in the UK, have a two year survival rate of less than 5%. Patients have a high objective response rate to SACT with useful symptomatic improvement.[248] Careful patient selection is crucial to avoid unnecessary toxicity. Combination SACT has been shown to be less toxic and more effective than single agent treatment with oral etoposide.[248]

8.6.1 SYSTEMIC ANTICANCER THERAPY IN OLDER PATIENTS

When considering the suitability of a patient for SACT, age and poor performance status should be seen as separate factors. A systematic review of 168 studies and a review of 21 studies in SCLC concluded that standard SACT should not be denied on the basis of age alone.[245, 249] Fit older patients should be offered combination SACT, as this has better survival rates than single agent SACT. The benefits of any kind of SACT for patients who are PS3 or 4 are unclear. **1++**

A **Combination intravenous SACT should be considered for patients with SCLC over 70 years of age with performance status 0-2.**

8.6.2 STANDARD REGIMENS

RCTs have shown that a platinum combination regimen results in improved survival when compared with anthracycline-based combinations in patients with SCLC.[250, 251] A regimen based on platinum agents and etoposide has proven efficacy and is one of the most commonly prescribed treatments in limited and extensive disease SCLC.[202, 252] **1+**

A **A regimen containing a platinum agent and etoposide is recommended for first line treatment of patients with SCLC.**

8.6.3 ALTERNATING REGIMENS

There is evidence that alternating regimens provide no additional benefit in terms of progression-free or overall survival, compared with standard SACT regimens.[253, 254]

8.6.4 HIGH DOSE/INTENSIFICATION OF SYSTEMIC ANTICANCER THERAPY

High dose/intensification of SACT has been studied in both limited and extensive disease SCLC. A review concluded that there was no evidence of benefit beyond six cycles of SACT, nor was there benefit from early or late dose intensification, but that shortening the treatment interval with the use of granulocyte-colony stimulating factor (GCSF) could improve median and two year survival.[255] Higher response rates have been obtained but at the expense of significant toxicity.[250]

8.6.5 DURATION OF SYSTEMIC ANTICANCER THERAPY

In patients with limited disease SCLC no survival benefit is gained from extending induction SACT beyond six cycles.[256] **1+**

A **In patients with SCLC the recommended number of systemic anticancer therapy cycles is three to six.**

8.6.6 SECOND LINE SYSTEMIC ANTICANCER THERAPY

Patients who respond to first line SACT and who have had at least six months disease- free survival are most likely to benefit from second line treatment.[250] **1++**

B **Second line systemic anticancer therapy in patients with SCLC should be considered depending on the duration of response to first line treatment and on patients' performance status and wishes.**

8.6.7 MAINTENANCE

The evidence does not support the use of continued induction therapy, oral etoposide, interferon or matrix metalloproteinase inhibitors as maintenance treatment following response to first line SACT.[256-258] **1+**

B **Maintenance systemic anticancer therapy following first line treatment is not recommended.**

9 Combined modalities

9.1 POSTOPERATIVE (ADJUVANT) RADIOTHERAPY IN PATIENTS WITH NSCLC UNDERGOING CURATIVE SURGERY

Postoperative radiotherapy (PORT) has been shown to reduce local recurrence in the radiotherapy arm.[259,260] The PORT meta-analysis suggests an adverse effect of radiotherapy on survival with a hazard ratio of 1.21 (95% CI 1.08 to 1.34), favouring surgery; two year survival with adjuvant radiotherapy was 48% versus 50% in the surgery alone group.[259] A subsequent RCT examined the effect of postoperative radiotherapy in pathological stage I patients and demonstrated a significant survival advantage in favour of radiotherapy (five year survival 67% versus 58%, p=0.048).[260] It is not clear whether the adverse effect of PORT on survival applies to postoperative radiotherapy using modern planning techniques and treatment technology. **1++**

Postoperative radiotherapy has traditionally been considered for those patients with incomplete resection of the primary tumour and for those patients requiring chest wall resection to remove the tumour. There is little evidence addressing these specific indications.

A **Patients with NSCLC who have had complete tumour resection should not receive postoperative radiotherapy, except as part of a randomised trial.**

✓ Postoperative radiotherapy may be considered in patients with incomplete resection.

9.2 CONCURRENT CHEMORADIOTHERAPY IN PATIENTS WITH NSCLC

Revised

In patients with locally advanced NSCLC, concurrent SACT and radiotherapy confers a significant survival benefit over sequential treatment (HR 0.84, 95% CI, 0.74 to 0.95; p=0.004; absolute survival benefit 4.5% at five years) or radiotherapy alone.[261,262] This benefit is seen at a cost of increased radiotherapy toxicity to the oesophagus. The optimal SACT and radiotherapy schedule remain unclear.[262] **1++**

A **Concurrent chemoradiotherapy should be administered to patients with locally advanced NSCLC** (suitable for radical radiotherapy) **who have a good performance status** (PS 0-1)**.**

✓ Treatment within a clinical trial is recommended.

9.3 CONCURRENT RADIOTHERAPY AND SACT IN PATIENTS WITH LIMITED DISEASE SCLC

The current evidence is conflicting with regard to the benefit of concurrent radiotherapy in limited disease SCLC.[263-269] Although the RCTs are good quality, the number of confounding variables and different outcome measures makes it difficult to reach a clear conclusion. There are positive studies showing benefit for 'early' radiotherapy. Many of the studies looked at 'early' versus 'late' with early and late being concurrent in some studies. The definition of 'early' varied between studies. It appears that the overall treatment time for radiotherapy, as well as the timing of the start date, is a factor in outcomes. There is some evidence that concurrent chemoradiation increases toxicity. **1+** **1-**

10 Palliative interventions

10.1 MANAGEMENT OF MALIGNANT PLEURAL EFFUSION

The optimal technique for pleurodesis in malignant pleural effusion has been investigated in a Cochrane review.[270] The main agent used in the UK for pleurodesis is talc. Talc appears to be the most effective sclerosant, with a relative risk for successful pleurodesis of 1.26 (95% CI 1.07 to 1.48) compared with bleomycin or tetracycline. Adult respiratory distress syndrome following talc pleurodesis has been reported as a complication in case reports but not in RCTs. Meta-analysis indicates there is no evidence of excess mortality with talc pleurodesis compared with other sclerosants. Thoracoscopic pleurodesis was found to be more effective than medical thoracostomy pleurodesis, with a relative risk of non-recurrence of an effusion of 1.19 (95% CI 1.04 to 1.36) in favour of thoracoscopic pleurodesis. There was no evidence for increased mortality following thoracoscopic pleurodesis. 1++

Revised There is evidence to support the use of tunnelled pleural catheters in the management of malignant pleural effusions when talc pleurodesis is not possible.[271-274] They provide a safe means of palliation of symptoms secondary to the effusion and enable the patient to be managed at home rather than hospital.[275] The main complications appear to be blockage or dislodgement of the catheter or seeding down the drain tract. In a retrospective audit seeding affected 6.7% of 45 patients.[276] Spontaneous pleuradhesis occurred in up to 25% of cases. Very few cases of pleural infection secondary to the drain have been reported.[276] 3

✓ Achieving complete lung re-expansion prior to pleurodesis remains the most important prerequisite for success.

A **Talc is the optimal sclerosant for thoracoscopic pleurodesis in patients with a malignant pleural effusion who are fit enough to undergo sedation or general anaesthesia.**

✓ In patients who are unfit for a thoracoscopic procedure, tube thoracostomy pleurodesis using talc slurry should be performed.

10.2 MANAGEMENT OF ENDOBRONCHIAL OBSTRUCTIONS

Revised A single RCT of different schedules for endobrachial brachytherapy for the management of endobronchial obstructions was reported in the NICE guideline on the diagnosis and management of lung cancer. Based on this RCT and expert opinion, NICE recommends:[18]

- monitoring (clinically and radiologically) for endobronchial obstruction when patients have large airway involvement to ensure treatment is offered early.
- offering external beam radiotherapy and/or endobronchial debulking or stenting to patients with impending endobronchial obstruction.
- that every cancer network should ensure that patients have rapid access to a team capable of providing interventional endobronchial treatments. 4

10.3 MANAGEMENT OF SUPERIOR VENA CAVA OBSTRUCTION

One systematic review of the management of superior vena cava obstruction (SVCO) including two randomised and 44 non-randomised studies was identified.[277] The poor quality of these studies and their heterogeneity meant that only a narrative review could be performed, rather than a formal statistical analysis.

10.3.1 SYSTEMIC ANTICANCER THERAPY AND RADIOTHERAPY

Systemic anticancer therapy or radiotherapy can provide relief from SVCO in 77% of patients with SCLC. In patients with NSCLC, SVCO was relieved in 63% following radiotherapy and in 59% following SACT. No specific SACT regimen was identified as being more effective than any other. Recurrence of SVCO following treatment was 17% in SCLC and 19% in NSCLC. Relapse occurred 1–16 months after initial treatment and median survival in SACT/radiotherapy studies ranged from 2–9.5 months.[277] 1+

10.3.2 STENTING

Endovascular stenting relieved symptoms of SVCO in 95% of patients, with recurrence in 11%. The median time to relapse was 1–2 months. Recanalisation was possible in the majority of patients, leading to a long term patency rate of 92%. Stent insertion appeared to provide faster relief from symptoms of SVCO than SACT or radiotherapy. It is unclear whether post-stenting anticoagulation prevents stent thromboses. Relapse of SVCO was higher in patients who had received thrombolysis prior to stent insertion (16% compared with 7%). Median survival in stent studies was 1.5–6.5 months, shorter than for SACT/radiotherapy studies, although stenting is often used in patients failing to respond to, or relapsing following initial treatment.[277] 1+

B **In patients with superior vena cava obstruction due to SCLC, SACT/radiotherapy is recommended as initial treatment, but stenting may be considered for relapse or persistent superior vena cava obstruction.**

✓ In patients with superior vena cava obstruction due to NSCLC, stenting may be considered as a primary treatment.

10.3.3 STEROIDS

It is not clear whether steroids have a role to play in the management of the acute presentation of SVCO. At present they are frequently used to manage radiation-induced oedema in thoracic radiotherapy despite the absence of evidence to support their use.

10.4 MANAGEMENT OF BONE METASTASES

Palliative radiotherapy is covered in section 7.7.

10.4.1 BISPHOSPHONATES

Revised In patients with bone metastases from lung cancer, treatment with a bisphosphonate improves pain control.[278-280] In an RCT, fewer skeletal related events (SRE) were seen in the group treated with zolendronic acid (36% *v* 46%) and time to SRE was longer (236 days *v* 155 days) compared to placebo.[279] This treatment is well tolerated. 1+ 1++

B **Patients with lung cancer who have symptomatic bone metastases should be considered for treatment with a bisphosphonate.**

11 Supportive and palliative care

11.1 INTRODUCTION

Supportive care is defined as care that "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".[281]

Palliative care is defined as "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".[281]

Specialist palliative care is defined as "the active total care of patients with progressive, far advanced disease and limited prognosis and their families, by a multiprofessional team who have undergone recognised specialist palliative care training. It provides physical, psychological, social and spiritual support, and will involve practitioners with a broad mix of skills."[282] Specialist palliative care is an integral component of the care of patients with advanced malignancy, required at varying times during their illness.

The General Medical Council has stated that every member of the medical profession requires generic palliative care skills.[283]

11.2 SPECIALIST PALLIATIVE CARE SERVICES

Three good quality systematic reviews, two RCTs, two cohort studies and a postal survey were identified.[284-291] The studies demonstrate that the involvement of palliative care teams results in improved quality of life, improved symptom control and a reduction in hospital readmission rates. Additional reported benefits include a reduction in the number of inpatient hospital days, patients spending more time at home, greater satisfaction amongst patients and carers, a reduction in overall cost and an increase in the number of patients dying where they wished.[291] **1+**

B **All patients with lung cancer should have access to a specialist palliative care team.**

No evidence was identified comparing different palliative care team models, for example, home care compared with hospice or hospital care settings.

✓ Specialist palliative care services should be available in the community setting to support patients who wish to die at home.

11.3 SYMPTOM MANAGEMENT

Patients with lung cancer experience more symptom distress than other types of cancer patient.[286] Patients with lung cancer frequently have comorbidities and multiple symptoms.

Symptom distress scoring at the time of diagnosis allows clinical interventions for symptom management to be tailored appropriately.[292] Increased symptom distress is strongly associated with greater psychological distress and poorer quality of life.[293] As symptom distress can impact on a patient's ability to perform activities of daily living, regular assessment of symptoms and needs, with timely referral to allied health professionals (AHPs), will assist patients in achieving the highest functional status and maintaining quality of life.[294] **4**

D **Symptoms should be assessed regularly and appropriate interventions initiated by the full multidisciplinary team.**

11.3.1 PAIN

Pain is one of the greatest sources of suffering in patients with lung cancer. The assessment and management of pain in patients with cancer is addressed in SIGN guideline 106: Control of pain in adults with cancer.[295]

11.3.2 FATIGUE

Cancer and many of its treatments can cause significant fatigue, impacting on patients' quality of life.[296,297] An essential component of managing fatigue is its recognition by healthcare professionals and the correction of known causal factors such as a poor sleep pattern, anaemia, drug reactions and depression. Guidelines on fatigue evaluation and management can be accessed via the Fatigue Coalition.[298]

✓ Regular multidisciplinary team assessment of fatigue should be made and interventions initiated.

11.3.3 ANXIETY AND DEPRESSION

Significant psychological distress has been reported in 43% of patients with lung cancer.[299] Counselling interventions may be effective in helping patients cope more effectively with the emotional symptoms associated with their disease but the most appropriate way of delivering these remains unclear.[300]

✓ All patients should undergo psychosocial assessment and have access to appropriate psychosocial and spiritual support.

11.3.4 BREATHLESSNESS AND COUGH

Studies have demonstrated improved management of dyspnoea following nursing or physiotherapy intervention.[291,301]

✓ Breathlessness clinics led by nurses or physiotherapists should be made available to all patients with lung cancer.

11.3.5 NUTRITIONAL ISSUES

Between 46% and 61% of patients with lung cancer have experienced weight loss by the time of diagnosis or the beginning of treatment.[302]

Disease or treatment related nutritional issues should be managed by the appropriate professionals from the multidisciplinary team.

Increasing oral nutritional intake in this group of patients has not been shown to improve weight gain, tumour response or survival.[285]

12 Multidisciplinary teams, follow up and communication

12.1 INTRODUCTION

The burden of lung cancer, its treatments and their related toxicities influence all aspects of quality of life for patients and their carers. It is important that the multidisciplinary team works to meet the needs of this patient group. Follow up should be modified throughout the patient's pathway of care to ensure a smooth progression of care and service provision. With up to 40% of patients reporting severe communication problems at the end of life,[303] and the recognised need for a patient-centred approach, effective communication throughout the cancer journey is now considered to be an essential component of care.

12.2 ROLE OF THE MULTIDISCIPLINARY TEAM

Multidisciplinary teams (MDTs) have been defined as "a group of health and social care professionals from a range of disciplines who meet regularly to discuss and agree plans of treatment and care for people with a particular type of cancer or problem, or in a particular location".[304] This definition implies the inclusion of primary care teams, site-specific cancer teams, therapy teams and specialist palliative care teams. **4**

The body of evidence evaluating the role of the MDT is generally poor, as there are ethical considerations surrounding comparative studies in this area. Studies are also hindered by a lack of clarity when defining the MDT. In Scotland, Managed Clinical Networks (MCNs) guide the formation and networking of appropriate teams.

Two cohort studies were identified.[284,305] One identified the importance of the MDT in providing a fast-track model to reduce waiting times. The second demonstrated the positive impact of nursing interventions. Two surveys were also identified which highlight the importance of the MDT in the assessment of patient needs, both physical and psychosocial.[306, 307] **4**

The report An Assessment of Need by The Allied Health Professions Palliative Care Project states that AHPs contribute positively to the quality of life of patients with oncology related palliative care needs, through rehabilitative and supportive interventions, and identifies a large number of patients for whom this need is not met.[294] **4**

D **All patients with a diagnosis of lung cancer should have their treatment and management planned and directed by a multidisciplinary team.**

D **Allied health professional services should be offered to all patients with lung cancer.**

✓
- Following diagnosis and staging, all new cases of lung cancer should be discussed in a multidisciplinary team meeting, attended if possible, by the respiratory physician, radiologist, pathologist, thoracic surgeon, oncologists, site-specific lung cancer nurses, allied healthcare professionals and pharmacists, with the aim of formulating a management plan for each patient.
- The diagnosis, staging and management plan should be explained by the physician and the nurse to the patient at the earliest opportunity, clearly and unambiguously, so that the patient is in full possession of all necessary information. A carer should be involved when appropriate. Provision of written as well as verbal information is best.

✓ Healthcare professionals have a responsibility to:
- provide and promote rapid access to an MDT
- respond sympathetically to emotional, physical, psychosocial and spiritual problems
- communicate and collaborate with primary, secondary and tertiary care settings.

12.3 FOLLOW UP

There is a paucity of good quality research in this area. One RCT was identified which compared nurse-led to physician-led follow up of patients with lung cancer who had completed their initial treatment and were expected to survive at least three months. Clinical nurse specialist-led follow up was as effective and led to greater patient satisfaction than physician-led follow up.[308] **1+**

A cohort study and two surveys exploring follow up also suggest that specialist nurse-led follow up can be as effective and lead to greater patient satisfaction than physician-led follow up.[290,309,310] Further research is required to substantiate these findings, as the benefits potentially relate to more open or improved access. **3**

The British Thoracic Society Lung Cancer Working Party recommends that respiratory physicians should "develop with their colleagues an explicit follow up policy within their cancer units, which is appropriate to local needs and resources and takes particular note of the wishes and interests of patients and their GPs. It should be clear to patients who their supervising consultant is".[311] **4**

B **Follow up by clinical nurse specialists should complement conventional arrangements.**

✓ The development of clinical nurse specialist posts should be encouraged, through resourcing and training, to facilitate best practice.

B **Hospital follow up should be continued where hospital treatment or specialist advice is still required, or whilst clinical trials are ongoing.**

- **After surgery, the surgeon should follow up all patients initially: later follow up should be according to local policy.**
- **After palliative therapy is completed, follow up should be agreed between the oncologist, respiratory physician, GP and palliative care team.**

✓ Written and verbal information on follow up should be shared between primary, secondary and tertiary care in keeping with best practice and MCN guidelines.

12.4 COMMUNICATION

A Cochrane review, an RCT, three cohort studies and a survey were identified that cover a wide range of issues related to communication skills, all demonstrating strongly that communication skills training for healthcare professionals is of lasting benefit. [290,307,312,313,314, 315] **1+ 2+ 3**

The following have all been shown to be potentially effective communication tools or strategies:

- health related quality of life measurements
- needs assessment tools
- recorded consultation
- audio of general information
- summary letter as follow up
- presence of support person
- actively encouraging questions and a question prompt list
- patient-held record.

A **Communication skills training should be provided across the multidisciplinary team.**

✓ Information needs should be resourced and provided using a variety of media, to meet individual patient/carer needs.

13 Provision of information

Revised This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing lung cancer with patients and carers and in guiding the production of locally produced information materials.

13.1 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

Clinical encounters with patients with lung cancer should facilitate patient choice about treatment decisions (assuming patients wish to participate in the decision making process). Healthcare professionals should bear in mind that patients and carers face an ever increasing amount of information at a time when the stress of their experience can make it extremely difficult to take necessary information on board.[18] At all times the amount of information given to patients and carers should be appropriate to their wishes and level of understanding, and be delivered in a way that is sensitive, understandable to them, and accurate. Asking patients and carers what they would like to know and checking what they have understood from the information they have been given is essential in this process.

Healthcare professionals should be aware that the breaking of bad news occurs more than once and requires the same sensitive approach each time (ie at diagnosis, during the treatment pathway and if a patient has a relapse).[18]

Initial presentation and referral

• Explain to patients that the symptoms they report may be caused by lung cancer or another condition.
• Advise patients of the need for referral to a specialist.
• Explain to patients that lung cancer is diagnosed by physical examination and one or more diagnostic tests including:
  o X-ray
  o CT scan
  o PET scan
  o bronchoscopy
  o biopsy.
• If the patient is a smoker discuss the benefits of smoking cessation.

Diagnosis

• Explain what lung cancer is and check the patient's understanding.
• Explain to patients that further tests may be done to 'stage' the cancer which helps to establish the extent to which the cancer has grown and perhaps spread.
• To aid patients making informed choices, discuss treatment options and offer written and verbal information outlining a clear pathway of how they will be treated and cared for. Include in this discussion:
  o treatment choices
  o side effects of treatment and management of these
  o treatment outcomes
  o referral to other specialists as required to manage toxicities of treatment.
• Allow sufficient time to discuss the following issues and ensure patients are involved in discussions:
  o aims of treatments
  o prognosis (include Advanced Care Planning if appropriate)
  o managing distress (including depression and anxiety).
• Ensure patients are aware of how they can access a clinical nurse specialist for support, advice and information. Provide information on further sources of support (*see section 13.2*).

Treatment
• Inform patients of treatment plans and advise them of the timeframe for treatment. • Discuss surgery/systemic anticancer therapy/radiotherapy, their procedures and adverse side effects. • Highlight that stopping smoking at this stage can improve prognosis. • Ensure patients are offered participation in a clinical trial when available and appropriate. • Discuss with patients how they are coping and managing distress (including depression and anxiety). • Explain the importance of attending ongoing follow-up appointments after discharge and inform them of how they are likely to be followed up, ie by whom, where and when. • Advise patients of where they can receive information about financial issues.
Follow up/end of treatment
• Give patients the opportunity to ask questions or discuss any concerns they may have. • Discuss the possibility of recurrence with patients, how they would like to be managed and advise them to report on specific symptoms. • Inform patients of the follow-up procedures for lung cancer, including tests and timeframes for these. • Allow discussion of the following issues with patients: o returning to work o how they are coping and managing distress (including depression and anxiety). • Reiterate information on sources of support (*see section 13.2*). • Highlight the benefits of exercise and healthy diet. • Discuss the following issues with patients who have had a relapse/disease progression: o treatment choices and outcomes o side effects of treatment and management of these o prognosis (include Advanced Care Planning if appropriate) o managing distress (including depression and anxiety).
Palliative care
• Offer to discuss end of life care with the patient when appropriate. • The following should be discussed with patients: o reason for and aim of palliative care o who is likely to be involved in their care o symptom management o Advance Care Planning if appropriate.

13.2 SOURCES OF FURTHER INFORMATION

ASH Scotland
8 Frederick Street, Edinburgh EH2 2HB
Tel: 0131 225 4725
www.ashscotland.org.uk • Email: ashscotland@ashscotland.org.uk

Action on Smoking and Health provides information on tobacco and health.

British Lung Foundation
73–75 Goswell Road, London EC1V 7ER
Helpline: 03000 030 555
www.blf.org.uk

The British Lung Foundation supports people affected with lung disease with support groups, specialist care and information.

Calman Cancer Support Centre
Cancer Support Scotland, Gartnavel Hospital Complex**, 1**053 Great Western Road, Glasgow G12 OYN
Freephone: 0800 652 4531 • Tel: 0141 337 8199
www.cancersupportscotland.org

Cancer Support Scotland provides emotional and practical support on a one-to-one basis and through community based groups. Complementary therapies are available.

Cancer Research UK
PO Box 123, 61 Lincoln's Inn Fields, London WC2A 3PX
Tel: 020 7242 0200
www.cancerresearchuk.org

Cancer Research UK funds research into cancer, campaigns on cancer issues and produces patient information leaflets.

CancerHelp UK
Tel: 0800 800 4040
www.cancerhelp.org.uk • www.cancerresearchuk.org/cancer-help

CancerHelp UK is a free information service about cancer and cancer care for people with cancer and their families. It is provided by Cancer Research UK. The site includes a comprehensive range of information including cancer prevention, diagnosis, treatment and follow up.

CLAN Cancer Support
120 Westburn Road, Aberdeen AB25 2QA
Tel: 01224 647000
www.clanhouse.org • Email: enquiries@clanhouse.org

CLAN provides emotional and practical support to people with cancer, families and carers in the northeast of Scotland, Orkney and Shetland.

Clydeside Action on Asbestos
245 High Street, Glasgow G4 0QR
Tel: 0141 552 8852
Email: peter@clydesideaction.co.uk

Clydeside Action on Asbestos is a charity which campaigns for, and provides support to, individuals and families of people who have been diagnosed with illnesses likely to have been caused by asbestos exposure.

Macmillan Cancer Support (Scotland)
132 Rose Street, Edinburgh EH2 3JD
Tel: 0808 808 00 00
www.macmillan.org.uk • Email: southscotland@macmillan.org.uk

The Scottish office of the UK charity, supports people with cancer (and their families) with practical, medical, emotional and financial advice.

Maggie's Centres Scotland
Maggie's Centres, 1st Floor, 1 Waterloo Street, Glasgow G2 6AY
Tel: 0300 123 1801
E-mail: enquiries@maggiescentres.org

Maggie's provides practical, emotional and social support to people with cancer, their family and friends. Built alongside NHS cancer hospitals and staffed with professional experts, Maggie's Centres are warm and welcoming, full of light and open space, with a big kitchen table at their heart.

Maggie's Dundee
Tom McDonald Avenue, Ninewells Hospital, Dundee DD2 1NH
Tel: 01382 632999 • Email: dundee@maggiescentres.org

Maggie's Edinburgh
The Stables, Western General Hospital, Crewe Road South, Edinburgh EH4 2XU
Tel: 0131 537 3131• Email: edinburgh@maggiescentres.org

Maggie's Fife
Victoria Hospital, Hayfield Road, Kirkcaldy KY2 5AH
Tel: 01592 647997 • Email: fife@maggiescentres.org

Maggie's Glasgow
Gartnavel General Hospital, 1053 Great Western Road, Glasgow G12 0YN
Tel: 0141 357 2269 • Email: glasgow@maggiescentres.org

Maggie's Highlands
Raigmore Hospital, Old Perth Road, Inverness IV2 3UJ
Tel: 01463 706306 • Email: highlands@maggiescentres.org

Maggie's Lanarkshire
Flat 78, Residential Accommodation, Wishaw General Hospital, 50 Netherton Road, Wishaw ML2 ODP
Tel: 01698 358392 • Email: lanarkshire@maggiescentres.org

Marie Curie Cancer Care (Scotland)
14 Links Place, Edinburgh EH6 7EB
Tel: 0800 716 146
www.mariecurie.org.uk

Marie Curie Cancer Care provides practical nursing care at home and specialist care across its Marie Curie centres.

National Lung Cancer Forum for Nurses
www.nlcfn.co.uk

The NLCFN provides information on lung cancer to patients, carers and health professionals.

NHS Inform
www.nhsinform.co.uk/cancer/tips

NHS Inform provides tailored information for the people of Scotland (TIPS), which allows patients and carers to customise their own cancer leaflet with information relevant to them. Details of local support services are also available. The site was developed in association with MacMillan Cancer Support.

North of Scotland Cancer Network (NOSCAN)
Rosehill Annexe, ARI Site, Cornhill Road, Aberdeen AB25 2ZG
Tel: 01224 552745
www.noscan.scot.nhs.uk

NOSCAN offers a range of support and advice to patients and families including support groups and written information.

Princess Royal Trust for Carers
Skypark 3, Suite l/2, 14/18 Elliott Place, Glasgow G3 8EP
Tel: 0300 123 2008
www.carers.org

The Princess Royal Trust for Carers provides information, advice and support for carers.

Roy Castle Lung Cancer Foundation
98 Holm Street, Glasgow, G2 6SY
Tel: 0333 323 7200 (option 2)
Email: info@roycastle.org • www.roycastle.org

The Roy Castle Lung Foundation provides a comprehensive support, information and advocacy service for people affected by lung cancer.

Smokeline
Tel: 0800 84 84 84
www.canstopsmoking.com

Smokeline provides advice and support on giving up smoking.

South East Scotland Cancer Network (SCAN)
Pentland House, 47 Robbs Road, Edinburgh EH14 1TY
Tel: 0131 465 7681
www.scan.scot.nhs.uk

SCAN offers a range of support and advice to patients and families including support groups and written information.

West of Scotland Cancer Network (WOSCAN)
1st Floor, St Mungo Building, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF
Tel: 0141 211 1145
www.woscan.scot.nhs.uk

WOSCAN offers a range of support and advice to patients and families including support groups and written information.

14 Implementing the guideline

Revised This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

14.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN.

14.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations were identified as having significant budgetary impact.

14.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The Scottish Government and Healthcare Improvement Scotland have published Quality Performance Indicators (QPIs) for lung cancer and these should form the basis of audit work in Scotland.[316]

14.4 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

The Scottish Medicines Consortium (SMC) advised that:

- Pemetrexed is accepted in combination with cisplatin for first line treatment of patients with locally advanced or metastatic (spreading) non-small cell lung cancer that does not affect squamous cells (cells that line the airways). It is restricted to use in patients with particular types of non-small cell lung cancer (adenocarcinoma or large cell carcinoma) (February 2010).
- Pemetrexed is accepted for restricted use within NHS Scotland for monotherapy for the second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology. It is restricted to use in patients with good performance status who would otherwise be eligible for treatment with docetaxel (September 2008).
- Pemetrexed is not recommended for monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum based chemotherapy. In a full submission, the manufacturer did not present a sufficiently robust economic case and their justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC (September 2010).The marketing authorisation for pemetrexed has recently been extended to allow its use as maintenance therapy in patients who have had first line treatment with cisplatin plus pemetrexed. The holder of the marketing authorisation has not made a submission to SMC regarding the use of this product in this setting (February 2012).

- Erlotinib is accepted for first line treatment of patients with locally advanced or metastatic non-small cell lung cancer with epidermal growth factor receptor activating mutations (January 2012).
- Erlotinib is accepted for restricted use within NHSScotland for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, after failure of at least one prior chemotherapy regimen. When prescribing erlotinib, factors associated with prolonged survival should be taken into account. No survival benefit or other clinically relevant effect of the treatment have been demonstrated in patients with epidermal growth factor receptor (EGFR)-negative tumours. It is restricted to use in patients who would otherwise be eligible for treatment with docetaxel monotherapy (June 2006).
- Erlotinib is not recommended as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after four cycles of standard platinum based first line chemotherapy. The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC (January 2011).

15 The evidence base

15.1 SYSTEMATIC LITERATURE REVIEW

Revised The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2005-2012. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

15.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to patients with lung cancer. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised by the SIGN Patient Involvement Officer and presented to the guideline development group.

15.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (*see Annex 1*). The following areas for further research have been identified:

- the efficacy of surgery for patients with stage IIIa and IIIb NSCLC
- the efficacy of surgery for patients with multilevel N2 disease to establish if any subgroups might benefit from the addition of surgery to SACT and radiotherapy
- the potential benefit of focal brain radiotherapy compared to surgery or whole brain irradiation in patients with NSCLC and one to three metastases
- the efficacy of stereotatic radiotherapy in patients with early NSCLC
- the efficacy of intensity modulated radiotherapy compared to conventional conformal radiotherapy
- trials looking at ways of reducing radiation morbidity.

15.3 REVIEW AND UPDATING

This guideline was issued in 2014 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

16 Development of the guideline

16.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at **www.sign.ac.uk**

16.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Ron Fergusson *(Chair)*	*Consultant in Respiratory Medicine, Western General Hospital, Edinburgh*
Mr Mohammed Asif	*Consultant Thoracic Surgeon, Golden Jubilee National Hospital, Clydebank*
Ms Juliet Brown	*Evidence and Information Scientist, SIGN*
Mr Eric Byrne	*Patient representative, Airdrie*
Miss Fiona Carnochan	*Associate Specialist in Thoracic Surgery, Royal Infirmary of Edinburgh*
Dr Scott Davidson	*Consultant Respiratory Physician, Southern General Hospital, Glasgow*
Dr Sai Han	*Consultant Nuclear Medicine Physician, West of Scotland PET Centre, Gartnavel General Hospital, Glasgow*
Dr Richard Jones	*Consultant Clinical Oncologist, Beatson West of Scotland Cancer Centre, Glasgow*
Professor Keith Kerr	*Consultant Pathologist, Aberdeen Royal Infirmary*
Dr Felicity Little	*Consultant Clinical Oncologist, Edinburgh Cancer Centre, Western General Hospital*
Ms Fiona MacLean	*Lead Clinical Pharmacist, New Victoria Hospital, Glasgow*
Dr Saeed Mirsadraee	*Senior Clinical Lecturer in Radiology, University of Edinburgh*
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Dr Beate Riedel	*Clinical Psychologist, Edinburgh Cancer Centre, Western General Hospital*
Ms Allison Smith	*Clinical Nurse Specialist, Gartnavel General Hospital, Glasgow*
Ms Ailsa Stein	*Programme Manager, SIGN*
Dr William Wallace	*Consultant Pathologist, Royal Infirmary of Edinburgh*
Mrs Lorraine Webster	*Macmillan Information Radiographer and Counsellor, Beatson West of Scotland Cancer Centre, Glasgow*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest. A register of interests is available on the contacts page of the SIGN website **www.sign.ac.uk**

Mrs Lesley Forsyth	*Events Coordinator*
Mrs Karen Graham	*Patient Involvement Officer*
Miss Gemma Hardie	*Distribution and Office Coordinator*
Mr Stuart Neville	*Publications Designer*
Miss Gaynor Rattray	*Guideline Coordinator*

16.3 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 80: Management of patients with lung cancer, on which this guideline is based.

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

Dr Robert Milroy	*Consultant Respiratory Physician, Glasgow Royal Infirmary*
Dr Joris Van der Horst	*Consultant Physician, Glasgow Royal Infirmary*

16.4 CONSULTATION AND PEER REVIEW

16.4.1 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Mrs Diana Borthwick	*Clinical Nurse Specialist, Western General Hospital, Edinburgh*
Dr Adam Dangoor	*Consultant Medical Oncologist, Bristol Haematology and Oncology Centre*
Mr Joel Dunning	*Consultant Cardiothoracic Surgeon, James Cook University Hospital, Middlesbrough*
Professor John Gosney	*Consultant Thoracic Pathologist, Royal Liverpool University Hospital*
Dr Matthew Hatton	*Clinical Oncologist, Weston Park Hospital, South Yorkshire*
Mr Eric Lim	*Consultant Thoracic Surgeon, Royal Brompton Hospital, London*
Dr Robert Milroy	*Consultant Respiratory Physician, Glasgow Royal Infirmary*
Ms Lydia Morrison	*Lung Cancer Nurse Specialist, Raigmore Hospital, Inverness*
Mr Mark Parsons	*Principal Clinical Pharmacist, Ninewells Hospital, Dundee*
Dr Mick Peake	*Consultant and Senior Lecturer in Respiratory Medicine, Glenfield Hospital, Leicester*
Dr Robert Rintoul	*Consultant in Respiratory Medicine, Papworth Hospital, Cambridge*
Professor Edwin van Beek	*Director, Clinical Research Imaging Centre, Royal Infirmary of Edinburgh*
Ms Orla Walsh	*Project Manager, National Cancer Control Programme, Dublin*

16.4.2 PUBLIC CONSULTATION

The draft guideline was available on the SIGN website for a month to allow all interested parties to comment. Comments from the public consultation were addressed alongside those of the specialist reviewers. All contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

	Association for the British Pharmaceutical Industry
Ms Tracey Bowden	*National Account Manager (Scotland and Northern Ireland), Pfizer Ltd, Surrey*
Ms Sarah Jones	*Medical and Scientific Affairs Manager, Boehringer Ingelheim Ltd, Bracknell*
Ms Mary MacLean	*Regional Cancer Care Pharmacist, West of Scotland Cancer Network, Glasgow*
Mr Greg Stevenson	*NHS National Programmes and Public Affairs Manager, Roche Products Ltd, Welwyn Garden City*
Ms Pratibha Suresh	*Technical Advisor, Eli Lilly and Company, Basingstoke*

16.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council membership page of the SIGN website **www.sign.ac.uk**

Dr Grant Baxter	*Royal College of Radiologists*
Professor Keith Brown	*Chair of SIGN; Co-Editor*
Dr Richard Herriot	*Royal College of Pathologists*
Dr Roberta James	*SIGN Programme Lead; Co-Editor*
Dr Norma Sidek	*Royal College of Radiologists*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

Abbreviations

AHP	allied health professionals
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
BRAF	v-raf murine sarcoma viral oncogene homolog B gene
BSC	best supportive care
CAV	cyclophosphamide, doxorubicin and vincristine
CHART	continuous hyperfractionated accelerated radiation therapy
CI	confidence interval
CPA	clinical pathology accreditation
CPD	continuous professional development
CT	computed tomography
EBUS	endobronchial ultrasound
EBUS-FNA	endobronchial ultrasound- fine needle aspiration
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EQA	external quality assurance
EUS	endoscopic ultrasound
EUS-FNA	endoscopic ultrasound fine needle aspiration
FDG	fluorodeoxyglucose
FEV_1	forced expiratory volume in one second
FN	false negative
FNA	fine needle aspiration
FOB	fibre optic bronchoscopy
FP	false positive
GCSF	granulocyte-colony stimulating factor
GMC	General Medical Council
HR	hazard ratio
HU	Houndsfield units
IHC	immunohistochemistry
IMRT	intensity modulated radiotherapy
KRAS	Kirsten rat sarcoma proto-oncogene
MA	marketing authorisation
MCN	managed clinical network
MDT	multidisciplinary team
MRI	magnetic resonance imaging

MTA	multiple technology appraisal
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
NSCLC	non-small cell lung cancer
NSCLC-NOS	NSCLS not otherwise specified; NSCLC which cannot be subtyped on morphological grounds
PCI	prophylactic cranial irradiation
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PFS	progression free survival
PORT	postoperative radiotherapy
ppo	postoperative predictive
PPV	positive predictive value
QPIs	quality performance indicators
RCT	randomised controlled trial
RR	relative risk
RT	radiotherapy
SABR	stereotactic ablative radiotherapy
SACT	systemic anticancer therapy
SCLC	small cell lung cancer
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SPC	summary of product characteristics
SRE	skeletal related events
SUV	standardised uptake value
SVCO	superior vena cava obstruction
TKI	tyrosine kinase inhibitors
TLCO	carbon monoxide transfer factor
TNM	tumour, nodes, metastases
UICC	International Union Against Cancer
US	ultrasound
VATS	video-assisted thoracoscopic surgery
WHO	World Health Organization

Annex 1

Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Key question		See guideline section
1.	In the following patient groups, is PET scan effective*?* Peripheral stage I disease on original CT scan Stage II to IIIb disease on original CT scan Outcomes: sensitivity, specificity, NPV, PPV	4.2, 5.3, 5.4
2.	In patients with stage II to IIIb disease what is the effectiveness of EBUS/EUS for diagnosis compared to mediastinoscopy? Consider: Staging Outcomes: sensitivity, specificity, NPV, PPV	4.7
3.	a) In patients with lung cancer how do cytological samples compare with tissue biopsy samples for tumour subtyping, immunohistochemistry and predictive markers assessed by FISH or mutational analysis? b) In patients with advanced (IIIb to stage IV) disease fit for systemic treatment, is there evidence for benefit of predictive marker testing at initial diagnosis? Outcomes: sensitivity, specificity, NPV, PPV	4.10
4.	In patients with brain metastases, how do MRI, CT scan, scintigraphy compare in terms of accuracy of staging/diagnosis? Outcomes: sensitivity, specificity, NPV, PPV	5.4.4
5.	In patients with suspected lung cancer how does CT guided biopsy compare with bronchoscopic techniques (radial ultrasound, x-ray guided, electro-navigation guided)? Outcomes: sensitivity, specificity, NPV, PPV, complications	4.2
6.	In patients with suspected lung cancer with a pleural effusion how effective are the following interventions in detecting metastatic malignancy? a) aspiration cytology b) pleural biopsy c) VATS pleural biopsy Outcomes: sensitivity, specificity, NPV, PPV, complications	4.6, 4.8
7.	In patients with suspected lung cancer and adrenal mass how does PET CT scan compare with MRI and ultrasound for diagnostic accuracy? Outcomes: sensitivity, specificity, NPV, PPV, complications	5.4.7
8.	In patients with NSCLC early stage disease, what is the effectiveness of stereotactic radiotherapy compared to surgery; standard radical radiotherapy; and radiofrequency ablation? Outcomes: median survival, 2-year survival, 5-year survival, progression-free survival, overall survival, response rate, declining lung function, pneumonitis, pulmonary fibrosis, quality of life	7.1.3

9.	In patients with NSCLC, what are the acceptable limits (fitness/lung function/ disease stage/tumour bulk/performance status) for radical radiotherapy? Outcomes: Median survival, 2-year survival, 5-year survival, progression-free survival, overall survival, response rate, declining lung function, pneumonitis, pulmonary fibrosis, quality of life	7.2
10.	In patients with NSCLC what is the evidence that intensity modulated radiotherapy (IMRT) is superior to conventional conformal radiotherapy? Outcomes: Local control, median survival, 2-year survival, 5-year survival, progression-free survival, overall survival, response rate, declining lung function, pneumonitis, pulmonary fibrosis, quality of life	7.1.4
11.	In patients with NSCLC with three or fewer brain metastases what is the role of whole brain irradiation versus focal radiotherapy versus surgery/metastatectomy? Outcomes: Median survival, 2-year survival, 5-year survival, progression-free survival, overall survival, response rate, quality of life	7.4
12.	In patients with advanced/extensive stage SCLC what is the evidence that prophylactic cranial irradiation (compared to no PCI) is beneficial? Outcomes: Local control, median survival, 2-year survival, 5-year survival, progression-free survival, overall survival, response rate, quality of life	7.6
13.	In patients with NSCLC (locally advanced or metastatic disease), what is the most effective first line systemic anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)? Outcomes: Overall survival, progression-free survival, toxicity, quality of life	8.2
14.	In patients with NSCLC (locally advanced or metastatic disease), what is the most effective second line systemic anticancer therapy (chemotherapy, targeted therapy, EGFR Inhibitors)? Outcomes: Overall survival, progression-free survival, toxicity, quality of life	8.4
15.	In patients with NSCLC (locally advanced or metastatic disease), is there any benefit of maintenance therapy (pemetrexed and erlotinib)? Outcomes: Overall survival, progression-free survival, toxicity, quality of life	8.3
16.	In patients with lung cancer what is the benefit of smoking cessation with and without anticancer treatment? Outcomes: overall survival, progression-free survival, toxicity, quality of life	3
17.	In patients with lung cancer with bone metastases, what is the evidence that bisphosphonates compared to no treatment with bisphosphonates? Outcomes: pain control, quality of life, skeletal related events (eg fractures)?	10.4
18.	In patients with NSCLC which subset derives benefit from adjuvant chemotherapy following curative resection? What are the optimal chemotherapy regimen/cycles? Outcomes: local control, median survival, 2-year survival, 5-year survival, progression-free survival, overall survival, response rate, quality of life	8.5
19.	In patients with NSCLC is concurrent radical chemoradiotherapy more effective than sequential chemoradiotherapy? Outcomes: local control, median survival, 2-year survival, 5-year survival, progression-free survival, overall survival, response rate, declining lung function, pneumonitis, pulmonary fibrosis, quality of life	9.2

20. In lung cancer patients undergoing surgery does case volume affect mortality? Consider: cardiothoracic versus thoracic surgeons, stage at resection Outcomes: recovery from procedure, accuracy of technique, 2-year survival, 5-year survival, progression-free survival, overall survival, pain/symptoms Techniques to consider: open/closed rates, positive resection rates lymph nodes, lobectomy, pneumonectomy, segmentectomy	6.1.1
21. In lung cancer patients undergoing lobectomy how does thoracotomy compare to the VATs approach? Outcomes: recovery from procedure, accuracy of technique, 2-year survival, 5-year survival, progression-free survival, overall survival, pain/symptoms	6.2.3
22. What is the optimal lymph node strategy at surgical resection? Compare discretionary sampling with systematic dissection with complete mediastinal lympadenectomy. Outcomes: accuracy of technique, 2-year survival, 5-year survival, progression-free survival, overall survival Consider: Lymph node sampling, systemic nodal dissection, complete mediastinal lymphanectomy, hylar lymph node	6.2.4
23. Should surgical resection be considered in subsets of stage 3a NSCLC compared to oncologic treatments such as radiotherapy, chemotherapy, chemoradiotherapy and neoadjuvant therapy? Outcomes: survival, quality of life	6.2.5
24. How does surgery and chemotherapy compare with chemotherapy alone in stage I SCLC? Outcomes: Tolerability of treatment, adverse effects, 2-year survival, 5-year survival, progression-free survival, overall survival	6.3.1
25. Should surgery be considered in patients with ppFEV$_1$ or ppDLCO <30% provided the risk of dyspnoea is explained to the patient compared to oncologic treatments such as radiotherapy, chemotherapy and chemoradiotherapy? Consider: perfusion scans and wedge resections in marginal cases. VAT resection in high risk groups Outcomes: Recovery from procedure, pain/symptoms, 2-year survival, 5-year survival, progression free survival, overall survival, dyspneoa	6.1

Annex 2

Staging

Staging of cancers applies a set of rules to express the extent of the disease and is used for prognostic and therapeutic purposes. Staging can be clinical (based on the results of clinical examination and radiological imaging) or pathological (based on histopathological findings following surgical resection of the tumour).

In non-small cell lung cancer two staging systems are widely used. The first, the TNM (tumour, nodes, metastases) was developed by the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) and is widely used for both clinical and pathological staging of lung cancer.[71] The second classification, uses the TNM system to classify patients into four stages (I –IV) according to prognosis.[71]

TNM Classification for lung cancer	
Tx	Positive cytology only
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Primary tumour ≤3 cm
T1a	≤2 cm
T1b	>2 to 3 cm
T2	Main bronchus ≥2 cm from carina, invades visceral pleura, partial atelectasis
T2a	>3 cm to 5 cm
T3	>7 cm; chest wall, diaphragm, pericardium, mediastinal pleura, main bronchus <2 cm from carina, total atelectasis, separate nodule(s) in same lobe
T4	Mediastinum, heart, great vessels, carina, trachea, oesophagus, vertebral body; separate tumour nodules in a different ipsilateral lobe
Nx	Lymph node status cannot be assessed
N0	No lymph node metastasis
N1	Metastasis in intrapulmonary, ipsilateral hilar and/or peribronchial lymph nodes
N2	Metastasis in ipsilateral mediastinal or subcarinal nodes
N3	Metastasis in contralateral mediastinal or hilar, scalene nodes or supraclavicular nodes
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe; pleural nodules or malignant or pericardial effusion
M1b	Distant metastasis

Stage grouping			
Occult carcinoma	Tx	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a,b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	M0	M0
	T1a,b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,b,T2a,b	N2	M0
	T3	N2	M0
	T3	N1,N2	M0
	T4	N0,N1	M0
Stage IIIB	T4	N2	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Small cell lung cancer

It is recommended that the TNM classification above is now used for staging SCLC patients. Studies in the literature in general use the former (limited/extensive) staging system.

Limited stage disease is defined as disease that is confined to a hemithorax and regional lymph nodes and that can be encompassed into a reasonable radiation port.

Extensive stage disease is defined as disease that exists beyond these limits.

Annex 3

Reliability of staging techniques[317]

Technique	False positive (%)	False negative (%)
CT for T3/4	32	18
CT for chest wall invasion	44	9
CT for mediastinal involvement	33	14
CT for N1	38	16
CT for N2/3	45	13
Mediastinoscopy for N2/3	-	9
PET for mediastinal lymphadenopathy	16	7
Clinical evaluation	60-70	30
Cranial CT in cI-III	5-10	5-10
Isotope bone scans	30-60	-
Chemical shift MRI for adrenal metastases	10	-
Percutaneous needle biopsy for adrenal metastases	-	10-20
PET for adrenal metastases	<5	<5
PET for distant metastases	>10	5

Annex 4

WHO/ECOG Performance Status[318]

0 Fully active. Able to carry on all pre-disease performance without restriction.

1 Restricted in physically strenuous activities but ambulatory and able to carry out work of a light and sedentary nature.

2 Ambulatory and capable of all self care but unable to carry out many work activities; up and about more than 50% waking hours.

3 Capable of only limited self care; confined to bed or a chair for more than 50% of waking hours.

4 Completely disabled; unable to carry out any self care; totally confined to bed or a chair.

www.ecog/org/general/perf_stat.html

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