NATIONAL CLINICAL EFFECTIVENESS COMMITTEE

National Patient Safety Office
Oifig Náisiúnta um Shábháilteacht Othar

Diagnosis, staging and treatment of patients with lung cancer

National Clinical Guideline No. 16

Summary

An Roinn Sláinte
DEPARTMENT OF HEALTH

November 2017

This National Clinical Guideline has been developed by the National Cancer Control Programme Guideline Development Group (GDG), within the HSE.

Using this National Clinical Guideline

This Guideline Summary should be read in conjunction with the full version National Clinical Guideline. The same number for appendices has been retained in both versions.

The full National Clinical Guidelines and Summary versions are available at http://health.gov.ie/national-patient-safety-office/ncec/national-clinical-guidelines/

This Summary National Clinical Guideline applies to adults (18 years or older) with newly diagnosed lung cancer, or, those that have a suspected diagnosis of lung cancer in a hospital setting.

This Summary National Clinical Guideline is intended for all health professionals involved in the diagnosis, staging and treatment of patients with lung cancer. While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

This Summary National Clinical Guideline is also relevant to those involved in clinical governance, in both primary and secondary care, to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline. Whilst the Summary National Clinical Guideline is focused on clinical care, it is expected to be of interest to patients with lung cancer and their significant others. Effort has been made to make this document more user friendly. A list of medical abbreviations used throughout the guideline can be found in Appendix 9: Glossary of terms and abbreviations.

Disclaimer

NCEC National Clinical Guidelines do not replace professional judgement on particular cases, whereby the clinician or health professional decides that individual guideline recommendations are not appropriate in the circumstances presented by an individual patient, or whereby an individual patient declines a recommendation as a course of action in their care or treatment plan. In these circumstances the decision not to follow a recommendation should be appropriately recorded in the patient's healthcare record.

Users of NCEC National Clinical Guidelines must ensure they have the current version (hardcopy, softcopy or App) by checking the website: http://health.gov.ie/national-patient-safety-office/ncec/

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1 Background

Cancer is a major healthcare challenge. Each year in Ireland, approximately 20,804 people are diagnosed with invasive cancer. Cancer is the second leading cause of death in Ireland after diseases of the circulatory system.

Deaths from cancer averaged about 8,655 deaths per year during 2011-2013, representing about 30% of all deaths in that period (NCRI, 2016).

Lung cancer was the single most common cause of cancer death in Ireland from 2011-2012 (See Section 3.1 Epidemiology). Averaging 1,827 deaths annually, lung cancer is the leading cause of cancer deaths in both sexes (NCRI, 2016). The incidence of lung cancer in Ireland is projected to rise more rapidly in females than in males. By 2040 the rate of lung cancer is projected to increase by 136% in females (Nordpred model) and 52% in males (NCRI, 2014).

Cancer incidence data from the National Cancer Registry Ireland (NCRI) and population projections from the Central Statistics Office (CSO) have been combined by the NCRI to estimate the number of new cancer cases expected in five year bands from 2015 to 2040. The total number of new invasive cancer cases (including non-melanoma skin cancer) is projected to increase by 84% for females and 107% for males between 2010 and 2040, based only on changes in population size and age distribution (demography). If trends in incidence since 1994 are also taken into account, the number of cases is expected to increase by between 86% and 125% for females (depending on the method of projection used) and by between 126% and 133% for males (NCRI, 2014).

In Ireland, there are eight hospitals designated as cancer centres and one satellite breast unit (Letterkenny General Hospital). A cancer centre is characterised by the geographic concentration of all oncology disciplines with sub-specialised expertise on a tumour specific/discipline basis to provide the critical mass and support to achieve best practice in cancer care.

As well as these designated cancer centres, other hospitals provide cancer services such as chemotherapy (Figure 1).

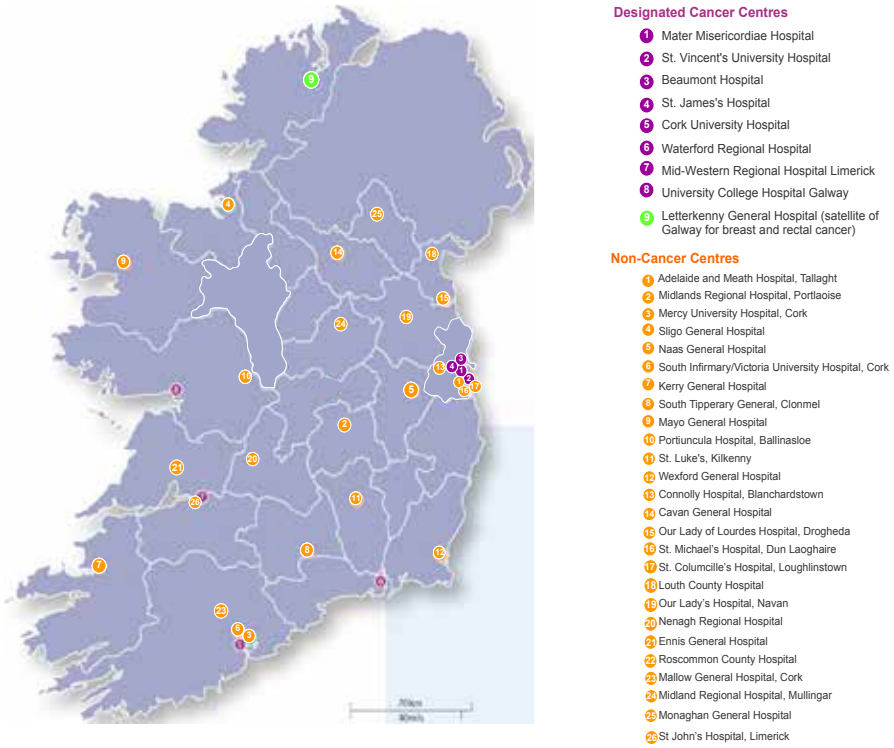

Figure 1 Cancer Services in Ireland

The National Cancer Control Programme (NCCP) engages regularly with the individual cancer centres and with Hospital Group structures. Discussion of performance data, improvement plans, resources including manpower, service planning and development takes place at regular review meetings between the NCCP and senior management at cancer centre and Hospital Group level. This provides an opportunity to share good practice from other cancer centres, if relevant. Where resource issues are identified, these are included in the service planning process. As specific issues arise in hospitals, these are managed by senior hospital management.

A Lead Clinician has been nominated for each of the common tumour sites (e.g. breast, lung, prostate, colorectal) in each of the designated cancer centres, and for rarer tumour sites (e.g. oesophageal cancer) in those centres which offer a service for that cancer. The Lead Clinician chairs the governance arrangements for their service within the cancer centre and participates in a National Leads forum for that tumour site. In order to operate as a cohesive national clinical network for the purpose of clinical audit, sharing of good practice and problem solving, the lead clinicians from the cancer centres meet collectively as a National Lead Clinicians Network. This supports consistency of care across the eight cancer centres.

The National Cancer Strategy (DoHC, 2006) recommended that national site-specific multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care. The principal objective of developing these guidelines is to improve the quality of care received by patients.

A Guideline Development Group was established to develop evidence based guidelines for the diagnosis, staging and treatment of patients with lung cancer.

The National Cancer Strategy 2017-2026 (DoH, 2017) recommends: *The NCCP will develop further guidelines for cancer care in line with National Clinical Effectiveness Committee (NCEC) standards.*

2 National Clinical Guideline recommendations

2.1 Summary of recommendations.

Section	Recommendation	Grade
Radiology	**2.2.1.1** Contrast enhanced CT scanning of the chest and upper abdomen to include the entire liver is recommended in all patients with suspected lung cancer, regardless of chest X-ray results.	**(B)**
	2.2.1.2 A tissue diagnosis of lung cancer should **not** be inferred from CT appearances alone.	**(D)**
	2.2.1.3 PET-CT is recommended for mediastinal and hilar lymph node staging in patients with potentially radically treatable non-small cell lung cancer (NSCLC) prior to invasive staging.	**(C)**
	2.2.1.4 In patients with PET activity in a mediastinal lymph node and normal appearing nodes by CT (and no distant metastases), sampling of the mediastinum is recommended over staging by imaging alone.	**(C)**
	2.2.2.1 Percutaneous FNA, TTNB, guided bronchoscopy and VATS are all appropriate first-line modalities for tissue diagnosis of peripheral lung nodules.	**(C)**
	2.2.2.2 While percutaneous TTNA/biopsy has a higher diagnostic yield, bronchoscopy (including guided approaches where available) may provide a diagnosis for peripheral lesions.	**(B)**
	2.2.3.1 In patients with clinical stage Ia tumours who are high risk surgical candidates, ablative techniques may be considered to achieve local control.	**(D)**
	2.2.4.1 Consider close follow-up for patients who have undergone treatment with curative intent (including surgery and radiotherapy), to include periodic radiological evaluation with CT.	**(C)**
	2.2.5.1 A negative PET-CT reliably excludes adrenal metastases in patients with NSCLC.	**(B)**
	2.2.5.2 In NSCLC patients with PET-CT positive for adrenal metastasis, histological confirmation should be considered unless there is overwhelming clinical and imaging evidence of widespread metastatic disease.	**(B)**
	2.2.5.3 In NSCLC patients with indeterminate adrenal lesions on PET-CT further assessment with adrenal specific CT or MRI criteria may be considered. If non-invasive imaging findings are indeterminate, adrenal sampling such as EUS-FNA, percutaneous biopsy or adrenalectomy may be considered.	**(D)**
	2.2.6.1 Offer patients with signs/symptoms suggestive of brain metastases a contrast-enhanced CT of the head followed by contrast-enhanced MRI if normal or MRI as an initial test.	**(B)**

Section	Recommendation	Grade
Radiology	**2.2.6.2** Offer MRI or CT of the head in patients with stage III NSCLC selected for treatment with curative intent.	**(C)**
	2.2.6.3 Do **not** routinely offer imaging of the brain in patients with stage I and II NSCLC.	**(C)**
	2.2.7.1 For patients with NSCLC with suspected bone metastasis, evaluation with PET-CT is recommended over bone scintigraphy or CT.	**(B)**
	2.2.7.2 Bone scintigraphy is not necessary when PET-CT has not shown bone metastases.	**(B)**
	2.2.8.1 In patients with clinically limited-stage small-cell lung cancer (SCLC), PET-CT is suggested to exclude occult metastases.	**(C)**
	2.2.9 Staging algorithm for patients with suspected lung cancer (Figure 2).	

Section	Recommendation	Grade
Respiratory Medicine	**2.3.1.1** Patients with central lesions (within proximal one-third of the hemithorax) alone (considered reachable by standard bronchoscopy) who are otherwise fit should undergo flexible bronchoscopy in order to establish a histological or cytological diagnosis.	**(B)**
	2.3.1.2 Visible tumours should be sampled using more than one technique to optimise sensitivity.	**(B)**
	2.3.1.3 Consider bronchoscopy to provide a diagnosis for peripheral lesions, although percutaneous FNA biopsy has a higher diagnostic yield.	**(B)**
	2.3.2.1 Endoscopic assessment of the mediastinal lymph nodes with EBUS-TBNA with or without EUS-FNA should be offered to patients with suspected lung cancer prior to mediastinoscopy.	**(A)**
	2.3.3.1 In patients being considered for active therapy, pleural effusion should be investigated with pleural aspiration.	**(C)**
	2.3.3.2 If pleural fluid cytology is negative, and treatment will change depending on the nature of the pleural fluid, pleural biopsy using image guided or thoracoscopic biopsy is recommended.	**(D)**
	2.3.4.1 In lung cancer patients with symptomatic (including breathlessness, haemoptysis and cough) malignant airway obstruction, any of the following therapeutic interventions may be considered: bronchoscopic debulking, tumour ablation modalities, airway stent placement and radiotherapy (external beam or brachytherapy).	**(D)**
	2.3.5 Staging algorithm for patients with suspected lung cancer (Figure 3).	

Section	Recommendation	Grade
Pathology	**2.4.1.1** Distinguishing between small-cell carcinoma and non-small cell carcinoma of the lung is recommended. For challenging cases, a diagnostic panel of immunohistochemical assays is recommended to increase the diagnostic accuracy.	**(B)**
	2.4.1.2 In individuals with pathologically diagnosed non-small cell lung cancer (NSLC), additional discrimination between adenocarcinoma and squamous cell carcinoma, even on cytologic material or small tissue samples is recommended.	**(B)**
	2.4.2.1 Endobronchial ultrasound rapid on-site evaluation (EBUS ROSE) should be made available whenever resources permit.	**(B)**
	2.4.2.2 Consider intra-operative frozen section analysis in primary diagnosis when preoperative diagnosis is not available.	**(C)**
	2.4.2.3 In selected cases intra-operative frozen section analysis for staging may be considered.	**(C)**
	2.4.3.1 Cytology samples can be used to provide material suitable for both NSCLC sub-typing and some molecular analysis, provided the samples are appropriately handled and processed.	**(B)**
	2.4.4.1 Fixation times of 6 to 12 hours for small biopsy samples and 8 to 18 hours for larger surgical specimens generally give best results, although expert consensus opinion is that fixation times of 6 to 48 hours should give acceptable results.	**(D)**

Section	Recommendation	Grade
Surgery	**2.5.1.1** For patients with clinical stage I and II non-small cell lung cancer (NSCLC) who are medically fit for surgical resection, a lobectomy rather than sublobar resection is recommended.	**(B)**
	2.5.2.1 For patients with clinical stage I NSCLC, video-assisted thoracic surgery (thoracoscopy) should be considered as an alternative to thoracotomy for anatomic pulmonary resection.	**(B)**
	2.5.3.1 Pulmonary function testing (spirometry, diffusion capacity, lung volume) should be performed in all patients being considered for surgical resection.	**(C)**
	2.5.3.2 Postoperative predictive values should be calculated using broncho-pulmonary segment counting. If a mismatch is suspected ventilation perfusion scan should be performed.	**(C)**
	2.5.3.3 Offer patients surgery if they have an FEV_1 & D_{LCO} within normal limits (postoperative predicted values >60%).	**(C)**
	2.5.3.4 Patients with ppo-FEV_1 and/or D_{LCO} <30% should have formal cardiopulmonary exercise testing with measurement of VO_2 max.	**(C)**

Section	Recommendation	Grade
Surgery	**2.5.3.5** Patients with ppo-FEV_1 and/or D_{LCO} >30% and <60% – supplementary functional exercise assessments should be considered.	**(D)**
	2.5.3.6 In patients with lung cancer being considered for surgery and a VO_2 max <15mL/kg/min predicted, it is recommended that they are counselled about minimally invasive surgery, sublobar resections or non-operative treatment options for their lung cancer.	**(C)**
	2.5.4.1 Lung cancer surgery remains the best opportunity for potential cure in patients with significant co-morbidity. Efforts to contain and manage that risk should start with preoperative scoring (thoracoscore) and should ideally include attendance at a preoperative assessment clinic, where practical.	**(D)**
	2.5.4.2 Seek a cardiology review in patients with an active cardiac condition or ≥3 risk factors or poor cardiac functional capacity.	**(C)**
	2.5.4.3 Offer surgery without further investigations to patients with ≤2 risk factors and good cardiac functional capacity.	**(B)**
	2.5.5.1 Age >80 years should not automatically preclude surgery. Decisions should be based on oncological stage, co-morbidity and physiological testing.	**(D)**
	2.5.6.1 Multifocal In patients with suspected or proven multifocal lung cancer (without mediastinal or extrapulmonary disease), curative-intent treatment may be considered, following discussion at a multidisciplinary team meeting.	**(D)**
	2.5.6.2 Synchronous In patients with suspected or proven synchronous primary lung cancer (without mediastinal or extrapulmonary disease), curative-intent treatment may be considered, following discussion at a multidisciplinary team meeting.	**(C)**
	2.5.7.1 Systematic mediastinal lymph node dissection should be performed in all patients having a lung cancer resection.	**(B)**
	2.5.8.1 In patients with malignant pleural effusion whose symptoms improved following drainage, a number of options are available depending on performance status and documentation of lung re-expansion: - In patients with good performance status with lung re-expansion, thoracoscopy with talc pleurodesis is recommended. **(C)** - In patients with non-expandable lung, tunnelled catheters may be considered. **(C)** - In patients with poor performance status with lung re-expansion, options include: tunnelled plerual catheter, serial thoracentesis, or bedside talc pleurodesis. **(D)**	
	2.5.9.1 In patients with an isolated brain metastasis and a synchronous resectable primary NSCLC, sequential resection of the primary tumour and definitive treatment of the brain metastasis may be considered, following discussion at a multidisciplinary team meeting.	**(C)**

Section	Recommendation	Grade
Surgery	**2.5.9.2** In patients with an isolated adrenal metastasis and a synchronous resectable primary NSCLC, sequential resection of the primary tumour and definitive treatment of the adrenal metastasis may be considered, following discussion at a multidisciplinary team meeting.	**(D)**
	2.5.10.1 Consider surgery as part of multimodality management in patients with T1–3 N2 (non-fixed, non-bulky, single zone) M0 disease.	**(C)**
	2.5.11.1 Patients with clinical stage I small-cell lung cancer (SCLC) and excellent performance status may be considered for resection following extensive staging investigation as part of a multimodality treatment regimen.	**(C)**

Section	Recommendation	Grade
Medical Oncology	**2.6.1.1 Preoperative chemoradiotherapy** For patients with non-small cell lung cancer (NSCLC) who are suitable for surgery, do **not** offer neoadjuvant chemoradiotherapy outside a clinical trial.	**(B)**
	2.6.1.2 Preoperative chemotherapy Following discussion at a multidisciplinary team meeting, appropriate patients with NSCLC who are suitable for surgery can be considered for neoadjuvant chemotherapy.	**(A)**
	2.6.2.1 Concurrent chemoradiotherapy should be administered to patients with locally advanced NSCLC (suitable for radical radiotherapy) who have a good performance status (0-1).	**(A)**
	2.6.3.1 Induction or consolidation chemotherapy are **not** routinely recommended for patients receiving concurrent radical chemoradiotherapy.	**(B)**
	2.6.4.1 Effectiveness of first-line cytotoxic chemotherapy In patients with a good performance status (PS) (i.e. Eastern Cooperative Oncology Group [ECOG] level 0 or 1) and stage IV NSCLC, a platinum-based chemotherapy regimen is recommended based on the survival advantage and improvement in quality of life (QOL) over best supportive care (BSC).	**(A)**
	2.6.4.2 Effectiveness of first-line cytotoxic chemotherapy In patients with stage IV NSCLC and a good performance status, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is **not** recommended because it provides no survival benefit and may be harmful.	**(A)**
	2.6.4.3 Effectiveness of first-line cytotoxic chemotherapy In patients receiving palliative chemotherapy for stage IV NSCLC, it is recommended that the choice of chemotherapy is guided by histological type of NSCLC.	**(B)**
	2.6.4.4 Effectiveness of first-line cytotoxic chemotherapy Bevacizumab plus platinum-based chemotherapy may be considered an option in carefully selected patients with advanced NSCLC. Risks and benefits should be discussed with patients before decision making.	**(B)**

Section	Recommendation	Grade
Medical Oncology	**2.6.4.5 Effectiveness of first-line targeted therapy** First-line single agent EGFR tyrosine kinase inhibitors (TKI) should be offered to patients with sensitising EGFR mutation positive NSCLC. Adding combination chemotherapy to TKI confers no benefit and should **not** be used.	**(A)**
	2.6.4.6 Effectiveness of first-line targeted therapy Crizotinib should be considered as first-line therapy in patients with ALK positive NSCLC tumours.	**(B)**
	2.6.5.1 In patients with stage IV non-squamous NSCLC who do not experience disease progression and have a preserved performance status after 4-6 cycles of platinum-based therapy, treatment with maintenance pemetrexed is suggested.	**(B)**
	2.6.5.2 In patients with stage IV NSCLC, switch maintenance therapy with chemotherapy agents other than pemetrexed has not demonstrated an improvement in overall survival and is **not** recommended.	**(B)**
	2.6.5.3 In patients with stage IV NSCLC who do not experience disease progression after 4-6 cycles of platinum-based double agent chemotherapy, there is insufficient evidence to recommend maintenance therapy with erlotinib.	**(B)**
	2.6.6.1 In elderly patients (age 70-79 years) with stage IV NSCLC who have good performance status and limited co-morbidities, treatment with a platinum doublet chemotherapy is recommended.	**(B)**
	2.6.6.2 In patients with stage IV NSCLC with a performance status of 2, single agent chemotherapy may be considered. Platinum doublet chemotherapy is suggested over single agent chemotherapy if the performance status of 2 is cancer related rather than co-morbidity associated.	**(B)**
	2.6.6.3 Unfit patients of any age (performance status (3-4)) do not benefit from cytotoxic chemotherapy. However if patients harbor an EGFR or ALK mutation positive tumour, they may be considered for treatment with targeted therapies.	**(C)**
	2.6.7.1 Second-line systemic anticancer therapy (SACT) with single agent drugs should be considered. The choice of agent to be used should be made on a case by case basis taking into account previous treatment, mutation status and co-morbidities.	**(B)**
	2.6.8.1 In patients with either limited-stage or extensive-stage small-cell lung cancer (SCLC), platinum-based chemotherapy with either cisplatin or carboplatin plus etoposide is recommended.	**(A)**
	2.6.8.2 Non-platinum combinations can be considered in patients with limited-stage and extensive-stage SCLC.	**(A)**
	2.6.9.1 There is no data to support maintenance therapy in limited-stage or extensive-stage SCLC.	**(C)**
	2.6.10.1 In patients with relapsed refractory SCLC, second-line therapy should be considered.	**(B)**

Section	Recommendation	Grade
Medical Oncology	**2.6.10.2** Re-initiation of the previously administered first-line chemotherapy regimen is recommended in patients with SCLC who relapse greater than six months from completion of initial chemotherapy.	**(B)**
	2.6.10.3 Single agent chemotherapy should be considered in patients with primary refractory SCLC to maintain or improve quality of life.	**(B)**

Section	Recommendation	Grade
Radiaton Oncology	**2.7.1.1** Every patient with early stage disease (T1-T2 N0 M0) should be evaluated for fitness for surgery. If unfit for surgery, or surgery is declined, patients should be considered for radical treatment, preferably SBRT/SABR or radical radiotherapy.	**(A)**
	2.7.1.2 Radiofrequency ablation (RFA) can be considered for patients with clinical stage Ia tumours who are not suitable for surgery following discussion at a multidisciplinary team meeting. (*Refer to Clinical question 2.2.3*).	**(D)**
	2.7.2.1 In patients receiving combined chemoradiotherapy standard fractionation should be used to deliver a radical dose equivalent to 60 – 66 Gy.	**(A)**
	2.7.2.2 When a radical dose is considered 3D-CRT is the minimum technique to be used.	**(B)**
	2.7.2.3 When available, CHART can be considered in patients with non-operable stage I-III non-small cell lung cancer (NSCLC) not receiving chemotherapy.	**(A)**
	2.7.3.1 Perform three-dimensional treatment planning in patients undergoing radical thoracic radiotherapy. 4DCT should be performed where available.	**(B)**
	2.7.3.2 The dose volume parameters for the organs at risk (e.g. oesophagus, lung) need to be taken into account. It is prudent to limit V_{20} to ≤30–35% and mean lung dose to ≤20–23 Gy (with conventional fractionation) if one wants to limit the risk of radiation pneumonitis to ≤20% in definitively treated patients with NSCLC.	**(B)**
	2.7.4.1 In patients with R1 resection, regardless of N status, postoperative radiotherapy (PORT) should be proposed sequentially delivering a radical dose of 60 Gy in 30 fractions.	**(B)**
	2.7.4.2 In patients with a pN2 stage and a complete resection there is no consensus to the benefit of PORT. If considered, PORT should be delivered at a dose of 50 Gy standard fractionation.	**(B)**
	2.7.4.3 PORT is **not** indicated in patients with a complete resection R0 and N0 disease.	**(B)**

Section	Recommendation	Grade
Radiaton Oncology	**2.7.5.1** Consolidation prophylactic cranial irradiation (PCI) is recommended in patients with limited-stage small-cell lung cancer (SCLC) having a response to chemoradiotherapy.	**(A)**
	2.7.5.2 In combined modality care, thoracic radiotherapy is recommended in patients with limited-stage SCLC and should be initiated as early as possible.	**(A)**
	2.7.5.3 Consolidation PCI is recommended in patients with extensive-stage SCLC having a response to chemotherapy.	**(A)**
	2.7.5.4 Consolidation thoracic radiotherapy may be considered in patients with extensive-stage SCLC having a response to chemotherapy.	**(A)**

Section	Recommendation	Grade
Palliative Care	**2.8.1.1** Patients with stage IV non-small cell lung cancer (NSCLC) should be offered concurrent specialist palliative care and standard oncological care at initial diagnosis.	**(B)**

Good practice point
Recommended best practice based on the clinical experience of the Guideline Development Group.

2.2 Radiology

The following are responsible for implementation of the radiology recommendation:
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

The literature used in the development of this guideline was based on the 7th edition of the Lung Cancer TNM staging system. The 8th edition of the TNM staging system was published in December 2016 (Brierley et al., 2016), this may lead to changes in recommendations over time, which should be taken into consideration at multidisciplinary team meetings.

Clinical question 2.2.1

In non-small cell lung cancer (NSCLC) patients with mediastinal and hilar adenopathy, what is the efficacy of CT (contrast and non-contrast) and PET-CT in the diagnosis of lung cancer?

Evidence summary
Two clinical guidelines (SIGN, 2014, NICE, 2011), and a Cochrane meta-analysis (Schmidt-Hansen et al., 2014) addressed this clinical question.

Two International guidelines (SIGN, 2014, NICE, 2011) recommend that patients with suspected lung cancer should undergo a contrast enhanced computed tomography (CT) (See Figure 2 'Staging algorithm in patients with suspected lung cancer'.)

> "Contrast enhanced CT scanning of the chest and abdomen is recommended in all patients with suspected lung cancer, regardless of chest X-ray results." [SIGN, 2014]

> "Patients with known or suspected lung cancer should be offered a contrast enhanced chest CT scan to further the diagnosis and stage the disease. The scan should also include the liver and adrenals." [NICE, 2011]

Hilar nodes (N1)
The reliability of CT, magnetic resonance imaging (MRI) and thoracoscopy in staging N1 nodes is poor (Roberts et al., 1999, Detterbeck and Jones, 2001, Glazer et al., 1985, Wain, 1993). This may be a concern if radical radiotherapy is being considered and the primary tumour is distant from the hilum. (SIGN, 2014)

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 (Detterbeck et al., 2001a). The false negative rate is higher with central tumours and adenocarcinomas (22% and 19%). (SIGN, 2014)

PET scanning of mediastinal nodes (N2/3)
18F-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography (FDG PET-CT) is more accurate than CT in detecting mediastinal nodal metastases in patients with NSCLC (Birim et al., 2005). The false negative rate of FDG PET in mediastinal nodes of 10 mm in short axis diameter on CT was very low (5%) (de Langen et al., 2006). (SIGN, 2014)

The false negative rate of FDG PET in mediastinal nodes >15 mm in short axis diameter on CT was relatively high (21%) (de Langen et al., 2006). 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 (ACCP, 2007, De Leyn et al., 2007). (SIGN, 2014)

The specificity of FDG PET in mediastinal nodal staging is approximately 80% (Silvestri et al., 2007). Given a relatively high false positive rate, FDG PET positive mediastinal nodes should be confirmed with nodal sampling, if this will alter management (Silvestri et al., 2007). (SIGN, 2014)

A Cochrane report (Schmidt-Hansen et al., 2014) included 45 prospective and retrospective studies that assessed the diagnostic accuracy of integrated PET-CT for diagnosing N2 disease in patients with

suspected resectable NSCLC. Two primary analyses were conducted as the criteria for test positivity – activity > background and SUVmax ≥ 2.5. The summary sensitivity and specificity estimates for activity > background test positivity were 77.4% (95% CI 65.3 to 86.1) and 90.1% (95% CI 85.3 to 93.5), respectively. The summary sensitivity and specificity estimates for SUVmax ≥ 2.5 were 81.3% (95% CI 70.2 to 88.9) and 79.4% (95% CI 70 to 86.5), respectively. Substantial heterogeneity was observed in both analyses. The study concluded that the sensitivity and specificity although reasonable, is insufficient to allow management based on PET-CT alone. PET-CT should form part of a clinical pathway supported by other investigations and cannot be used as a stand-alone test.

Recommendation 2.2.1.1	**Grade**
Contrast enhanced CT scanning of the chest and upper abdomen to include the entire liver is recommended in all patients with suspected lung cancer, regardless of chest X-ray results.	**B**

Recommendation 2.2.1.2	**Grade**
A tissue diagnosis of lung cancer should **not** be inferred from CT appearances alone.	**D**

Recommendation 2.2.1.3	**Grade**
PET-CT is recommended for mediastinal and hilar lymph node staging in patients with potentially radically treatable non-small cell lung cancer (NSCLC) prior to invasive staging.	**C**

Recommendation 2.2.1.4	**Grade**
In patients with PET activity in a mediastinal lymph node and normal appearing nodes by CT (and no distant metastases), sampling of the mediastinum is recommended over staging by imaging alone.	**C**

Good practice point
In the presence of hilar and mediastinal PET positive adenopathy the highest stage node should be biopsied to confirm metastic spread.

Clinical question 2.2.2

In patients with peripheral lung nodules, what is the efficacy of the following tests in the diagnosis of lung cancer?

- **Percutaneous fine needle aspiration (FNA) and transthoracic needle biopsy (TTNB)**
- **Guided bronchoscopy**
- **Video-assisted thoracoscopic surgery (VATS)**

Evidence summary

Two clinical guidelines (SIGN, 2014, NICE, 2011), a meta-analysis (Wang Memoli et al., 2012) and a systematic review (Yao et al., 2012) addressed this clinical question.

Percutaneous fine needle aspiration and Transthoracic needle biopsy

Transthoracic needle biopsy is used to obtain diagnostic samples from lesions that are not accessible via the bronchial tree and where there is no obvious lymph node involvement. This is usually where there are one or more peripheral lesions. CT is used to guide biopsy where lesions are in difficult to reach locations or where they are completely surrounded by aerated lung. Ultrasound is used where the lesion abuts the chest wall and is visible on ultrasound. (NICE, 2011)

Percutaneous FNA/biopsy is a highly sensitive technique for diagnosing lung cancer (sensitivity of 88–92%) (Schreiber and McCrory, 2003, Detterbeck and Rivera, 2001b). Fine needle aspirations can be guided by fluoroscopy, ultrasound, CT or 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 (Detterbeck and Rivera, 2001b). 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 (Detterbeck and Rivera, 2001b). (SIGN, 2014)

Yao et al. (2012) performed a systematic review which compared fine needle aspiration biopsy (FNA) with core-needle biopsy (CB) for diagnostic characteristics and yields for diagnosing lung cancer in patients with lung lesions. For overall diagnostic characteristics (benign vs. malignant) of FNA and CB, the ranges of sensitivity, specificity and of accuracy are displayed in Table 1. For specific diagnostic characteristics of FNA and CB (identifying the histologic subtype of malignancies or the specific benign diagnoses), the ranges of sensitivity, specificity and of accuracy are displayed in Table 2. Compared with FNA, CB did not result in a higher complication rate (pneumothorax or haemoptysis).

Table 1. Overall diagnostic characteristics (benign vs. malignant) of FNA and CB

	Fine needle aspiration biopsy	Core-needle biopsy
Sensitivity	81.3%-90.8%	85.7%-97.4%
Specificity	75.4%-100.0%	88.6%-100.0%
Accuracy	79.7%-91.8%	89.0%-96.9%

Table 2. For specific diagnostic characteristics of FNA and CB

	Fine needle aspiration biopsy	Core-needle biopsy
Sensitivity	56.3%-86.5%	56.5%-88.7%
Specificity	6.7%-57.1%	52.4%-100.0%
Accuracy	40.4%-81.2%	66.7%-93.2%

Guided bronchoscopy

A recent meta-analysis (Wang Memoli et al., 2012) was undertaken to determine the overall diagnostic yield of guided bronchoscopy using one or a combination of electromagnetic navigation bronchoscopy (ENB), virtual bronchoscopy (VB), radial endobronchial ultrasound (R-EBUS), ultrathin bronchoscope, and guide sheath. A total of 3,052 lesions from 39 studies were included. The pooled diagnostic yield was 70%, which is higher than the yield for traditional transbronchial biopsy. The yield increased as the lesion size increased. The pneumothorax rate was 1.5%, which is significantly smaller than that reported for transthoracic needle aspiration (TTNA). The results showed that the diagnostic yield of guided bronchoscopic techniques is better than that of traditional transbronchial biopsy. Although the yield remains lower than that of TTNA, the procedural risk is lower. However guided bronchoscopy allows both sampling of mediastinal lymph nodes and peripheral lung nodules in appropriately selected patients during the same procedure. Guided bronchoscopy may be an alternative or be complementary to TTNA for tissue sampling of pulmonary nodules, but further study is needed to determine its role in the evaluation of peripheral pulmonary lesions.

Flexible bronchoscopy has a lower diagnostic sensitivity for peripheral lesions compared with central lesions. Fluoroscopy may improve the diagnostic yield of bronchoscopy in sampling peripheral lesions but diagnostic yield remains lower than TTNA/biopsy (Detterbeck and Rivera, 2001a, Schreiber and McCrory, 2003). (SIGN, 2014)

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 (Mack et al., 1993, Mitruka et al., 1995). It has a low complication rate (0.8% open conversion rate). (SIGN, 2014)

VATS should be performed by a well trained thoracic surgeon with extensive open experience in a recognised VATS unit (Ferguson and Walker, 2006). (SIGN, 2014)

While the above options are acceptable (see Figure 2 – 2.2.9 Staging algorithm for patients with suspected lung cancer), they will depend on multiple factors including; patient comorbidities, patient preference, local availability and expertise and size and location of the nodule.

Recommendation 2.2.2.1	**Grade**
Percutaneous FNA, TTNB, guided bronchoscopy and VATS are all appropriate first-line modalities for tissue diagnosis of peripheral lung nodules.	**C**

Recommendation 2.2.2.2	**Grade**
While percutaneous TTNA/biopsy has a higher diagnostic yield, bronchoscopy (including guided approaches where available) may provide a diagnosis for peripheral lesions.	**B**

Good practice point

In the presence of hilar and mediastinal PET positive adenopathy the highest stage node should be biopsied to confirm metastatic spread.

Clinical question 2.2.3

In NSCLC patients with early stage disease who are high risk surgery candidates, what is the effectiveness of ablative techniques?

Evidence summary

A clinical guideline (Lim et al., 2010) and two retrospective studies (Lanuti et al., 2012, Hiraki et al., 2011) addressed this clinical question.

Radiofrequency ablation (RFA) for primary lung tumours has developed as a minimally invasive treatment for both radical treatment and palliation. It is well tolerated and complication rates are low. The treatment can be delivered in a single session, usually requiring only a short admission. RFA is suitable for small tumours, usually of 3 cm diameter or less, although larger lesions may be considered suitable in certain circumstances. (Lim et al., 2010)

No data have been published so far on the combination of RFA with chemotherapy for early stage non-small cell lung cancer. (Lim et al., 2010)

Lanuti et al. (2012) performed 55 ablations in 45 patients (age, 51 to 89 years) with stage I NSCLC. At a median follow-up of 32 months, locoregional recurrence (LRR) occurred in 21 (38%) within a mean of 12±10 (range, 1-44) months from RFA. Recurrence was observed locally in the tumour bed in 18 (33%), in regional nodes in 4 (7%), and distant in 2 (4%). The mean maximal tumour diameter was 2.3±1.3 (range, 0.7 to 4.5) cm. In tumours exceeding 3 cm, 10 (80%) were associated with LRR. Recurrent lesions were treated with repeat RFA (5), radiotherapy (8), chemoradiotherapy (5), and chemotherapy (2). Local control was achieved by repeat RFA in 2 of 5 (40%) or by radiotherapy in 8 lesions (100%), with 2 regional nodal failures (median follow-up, 40±13 months). Overall survival among patients who did or did not experience LRR was similar (32% to 35%). Repeat RFA was not associated with any significant complications or procedure-related 30-day mortality. The authors concluded lung RFA is associated with increased rates of local failure in tumours exceeding 3 cm and in contact with larger segmental vessels. However, patients with local failure can be promptly salvaged with stereotactic ablative radiation therapy (SBRT/SABR) or repeat RFA, without detriment to overall survival.

A retrospective cohort study (Hiraki et al., 2011) comprising of 50 non-surgical candidates (29 men and 21 women; mean age, 74.7 years) with clinical stage I (Ia, n = 38; Ib, n = 12) histologically proven non–small cell lung cancer treated a total of 52 tumours with 52 ablation sessions. The median follow-up period was 37 months. Local progression was observed in 16 (31%) of the 52 tumours. The median survival time was 67 months. The overall, cancer-specific, and disease-free survivals were 94%, 100%, and 82% at 1 year, 86%, 93%, and 64% at 2 years, and 74%, 80%, and 53% at 3 years, respectively. The authors concluded RFA of clinical stage I non–small cell lung cancer was minimally invasive and provided promising patient survival, although the local efficacy needs to be improved.

Recommendation 2.2.3.1	**Grade**
In patients with clinical stage Ia tumours who are high risk surgical candidates, ablative techniques may be considered to achieve local control.	**D**

Good practice point

Radiofrequency ablation should only be considered for patients following discussion at a multidisciplinary team meeting.

Clinical question 2.2.4

For patients with NSCLC who have undergone surgical resection or radiotherapy with curative intent, is there a role for imaging surveillance?

Evidence summary

A meta-analysis (Calman et al., 2011) addressed this clinical question.

A meta-analysis examined the role of follow-up in patients with lung cancer (Calman et al., 2011). The study included eight observational studies and one randomised trial, the primary outcomes were overall survival and survival comparing symptomatic and asymptomatic recurrence. Six studies examined survival in patients with lung cancer comparing more intensive versus less-intensive follow-up programmes (Benamore et al., 2007, Moore et al., 2002, Sugiyama et al., 2008, Younes et al., 1999, Virgo et al., 1995, Zieren et al., 1994). The studies of follow-up care after potentially curative resection included patients with stages I to III disease, reflecting the stage of disease deemed appropriate for curative intent treatment. They showed a general trend for improvement in survival favoured more intensive follow-up: Hazard Ratio (HR) 0.83 (0.66 –1.05), but this was not statistically significant (p=0.13). Between-study heterogeneity was low. High rates of relapse (between 21% and 71%) were reported even when curative treatment was intended. In the curative intent subgroup, all the studies found that asymptomatic recurrence was associated with a significantly longer survival time: HR 0.61 (0.50–0.74) (p<0.01), with a low level of heterogeneity. The study concluded that there is scope for further research in lung cancer follow-up of patients after different treatment regimes.

Recommendation 2.2.4.1	Grade
Consider close follow-up for patients who have undergone treatment with curative intent (including surgery and radiotherapy), to include periodic radiological evaluation with CT.	C

Good practice point
The evidence for this practice is limited and the optimal scanning interval remains to be determined.

Good practice point
Schedule choice of radiological investigation should be discussed at multidisciplinary team meeting, and follow-up should include clinical evaluation with consideration of symptoms, quality of life, co-morbidities and smoking cessation (see Tools on smoking cessation in Appendix 3: Summary of the tools to assist in the implementation of this National Clinical Guideline).

Good practice point
Patients should be advised of the benefits of smoking cessation.

Clinical question 2.2.5

For patients with NSCLC which of the following tests is most accurate for detecting metastatic spread to indeterminate adrenal nodules/masses: chemical shift MRI, non-contrast CT, PET-CT?

Evidence summary
A current guideline (SIGN, 2014) addressed this clinical question.

An adrenal adenoma can be reliably diagnosed by chemical shift magnetic resonance imaging (MRI), unenhanced computed tomography (CT) and delayed contrast-enhanced CT, making these suitable techniques for excluding metastases (Detterbeck et al., 2001b, Detterbeck et al., 2001c). Percutaneous needle biopsy has an overall complication rate of 8-9% with 3-4% having major complications (e.g. pneumothorax or significant haemorrhage) (Welch et al., 1994). At less than 5%, positron emission tomography (PET) scanning appears to have the lowest false positive (FP) and false negative (FN) rates for adrenal metastases (Detterbeck et al., 2001c). (SIGN, 2014)

In a meta-analysis, FDG positron emission tomography-computed tomography (PET-CT) was found to be highly sensitive (97%) and specific (91%) in differentiating malignant from benign adrenal disease although studies were highly heterogeneous (Boland et al., 2011). Although FDG PET-CT interpretation criteria varied, there was no significant difference in their accuracy. Several primary studies also showed high sensitivity and specificity of FDG PET-CT in adrenal staging in lung cancers (Cho et al., 2011, Lu et al., 2010). No trials of head- to-head comparison of PET-CT, MRI and ultrasound were identified. (SIGN, 2014)

High FDG activity in an adrenal mass has high specificity for metastasis although there are variations in FDG PET-CT interpretation criteria (visual analysis, standardised uptake value (SUV), SUV ratio etc) (Boland et al., 2011, Lu et al., 2010, Brady et al., 2009, Kumar et al., 2004). EUS-FNA has also been shown to be effective in adrenal staging especially of the left adrenal gland (Bodtger et al., 2009, DeWitt et al., 2007). (SIGN, 2014)

Recommendation 2.2.5.1	**Grade**
A negative PET-CT reliably excludes adrenal metastases in patients with NSCLC.	**B**

Recommendation 2.2.5.2	**Grade**
In NSCLC patients with PET-CT positive for adrenal metastasis, histological confirmation should be considered unless there is overwhelming clinical and imaging evidence of widespread metastatic disease.	**B**

Recommendation 2.2.5.3	**Grade**
In NSCLC patients with indeterminate adrenal lesions on PET-CT further assessment with adrenal specific CT or MRI criteria may be considered. If non-invasive imaging findings are indeterminate, adrenal sampling such as EUS-FNA, percutaneous biopsy or adrenalectomy may be considered.	**D**

Clinical question 2.2.6

For patients with NSCLC which of the following tests is most accurate for detecting brain metastases: MRI, CT, PET-CT?

Evidence summary

Two clinical guidelines (SIGN, 2014, Lim et al., 2010) addressed this clinical question.

CT

Contrast-enhanced CT is the most commonly used imaging method to detect brain metastases and is as reliable as non-contrast-enhanced MRI (Hatter et al., 1994, Kormas et al., 1992, Ichinose et al., 1989, Ferrigno and Buccheri, 1994, Akeson et al., 1995, Taphoorn et al., 1989, Sze et al., 1988, Davis et al., 1991). 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 (Kormas et al., 1992, Ichinose et al., 1989). In patients with N2 disease who are still being considered for curative treatment, a CT scan of the head is warranted (Kormas et al., 1992). (SIGN, 2014)

MRI

MRI of the brain detects more and smaller lesions than CT (Yokoi et al., 1999, Davis et al., 1991). The prevalence of cerebral metastases may be influenced by both stage and cell type. In patients with clinical features suggestive of intracranial pathology, CT may be the preferred first test because it is generally more easily accessed than MRI. However, a normal CT scan of the head should always be followed by an MRI owing to the better sensitivity of MRI. The use of routine MRI in staging patients with negative clinical evaluation findings has not been adequately studied. In the post-PET era it may be prudent to consider cerebral imaging, using contrast-enhanced MRI or CT if contraindicated, in patients with stage III non-small cell lung cancer. (Lim et al., 2010)

PET-CT

The main limitations of PET–CT scanning is that high glucose metabolism in the brain and kidney makes evaluation of metastases at these sites difficult and unreliable. (SIGN, 2014)

Recommendation 2.2.6.1	**Grade**
Offer patients with signs/symptoms suggestive of brain metastases, a contrast-enhanced CT of the head followed by contrast-enhanced MRI if normal or MRI as an initial test.	**B**

Recommendation 2.2.6.2	**Grade**
Offer MRI or CT of the head in patients with stage III NSCLC selected for treatment with curative intent.	**C**

Recommendation 2.2.6.3	**Grade**
Do **not** routinely offer imaging of the brain in patients with stage I and II NSCLC.	**C**

Clinical question 2.2.7

For patients with NSCLC which of the following tests is most accurate for detecting bone metastases: isotope bone scan, CT, MRI, PET-CT?

Evidence summary
Clinical guidelines (SIGN, 2014, NICE, 2011, Lim et al., 2010) addressed this clinical question.

Bone Scanning
Four studies of low to moderate quality examined the accuracy of bone scintigraphy ± single-photon emission computed tomography (SPECT) in detecting bone metastases due to lung cancer (Cheran et al., 2004, Hetzel et al., 2003, Song et al., 2009, Takenaka et al., 2009). The sensitivity, specificities and accuracies of bone scintigraphy reported by these studies ranged between 52-96%, 83-99% and 81-95%, respectively. (NICE, 2011)

Technetium-99m (99mTc) bone scanning has a high false positive rate (30 to 60%). Compared to conventional isotope bone scanning, PET-CT is more specific and sensitive (NICE, 2011). Tc-99m nuclear bone scans may be helpful if a PET scan is not indicated and symptoms of bone metastases are present. A positive bone scan should be confirmed by additional studies (e.g. X-ray, MRI, biopsy). (SIGN, 2014)

PET is more sensitive in detecting bone metastases than conventional bone scintigraphy (Hsia et al., 2002), and PET-CT is likely to be superior. The role of bone scintigraphy is limited to those with a high clinical suspicion of metastatic disease as a positive result will effectively exclude a patient from further radical treatment. (Lim et al., 2010)

PET-CT
Two studies of low-moderate quality examined the accuracy of PET-CT in M-staging (Song et al., 2009, Takenaka et al., 2009), and found that the sensitivities, specificities and overall accuracy of PET-CT to be between 94-96%, 86-99% and 89-98% for bone metastases detection, respectively (NICE, 2011).

MRI
One study (Takenaka et al., 2009) examined the ability of MRI to detect bone metastases and reported sensitivities, specificities and accuracies of 64-96%, 79-90% and 83-91%, respectively, for bone metastasis detection. (NICE, 2011)

MRI has an established role in problem solving isolated boney abnormalities identified by other imaging.

Recommendation 2.2.7.1	**Grade**
For patients with NSCLC with suspected bone metastasis, evaluation with PET-CT is recommended over bone scintigraphy or CT.	**B**

Recommendation 2.2.7.2	**Grade**
Bone scintigraphy is not necessary when PET-CT has not shown bone metastases.	**B**

Clinical question 2.2.8

In patients with limited-stage small-cell lung cancer (SCLC) on diagnostic CT, does PET-CT change management?

Evidence summary

A meta-analysis (Gould et al., 2001), two prospective studies (Brink et al., 2004, Bradley et al., 2004) and a focused review (Kalemkerian and Gadgeel, 2013) addressed this clinical question.

A meta-analysis to estimate the diagnostic accuracy of FDG-PET for malignant focal pulmonary lesions (Gould et al., 2001) found FDG-PET is an accurate non-invasive imaging test for diagnosis of pulmonary nodules and larger mass lesions, although few data exist for nodules smaller than 1 cm in diameter. In current practice, FDG-PET has high sensitivity and intermediate specificity for malignancy.

Brink et al. (2004) performed FDG-PET in 120 consecutive patients with SCLC during primary staging. Complete agreement between FDG-PET results and other staging procedures was observed in 75 patients. Differences occurred in 45 patients at 65 sites. In 47 sites the FDG-PET results were proven to be correct, and in ten, incorrect. In the remaining eight sites, the discrepancies could not be clarified. In 14/120 patients, FDG-PET caused a stage migration, correctly upstaging ten patients to extensive disease and downstaging three patients by not confirming metastases of the adrenal glands previously suspected on CT. Only 1/120 patients was incorrectly staged by FDG-PET, owing to failure to detect brain metastases. In all cases the stage migration led to a significant change in the treatment protocol. Sensitivity of FDG-PET was significantly superior to that of CT in the detection of extrathoracic lymph node involvement (100% vs 70%, specificity 98% vs 94%) and distant metastases except to the brain (98% vs 83%, specificity 92% vs 79%). However, FDG-PET was significantly less sensitive than cranial MRI/CT in the detection of brain metastases (46% vs 100%, specificity 97% vs 100%).

Bradley et al. (2004) prospectively performed pretreatment FDG-PET on 24 patients determined by conventional staging methods to have limited-stage SCLC. FDG-PET correctly upstaged two (8.3%) of 24 patients to extensive-stage disease (95% CI, 1.03% to 27.0%). PET correctly identified tumour in each SCLC mass (primary or nodal) that was suspected on CT imaging, thus giving a lesion-based sensitivity relative to CT of 100%. PET identified unsuspected regional nodal metastasis in six (25%) of 24 patients, and the radiation therapy plan was significantly altered to include the PET-positive/CT-negative nodes within the high-dose region in each of these patients. The authors concluded FDG-PET has high sensitivity for SCLC and appears to be of value for initial staging and treatment planning of patients with presumed limited-stage disease.

A focused review published in the Journal of the National Comprehensive Cancer Network (Kalemkerian and Gadgeel, 2013) included 14 studies comparing pretreatment FDG-PET with conventional staging procedures for the initial staging of patients with SCLC. Seven studies evaluated changes in initial management based on PET-CT in patients with SCLC (Kamel et al., 2003, Bradley et al., 2004, Blum et al., 2004, Kut et al., 2007, van Loon et al., 2008, van Loon et al., 2010). Overall, PET findings led to a change in initial management in 28% (range, 0%–47%) of 211 patients. Of the 59 patients with a change in management, 32% underwent an alteration in the general treatment plan as a result of stage shift, whereas 68% had changes in the extent of the radiation field for the treatment of limited-stage SCLC. The study concluded that PET-CT can improve both staging accuracy and treatment planning in patients with SCLC, although further prospective studies are needed to fully define its role.

Recommendation 2.2.8.1	**Grade**
In patients with clinically limited-stage small-cell lung cancer (SCLC), PET-CT is suggested to exclude occult metastases.	**C**

Good practice point
MRI or CT of brain is also recommended.

2.2.9 Staging algorithm for patients with suspected lung cancer

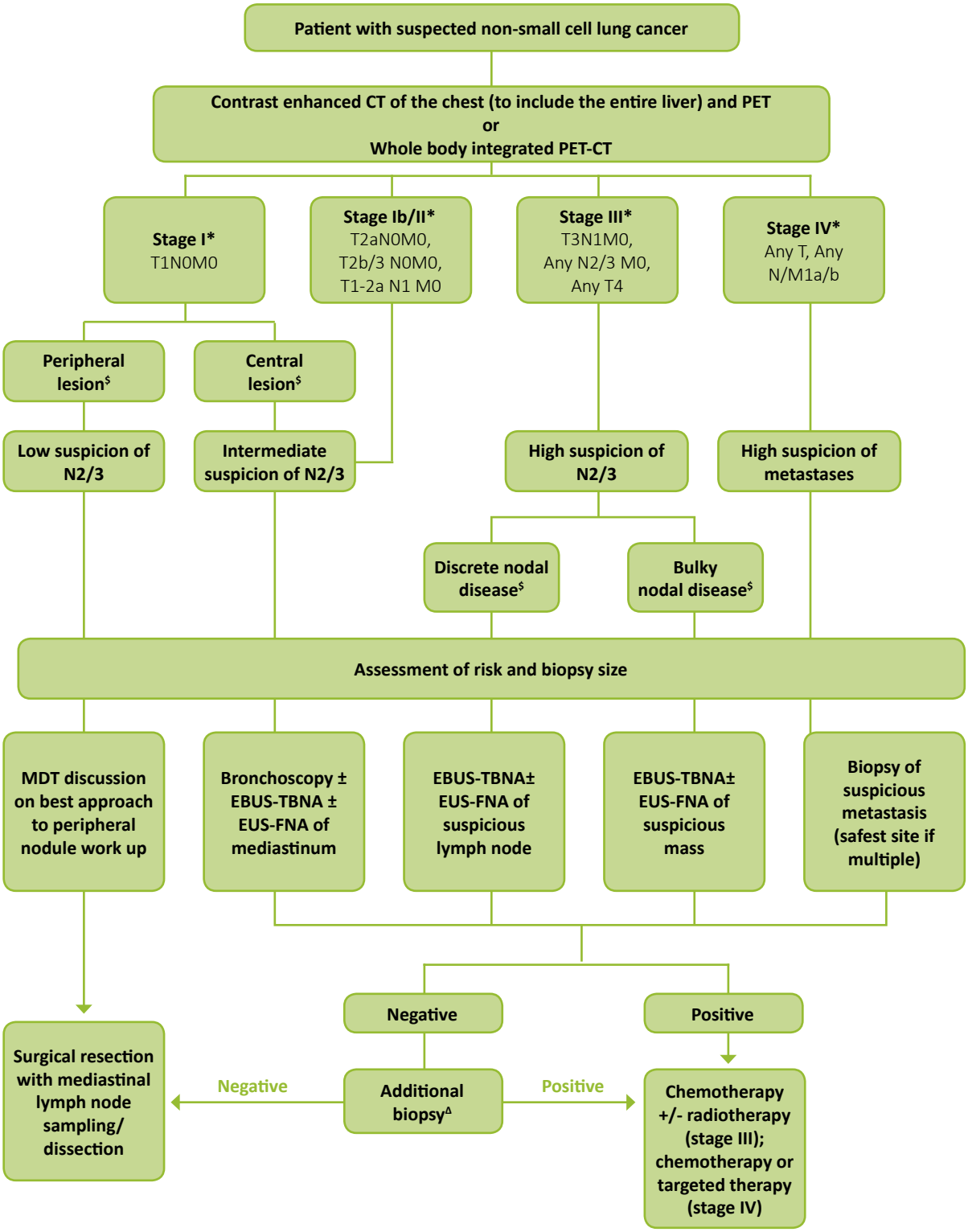

Figure 2. Staging algorithm in patients with suspected lung cancer. Modified from (Thomas and Gould, 2016).

For explanatory notes, see over page.

* Please note that this refers to the 7th edition of the IASLC TNM staging system.

$ Definitions:

Peripheral lesions	Normal mediastinal and N1 nodes (<1cm) and a peripheral tumour (within outer two-thirds of hemithorax) (Silvestri et al., 2013).
Central lesions	Normal mediastinal nodes (<1cm) but enlarged N1 nodes (≥ 1cm) or a central tumour (with proximal one-third of the hemithorax) (Silvestri et al., 2013).
Bulky nodal disease	Correlates with the radiographic group A, as described in the American College of Chest Physicians (ACCP) evidence-based Clinical Practice Guidelines (Silvestri et al., 2013). This group is defined as mediastinal infiltration, where the discrete lymph nodes cannot be distinguished or measured.
Discrete nodal disease	Correlates to radiographic group B, as described in the American College of Chest Physicians (ACCP) evidence-based Clinical Practice Guideline (Silvestri et al., 2013). This group is defined as patients with mediastinal node enlargement, in whom the size of the discrete nodes can be measured.

Δ Mediastinoscopy/video assisted mediastinoscopy/extended cervical mediastinoscopy/oesophageal ultrasound

2.3 Respiratory Medicine

Responsibility for the implementation of respiratory medicine recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

The literature used in the development of this guideline was based on the 7th edition of the Lung Cancer TNM staging system. The 8th edition of the TNM staging system was published in December 2016 (Brierley et al., 2016), this may lead to changes in recommendations over time, which should be taken into consideration at multidisciplinary team meetings.

Clinical question 2.3.1

What is the efficacy of bronchoscopy in identifying lung cancer?

Evidence summary

A clinical guideline (SIGN, 2014) addressed this clinical question.

The value of bronchoscopy depends on the location of the primary tumour. Peripheral tumours in subsegmental bronchi may not be visible. (SIGN, 2014)

The evidence base for the role of bronchoscopy in both central and peripheral tumours comes from two large systematic reviews (Detterbeck and Rivera, 2001a, Schreiber and McCrory, 2003). (SIGN, 2014)

Central tumours

Central lesions are defined as normal mediastinal nodes (<1cm) but enlarged N1 nodes (≥ 1cm) or a central tumour (within proximal one-third of the hemithorax) (Silvestri et al., 2013).

Flexible bronchoscopy has good diagnostic sensitivity (83% to 88%) for central lesions (Detterbeck and Rivera, 2001a, Schreiber and McCrory, 2003). Sampling using multiple techniques gives the highest diagnostic yield. As a single procedure, bronchial biopsy is the most reliable. Table 3 shows the variation in sensitivity for each method. (SIGN, 2014)

Table 3. Percentage diagnostic sensitivity in central tumours

Technique	% Sensitivity	
	Detterbeck and Rivera, 2001a	Schreiber et al., 2003
Biopsy	83	74
Brushing	64	59
Washing	48	48
All three modalities	83	88

Peripheral tumours

Peripheral lesions are defined as normal mediastinal and N1 nodes (<1cm) and a peripheral tumour (within outer two-thirds of hemithorax) (Silvestri et al., 2013).

Flexible bronchoscopy has a lower diagnostic sensitivity for peripheral lesions compared with central lesions (see Table 3 and Table 4). Fluoroscopy may improve the diagnostic yield of bronchoscopy in sampling peripheral lesions but diagnostic yield remains lower than percutaneous fine needle aspiration (FNA) biopsy (Detterbeck and Rivera, 2001a, Schreiber and McCrory, 2003). (SIGN, 2014)

Table 4. Percentage diagnostic sensitivity in peripheral tumours

Technique	% Sensitivity	
	Detterbeck and Rivera, 2001a	Schreiber et al., 2003
Biopsy	60	46
Brushing	48	52
Washing	37	43
All three modalities	66	69

There is international consensus (Detterbeck et al., 2013, Sanchez de Cos et al., 2011, De Leyn et al., 2014) that patients with a central lesion and radiographically normal mediastinum by PET-CT should undergo EBUS evaluation (See Figure 3 'Staging algorithm for patients with suspected lung cancer').

Recommendation 2.3.1.1	**Grade**
Patients with central lesions (within proximal one-third of the hemithorax) alone (considered reachable by standard bronchoscopy) who are otherwise fit should undergo flexible bronchoscopy in order to establish a histological or cytological diagnosis.	**B**

Recommendation 2.3.1.2	**Grade**
Visible tumours should be sampled using more than one technique to optimise sensitivity.	**B**

Recommendation 2.3.1.3	**Grade**
Consider bronchoscopy to provide a diagnosis for peripheral lesions, although percutaneous FNA biopsy has a higher diagnostic yield.	**B**

Good practice point
In patients with central lesions and negative mediastinum on PET-CT, consideration should be given to EBUS evaluation of mediastinum before definitive therapy.

Clinical question 2.3.2

In patients with mediastinal adenopathy: What is the efficacy of EBUS, EBUS/EUS and mediastinoscopy in the diagnosis of lung cancer?

Evidence summary

Two clinical guidelines (SIGN, 2014, Lim et al., 2010) addressed this clinical question.

Endoscopic sampling of the mediastinal lymph nodes

Assessing the mediastinum with endobronchial ultrasound fine needle aspiration (EBUS-FNA) and endoscopic ultrasound fine needle aspiration (EUS-FNA) offers a less invasive technique with higher sensitivity (94% vs 79%) and negative predicted probability (93% vs 86%) than surgical staging alone (Sharples et al., 2012). The technique is associated with low risk and less need for general anaesthesia and thoracotomy. The use of these techniques readily allows for repeat sampling of the mediastinum which is simpler than repeat mediastinoscopy (Yasufuku et al., 2011). (SIGN, 2014)

Mediastinoscopy

The indications for cervical mediastinoscopy have evolved with the increasing availability of PET, EBUS, EUS and broader selection criteria for surgery. With a sensitivity of 85% for PET imaging, many consider that confirmatory mediastinoscopy and lymph node biopsies are not required following a 'negative' PET. Microscopic N2 disease may have a better prognosis, but this will only be confirmed if appropriate lymph node sampling is performed. Although the specificity of PET is high, minimally invasive sampling followed by mediastinoscopy is indicated to screen for false positive results in order not to deny the small proportion of patients the potential of radical treatment. As broader selection criteria are in place, the clinical utility of pretreatment lymph node staging has evolved to assess the location and number of lymph stations that are involved rather than the presence or absence of mediastinal lymph node metastases. (Lim et al., 2010)

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 (Best et al., 1987). (SIGN, 2014)

Recommendation 2.3.2.1	Grade
Endoscopic assessment of the mediastinal lymph nodes with EBUS-TBNA with or without EUS-FNA should be offered to patients with suspected lung cancer prior to mediastinoscopy.	**A**

Good practice point

Negative EBUS does not entirely exclude nodal disease. Surgical staging is still indicated where EBUS-TBNA (EBUS-FNA) is negative if clinical suspicion of mediastinal nodal disease remains high.

Clinical question 2.3.3

In patients with pleural effusion and suspected lung cancer, what is the efficacy of pleural sampling in the diagnosis of lung cancer?

Evidence summary

A clinical guideline (SIGN, 2014) and a retrospective diagnostic study (Bielsa et al., 2008) addressed this clinical question.

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 (Dales et al., 1990). Some patients may require thoracoscopic biopsy to confirm pleural malignancy as aspiration and closed biopsy alone may be insufficient. (SIGN, 2014)

In instances where the first cytological analysis is not conclusive, a retrospective analysis of 1,427 patients with pleural effusion, including 466 patients with malignant pleural effusion (Bielsa et al., 2008) concluded that at least one more specimen should be submitted immediately for cytologic analysis and that delaying this secondary analysis will lead to a low diagnostic yield.

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%) (Metintas et al., 2010). (SIGN, 2014)

Recommendation 2.3.3.1	**Grade**
In patients being considered for active therapy, pleural effusion should be investigated with pleural aspiration.	**C**

Recommendation 2.3.3.2	**Grade**
If pleural fluid cytology is negative, and treatment will change depending on the nature of the pleural fluid, pleural biopsy using image guided or thoracoscopic biopsy is recommended.	**D**

Good practice point
Aim for 50 ml of pleural fluid and cell block preparation.

Clinical question 2.3.4

What is the role of palliative interventions in the management of malignant airway obstruction?

Evidence summary

A clinical guideline (NICE, 2011) and an UpToDate® review (Herth et al., 2016) addressed this clinical question.

There are a range of treatments to prevent or treat airway obstruction including conventional external beam radiotherapy, endobronchial surgical debulking of the cancer, stenting and endoscopic endobronchial treatments.

Choosing among the interventions is dependent upon factors including the nature of the lesion, predicted response to therapy, operator experience, available expertise, patient prognosis or health status, patient preference, and the ability of the patient to tolerate a selected procedure (Ernst et al., 2004, Bolliger et al., 2002, Ernst et al., 2003, Stephens and Wood, 2000, Seijo and Sterman, 2001). (Herth et al., 2016 - UpToDate®).

Endobronchial surgical debulking of the cancer can be undertaken using either rigid or flexible bronchoscopy. Advantages of rigid bronchoscopic procedures under general anaesthesia include the ability to remove large pieces of cancer, maintain adequate ventilation, and allow control of large volume haemorrhage. Nonetheless, flexible bronchoscopy is increasingly used for debulking procedures. These treatments are usually given to palliate symptoms and improve quality of life, but in some patients, relief of endobronchial obstruction will allow assessment for subsequent treatment with curative intent. (NICE, 2011)

Endobronchial techniques available are either a) used to debulk the cancer (brachytherapy, electrocautery, cryotherapy, thermal laser ablation and photodynamic therapy) or b) used to maintain/re-establish airway patency (endobronchial stenting). Thermal ablation, surgical debulking and stent insertion were all favoured options where immediate relief of endobronchial obstruction is required, especially if there is a relatively large cancer. Endobronchial debulking procedures are generally not suitable in cases where the predominant cause of airway obstruction is extrinsic compression. In such cases airway stenting to maintain/re-establish airway patency and/or external beam radiotherapy aimed at treating the surrounding cancer may be considered. External beam radiotherapy is effective in around two-thirds of patients and is less invasive than the other endobronchial treatments (NICE, 2011).

Recommendation 2.3.4.1	**Grade**
In lung cancer patients with symptomatic (including breathlessness, haemoptysis and cough) malignant airway obstruction, any of the following therapeutic interventions may be considered: bronchoscopic debulking, tumour ablation modalities, airway stent placement and radiotherapy (external beam or brachytherapy).	**D**

2.3.5 Staging algorithm for patients with suspected lung cancer

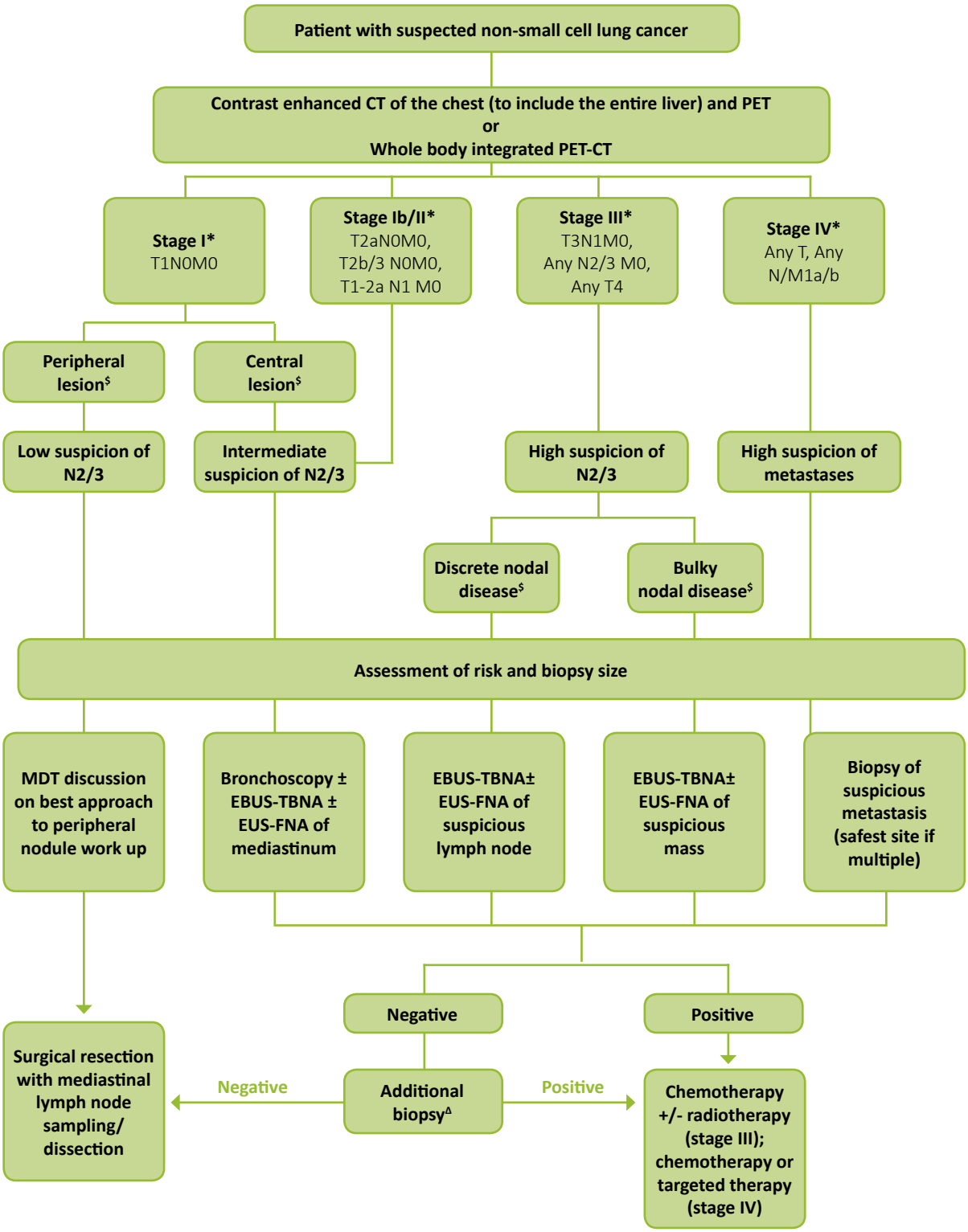

Figure 3. Staging algorithm in patients with suspected lung cancer. Modified from (Thomas and Gould, 2016).

For explanatory notes, see over page.

* Please note that this refers to the 7th edition of the IASLC TNM staging system.

$ Definitions:

Peripheral lesions	Normal mediastinal and N1 nodes (<1cm) and a peripheral tumour (within outer two-thirds of hemithorax) (Silvestri et al., 2013).
Central lesions	Normal mediastinal nodes (<1cm) but enlarged N1 nodes (≥ 1cm) or a central tumour (with proximal one-third of the hemithorax) (Silvestri et al., 2013).
Bulky nodal disease	Correlates with the radiographic group A, as described in the American College of Chest Physicians (ACCP) evidence-based Clinical Practice Guidelines (Silvestri et al., 2013). This group is defined as mediastinal infiltration, where the discrete lymph nodes cannot be distinguished or measured.
Discrete nodal disease	Correlates to radiographic group B, as described in the American College of Chest Physicians (ACCP) evidence-based Clinical Practice Guideline (Silvestri et al., 2013). This group is defined as patients with mediastinal node enlargement, in whom the size of the discrete nodes can be measured.

Δ Mediastinoscopy/video assisted mediastinoscopy/extended cervical mediastinoscopy/oesophageal ultrasound

2.4 Pathology

Responsibility for the implementation of pathology recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

The literature used in the development of this guideline was based on the 7th edition of the Lung Cancer TNM staging system. The 8th edition of the TNM staging system was published in December 2016 (Brierley et al., 2016), this may lead to changes in recommendations over time, which should be taken into consideration at multidisciplinary team meetings.

Pathology Terminology & Reporting
Guidance on the appropriate terminology for use in Biopsy/Cytological/Resections specimen reports is covered by the RCPath reporting proforma template (RCPath, 2016) and further detailed in the WHO Classification of Tumours of the Heart, Lung, Pleura Thymus and Heart (4th Edition, 2015).

Lung resection specimens
When reporting lung resection specimens use the information/terminology of the current RCPath template (Appendix - Histopathology reporting proforma for lung cancer resection specimens).

Lung biopsy/cytology specimens
When reporting lung biopsy/cytology specimens use the information/terminology of the current RCPath template (Appendix - Reporting proforma for lung cancer biopsy/cytology specimens.)

Good practice point
A comment should be included if there is insufficient tissue for molecular analysis in non-squamous non-small cell lung cancer (NSCLC).

Good practice point
The term bronchioloalveolar carcinoma (BAC) should be discontinued.

Clinical question 2.4.1

a) **What is the benefit of histopathological analysis for small-cell lung cancer (SCLC) vs non-small cell lung cancer (NSCLC)?**
b) **When should immunohistochemical analysis be performed?**
c) **What is the best panel(s) of immunohistochemical stains for NSCLC subtypes?**

Evidence summary
Clinical guidelines (Travis et al., 2011, SIGN, 2014) a diagnostic study (Bishop et al., 2010) and a review (Travis, 2002) addressed this clinical question.

a) Benefit of histopathological analysis for SCLC and NSCLC
Lung cancer can be divided into many subtypes, the most important distinction is between SCLC and NSCLC, this is important because of the major clinical differences in presentation, metastatic spread and response to therapy. Another important feature of the pathology of lung cancer is histologic heterogeneity, which consists of a mixture of histologic types that represents the derivation of lung cancer from a pluripotent stem cell. (Travis, 2002)

b) Purpose of immunohistochemical analysis
Immunohistochemistry should be used in all NSCLC cases which cannot be sub-typed on morphological grounds. (SIGN, 2014)

In cases where a specimen shows NSCLC lacking either definite squamous or adenocarcinoma morphology, immunohistochemistry may refine diagnosis (Travis et al., 2011).

Immunohistochemistry has been routinely used for separating metastatic tumours from primary lung cancers especially in patients with no known primary tumours, it is also becoming more important in the classification of primary lung tumours. Indeed, recent advances in targeted therapies (e.g. tyrosine kinase inhibitors and angiogenesis inhibitors) have made the distinction between adenocarcinomas and squamous cell carcinomas of the lung even more important (Besse et al., 2007, Cohen et al., 2007, Herbst, 2006, Herbst and Sandler, 2008, Johnson et al., 2004, Lam and Watkins, 2007) because not only are tyrosine kinase inhibitors more efficacious in adenocarcinomas than in squamous cell carcinomas, but also the use of antiangiogenic modalities can be associated with life-threatening pulmonary haemorrhage in squamous cell carcinomas (Besse et al., 2007, Herbst, 2006). (Bishop et al., 2010)

c) Immunohistochemical panel(s)
At the present time, thyroid transcription factor-1 (TTF-1) seems to be the single best marker for adenocarcinoma. TTF-1 provides the added value of serving as a pneumocyte marker that can help confirm a primary lung origin in 75 to 85% of lung adenocarcinomas (Motoi et al., 2008, Yatabe et al., 2002, Lau et al., 2002). This can be very helpful in addressing the question of metastatic adenocarcinoma from other sites such as the colon or breast. Diastase-periodic acid Schiff or mucicarmine mucin stains may also be of value. p63 is consistently reported as a reliable marker for squamous histology and CK5/6 also can be useful (Loo et al., 2010, Nicholson et al., 2010, Camilo et al., 2006, Wu et al., 2003, Chu and Weiss, 2002, Ordonez, 2000, Kaufmann and Dietel, 2000, Kargi et al., 2007, Khayyata et al., 2009). (Travis et al., 2011)

Napsin A appears to be a useful marker when used in combination with TTF-1 as it provides increased sensitivity and specificity for both classifying primary lung tumours as adenocarcinoma and for identifying lung origin in the setting of a metastatic adenocarcinoma (Bishop et al., 2010).

It is possible that cocktails of nuclear and cytoplasmic markers (TTF-1/CK5/6 or p63/napsin-A) may allow for use of fewer immunohistochemical studies of multiple antibodies (Rossi et al., 2009a). (Travis et al., 2011)

Strategic use of small biopsy and cytology samples is important, i.e., use the minimum specimen necessary for an accurate diagnosis, to preserve as much tissue as possible for potential molecular studies (Suh et al., 2011). Methods that use substantial amounts of tissue to make a diagnosis of adenocarcinoma versus squamous cell carcinoma, such as large panels of immunohistochemical stains or molecular studies, may not provide an advantage over routine light microscopy with a limited immunohistochemical workup (Rossi et al., 2009b). (Travis et al., 2011)

Immunohistochemical stains to distinguish between primary lung adenocarcinoma and squamous cell carcinoma are p63, p40, CK 5/6 (present in squamous cell carcinoma) and TTF-1, Napsin A (present in adenocarcinoma).

Every effort should be made, during the diagnostic phase, to preserve tumour material for molecular biomarker analysis. (SIGN, 2014)

Recommendation 2.4.1.1	**Grade**
Distinguishing between small-cell carcinoma and non-small cell carcinoma of the lung is recommended. For challenging cases, a diagnostic panel of immunohistochemical assays is recommended to increase the diagnostic accuracy.	**B**

Recommendation 2.4.1.2	**Grade**
In individuals with pathologically diagnosed non-small cell cancer (NSCLC), additional discrimination between adenocarcinoma and squamous cell carcinoma, even on cytologic material or small tissue samples is recommended.	**B**

Good practice point
Recommended immunohistochemical stains to distinguish between NSCLC/SCLC/Lymphoma include: Keratin, CD56, TTF – 1, CD45, Ki – 67 and synaptophysin.

Good practice point
Use of neuron specific enolase (NSE) is **not** recommended.

Good practice point
Recommended immunohistochemical stains to distinguish between primary lung adenocarcinoma and squamous cell carcinoma are p63, p40, CK 5/6 (present in squamous cell carcinoma) and TTF-1, Napsin A (present in adenocarcinoma).

Good practice point
Judicious use of tissue is extremely important and non- discriminatory immunostains and levels should be avoided.

Clinical question 2.4.2

What is the efficacy of the following diagnostic tools in identifying and staging lung cancer?
- **ROSE at EBUS**
- **Frozen section**

Evidence summary
A clinical guideline (Travis et al., 2011), two randomised controlled trials (Oki et al., 2013, Trisolini et al., 2011) and a diagnostic study (Marchevsky et al., 2004) addressed this clinical question.

ROSE at EBUS
A randomised controlled trial (RCT) was conducted in 2013 (Oki et al., 2013) to evaluate the efficacy of rapid on-site evaluation (ROSE) during endobronchial ultrasound guided-transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of lung cancer. One hundred and twenty patients suspected of having lung cancer with hilar/mediastinal lymphadenopathy were randomised to undergo EBUS-TBNA with or without ROSE. The sensitivity and accuracy for diagnosing lung cancer were 88% and 89% in the ROSE group, and 86% and 89% in the non-ROSE group, respectively. No complications were associated with the procedures. Additional procedures including EBUS-TBNA for lesions other than the main target lesion and/or transbronchial biopsy in the same setting were performed in 11% of patients in the ROSE group and 57% in the non-ROSE group ($p<0.001$). Mean puncture number was significantly lower in the ROSE group (2.2 vs. 3.1 punctures, $p<0.001$), and mean bronchoscopy time was similar between both groups (22.3 vs. 22.1 min, $p=0.95$). The authors concluded that ROSE during EBUS-TBNA is associated with a significantly lower need for additional bronchoscopic procedures and puncture number.

In addition an RCT of 168 patients with enlarged lymph nodes were randomised to undergo TBNA with or without ROSE (Trisolini et al., 2011). There was no significant difference between the TBNA group and the ROSE group in terms of diagnostic yield (75% vs 78%, respectively; $p=0.64$), and percentage of adequate specimens (87% vs 78%, respectively; $p=0.11$). However, similar to the findings reported by Oki et al. (2013), the complication rate of bronchoscopy was significantly lower in patients undergoing on-site review (6% vs 20%; $p=0.01$), whereas the complication rate of TBNA was similar among the study groups.

Frozen section
For a limited resection to be adequate oncologically, a precise pre- and intra-operative diagnosis is critical. The accuracy of intra-operative frozen section analysis in determining whether small lung adenocarcinomas have an invasive component still needs to be defined. The predictive value of frozen section ranges from 93% to 100% but not all articles clearly report the accuracy of frozen section analysis (Yamato et al., 2001, Yamada and Kohno, 2004, Yoshida et al., 2005, Watanabe et al., 2005). In addition, evaluation of margins by frozen section may be problematic, especially when stapler cartridges have been used on both sides. Scraping or washing of staple lines with subsequent cytological analysis has been attempted (Higashiyama et al., 2003, Utsumi et al., 2010). When a sublobar resection is performed, frozen section analysis of an interlobar, hilar, or any suspicious lymph node is a useful staging evaluation, and when positive nodes are found, a lobectomy is indicated when there is no functional cardiopulmonary limitation. (Travis et al., 2011)

Marchevsky et al., (2004) reviewed the frozen section diagnoses of 183 consecutive pulmonary nodules smaller than 1.5 cm in diameter and calculated the sensitivity, specificity, and predictive values of this diagnostic procedure. One hundred and seventy four nodules were correctly classified by frozen section as neoplastic or non-neoplastic, six lesions were diagnosed equivocally, and two neoplasms were missed owing to sampling errors. The sensitivities for a diagnosis of neoplasia were 86.9% and 94.1% for nodules smaller than 1.1 cm in diameter and measuring 1.1 to 1.5 cm, respectively. The diagnostic accuracy of frozen sections was significantly better in nodules larger than 1.0 cm in diameter ($p=0.05$). There were no false-positive diagnoses of malignancy, resulting in 100% specificity.

Intraoperative consultation with frozen section is a sensitive and specific procedure for the diagnosis of malignancy from small pulmonary nodules. The distinction between lepidic pattern adenocarcinoma and atypical adenomatous hyperplasia, and of small peripheral carcinoid tumours from other lesions, can be difficult by frozen section (Marchevsky et al., 2004).

Recommendation 2.4.2.1	**Grade**
Endobronchial ultrasound rapid on-site evaluation (EBUS ROSE) should be made available whenever resources permit.	**B**

Recommendation 2.4.2.2	**Grade**
Consider intra–operative frozen section analysis in primary diagnosis when preoperative diagnosis is not available.	**C**

Recommendation 2.4.2.3	**Grade**
In selected cases intra-operative frozen section analysis for staging may be considered.	**C**

Clinical question 2.4.3

In patients with NSCLC, how do cytological samples compare with tissue biopsy samples for tumour sub-typing, immunohistochemistry and predictive markers assessed by FISH or mutational analysis?

Evidence summary

Two clinical guidelines (Travis et al., 2011, Lindeman et al., 2013) addressed this clinical question.

Cytology is a powerful tool in the diagnosis of lung cancer, in particular in the distinction of adenocarcinoma from squamous cell carcinoma (Rivera et al., 2007). In a recent study of 192 preoperative cytology diagnoses, definitive versus favoured versus unclassified diagnoses were observed in 88% versus 8% versus 4% of cases, respectively (Rekhtman et al., 2011). When compared with subsequent resection specimens, the accuracy of cytologic diagnosis was 93% and for definitive diagnoses, it was 96%. For the adenocarcinoma and squamous cell carcinoma cases, only 3% of cases were unclassified, and the overall accuracy was 96%. When immunohistochemistry was used in 9% of these cases, the accuracy was 100% (Rekhtman et al., 2011). (Travis et al., 2011)

Whenever possible, cytology should be used in conjunction with histology in small biopsies (Nicholson et al., 2010, Sigel et al., 2011). In another study where small biopsies were evaluated in conjunction with cytology for the diagnosis of adenocarcinoma versus squamous cell carcinoma versus unclassified non-small cell lung cancer-not otherwise specified (NSCLC-NOS), the result for cytology was 70% versus 19% versus 11% and for biopsies, it was 72%, 22%, and 6%, respectively (Sigel et al., 2011). Still when cytology was correlated with biopsy, the percentage of cases diagnosed as NSCLC-NOS was greatly reduced to only 4% of cases (Sigel et al., 2011). In a small percentage of cases (<5%), cytology was more informative than histology in classifying tumours as adenocarcinoma or squamous cell carcinoma (Sigel et al., 2011). The factors that contributed the greatest to difficulty in a specific diagnosis in both studies were poor differentiation, low specimen cellularity, and squamous histology (Rekhtman et al., 2011, Sigel et al., 2011). (Travis et al., 2011)

Small biopsies and/or cytologic samples including pleural fluids can be used for many molecular analyses (Rekhtman et al., 2011, Zhang et al., 2008, Wu et al., 2008, Li et al., 2008, Lim et al., 2009, Savic et al., 2008, Miller et al., 2008, Kimura et al., 2006, Borczuk et al., 2004, Zudaire et al., 2008, Gordon et al., 2003, Solomon et al., 2010, Asano et al., 2006, Otani et al., 2008). Epidermal growth factor receptor (EGFR) mutation testing and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation testing are readily performed on these specimens (Rekhtman et al., 2011, Sigel et al., 2011, Zhang et al., 2008, Li et al., 2008, Lim et al., 2009, Savic et al., 2008, Miller et al., 2008, Kimura et al., 2006, Solomon et al., 2010, Asano et al., 2006, Otani et al., 2008). Formalin fixed paraffin-embedded samples can be used effectively for polymerase chain reaction-based mutation testing and for fluorescence in situ hybridisation (FISH) or chromogenic in situ hybridisation (CISH) testing for gene amplification and for immunohistochemistry. Cytology smears can be analysed for immunohistochemical and certain molecular studies, but it is far preferable if cell blocks are available. (Travis et al., 2011)

Specimen requirements for anaplastic lymphoma kinase fluorescence in situ hybridisation (ALK FISH) are generally similar to those for EGFR mutation testing: formalin fixation is acceptable, specimens should have enough cancer cells to analyse clearly, and DNA-damaging fixatives or acidic decalcifying agents should be avoided, as should specimens with abundant necrosis. Unlike EGFR mutation testing, however, FISH testing can be problematic when performed on alcohol fixed samples. (Lindeman et al., 2013)

Recommendation 2.4.3.1	**Grade**
Cytology samples can be used to provide material suitable for both NSCLC sub-typing and some molecular analysis, provided the samples are appropriately handled and processed.	**B**

Good practice point
When paired cytology and biopsy specimens exist, a review of both modalities is advised if there is discordance.

Good practice point
In general, immunohistochemistry work-up should not be duplicated on both samples.

Good practice point
ALK FISH can be problematic when performed on alcohol-fixed samples.

Clinical question 2.4.4

What are optimal formalin fixation times for future molecular diagnostics?

Evidence summary

A clinical guideline (Lindeman et al., 2013) addressed this clinical question.

Processing specimens for epidermal growth factor receptor (EGFR) mutation testing

The relatively broad time range of specimen fixation found in pathology practice usually has no effect on morphologic details, but longer durations of fixation adversely affect the quality of nucleic acid (Srinivasan et al., 2002). Fixation times of 6 to 12 hours for small biopsy samples and 8 to 18 hours for larger surgical specimens generally give best results, although expert consensus opinion is that fixation times of 6 to 48 hours should give acceptable results (Wolff et al., 2007, College of American Pathologists, 2012). This is a generalisation, however, and the effect of extreme fixation times should be assessed by each laboratory during validation. This knowledge should be incorporated into the interpretation and reporting of molecular pathology results when fixation times are extreme. (Lindeman et al., 2013)

Methods for anaplastic lymphoma kinase (ALK) testing

Specimen requirements for anaplastic lymphoma kinase fluorescence in situ hybridisation (ALK FISH) are generally similar to those for EGFR mutation testing: formalin fixation is acceptable, specimens should have enough cancer cells to analyse clearly, and DNA-damaging fixatives or acidic decalcifying agents should be avoided, as should specimens with abundant necrosis. (Lindeman et al., 2013)

Recommendation 2.4.4.1	Grade
Fixation times of 6 to 12 hours for small biopsy samples and 8 to 18 hours for larger surgical specimens generally give best results, although expert consensus opinion is that fixation times of 6 to 48 hours should give acceptable results.	**D**

2.5 Surgery

Responsibility for the implementation of surgery recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

The literature used in the development of this guideline was based on the 7th edition of the Lung Cancer TNM staging system. The 8th edition of the TNM staging system was published in December 2016 (Brierley et al., 2016), this may lead to changes in recommendations over time, which should be taken into consideration at multidisciplinary team meetings.

Clinical question 2.5.1

In patients with stage I & II non-small cell lung cancer (NSCLC) how does the extent of lung resection effect outcomes?

Evidence summary

A clinical guideline (SIGN, 2014) and a prospective, multicentre, randomised trial (Ginsberg and Rubinstein, 1995) addressed this clinical question.

Lobectomy is an anatomical resection of the lung which includes resection of the lymphatic drainage, N1 and N2 nodes.

Sublobar resections include segmentectomy and wedge resections and may not deliver complete lymphatic drainage with N1 clearance. Segmentectomy and wedge resection procedures are not consistently defined in the literature making comparative review of outcomes difficult to interpret.

In 1995, the Lung Cancer Study Group reported on the only randomised trial of elective sublobar resection vs. lobectomy (Ginsberg and Rubinstein, 1995). This prospective, multicentre randomised trial compared limited resection with lobectomy for patients with peripheral T1 N0 non-small cell lung cancer documented at operation, 247 of 276 randomised patients were considered eligible for analysis. No significant differences were observed for all stratification variables, selected prognostic factors, perioperative morbidity, mortality, or late pulmonary function. In patients undergoing limited resection, there was an observed 75% increase in recurrence rates (p=0.02, one-sided) attributable to an observed tripling of the local recurrence rate (p=0.008 two-sided), an observed 30% increase in overall death rate (p=0.08, one-sided), and an observed 50% increase in death with cancer rate (p=0.09, one-sided) compared to patients undergoing lobectomy (p=0.10, one-sided was the predefined threshold for statistical significance for this equivalency study). The authors concluded that when compared with lobectomy, limited pulmonary resection does not confer improved perioperative morbidity, mortality, or late postoperative pulmonary function. Because of the higher death rate and locoregional recurrence rate associated with limited resection, lobectomy still must be considered the surgical procedure of choice for patients with peripheral T1 N0 non-small cell lung cancer.

Lobectomy is preferred to sub-lobar resection and segmentectomy is superior to non-anatomical wedge resection on the basis of a reduced recurrence rate (Ginsberg and Rubinstein, 1995), except in patients who are of marginal fitness (SIGN, 2014).

Lobectomy remains the procedure of choice for fit patients. (SIGN, 2014)

Recommendation 2.5.1.1	**Grade**
For patients with clinical stage I and II non-small cell lung cancer (NSCLC) who are medically fit for surgical resection, a lobectomy rather than sublobar resection is recommended.	**B**

Good practice point

Offer more extensive surgery (bronchoangioplastic surgery, bilobectomy, pneumonectomy) if anatomically required to achieve clear margins.

Clinical question 2.5.2

In patients with clinical stage I NSCLC undergoing lobectomy, how does video-assisted thoracic surgery (VATS) compare to thoracotomy?

Evidence summary

A clinical guideline (SIGN, 2014) addressed this clinical question.

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 (Ng et al., 2007, Paul et al., 2010, Whitson et al., 2008, Flores et al., 2009). Survival rates at two and five years are comparable (Whitson et al., 2008, Flores et al., 2009, Yang et al., 2009). 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 (Cattaneo et al., 2008). All evidence identified related to stage I disease rather than later stages. VATS is comparable to open surgery for systematic node dissection in terms of numbers of nodes dissected, operative mortality, morbidity and recurrence (Watanabe et al., 2005). (SIGN, 2014)

Recommendation 2.5.2.1	Grade
For patients with clinical stage I NSCLC, video-assisted thoracic surgery (thoracoscopy) should be considered as an alternative to thoracotomy for anatomic pulmonary resection.	**B**

Clinical question 2.5.3

Which pulmonary function tests should be used to determine fitness for resection?

Evidence summary

Two clinical guidelines (SIGN, 2014, Lim et al., 2010) addressed this clinical question.

Evaluation of lung function is an important aspect of preoperative assessment to estimate the risk of operative mortality and impact of lung resection on quality of life, especially in relation to unacceptable post-resection dyspnoea. (Lim et al., 2010)

FEV_1/D_{LCO}

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 (T_{LCO}) for surgery. Many of these studies had small sample sizes (Lim et al., 2010). To increase resection rates it may be necessary to look at patients with ppo FEV_1 and T_{LCO} of less than 30%. It may also be important to consider patients with poor FEV_1s preoperatively, such as patients considered for lung reduction surgery (Lim et al., 2006). These patients would represent a select group and would need careful preoperative assessment which may involve perfusion scanning and pulmonary artery pressure measurement (Lim et al., 2010). (SIGN, 2014)

Patients who perform well at the six minute walk or shuttle test, but have ppo FEV_1 or T_{LCO} 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 (Ginsberg and Rubinstein, 1994). (SIGN, 2014)

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. (SIGN, 2014)

VO_2 max

A meta-analysis has confirmed the finding that lower levels of VO_2 max are associated with increasing 'complications' after lung resection (Benzo et al., 2007). However, numerous values have been used to define 'prohibitive risk' for lung surgery, and the studies are difficult to interpret owing to the widespread use of composite endpoints. When scrutinised, individual endpoints included lobar collapse, high levels of carbon dioxide tension (PCO_2), arrhythmia and readmission to ICU. It is doubtful that many patients would consider the risk of developing these complications as 'prohibitive' for surgical resection. (Lim et al., 2010)

With sample sizes ranging from 8 to 160 patients (Benzo et al., 2007) and an average death rate of 2.6% for lobectomy, the discriminating cut-off points for VO_2 max to predict death is likely to be poor and, without valid risk adjustment, it is not possible to estimate an independent contribution of VO_2 max. The arbitrary use of cut-off values for defining patient groups with no adverse outcome carries a large degree of imprecision; for example, the 95% binomial CI of no adverse outcomes in a typical sample of 30 patients would be 0-13.6%. (Lim et al., 2010)

Perhaps the best conducted study was the Cancer and Leukemia Group B (CALBG) Protocol 9238 in which 403 patients were classified into low, high and very high risk groups. Of the 68 patients in the very high risk group (VO_2 max <15 ml/ kg/min), surgery was only undertaken at the 'physician's discretion' with an operative mortality rate of 4% and no difference in postoperative complication rate. A central message from this study was that, in patients in the very high risk subgroup who underwent lung resection, the median survival was 36 months compared with 15.8 months for those in the same risk group who did not undergo surgical resection ($p<0.001$) (Loewen et al., 2007). The evidence for cardiopulmonary exercise

testing providing a useful definition of 'high risk' is therefore limited and there are no data available to show how it can help predict unacceptable levels of postoperative dyspnoea. (Lim et al., 2010)

Stair Test

A number of authors have reported on the association between stair climbing and surgical outcomes (Holden et al., 1992, Olsen et al., 1991, Von Nostrand et al., 1968, Girish et al., 2001, Brunelli et al., 2002). However, the data are difficult to interpret as there is a lack of standardisation of the height of the stairs, the ceiling heights, different parameters used in the assessment (e.g. oxygen saturations, extent of lung resection) and different outcomes. (Lim et al., 2010)

Shuttle Walk

The shuttle walk test is the distance measured by walking a 10 m distance usually between two cones at a pace that is progressively increased. This test has good reproducibility and correlates well with formal cardiopulmonary exercising testing (VO_2 max) (Singh et al., 1994, Morgan, 1989). Previous British Thoracic Society (BTS) recommendations that the inability to walk 25 shuttles classifies patients as high risk has not been reproduced by a prospective study (Win et al., 2004). Some authors report that shuttle walk distance may be useful to stratify low-risk groups (ability to walk >400 m) who would not need further formal cardiopulmonary exercise testing (Win et al., 2006). (Lim et al., 2010)

Recommendation 2.5.3.1	**Grade**
Pulmonary function testing (spirometry, diffusion capacity, lung volume) should be performed in all patients being considered for surgical resection.	**C**

Recommendation 2.5.3.2	**Grade**
Postoperative predictive values should be calculated using broncho-pulmonary segment counting. If a mismatch is suspected ventilation perfusion scan should be performed.	**C**

Recommendation 2.5.3.3	**Grade**
Offer patients surgery if they have an FEV_1 & D_{LCO} within normal limits (postoperative predicted values >60%).	**C**

Recommendation 2.5.3.4	**Grade**
Patients with ppo-FEV_1 and/or D_{LCO} <30% should have formal cardiopulmonary exercise testing with measurement of VO_2 max.	**C**

Recommendation 2.5.3.5	**Grade**
Patients with ppo-FEV_1 and/or D_{LCO} >30% and <60% – supplementary functional exercise assessments should be considered.	**D**

Recommendation 2.5.3.6	**Grade**
In patients with lung cancer being considered for surgery and a VO_2 max <15mL/kg/min predicted, it is recommended that they are counselled about minimally invasive surgery, sublobar resections or non-operative treatment options for their lung cancer.	**C**

Clinical question 2.5.4

In patients with lung cancer, how should non-pulmonary co-morbidity influence surgical selection?

Evidence summary

A clinical guideline (Lim et al., 2010) and a validation study (Falcoz et al., 2007) addressed this clinical question.

Patient demographics and risk-factors for lung cancer contribute to significant co-morbidities in our surgical candidate population. This has implications for surgical case selection and outcomes.

For patients who had undergone prior coronary bypass surgery, the risk of death and myocardial infarction was observed to be reduced from 5.8% and 1.9% to 2.4% and 1.2%, respectively (Eagle et al., 1997). (Lim et al., 2010)

The current evidence base that guides clinical management of the specific thoracic surgical patient with coronary artery disease is limited. (Lim et al., 2010)

Thoracoscore is a multifactorial risk assessment model to predict in-hospital mortality in various thoracic procedures. The model was first published by the French Society of Thoracic and Cardiovascular Surgery (Falcoz et al., 2007). Thoracoscore is recommended for use in the UK by the 'British Thoracic Society' and the 'National Institute for Health and Care Excellence' (NICE). However, a recent multicentre prospective study (Sharkey et al., 2015) aimed to evaluate Thoracoscore as a valid tool for use in patients undergoing lung resection at six UK centres. They found the mean thoracoscore was 2.66%, almost double the observed mortality of 1.38%. However, mean thoracoscore for the patients who died was statistically significantly higher than those who survived, 4.01% versus 2.64% ($p<0.001$).

A history (including assessment of functional status), physical examination and resting ECG are prerequisites for cardiac risk assessment. All patients with an audible murmur or unexplained dyspnoea should also have an echocardiogram. The first step in cardiac risk assessment is to identify patients with an active cardiac condition, as they all require evaluation by a cardiologist and correction before surgery. (Lim et al., 2010)

In patients who do not have an active cardiac condition, risk assessment is performed using the revised cardiac index.

Table 5, shows a validated model with receiver operator characteristic (ROC) area under the curve (AUC) of 0.81 (Lee et al. 1999). (Lim et al., 2010)

Table 5. Revised cardiac risk index

Number of Factors	Risk of Major Cardiac Complication*
0	0.4%
1	1%
2	7%
≥3	11%

Risk factors: high-risk type of surgery (includes all thoracic surgery), ischaemic heart disease, history of congestive cardiac failure, history of cerebrovascular disease, insulin therapy for diabetes, preoperative serum creatinine >177 mmol/l.

*Cardiac complications defined as myocardial infarction, pulmonary oedema, ventricular fibrillation or primary cardiac arrest, complete heart block. The risks have been quoted from the validation cohort.

Patients with ≤2 risk factors and good cardiac functional capacity (able to climb a flight of stairs without cardiac symptoms) can proceed to surgery without further investigations. Patients with poor cardiac functional capacity or with ≥3 risk factors should have further investigations to screen for reversible cardiac ischaemia (e.g. exercise stress testing, exercise thallium scan) and, if necessary, cardiology review prior to surgery. (Lim et al., 2010)

Recommendation 2.5.4.1	**Grade**
Lung cancer surgery remains the best opportunity for potential cure in patients with significant co-morbidity. Efforts to contain and manage that risk should start with preoperative scoring (thoracoscore) and should ideally include attendance at a preoperative assessment clinic, where practical.	**D**

Recommendation 2.5.4.2	**Grade**
Seek a cardiology review in patients with an active cardiac condition or ≥3 risk factors or poor cardiac functional capacity.	**C**

Recommendation 2.5.4.3	**Grade**
Offer surgery without further investigations to patients with ≤2 risk factors and good cardiac functional capacity.	**B**

Good practice point
All anatomically resectable patients should be seen by a surgeon before they are deemed surgically unfit.

Clinical question 2.5.5

Should lung cancer surgery be offered to octogenarians?

Evidence summary

A clinical guideline (British Thoracic Society, 2001) and a non-systematic review (Weinmann et al., 2003) addressed this clinical question.

Most studies in octogenarians (80 years and over) are small and involve patients presenting with stage I disease treated by lobectomy or more limited resection. Earlier studies suggested a high perioperative mortality rate (Shirakusa et al., 1989) but more recent reports suggest this has fallen, reflecting a similar fall in operative mortality seen previously in less elderly patients (Tanita et al., 1995; Pagni et al., 1997). (British Thoracic Society, 2001)

A non-systematic review of 37 studies of surgery in the elderly with NSCLC (Weinmann et al., 2003) concluded that careful preoperative assessment of a patient including vigorous techniques of improvement of their physical and mental status are a must for a successful treatment outcome in elderly patients with lung cancer.

Recommendation 2.5.5.1	Grade
Age >80 years should not automatically preclude surgery. Decisions should be based on oncological stage, co-morbidity and physiological testing.	**D**

Clinical question 2.5.6

In patients with NSCLC what is the optimum surgical approach for?

a) Multifocal tumours

b) Synchronous tumours

Evidence summary

A clinical guideline (Kozower et al., 2013) addressed this clinical question.

Multifocal

The literature is limited in this area and pathological definitions have evolved recently.

The approach used here is to define such patients according to clinical features as opposed to pathologic features, which generally are not available until after treatment (i.e., resection) has been carried out. Multifocal lung cancers (MFLCs) are defined as multiple lesions arising from ground glass opacities (GGOs), which may have or develop a solid component. There may be a limited number or multiple lesions. The following patients are also included: those with a GGO lesion suspected or proven to be malignant and other small GGO lesions that are more likely adenomatous alveolar hyperplasia (AAH) than an invasive carcinoma because data suggest that AAH is a precursor to such tumours (Kakinuma et al., 2004, Nakata et al., 2004, Travis et al., 2005). Including such patients also satisfies the need for a clinically applicable definition. At the other end of the spectrum are patients with an infiltrative pattern of disease either confined to a particular area (segment or lobe) or appearing diffusely in the lung parenchyma (also called pneumonic type of adenocarcinoma). These conditions should also be included among multifocal cancers. (Kozower et al., 2013)

There is a growing body of data that demonstrates excellent survival after resection of small solitary GGO lesions (Howington et al., 2013). Furthermore, data support that sublobar resection of single lesions presenting as a GGO is adequate. Much fewer data have been published on the outcome of patients with multiple cancers presenting as GGO lesions (i.e., multifocal cancers). Good survival and a low recurrence rate after resection of MFLC have been reported (Kim et al., 2009, Park et al., 2009). (Kozower et al., 2013)

It is reasonable to suggest that limited resection of MFLCs should be performed. This is supported by the good outcomes of limited resection for single GGO lesions (Howington et al., 2013), the perception of a decreased propensity for nodal and systemic metastases, an increased propensity to develop new pulmonary foci of cancer, and the need to preserve lung parenchyma when patients present with multiple lesions. The good survival that is reported after resection argues for an aggressive, curative-intent approach rather than palliative treatment. (Kozower et al., 2013)

Often, patients with MFLC also have lesions not believed to be malignant (i.e. < 10 mm pure GGO lesions, which are AAH in the majority). We suggest that these patients be approached according to the data available for isolated lesions with the same characteristics (Pastorino et al., 2003). Lesions that are sufficiently suspicious of being malignant should prompt treatment, whereas those that are not should continue to be observed. (Kozower et al., 2013)

Synchronous

The term synchronous tumour refers to two separate primary lung cancers occurring at the same time. The distinction from metastatic disease may be clear when there are two separate histological subtypes. Where the same subtype is in both lesions, the criteria proposed by Martini and Melamed (1975) can be useful (Kozower et al., 2013).

The survival of patients with synchronous primary lung cancer is fairly variable, suggesting that a thoughtful approach is necessary in classifying two synchronous foci of cancer as two separate primary lung cancers. (Kozower et al., 2013)

Approximately 60% of synchronous primary lung cancer reported in the past 25 years are squamous cell cancers, and in about 60% of the cases, the tumours are of the same histologic type (Van Bodegom et al., 1989, Deschamps et al., 1990, Rosengart et al., 1991, Antakli et al., 1995, Ribet and Dambron, 1995, Lee et al., 2008, Ferguson et al., 1985). (Kozower et al., 2013)

The average 5-year survival of patients who undergo resection is only about 25%, and that of patients with pathological stage I disease is about 40%. Nevertheless, this appears to be better than the natural history of untreated lung cancer (Detterbeck and Gibson, 2008). In the absence of distant metastases, lymph node involvement, or evidence that the second focus of cancer is a metastasis, resection is preferable to observation according to the available data. (Kozower et al., 2013)

Recommendation 2.5.6.1	**Grade**
Multifocal In patients with suspected or proven multifocal lung cancer (without mediastinal or extrapulmonary disease), curative-intent treatment may be considered, following discussion at a multidisciplinary team meeting.	**D**

Recommendation 2.5.6.2	**Grade**
Synchronous In patients with suspected or proven synchronous primary lung cancers (without mediastinal or extrapulmonary disease), curative-intent treatment may be considered, following discussion at a multidisciplinary team meeting.	**C**

Clinical question 2.5.7

In patients with NSCLC, what is the optimal lymph node strategy at surgical resection?

Evidence summary

A clinical guideline (Lim et al., 2010) and a randomised controlled trial (Darling et al., 2011) addressed this clinical question.

The British Thoracic Society states that systematic mediastinal lymph node dissection is the removal of all present and accessible N1 and N2 lymph nodes. The Union for International Cancer Control (UICC) recommends that at least six lymph node stations should be removed or sampled before the confirmation of pN0 status (Goldstraw, 2009). Three of these nodes/stations should be mediastinal (including the subcarinal station) and three should be from N1 stations (Lim et al., 2010).

There is considerable variation in practice, from no lymph node sampling through lobe-specific sampling to systematic nodal dissection. Postoperative morbidity is usually cited against the use of routine systematic nodal dissection and, in response to this, the results of the American ACOSOG Z30 trial confirm that patients randomised to complete mediastinal lymphadenectomy had little added morbidity compared with those who underwent lymph node sampling (Allen et al., 2006). Two trials comparing systematic nodal dissection with lymph node sampling reported better survival in patients randomised to systematic nodal dissection (Izbicki et al., 1995, Wu et al., 2002). (Lim et al., 2010)

Mediastinal lymph node dissection (MLND) does not improve long-term survival in patients with early-stage (T1 or T2, N0 or nonhilar N1) NSCLC who have pathologically negative mediastinal and hilar nodes after rigorous systematic preresection lymph node sampling. In such patients, mediastinal lymph node dissection also does not affect the rate of local or regional recurrence. Darling et al. states that the results do not apply to patients with T3 or T4 tumours or those with known hilar or N2 disease because they were not included in the study. Staging by PET-CT or CT alone is not equivalent to the invasive staging performed in this study, and surgeons cannot use this study to justify excluding invasive mediastinal staging from their evaluation of patients with early-stage NSCLC. (Darling et al., 2011)

Mediastinal lymph node dissection provides patients with the most accurate staging and the opportunity for adjuvant therapy if occult metastatic disease is present. Because current preoperative staging cannot definitively identify patients with mediastinal lymph node involvement, and because patients with known hilar or mediastinal disease (N2) or with T3 or T4 tumours may benefit from mediastinal lymph node dissection because the pre-test probability of N2 disease is higher, we still recommend that all patients with resectable NSCLC undergo mediastinal lymph node dissection because the procedure does not increase mortality or morbidity. (Darling et al., 2011)

Recommendation 2.5.7.1	**Grade**
Systematic mediastinal lymph node dissection should be performed in all patients having a lung cancer resection.	**B**

Clinical question 2.5.8

In patients with malignant pleural effusion associated with lung cancer, what is the best treatment strategy?

Evidence summary

A clinical guideline (SIGN, 2014) and an UpToDate® review (Light and Doelken, 2015) addressed this clinical question.

In patients with malignant pleural effusion whose symptoms improve following fluid drainage, a number of options are available depending on performance status and documentation of lung re-expansion. (Light and Doelken, 2015)

The optimal technique for pleurodesis in malignant pleural effusion has been investigated in a Cochrane review (Shaw and Agarwal, 2004). 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. (SIGN, 2014)

There is evidence to support the use of tunnelled pleural catheters in the management of malignant pleural effusions when talc pleurodesis is not possible (Sabur et al., 2013, Suzuki et al., 2011, Thornton et al., 2010, Tremblay and Michaud, 2006). 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 (Sudharshan et al., 2011). 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 (Janes et al., 2007). Spontaneous pleurodesis occurred in up to 25% of cases. Very few cases of pleural infection secondary to the drain have been reported (Janes et al., 2007). Achieving complete lung re-expansion prior to pleurodesis remains the most important prerequisite for success. (SIGN, 2014)

Serial thoracentesis is commonly practiced.

Recommendation 2.5.8.1	Grade
In patients with malignant pleural effusion whose symptoms improved following drainage, a number of options are available depending on performance status and documentation of lung re-expansion:	
- In patients with good performance status with lung re-expansion, thoracoscopy with talc pleurodesis is recommended.	**C**
- In patients with non-expandable lung, tunnelled catheters may be considered.	**C**
- In patients with poor performance status with lung re-expansion, options include: tunnelled pleural catheter, serial thoracentesis, or bedside talc pleurodesis.	**D**

Clinical question 2.5.9

Should surgical resection be considered in patients with NSCLC, who have treatable isolated brain or adrenal metastases at the time of presentation?

Evidence summary

A best evidence topic (Modi et al., 2009) including eleven retrospective studies (1,035 patients) addressed the treatment of brain metastases, and a retrospective study (Raz et al., 2011) addressed the issue of treatment of adrenal metastases in this clinical question.

Brain metastasis

A best evidence topic (Modi et al., 2009) including eleven retrospective studies (Bonnette et al., 2001, Getman et al., 2004, Penel et al., 2001, Mussi et al., 1996, Iwasaki et al., 2004, Girard et al., 2006, Wronski et al., 1995, Mozami et al., 2002, Furak et al., 2005, Billing et al., 2001, Abrahams et al., 2001) addressed the issue of surgical resection of the primary tumour in patients with NSLC and cerebral metastases. In these studies, the median survival for the curative intent groups (bifocal therapy ± adjuvant treatment) ranged from 19 to 27 months (mean=23.12±3.3 months) and at 1, 2 and 5 years from 56% to 69% (mean= 63.9±5.6%), 28% to 54% (mean= 38.7±11%) and 11% to 24% (mean=18±5.7%), respectively. In comparison, the median and 1-year survival of the palliative groups were 7.1–12.9 months (mean=10.3±2.9 months) and 33–39.7% (mean= 35.3±3.8%), respectively. The study concluded that in the absence of mediastinal lymph node involvement, surgical resection of NSCLC with complete resection of the brain metastasis improves prognosis.

Adrenal

Raz et al. (2011) identified 37 patients with isolated adrenal metastasis from NSCLC. Twenty patients underwent adrenalectomy. Patients did not undergo adrenalectomy owing to suspicion of N2 disease, medical comorbidities, or patient preference. Seven patients (35%) treated surgically had tumours that were ipsilateral to their primary tumour, and eight (40%) had metachronous metastases. Five-year overall survival was 34% for patients treated operatively and 0% for patients treated nonoperatively p=0.002). Among patients treated with adrenalectomy, patients with ipsilateral metastases had a 5-year survival of 83% compared with 0% for patients with contralateral metastases (p=0.003). Patients without mediastinal nodal disease had a 5-year survival of 52% compared with 0% for patients with mediastinal nodal disease (p=0.008). Survival of patients who underwent adrenalectomy for synchronous and metachronous adrenal metastases was not significantly different (p=0.81). Surgical resection of isolated adrenal metastasis from lung cancer provides a survival benefit in well-selected patients compared with nonoperative management. No patient with contralateral adrenal metastases or mediastinal nodal disease survived long term after adrenalectomy. The time interval between treatment of the primary lung cancer and adrenal metastasis was not significantly associated with survival, but the cohort size was small.

Recommendation 2.5.9.1	**Grade**
In patients with an isolated brain metastasis and a synchronous resectable primary NSCLC, sequential resection of the primary tumour and definitive treatment of the brain metastasis may be considered, following discussion at a multidisciplinary team meeting.	**C**

Recommendation 2.5.9.2	**Grade**
In patients with an isolated adrenal metastasis and a synchronous resectable primary NSCLC, sequential resection of the primary tumour and definitive treatment of the adrenal metastasis may be considered, following discussion at a multidisciplinary team meeting.	**D**

Good practice point

The management of these patients should be discussed at a multidisciplinary team meeting including the role of systemic therapy.

Clinical question 2.5.10

Should surgical resection be considered as part of the multimodality treatment of patients with stage IIIa (N2) NSCLC?

Evidence summary
Two clinical guidelines (Lim et al., 2010, SIGN, 2014) addressed this clinical question.

N2 disease describes any metastatic involvement of ipsilateral or subcarinal mediastinal nodes. This term encompasses a spectrum of disease from micrometastatic disease in one node to extranodal extension from malignant disease in several lymph node stations and therefore the management of N2 disease should take this into consideration. (Lim et al., 2010)

The IASLC Lung Cancer Staging Project identified that overall disease burden (in the lymph nodes) had more influence on prognosis than anatomical site of lymph node involvement (Rusch et al., 2007); hence nodal stations are now consolidated into lymph node zones (Rusch et al., 2009). The prognosis of single zone N2 disease (N2a) was better than multi-zone N2 (N2b) disease with post-resection 5-year survivals of 34% and 20%, respectively ($p<0.001$) (Rusch et al., 2007). (Lim et al., 2010)

Single zone N2 disease
Resection may be considered in patients with single zone N2 disease as survival is similar to patients with multi-zone N1b disease (Rusch et al., 2007). (Lim et al., 2010)

Multi-zone disease
Patients with bulky or fixed N2 disease are not considered for surgery and are treated by combinations of chemotherapy, radical radiotherapy or concurrent chemoradiotherapy. (Lim et al., 2010)

A number of retrospective case series with relatively small numbers (30–100 cases) have been published detailing the clinical outcomes achieved following surgery in selected patients with stage IIIa disease (Detterbeck, 2001). Patients were managed using a multimodality approach that included preoperative chemotherapy and occasionally radiotherapy. Most studies suggested a survival benefit with a chemotherapy plus surgical resection protocol, compared with contemporary non-surgical management. (SIGN, 2014)

Patients who are suitable for surgery should have non-fixed, non-bulky disease and should be expected to tolerate multimodality treatment (Lim et al., 2010).

Recommendation 2.5.10.1	Grade
Consider surgery as part of multimodality management in patients with T1–3 N2 (non-fixed, non-bulky, single zone) M0 disease.	C

Clinical question 2.5.11

In patients with small-cell lung cancer (SCLC) what is the role of surgery?

Evidence summary
A clinical guideline (SIGN, 2014) addressed this clinical question.

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 (Lad et al., 1994). (SIGN, 2014)

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 (Lim et al., 2008, Vallières et al., 2009, Weksler et al., 2012), but further research is required before strong conclusions can be drawn. (SIGN, 2014)

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. 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 (Fujimori et al., 1997, Shepherd et al., 1989, Davis et al., 1993, Schreiber et al., 2010).

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 (Fujimori et al., 1997, Shepherd et al., 1989, Davis et al., 1993). (SIGN, 2014)

Recommendation 2.5.11.1	**Grade**
Patients with clinical stage I small-cell lung cancer (SCLC) and excellent performance status may be considered for resection following extensive staging investigation as part of a multimodality treatment regimen.	**C**

2.6 Medical Oncology

Responsibility for the implementation of medical oncology recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

The literature used in the development of this guideline was based on the 7th edition of the Lung Cancer TNM staging system. The 8th edition of the TNM staging system was published in December 2016 (Brierley et al., 2016), this may lead to changes in recommendations over time, which should be taken into consideration at multidisciplinary team meetings.

Clinical question 2.6.1

In patients with non-small cell lung cancer (NSCLC) (excluding pancoast tumours) having curative surgery, how effective is preoperative (neoadjuvant) chemotherapy or chemoradiotherapy?

Evidence summary

A clinical guideline (Bezjak et al., 2015) and a meta-analysis (NSCLC Meta-analysis Collaborative Group, 2014) addressed this clinical question.

Preoperative chemotherapy

A recent meta-analysis (NSCLC Meta-analysis Collaborative Group, 2014) of individual participant data from 15 randomised control trials (2,385 patients) aimed to establish the effect of preoperative chemotherapy for patients with resectable NSCLC. The study showed a significant benefit of preoperative chemotherapy on survival (hazard ratio (HR) 0.87, 95% CI 0.78–0.96, p=0.007), a 13% reduction in the relative risk of death (no evidence of a difference between trials; p=0.18, I^2=25%). This finding represents an absolute survival improvement of 5% at 5 years, from 40% to 45%. Recurrence-free survival (HR 0.85, 95% CI 0.76–0.94, p=0.002) and time to distant recurrence (0.69, 0.58–0.82, p<0.0001) results were both significantly in favour of preoperative chemotherapy although most patients included were stage Ib–IIIa. Findings, which are based on 92% of all patients who were randomised, and mainly stage Ib–IIIa, show preoperative chemotherapy significantly improves overall survival, time to distant recurrence, and recurrence free survival in resectable NSCLC. The findings suggest this is a valid treatment option.

Preoperative chemoradiotherapy

The American Society for Radiation Oncology guideline states that there is no level I evidence recommending the use of induction radiotherapy (or chemoradiotherapy) followed by surgery for patients with resectable stage III NSCLC. (Bezjak et al., 2015)

Recommendation 2.6.1.1	**Grade**
Preoperative chemoradiotherapy For patients with non-small cell lung cancer (NSCLC) who are suitable for surgery, do **not** offer neoadjuvant chemoradiotherapy outside a clinical trial.	**B**

Recommendation 2.6.1.2	**Grade**
Preoperative chemotherapy Following discussion at a multidisciplinary team meeting, appropriate patients with NSCLC who are suitable for surgery can be considered for neoadjuvant chemotherapy.	**A**

Good practice point
This evidence does not apply to pancoast tumours.

Clinical question 2.6.2

In patients with locally advanced NSCLC having radical radiotherapy, is concurrent chemoradiotherapy more effective than sequential chemoradiotherapy?

Evidence summary

A clinical guideline (SIGN, 2014) addressed this clinical question.

In patients with locally advanced NSCLC, concurrent systemic anti cancer therapy 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 (Aupérin et al., 2010, O'Rourke et al., 2010). This benefit is seen at a cost of increased radiotherapy toxicity to the oesophagus. The optimal chemotherapy and radiotherapy schedule remain unclear (O'Rourke et al., 2010). (SIGN, 2014)

Recommendation 2.6.2.1	Grade
Concurrent chemoradiotherapy should be administered to patients with locally advanced NSCLC (suitable for radical radiotherapy) who have a good performance status (0-1).	**A**

Good practice point

A sequential approach may be chosen for patients considered at higher risk for toxicity or in patients with good performance status for other clinical reasons such as: the reduction in the radiotherapy field obtained if radiation is preceded by chemotherapy.

Clinical question 2.6.3

In patients with locally advanced NSCLC having concurrent radical chemoradiotherapy, what is the effectiveness of:

a) Induction (first-line) chemotherapy

b) Consolidation chemotherapy

Evidence summary

A clinical guideline (NICE, 2011) and a randomised controlled trial (Ahn et al., 2015) addressed this clinical question.

The NICE (2011) guideline discusses three studies examining the effectiveness of the following interventions:

Study	Intervention
Vokes et al., 2007	Concurrent chemoradiation ± induction chemotherapy
Hanna et al., 2008	Concurrent chemoradiation ± consolidation chemotherapy
Kelly et al., 2008	Concurrent chemoradiation + consolidation chemotherapy ± maintenance chemotherapy

In an RCT of moderate quality Vokes et al. (2007) found no effect of induction chemotherapy on survival, disease-free survival or toxicity other than higher rates of grade 4 maximum toxicity and grade 3-4 absolute neutrophil count (ANC) in the patients who received induction treatment. Apart from higher rates of grade 3-5 infections and pneumonitis in the patients who received consolidation chemotherapy, Hanna et al. (2008) did not find any effect of consolidation chemotherapy on survival, progression-free survival or treatment-related deaths in an RCT of low-moderate quality. Kelly et al. (2008) in a low-moderate quality RCT found that although progression-free survival did not differ between the treatment groups, maintenance gefitinib was associated with significantly shorter survival than placebo. (NICE, 2011)

A recent randomised phase III trial aimed to determine the efficacy of consolidation chemotherapy with docetaxel and cisplatin (DP) after concurrent chemoradiotherapy with the same agents in locally advanced non-small cell lung cancer (Ahn et al., 2015). Patients were randomised to an observation arm (n=211) or a consolidation arm (n=209). In the observation arm patients received concurrent chemoradiotherapy with docetaxel (20 mg/m^2) and cisplatin (20 mg/m^2) every week for 6 weeks with a total dose of 66 Gy of thoracic radiotherapy in 33 fractions. In the consolidation arm patients received the same concurrent chemoradiotherapy followed by three cycles of DP (35 mg/m^2 each on days 1 and 8, every 3 weeks). In the consolidation arm, 143 patients (68%) received consolidation chemotherapy, of whom 88 (62%) completed three planned cycles. The median PFS was 8.1 months in the observation arm and 9.1 months in the consolidation arm (HR 0.91; 95% CI, 0.73 to 1.12; p=0.36). Median overall survival times were 20.6 and 21.8 months in the observation and consolidation arms, respectively (HR 0.91, 95% CI, 0.72 to 1.25; p=0.44). The study concluded that consolidation chemotherapy after concurrent chemoradiotherapy with weekly DP in locally advanced non-small cell lung cancer failed to further prolong PFS and concurrent chemoradiotherapy alone should remain the standard of care.

Recommendation 2.6.3.1	Grade
Induction or consolidation chemotherapy are **not** routinely recommended for patients receiving concurrent radical chemoradiotherapy.	**B**

Good practice point

Ensure patients are offered participation in a clinical trial when available and appropriate.

Clinical question 2.6.4

In patients with advanced/stage IV NSCLC what is the effectiveness of first-line chemotherapy and is there any evidence that particular regimens or drugs are more effective or less toxic than others?

Evidence summary

A Cochrane review (NSCLC Collaborative Group, 2010) and two randomised studies (Delbaldo et al., 2007, Scagliotti et al., 2008,) addressed the effectiveness of chemotherapy in patients with advanced NSCLC.

Effectiveness of first-line cytotoxic chemotherapy

A Cochrane review (NSCLC Collaborative Group, 2010) assessed the effect on survival of supportive care and chemotherapy versus supportive care alone in advanced NSCLC. Survival analyses, based on 2,533 deaths and 2,714 patients from 16 trials show a highly statistically significant benefit of chemotherapy on survival (HR 0.77; 95% CI 0.71 to 0.83, p<0.0001) translating to an absolute improvement of 9% at 12 months, increasing survival from 20% to 29% or an absolute increase in median survival of 1.5 months (from 4.5 months to 6 months). There was some evidence of heterogeneity between the trials (p=0.02, I^2 = 47%).

A meta-analysis of randomised controlled trials evaluated the clinical benefit of adding a drug to single agent or 2-agent chemotherapy regimen in patients with advanced NSCLC (Delbaldo et al., 2007). In total, 57 trials (11,160 patients) were analysed. In the trials comparing a doublet regimen with a single-agent regimen, a significant increase was observed in tumour response (OR, 0.42; 95% confidence interval [CI], 0.37-0.47; p<0.001) and 1-year survival (OR, 0.80; 95% CI, 0.70-0.91; p<0.001) in favour of the doublet regimen. The median survival ratio was 0.83 (95% CI, 0.79-0.89; p<0.001). An increase was also observed in the tumour response rate (OR, 0.66; 95% CI, 0.58- 0.75; p<0.001) in favour of the triplet regimen, but not for 1-year survival (OR, 1.01; 95% CI, 0.85-1.21; p=0.88). The median survival ratio was 1.00 (95% CI, 0.94-1.06; p=0.97). The study concluded that in patients with advanced NSCLC a second drug improved tumour response and survival rate and that adding a third drug had a weaker effect on tumour response and no effect on survival.

A non inferiority, phase III, randomised study (Scagliotti et al., 2008) compared the overall survival of cisplatin/pemetrexed with cisplatin/gemcitabine in chemotherapy-naive patients with advanced NSCLC. Overall survival for patients randomly assigned to cisplatin/pemetrexed was noninferior to the overall survival of patients assigned to cisplatin/gemcitabine (median overall survival, 10.3 vs. 10.3 months; HR 0.94, 95% CI, 0.84 to 1.05). However, in patients with adenocarcinoma randomly assigned to cisplatin/pemetrexed, survival was significantly better than for those assigned to cisplatin/gemcitabine (12.6 v 10.9 months, respectively; p=0.03). This is supported by a recent meta-analysis (Pilkington et al., 2015) that combined the results from Scalgliotti et al. (2009) and Gronberg et al. (2009) and found that in patients with non-squamous disease, there is evidence that pemetrexed+platinum increases OS compared with gemcitabine+platinum (MA: HR 0.85, 95% CI 0.73 to 1.00; MTC-1: HR 0.85, 95% CI 0.74 to 0.98).

A number of phase II/III trials (Johnson et al., 2004, Sandler et al., 2006, Reck et al., 2009, Herbst et al., 2007, Niho et al., 2012) looked at the addition of bevacizumab in combination with chemotherapy. Additionally, four meta-analyses (Soria et al., 2013, Botrel et al., 2011, Cao et al., 2012, Lima et al., 2011) have addressed this issue, they broadly agree that the addition of bevacizumab to chemotherapy in patients with advanced NSCLC improves OS, PFS and RR. However, the absolute benefits are small and the adverse effects of treatment are considerable.

Effectiveness of first-line targeted therapy

A Cochrane review (Greenhalgh et al., 2016) and a phase III trial (Solomon et al., 2014) addressed the effectiveness of first-line targeted therapy in patients with advanced NSCLC.

The Guideline Development Group highlighted this as a rapidly evolving area of research.

EGFR

A recent Cochrane review (Greenhalgh et al., 2016) assessed the clinical effectiveness of EGFR TKI therapies in the first-line treatment of patients with EGFR mutation positive (M+) NSCLC compared with cytotoxic chemotherapy (used alone or in combination) and best supportive care. The study found that erlotinib, gefitinib, and afatinib are all active agents in EGFR M+ NSCLC patients, and demonstrate an increased tumour response rate and prolonged progression-free survival compared to cytotoxic chemotherapy.

Intervention		Control	Relative effect (95% CI)	
			Overall Survival	PFS
Erlotinib	vs.	Cytotoxic chemotherapy	HR 0.95 (0.75 to 1.22)	HR 0.30 (0.24 to 0.38)
Gefitinib	vs.	Paclitaxel + carboplatin	HR 0.95 (0.77 to 1.18)	HR 0.39 (0.32 to 0.48)
Afatinib	vs.	Cytotoxic chemotherapy	HR 0.93 (0.74 to 1.17)	HR 0.42 (0.34 to 0.53)

Adapted from (Greenhalgh et al., 2016)

Greenhalgh et al. (2016) concluded that erlotinib, gefitinib, and afatinib are effective in prolongation of PFS but not OS in EGFR M+ NSCLC patients with acceptable toxicity. Quality of life and response are closely linked, and the available data would favour selection of TKIs over chemotherapy as first-line treatment based on both these criteria. The review included six trials that measured quality of life for participants with EGFR M+ tumours by a number of different methods (two comparing afatinib with cytotoxic chemotherapy, two comparing erlotinib with cytotoxic chemotherapy, and two comparing gefitinib with cytotoxic chemotherapy); all six trials reported a beneficial effect of the TKI compared to cytotoxic chemotherapy. All three TKIs showed symptom palliation of cough, pain, and dyspnoea, although the methodology used was not standardised.

The majority of trials included people with a performance status (PS) of 1 and 2, but the data on AEs suggest that some PS 3 as well as elderly patients might tolerate the agents better than cytotoxic chemotherapy (Chen et al., 2012, Reck et al., 2010).

ALK

Solomon et al. (2014) conducted an open-label, phase III trial comparing crizotinib treatment with pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced ALK-positive NSCLC. Progression-free survival was significantly longer with crizotinib than with chemotherapy (median, 10.9 months vs. 7.0 months; hazard ratio for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; p<0.001). Objective response rates were 74% and 45%, respectively (p<0.001). Median overall survival was not reached in either group (hazard ratio for death with crizotinib, 0.82; 95% CI, 0.54 to 1.26; p=0.36); the probability of 1-year survival was 84% with crizotinib and 79% with chemotherapy. The most common adverse events of any cause for which the incidence was at least 5 percentage points higher in the crizotinib group than in the chemotherapy group were vision disorder (occurring in 71% of the patients), diarrhoea, (in 61%), and odema (in 49%); and the events for which the incidence was at least 5 percentage points higher in the chemotherapy group than in the crizotinib group were fatigue (occurring in 38% of the patients), anaemia (in 32%), and neutropenia (in 30%). There was a significantly greater overall improvement from baseline in global quality of life among patients who received crizotinib than among those who received chemotherapy (p<0.001). The study concluded that

crizotinib was superior to standard first-line pemetrexed-plus-platinum chemotherapy in patients with previously untreated advanced ALK-positive NSCLC.

Recommendation 2.6.4.1	Grade
Effectiveness of first-line cytotoxic chemotherapy In patients with a good performance status (PS) (i.e. Eastern Cooperative Oncology Group [ECOG] level 0 or 1) and stage IV NSCLC, a platinum-based chemotherapy regimen is recommended based on the survival advantage and improvement in quality of life (QOL) over best supportive care (BSC).	**A**

Recommendation 2.6.4.2	Grade
Effectiveness of first-line cytotoxic chemotherapy In patients with stage IV NSCLC and a good performance status, two-drug combination chemotherapy is recommended. The addition of a third cytotoxic chemotherapeutic agent is **not** recommended because it provides no survival benefit and may be harmful.	**A**

Recommendation 2.6.4.3	Grade
Effectiveness of first-line cytotoxic chemotherapy In patients receiving palliative chemotherapy for stage IV NSCLC, it is recommended that the choice of chemotherapy is guided by histological type of NSCLC.	**B**

Recommendation 2.6.4.4	Grade
Effectiveness of first-line cytotoxic chemotherapy Bevacizumab plus platinum-based chemotherapy may be considered an option in carefully selected patients with advanced NSCLC. Risks and benefits should be discussed with patients before decision making.	**B**

Recommendation 2.6.4.5	Grade
Effectiveness of first-line targeted therapy First-line single agent EGFR tyrosine kinase inhibitors (TKI) should be offered to patients with sensitising EGFR mutation positive NSCLC. Adding combination chemotherapy to TKI confers no benefit and should **not** be used.	**A**

Recommendation 2.6.4.6	Grade	Resource implication:
Effectiveness of first-line targeted therapy Crizotinib should be considered as first-line therapy in patients with ALK positive NSCLC tumours.	**B**	Crizotinib is licensed for this indication in the Republic of Ireland but is not currently reimbursed. The HSE reimbursement application is expected to be submitted in 2017.

Good practice point
Ensure patients are offered participation in a clinical trial when available and appropriate.

Good practice point
Patients should be referred for assessment by the palliative care service.

Clinical question 2.6.5

In patients with advanced/stage IV NSCLC is there any evidence for maintenance systemic therapy?

Evidence summary

Two clinical guidelines (SIGN, 2014, and Kulkarni et al., 2015- Cancer Care Ontario) addressed this clinical question.

The Cancer Care Ontario Guideline Development Group (Kulkarni et al., 2015) conducted a meta-analysis of three RCTs (Ciuleanu et al., 2009, Paz-Ares et al., 2012, Rittmeyer et al., 2013). They found that patients randomised to pemetrexed as maintenance therapy had longer overall survival compared with those who did not receive maintenance pemetrexed therapy (HR 0.78; 95% confidence interval [CI], 0.69 to 0.89; p=0.0003, I^2=0%). At a baseline risk of 51% at 12 months, there would be 8% (83 per 1000) fewer deaths at 12 months (95% CI from 40 fewer to 121 fewer) for patients who received pemetrexed maintenance therapy.

The three RCTs reported on quality of life and found either no difference in the majority of scores or significant delays in symptom deterioration in favour of patients who received pemetrexed maintenance treatment (Ciuleanu et al., 2009, Paz-Ares et al., 2012, Rittmeyer et al., 2013). (Kulkarni et al., 2015)

A significant interaction was observed between histology (squamous versus non-squamous carcinoma) and treatment for progression-free survival and overall survival in Ciuleanu 2009. The two other RCTs included only patients with non-squamous histology (Barlesi et al., 2013, Paz-Ares et al., 2013). Meta-analysis with these two RCTs, plus the data from patients with non-squamous carcinoma from Ciuleanu 2009, found that patients with non-squamous cell histology who received pemetrexed as maintenance therapy had longer OS (HR 0.74; 95% CI, 0.64 to 0.86; p<0.0001) and PFS (HR 0.51; 95% CI, 0.41 to 0.63; p<0.00001) compared with those who did not receive pemetrexed as maintenance therapy. (Kulkarni et al., 2015)

Erlotinib maintenance treatment provided a statistically significant increase in progression-free survival and overall survival in patients treated with standard first-line platinum-based chemotherapy, 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) (Cappuzzo et al., 2010). (SIGN, 2014)

Recommendation 2.6.5.1	**Grade**
In patients with stage IV non-squamous NSCLC who do not experience disease progression and have a preserved performance status after 4-6 cycles of platinum-based therapy, treatment with maintenance pemetrexed is suggested.	**B**

Recommendation 2.6.5.2	**Grade**
In patients with stage IV NSCLC, switch maintenance therapy with chemotherapy agents other than pemetrexed has not demonstrated an improvement in overall survival and is **not** recommended.	**B**

Recommendation 2.6.5.3	Grade
In patients with stage IV NSCLC who do not experience disease progression after 4-6 cycles of platinum-based double agent chemotherapy, there is insufficient evidence to recommend maintenance therapy with erlotinib.	**B**

Good practice point
Ensure patients are offered participation in a clinical trial when available and appropriate.

Clinical question 2.6.6

In patients with advanced/stage IV NSCLC aged over 70, and/or with poor performance status, what is the effectiveness of first-line therapy?

Evidence summary

A clinical guideline (NCCN, V8 2017), a Cochrane review (Santos et al., 2015) and a randomised phase III trial (Zukin et al., 2013) addressed this clinical question.

Poor performance status

A multicentre phase III randomised trial (Zukin et al., 2013) compared single-agent pemetrexed versus combination carboplatin/pemetrexed as first-line management in patients with advanced NSCLC and a ECOG performance status of 2. The analysis included 205 patients, 102 patients assigned to receive pemetrexed and 103 assigned to receive carboplatin/pemetrexed. However, the guideline development group noted that the prevalence of comorbidities amongst patients in the trial was low in both arms. Although the median number of cycles was four in both arms, only 53.9% of patients in the pemetrexed arm completed the prescribed four cycles compared with 70.9% in the carboplatin/pemetrexed arm (p=0.012). Best response could not be determined in 34.4% and 23.3% of patients in the pemetrexed and carboplatin/pemetrexed arms, respectively, due to the lack of confirmation by response evaluation criteria in solid tumours (RECIST). Among evaluable patients, objective response rates were 10.5% in the pemetrexed arm (seven of 67) and 24% in the carboplatin/pemetrexed arm (19 of 79; p=0.032). The 6- and 12-month PFS rates were 18.4% and 2% versus 48.9% and 17%, respectively. The OS distributions were statistically significant in favour of the combination arm (HR 0.62; 95% CI, 0.46 to 0.83; p=0.001). However, there were four documented treatment-related deaths in the combination arm (3.9%) and the frequency of grades 3 and 4 anaemia (3.9% v 11.7%), neutropenia (1.0% v 6.8%), and thrombocytopenia (0% v 1.0%) were higher in the combination arm. The study concluded that combination chemotherapy with carboplatin/pemetrexed is superior to single-agent therapy in patients with advanced NSCLC and an ECOG performance status of 2, combination therapy should be offered to these patients.

The National Comprehensive Cancer Network (NCCN, V8 2017) guideline states that unfit patients of any age (performance status (3-4) do not benefit from cytotoxic treatments, except erlotinib, afatinib, or gefitinib for EGFR mutation-positive and crizotinib for ALK-positive tumours of non-squamous NSCLC or NSCLC NOS. (NCCN, V8 2017)

Elderly patients

A recent Cochrane review (Santos et al., 2015) aimed to assess the effectiveness and safety of different cytotoxic chemotherapy regimens for previously untreated elderly patients with advanced (stage IIIb and IV) NSCLC. The study included 51 trials: non-platinum single-agent therapy versus non-platinum combination therapy (seven trials) and non-platinum combination therapy versus platinum combination therapy (44 trials). The reviews results were as follows:

Non-platinum single-agent versus non-platinum combination therapy

Low-quality evidence suggests that these treatments have similar effects on overall survival (HR 0.92, 95% confidence interval (CI) 0.72 to 1.17; participants = 1062; five RCTs), one year OS (risk ratio (RR) 0.88, 95% CI 0.73 to 1.07; participants = 992; four RCTs), and PFS (HR 0.94, 95% CI 0.83 to 1.07; participants = 942; four RCTs). Non-platinum combination therapy may better improve ORR compared with non-platinum single-agent therapy (RR 1.79, 95% CI 1.41 to 2.26; participants = 1014; five RCTs; low-quality evidence). (Santos et al., 2015)

Differences in effects on major adverse events between treatment groups were as follows: anemia: RR 1.10, 95% CI 0.53 to 2.31; participants = 983; four RCTs; very low-quality evidence; neutropenia: RR 1.26, 95% CI 0.96 to 1.65; participants = 983; four RCTs; low-quality evidence; and

thrombocytopenia: RR 1.45, 95% CI 0.73 to 2.89; participants = 914; three RCTs; very low-quality evidence. (Santos et al., 2015)

Non-platinum therapy versus platinum combination therapy

Platinum combination therapy probably improves OS (HR 0.76, 95% CI 0.69 to 0.85; participants = 1705; 13 RCTs; moderate quality evidence), 1 year OS (RR 0.89, 95% CI 0.82 to 0.96; participants = 813; 13 RCTs; moderate-quality evidence), and ORR (RR 1.57, 95% CI 1.32 to 1.85; participants = 1432; 11 RCTs; moderate-quality evidence) compared with non-platinum therapies. Platinum combination therapy may also improve PFS, although our confidence in this finding is limited because the quality of evidence was low (HR 0.76, 95% CI 0.61 to 0.93; participants = 1273; nine RCTs). (Santos et al., 2015)

Effects on major adverse events between treatment groups were as follows:
anaemia: RR 2.53, 95% CI 1.70 to 3.76; participants = 1437; 11 RCTs; low-quality evidence; thrombocytopenia: RR 3.59, 95% CI 2.22 to 5.82; participants = 1260; nine RCTs; low-quality evidence; fatigue: RR 1.56, 95% CI 1.02 to 2.38; participants = 1150; seven RCTs; emesis: RR 3.64, 95% CI 1.82 to 7.29; participants = 1193; eight RCTs; and peripheral neuropathy: RR 7.02, 95% CI 2.42 to 20.41; participants = 776; five RCTs; low-quality evidence. (Santos et al., 2015)

Recommendation 2.6.6.1	**Grade**
In elderly patients (age 70-79 years) with stage IV NSCLC who have good performance status and limited co-morbidities, treatment with a platinum doublet chemotherapy is recommended.	**B**

Recommendation 2.6.6.2	**Grade**
In patients with stage IV NSCLC with a performance status of 2, single agent chemotherapy may be considered. Platinum doublet chemotherapy is suggested over single agent chemotherapy if the performance status of 2 is cancer related rather than co-morbidity associated.	**B**

Recommendation 2.6.6.3	**Grade**
Unfit patients of any age (performance status (3-4)) do not benefit from cytotoxic chemotherapy. However if patients harbor an EGFR or ALK mutation positive tumour, they may be considered for treatment with targeted therapies.	**C**

Good practice point
A comprehensive geriatric assessment should be considered in patients over 70 years.

Good practice point
In patients with stage IV NSCLC, who are 80 years or over, the benefit of chemotherapy is unclear and should be decided based on individual circumstances.

Good practice point
Ensure patients are offered participation in a clinical trial when available and appropriate.

Good practice point
Patients should be referred for assessment by the palliative care service.

Clinical question 2.6.7

In patients with advanced/stage IV NSCLC how effective is second and third-line therapy in patients with NSCLC who progress and relapse?

Evidence summary

This is a rapidly evolving area of research. Not all treatments discussed in the evidence summary are currently reimbursed in Ireland.[1]

In patients with advanced NSCLC who have received platinum as part of their first-line treatment randomised evidence does not support the use of combination chemotherapy as second-line treatment (Di Maio et al., 2009).

The following single agent treatments have shown benefit in clinical trials as second and/or third-line treatment:

Docetaxel		
Patient population:	**Study/Author:**	**Results:**
Patients with performance status (PS) of 0 to 2 and stage IIIb/IV NSCLC previously treated with a platinum-based chemotherapy regimen.	(Shepherd et al., 2000) **Intervention:** Docetaxel **Comparison:** Best Supportive Care	Time to progression was longer for docetaxel patients than for best supportive care patients (10.6 v 6.7 weeks, respectively; p<.001), as was median survival (7.0 v 4.6 months; log-rank test, p=.047).
Pemetrexed (non squamous histology only)		
Patient population:	**Study/Author:**	**Results:**
Patients with advanced NSCLC, PS 0-2, previously treated with chemotherapy.	(Hanna et al., 2004) **Intervention:** Pemetrexed **Comparison:** Docetaxel	Median progression-free survival was 2.9 months for each arm, and median survival time was 8.3 versus 7.9 months (p=not significant) for pemetrexed and docetaxel, respectively.
Erlotinib		
Patient population:	**Study/Author:**	**Results:**
Patients with advanced NSCLC previously treated with a platinum-based chemotherapy, and wild-type EGFR.	(Garassino et al., 2013) **Intervention:** Erlotinib **Comparison:** Docetaxel	Median overall survival was 8.2 months (95% CI 5.8–10.9) with docetaxel versus 5.4 months (4.5–6.8) with erlotinib (adjusted HR 0.73, 95% CI 0.53–1.00; p=0.05). Progression-free survival was significantly better with docetaxel than with erlotinib: median progression-free survival was 2.9 months (95% CI 2.4–3.8) with docetaxel versus 2.4 months (2.1–2.6) with erlotinib (adjusted HR 0.71, 95% CI 0.53–0.95; p=0.02).

[1] The process for reimbursement is outlined on page 130.

Erlotinib (cont.)		
Patient population:	**Study/Author:**	**Results:**
Patients with stage IIIb or IV NSCLC, previous treatment with chemotherapy, and performance status of 0 to 2 were eligible.	(Kawaguchi et al., 2014) **Intervention:** Erlotinib **Comparison:** Docetaxel	Median progression-free survival for erlotinib versus docetaxel was 2.0 *v* 3.2 months (HR 1.22; 95% CI, 0.97 to 1.55; p=.09), and median OS was 14.8 *v* 12.2 months (HR 0.91; 95% CI, 0.68 to 1.22; p=.53), respectively.
Patient population:	**Study/Author:**	**Results:**
Patients with NSCLC that progressed on first-line, platinum-doublet chemotherapy.	(Ciuleanu et al., 2012) **Intervention:** Erlotinib **Comparison:** Chemotherapy (standard docetaxel or pemetrexed regimens, at the treating investigators' discretion)	Median overall survival was 5.3 months (95% CI 4.0–6.0) with erlotinib and 5.5 months (4.4–7.1) with chemotherapy (HR 0.96, 95% CI 0.78–1.19; log-rank p=0.73). Median PFS in the erlotinib group was 6.3 weeks (95% CI 6.1–6.9) versus 8.6 weeks (7.1–12.1) in the chemotherapy group. There was no statistically significant difference in PFS between the two treatment groups (HR 1.19, 95% CI 0.97–1.46; p=0.089).
Patient population:	**Study/Author:**	**Results:**
Patients with stage IIIb or IV NSCLC, with performance status from 0 to 3, were eligible if they had received one or two prior chemotherapy regimens.	(Shepherd et al., 2005) **Intervention:** Erlotinib **Comparison:** Placebo	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.
Afatinib (Squamous histology only)		
Patient population:	**Study/Author:**	**Results:**
Stage IIIb or IV squamous cell carcinoma of the lung who had progressed after at least four cycles of platinum-based-chemotherapy.	(Soria et al., 2015) **Intervention:** Afatinib **Comparison:** Erlotinib	Median progression-free survival was 2.6 months (95% CI 2.0–2.9) with afatinib and 1.9 months (1.9–2.1) with erlotinib (HR 0.81 [95% CI 0.69–0.96]; p=0.0103). Median overall survival was 7.9 months (95% CI 7.2–8.7) in the afatinib group and 6.8 months (5.9–7.8) in the erlotinib group (HR 0.81 [95% CI 0.69–0.95]; p=0.0077).
Patient population:	**Study/Author:**	**Results:**
Patients with stage IIIb or IV adenocarcinoma and an ECOG PS of 0–2 who had received one or two previous chemotherapy regimens and had disease progression after at least 12 weeks of treatment with erlotinib or gefitinib.	(Miller et al., 2012) **Intervention:** Afatinib **Comparison:** Placebo	Median overall survival was 10.8 months (95% CI 10.0–12.0) in the afatinib group and 12.0 months (10.2–14.3) in the placebo group (HR 1.08, 95% CI 0.86–1.35; p=0.74). Median progression-free survival was longer in the afatinib group (3.3 months, 95% CI 2.79–4.40) than it was in the placebo group (1.1 months, 0.95–1.68; HR 0.38, 95% CI 0.31–0.48; p<0.0001).

Nivolumab		
Patient population:	**Study/Author:**	**Results:**
Patients with non-squamous NSCLC that had progressed during or after platinum-based doublet chemotherapy.	(Borghaei et al., 2015) **Intervention:** Nivolumab **Comparison:** Docetaxel	Median overall survival was 12.2 months (95% CI, 9.7 to 15.1) with nivolumab and 9.4 months (95% CI, 8.1 to 10.7) with docetaxel, representing a 28% lower risk of death with nivolumab (HR 0.72; 95% CI, 0.60 to 0.88; p<0.001). The median progression-free survival was 2.3 months (95% CI, 2.2 to 3.3) in the nivolumab group and 4.2 months (95% CI, 3.5 to 4.9) in the docetaxel group.
Patient population:	**Study/Author:**	**Results:**
Patients with advanced squamous-cell NSCLC who have disease progression during or after first-line chemotherapy.	(Brahmer et al., 2015) **Intervention:** Nivolumab **Comparison:** Docetaxel	The median overall survival was 9.2 months (95% confidence interval [CI], 7.3 to 13.3) with nivolumab versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel. The median progression-free survival was 3.5 months with nivolumab versus 2.8 months with docetaxel (HR for death or disease progression, 0.62; 95% CI, 0.47 to 0.81; p<0.001).
Pembrolizumab (PDL1 positive)		
Patient population:	**Study/Author:**	**Results:**
Patients with previously treated, PD-L1-positive, advanced NSCLC.	(Herbst et al., 2016) **Intervention:** Pembrolizumab (2 mg/kg) Pembrolizumab (10 mg/kg) **Comparison:** Docetaxel	Overall survival was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (HR 0.71, 95% CI 0.58–0.88; p=0.0008) and for pembrolizumab 10 mg/kg versus docetaxel (0.61, 0.49–0.75; p<0.0001). Median progression-free survival was 3.9 months with pembrolizumab 2 mg/kg, 4.0 months with pembrolizumab 10 mg/kg, and 4.0 months with docetaxel, with no significant difference for pembrolizumab 2 mg/kg versus docetaxel (0.88, 0.74–1.05; p=0.07) or for pembrolizumab 10 mg/kg versus docetaxel (HR 0.79, 95% CI 0.66–0.94; p=0.004).

The following single agents have also shown benefit as second/third-line treatment in patients with ALK positive tumours:

Crizotinib		
Patient population:	**Study/Author:**	**Results:**
Patients with locally advanced or metastatic ALK-positive lung cancer who had received one prior platinum-based regimen.	PROFILE 1007 (Shaw et al., 2013) **Intervention:** Crizotinib **Comparison:** Pemetrexed or Docetaxel	The median progression-free survival was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group (HR for progression or death with crizotinib, 0.49; 95% CI, 0.37 to 0.64; p<0.001). The median overall survival was 20.3 months (95% CI, 18.1 to not reached) with crizotinib and 22.8 months (95% CI, 18.6 to not reached) with chemotherapy (HR for death in the crizotinib group, 1.02; 95% CI, 0.68 to 1.54; p=0.54)

Ceritinib (previously treated with crizotininb)		
Patient population:	**Study/Author:**	**Results:**
Patients with ALK-rearranged locally advanced or metastatic cancer that progressed despite standard therapy.	ASCEND-1, - Phase I study, - (Kim et al., 2016, Shaw et al., 2014) **Intervention:** Ceritinib **Comparison:** –	An overall response was reported in 60 (72% [95% CI 61–82]) of 83 ALK inhibitor-naive patients and 92 (56% [49–64]) of 163 ALK inhibitor-pretreated patients. Median duration of response was 17.0 months (95% CI 11.3–non-estimable [NE]) in ALK inhibitor-naive patients and 8.3 months (6.8–9.7) in ALK inhibitor-pretreated patients. Median progression-free survival was 18.4 months (95% CI 11.1–NE) in ALK inhibitor-naive patients and 6.9 months (5.6–8.7) in ALK inhibitor pretreated patients.
Alectinib (previously treated with crizotinib)		
Patient population:	**Study/Author:**	**Results:**
Patients with locally advanced or metastatic ALK-rearranged NSCLC who had experienced progression while receiving crizotinib.	(Ou et al., 2016) - Phase II study **Intervention:** Alectinib **Comparison:** –	ORR by independent review committee (IRC) was 50% (95% CI, 41% to 59%), and the median duration of response (DOR) was 11.2 months (95% CI, 9.6 months to not reached). Median IRC-assessed progression-free survival for all 138 patients was 8.9 months (95% CI, 5.6 to 11.3 months).
Patient population:	**Study/Author:**	**Results:**
Patients with stage IIIb–IV, ALK-positive NSCLC who progressed on previous crizotinib.	(Shaw et al., 2016) - Phase II study **Intervention:** Alectinib **Comparison:** –	At the time of the primary analysis (median follow-up 4.8 months [IQR 3.3–7.1]), 33 of 69 patients with measurable disease at baseline had a confirmed partial response; thus, the proportion of patients achieving an objective response by the independent review committee was 48% (95% CI 36–60).

The following single agent has also shown benefit as second/third-line treatment in patients with EGFR positive tumours:

Osimertinib (T790M mutation positive)		
Patient population:	**Study/Author:**	**Results:**
Patients with advanced lung cancer who had radiologically documented disease progression after previous treatment with EGFR tyrosine kinase inhibitors.	(Janne et al., 2015) - Phase I study **Intervention:** Osimertinib **Comparison:** –	Among 127 patients with centrally confirmed EGFR T790M who could be evaluated for response, the response rate was 61% (95% CI, 52 to 70). In contrast, among 61 patients without centrally detectable EGFR T790M who could be evaluated for response, the response rate was 21% (95% CI, 12 to 34). The median progression-free survival was 9.6 months (95% CI, 8.3 to not reached) in EGFR T790M–positive patients and 2.8 months (95% CI, 2.1 to 4.3) in EGFR T790M–negative patients.

Osimertinib (T790M mutation positive) cont.		
Patient population:	**Study/Author:**	**Results:**
Patients with T790M-positive advanced non–small cell lung cancer, who had disease progression after first-line EGFR-TKI therapy.	Mok et al., 2017 - Phase III study **Intervention:** Osimertinib **Comparison:** Pemetrexed plus either carboplatin or cisplatin	The median duration of progression-free survival was significantly longer with osimertinib than with platinum therapy plus pemetrexed (10.1 months vs. 4.4 months; HR; 0.30; 95% confidence interval [CI], 0.23 to 0.41; p<0.001). The objective response rate was significantly better with osimertinib (71%; 95% CI, 65 to 76) than with platinum therapy plus pemetrexed (31%; 95% CI, 24 to 40) (odds ratio for objective response, 5.39; 95% CI, 3.47 to 8.48; p<0.001).

Recommendation 2.6.7.1	**Grade**
Second-line systemic anticancer therapy (SACT) with single agent drugs should be considered. The choice of agent to be used should be made on a case by case basis taking into account previous treatment, mutation status and co-morbidities.	**B**

Good practice point
This is a rapidly evolving area; please refer to the NCCP protocols for the latest information.

Good practice point
In all cases if patients are eligible for entry into clinical trials, it is recommended.

Clinical question 2.6.8

Is there any evidence that particular regimens or drugs are more effective or less toxic than others for the first-line treatment of limited-stage and extensive-stage small-cell lung cancer (SCLC)?

Evidence summary
A Cochrane review (Amarasena et al., 2015) addressed this clinical question.

Amarasena et al. (2015) aimed to determine the effectiveness of platinum chemotherapy regimens compared with non-platinum chemotherapy regimens in the treatment of SCLC with respect to survival, tumour response, toxicity and quality of life.

Survival at 24 months
There was no statistically significant difference between interventions (RR 1.06, 95% CI 0.85 to 1.31). There was no substantial heterogeneity present in the data (I^2 = 31%).

Subgroup LD-SCLC:
Nine studies reported data from 12-month survival comparisons for participants with limited disease, involving 1,209 participants. Of these, 597 received a platinum-based and 612 received a non-platinum based regimen. At 24 months, 255 participants were alive: 133 from the platinum-based arm and 122 from the non-platinum based arm. There was no statistically significant difference between interventions (RR 1.07, 95% CI 0.7 to 1.65). There was substantial heterogeneity present in the data (I^2 = 57%).

Subgroup ED-SCLC:
Fifteen studies reported data from 24-month survival comparisons for participants with extensive disease, involving 2,381 participants. Of these, 1,200 received a platinum-based and 1,181 received a non-platinum-based regimen. There was no statistically significant difference between interventions (RR 1.11, 95% CI 0.71 to 1.75). There was substantial heterogeneity present in the data (I^2 = 35%).

Complete response
There was a statistically significant effect favouring platinum-based chemotherapy regimens (RR 1.32, 95% CI 1.14 to 1.54). There was no substantial heterogeneity present in the data (I^2 = 46%)

Subgroup LD-SCLC:
There was a statistically significant effect favouring platinum-based regimens (RR 1.19, 95% CI 1.02 to 1.40). There was no heterogeneity (I^2 = 0%).

Subgroup ED-SCLC:
There was a statistically significant effect, favouring platinum-based chemotherapy regimens (RR 1.45, 95% CI 1.17 to 1.80). There was no substantial heterogeneity present in the data (I^2 = 24%).

The effect on quality of life could not be adequately assessed.

Many other combinations have been evaluated in patients with extensive-stage disease, with little consistent evidence of benefit when compared with EP. While phase III data exists regarding irinotecan and platinum combinations (Lara et al., 2009, Hanna et al., 2006, Noda et al., 2002, Hermes et al., 2008) they do not appear superior with potentially significant toxicity.

Recommendation 2.6.8.1	**Grade**
In patients with either limited-stage or extensive-stage small-cell lung cancer (SCLC), platinum-based chemotherapy with either cisplatin or carboplatin plus etoposide is recommended.	**A**

Recommendation 2.6.8.2	**Grade**
Non-platinum combinations can be considered in patients with limited-stage and extensive-stage SCLC.	**A**

Good practice point
Ensure patients are offered participation in a clinical trial when available and appropriate.

Good practice point
Patients should be referred for assessment by the palliative care service.

Clinical question 2.6.9

In patients with limited-stage and extensive-stage SCLC is there any role for maintenance chemotherapy?

Evidence summary

A meta-analysis (Zhou et al., 2013) addressed this clinical question.

A meta-analysis (Zhou et al., 2013) reported that maintenance chemotherapy did not prolong overall survival (HR 0.87; 95% CI: 0.71–1.06; p=0.172). Overall, maintenance chemotherapy was associated with a 13% improvement in OS, but the difference was not statistically significant and there was significant heterogeneity in the included studies. The authors noted that the results were not affected by exclusion of any specific trial.

Recommendation 2.6.9.1	Grade
There is no data to support maintenance therapy in limited-stage or extensive-stage SCLC.	**C**

Clinical question 2.6.10

How effective is second-line systemic therapy in patients with SCLC who progress and relapse?

Evidence summary

Two randomised phase III trials (O'Brien et al., 2006, von Pawel et al., 2014) addressed this clinical question.

For patients with small-cell lung cancer, further chemotherapy is routinely considered at relapse after first-line therapy. However, proof of clinical benefit has not been documented. (O'Brien et al., 2006)

O'Brien et al. (2006) randomly assigned patients with relapsed SCLC not considered as candidates for standard intravenous therapy to best supportive care (BSC) alone (n = 70) or oral topotecan (2.3 mg/m^2/d, days 1 through 5, every 21 days) plus BSC (topotecan; n = 71). In the intent-to-treat population, survival was prolonged in the topotecan group (log-rank p=0.0104). Median survival with BSC was 13.9 weeks (95% CI, 11.1 to 18.6) and with topotecan, 25.9 weeks (95% CI, 18.3 to 31.6). Statistical significance for survival was maintained in a subgroup of patients with a short treatment-free interval (≤ 60 days). Response to topotecan was 7% partial and 44% stable disease. Patients on topotecan had slower quality of life deterioration and greater symptom control. Principal toxicities with topotecan were haematological: grade 4 neutropenia, 33%; grade 4 thrombocytopenia, 7%; and grade 3/4 anaemia, 25%. Comparing topotecan with BSC, infection grade 2 was 14% versus 12% and sepsis 4% versus 1%; other grade 3/4 events included vomiting 3% versus 0, diarrhoea 6% versus 0, dyspnoea 3% versus 9%, and pain 3% versus 6%. Toxic deaths occurred in four patients (6%) in the topotecan arm. All cause mortality within 30 days of random assignment was 13% on BSC and 7% on topotecan. Chemotherapy with oral topotecan is associated with prolongation of survival and quality of life benefit in patients with relapsed SCLC.

von Pawel et al. (2014) randomly assigned 637 patients with refractory or sensitive SCLC at a ratio of 2:1 to 21-day cycles of amrubicin 40 mg/m^2 intravenously (IV) on days 1 to 3 or topotecan 1.5 mg/m^2 IV on days 1 to 5. Median OS was 7.5 months with amrubicin versus 7.8 months with topotecan (HR 0.880; p=0.170); in refractory patients, median OS was 6.2 and 5.7 months, respectively (HR 0.77; p=0.047). Median PFS was 4.1 months with amrubicin and 3.5 months with topotecan (HR 0.802; p=0.018). ORR was 31.1% with amrubicin and 16.9% with topotecan (odds ratio, 2.223; p<0.001). Grade ≥ 3 treatment-emergent adverse events in the amrubicin and topotecan arms were: neutropenia (41% v 54%; p=0.004), thrombocytopenia (21% v 54%; p<0.001), anaemia (16% v 31%; p<0.001), infections (16% v 10%; p=0.043), febrile neutropenia (10% v 3%; p=0.003), and cardiac disorders (5% v 5%; p=0.759); transfusion rates were 32% and 53% (p<0.001), respectively. NQO1 polymorphisms did not influence safety outcomes. Amrubicin had demonstrable activity and a safety profile comparable to that of topotecan in patients with SCLC. Amrubicin also demonstrated higher response rates and a minimal survival advantage of 2 weeks in patients with refractory disease.

Recommendation 2.6.10.1	**Grade**
In patients with relapsed refractory SCLC, second-line therapy should be considered.	**B**

Recommendation 2.6.10.2	**Grade**
Re-initiation of the previously administered first-line chemotherapy regimen is recommended in patients with SCLC who relapse greater than six months from completion of initial chemotherapy.	**B**

Recommendation 2.6.10.3	**Grade**
Single agent chemotherapy should be considered in patients with primary refractory SCLC to maintain or improve quality of life.	**B**

2.7 Radiation Oncology

Responsibility for the implementation of radiation oncology recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

The literature used in the development of this guideline was based on the 7th edition of the Lung Cancer TNM staging system. The 8th edition of the TNM staging system was published in December 2016 (Brierley et al., 2016), this may lead to changes in recommendations over time, which should be taken into consideration at multidisciplinary team meetings.

Clinical question 2.7.1

In patients with non-small cell lung cancer (NSCLC) early stage disease (T1-T2 N0 M0) who are unfit for surgery, what is the effectiveness of stereotactic radiotherapy, standard radical radiotherapy and radiofrequency ablation?

Evidence summary

Two clinical guidelines (NICE, 2011, Vansteenkiste et al., 2013) and a retrospective study (Ambrogi et al., 2015) addressed this clinical question.

Crabtree et al. (2010) found that among their group of patients with clinical stage I NSCLC significantly more patients who had received surgical treatment were alive at 3 years than patients who had received SBRT/SABR. The treatment groups did not differ in terms of 3-year cancer-specific survival or local control. When the analyses were limited to patients with clinical stage Ia 3-year disease-free survival did not differ significantly between the SBRT/SABR (n = 57) and surgery (n = 288) patients, but the surgery patients achieved significantly higher rates of local control at 3 years compared to the SBRT/SABR patients. Analysis of the patients with clinical stage Ib found no differences in 3-year disease-free survival or local control between the SBRT/SABR (n = 19) and surgery (n = 174) patients. In a separate series of analyses the authors attempted to address the baseline differences between the treatment groups in terms of age, clinical T stage, comorbidities and % predicted FEV_1 and D_{LCO} by matching surgery patients to the SBRT/SABR patients. Subsequent matched-patient analyses revealed no differences between the groups in terms of overall survival, disease-specific survival, or local control. No treatment-related deaths occurred as a consequence of SBRT although some other complications were associated with the treatment. In the surgery group, the operative mortality rate was 15/462 patients and 179/462 patients experienced complications associated with the surgical treatment. (NICE, 2011)

Grills et al. (2010) reported that rates of freedom from any failure, causes-specific survival, distant metastasis and local, regional, and loco-regional recurrence did not differ significantly between patients with stage I NSCLC who had received treatment with either SBRT/SABR or wedge resection, but the overall survival rate was significantly higher in the surgery patients than in those patients who had received SBRT/SABR. A second set of analyses excluding patients with pT4, synchronous primary or no biopsy revealed similar results with the exception of the loco-regional occurrence rate which was now significantly higher in the patients who had received surgery. Multivariate analyses showed that in the patients who had received SBRT/SABR squamous histology and the presence of synchronous primary tumour were significant predictors of distant metastasis and in the patients who had received wedge resection, visceral pleural invasion and stage Ib were significant predictors of distant metastasis. In addition, in all patients, age > 71 years was a significant predictor of overall survival. No treatment-related deaths were observed as a consequence of either treatment, but a number of adverse events were associated with both treatments. (NICE, 2011)

In patients unfit for surgery, SBRT/SABR is the treatment of choice for peripherally located stage I NSCLC (if SBRT/SABR is not available, a hypofractionated radiotherapy schedule with a high biologically equivalent dose is advised). (Vansteenkiste et al., 2013)

SBRT/SABR has led to improved population-based survival in elderly patients (Haasbeek et al., 2012), and the convenience of this outpatient therapy over three to eight visits has also led to a reduction in the proportion of untreated patients. The SBRT/SABR dose should be to a biologically equivalent tumour dose of ≥100 Gy, prescribed to the encompassing isodose. (Vansteenkiste et al., 2013)

A systematic review comparing outcomes of SBRT/SABR and surgery in patients with severe COPD revealed a higher 30-day mortality following surgery but similar OS at 1 and 3 years (Palma et al., 2012). Analysis of SBRT/SABR outcomes in 676 patients found a median OS of 40.7 months, and actuarial 5-year

rates of initial local, regional and distant recurrence of 10.5%, 12.7% and 19.9%, respectively (Senthi et al., 2012). A systematic review of SABR in centrally located tumours found local control rates of >85% with biologically equivalent doses ≥100 Gy (Senthi et al., 2013). The risk of high grade toxic effect was <9% when the biologically equivalent normal tissue dose was ≤210 Gy. Prospective trials of SBRT/SABR versus primary resection are now underway. (Vansteenkiste et al., 2013)

Radiofrequency ablation

Ambrogi et al. (2015) compared RFA and wedge resection in terms of disease recurrence and survival, as intent-to-treat therapy for stage I NSCLC in 121 marginal or non-surgical candidates.

Over a 7 year period, 59 patients were treated for stage I NSCLC with wedge resection and 62 with RFA. At a median follow-up of 36 and 42 months for wedge resection and for RFA (p=0.232), local recurrence rate was 2 and 23%, respectively (p=0.002). The 1-, 2- and 5-year overall survival (disease-free interval) rates were 100% (96%), 96% (90%) and 52% (76%) for wedge resection, and 93% (87%), 72% (63%), and 35% (55%) for RFA (p=0.044 and p=0.01, respectively). None of the analysed parameters was found to be risk factor for disease recurrence and survival, except stage T2, which significantly affected disease-recurrence, overall and cancer-related survival and disease-free interval in the RFA group.

Nevertheless, the debate seems open for patients with stage Ia disease. In these cases, RFA seems to have equivalent outcomes compared with wedge resection, thus the selection of patients is more challenging due to the acceptable risk level, which depends also on the different success rate of the non-surgical alternative therapies. Further prospective randomised studies are necessary, in order to clearly compare the outcomes of different modality therapies, but also to better define patients considered at high risk. (Ambrogi et al., 2015)

There is some evidence to show radiofrequency ablation can achieve local tumour control in patients with clinical stage Ia tumours; however there are no published studies that determine its utility compared to other management strategies and further clinical trials comparing RFA to other local therapies are therefore needed.

Recommendation 2.7.1.1	**Grade**
Every patient with early stage disease (T1-T2 N0 M0) should be evaluated for fitness for surgery. If unfit for surgery or surgery is declined, patients should be considered for radical treatment, preferably SBRT/SABR or radical radiotherapy.	**A**

Recommendation 2.7.1.2	**Grade**
Radiofrequency ablation (RFA) can be considered for patients with clinical stage Ia tumours who are not suitable for surgery following discussion at a multidisciplinary team meeting. (Refer to *Clinical question 2.2.3*).	**D**

Good practice point

If SBRT/SABR is not available or not feasible radical radiotherapy may be considered.

Clinical question 2.7.2

In patients with stage I-III NSCLC undergoing radical external beam radiation therapy what is the role and effectiveness of the following:

a) **New technology (IMRT/4DCT - breathing adapted radiotherapy)**
b) **Altered radiation fractionation schedules (Hyper and/or accelerated fractionation)**
c) **Dose**

Evidence summary

Three clinical guidelines (NICE, 2011, SIGN, 2014, Vansteenkiste et al., 2013), two retrospective studies (Cole et al., 2014, Liao et al., 2010) and an individual patient data meta-analysis (Mauguen et al., 2012) addressed this clinical question.

a) New technology

Newer technologies can reduce target volumes and hence normal tissue toxicity and can allow dose escalation to take place with the goal of increasing the biologically effective dose (BED) to a level to achieve maximal tumour treatment with acceptable toxicity outcomes (De Ruysscher et al., 2012, Machtay et al., 2012). Using isotoxic dose escalation, 4D planning in this study would allow, on average, an additional increase in total dose by a factor of 1.19 compared with 3D planned dose escalation. For 55 Gy in 20 fractions with a BED of 70.13 Gy_{10} this would mean an average increase to a BED of 83.3 Gy_{10}. Some studies suggest that an increase in absolute dose of 1 Gy is associated with a 3% reduction in death (Kong et al., 2005). By optimising dose prescription, potential gains for the patient in tumour control probability (TCP) can be realised while balancing the risk of acceptable normal tissue complication probability (NTCP) (Machtay et al., 2012). Mean Lung Dose (MLD) was lower for 19/20 of 4D planned cases, with an average reduction from 13.1 Gy to 11.1 Gy. This reduction in MLD can allow for dose escalation and where this is not possible, such as for conventional treatments that are not adapted or escalated, could theoretically lead to lower lung toxicity rates. (Cole et al., 2014)

Four-dimensional computed tomography (4DCT) based plans had lower planning target volume (PTV), a lower dose to organs at risk and lower predicted NTCP rates on LKB modelling ($p<0.006$). The clinical algorithm showed no difference for predicted 2-year survival and dyspnoea rates between the groups, but did predict for lower oesophageal toxicity with 4DCT plans ($p=0.001$). There was no correlation between LKB modelling and the clinical algorithm for lung toxicity or survival. Dose escalation was possible in 15/20 cases, with a mean increase in dose by a factor of 1.19 (10.45 Gy) using 4DCT compared with 3DCT plans. (Cole et al., 2014)

4DCT can theoretically improve therapeutic ratio and dose escalation based on dosimetric parameters and mathematical modelling. However, when individual characteristics are incorporated, this gain may be less evident in terms of survival and dyspnoea rates.

4DCT allows potential for isotoxic dose escalation, which may lead to improved local control and better overall survival. (Cole et al., 2014)

Mean follow-up times in the 4DCT/IMRT and CT/3DCRT groups were 1.3 (range, 0.1–3.2) and 2.1 (range, 0.1–7.9) years, respectively. The hazard ratios for 4DCT/IMRT were <1 for all disease end points; the difference was significant only for OS. The toxicity rate was significantly lower in the IMRT/4DCT group than in the CT/ 3DCRT group. V_{20} was significantly higher in the 3DCRT group and was a significant factor in determining toxicity. Freedom from DM was nearly identical in both groups. (Liao et al., 2010)

Treatment with 4DCT/IMRT was at least as good as that with 3DCRT in terms of the rates of freedom from locoregional progression (LRP) and distant metastasis (DM). There was a significant reduction in toxicity and a significant improvement in OS. (Liao et al., 2010)

b) Altered radiation fractionation schedules

One study of low quality was identified that examined the effectiveness of induction chemotherapy + hyperfractionated accelerated radiotherapy (HART) relative to the effectiveness of induction chemotherapy + standard once-daily RT in patients with stage IIIa and IIIb NSCLC (Belani et al., 2005). Overall survival, progression-free survival, response and incidence of grade 3 and above toxicities did not differ between the treatment groups. (NICE, 2011)

The European Society for Medical Oncology (ESMO) (Vansteenkiste et al., 2013) recommends the use of accelerated radiotherapy (e.g. 66Gy in 24 fractions) based on the results of a meta-analysis conducted by Maugen et al. (2012). The meta-analysis included individual patient data from phase III trials, it found that modified fractionation improved OS as compared with conventional schedules (hazard ratio (HR) = 0.88, 95% CI, 0.80 to 0.97; p=.009), resulting in an absolute benefit of 2.5% (8.3% to 10.8%) at 5 years. In both NSCLC and SCLC, the use of modified radiotherapy increased the risk of acute oesophageal toxicity (odds ratio [OR] = 2.44 in NSCLC and OR = 2.41 in SCLC; p<.001) but did not have an impact on the risk of other acute toxicities. The study concluded that patients with nonmetastatic NSCLC derived a significant OS benefit from accelerated or hyperfractionated radiotherapy; a similar but non-significant trend was observed for SCLC.

The Scottish Intercollegiate Guideline Network (SIGN) looked at hyperfractionated and/or accelerated radiotherapy in stage III NSCLC. They identified a meta-analysis and two RCTs (Lung Cancer Disease Group, 2000, Sause et al., 2000, Saunders et al., 1999) that suggest a survival benefit for accelerated and hyperfractionated radical radiation therapy compared with conventional radiotherapy. No benefit was observed for hyperfractionated radical radiation therapy of standard time length over conventional radiotherapy (SIGN, 2014).

Saunders et al. (1997) showed that continuous hyperfractionated accelerated radiation therapy (CHART) is more effective than 60 Gy over six weeks in patients with disease stage I to III not receiving chemotherapy.

c) Dose

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 (Rowell and Williams, 2004, Qiao et al., 2003). 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. (SIGN 2014)

Recommendation 2.7.2.1	**Grade**
In patients receiving combined chemoradiotherapy standard fractionation should be used to deliver a radical dose equivalent to 60 – 66 Gy.	**A**

Recommendation 2.7.2.2	**Grade**
When a radical dose is considered, 3D-CRT is the minimum technique to be used.	**B**

Recommendation 2.7.2.3	**Grade**
When available, CHART can be considered in patients with non-operable stage I-III non-small cell lung cancer (NSCLC) not receiving chemotherapy.	**A**

Good practice point
4DCT should be used when available.

Clinical question 2.7.3

In patients with stage III NSCLC undergoing radical three-dimensional conformal radiotherapy (3DCRT):

a) What are the most useful predictors of lung and oesophageal toxicity?

b) What are the most useful measures to reduce toxicity: clinical/technical?

Evidence summary

Two clinical guidelines (SIGN, 2014, Lim et al., 2010), two retrospective studies (Cole et al., 2014, Liao et al., 2010) and a review (Marks et al., 2010) addressed this clinical question.

A clinical oncologist specialising in lung oncology should determine suitability for radical radiotherapy, taking into account performance status and comorbidities. (SIGN, 2014)

When planning radical radiotherapy to the thorax it is crucial to take into account the dose delivered to the normal lung tissue, oesophagus, spinal cord and heart. In order to ensure the maximum sparing of normal tissues, three-dimensional treatment planning is mandatory (Senan et al., 2004). However, defining limits of dose tolerated by these tissues is complex as these limits vary according to the total dose delivered, fractionation regimen and use of concurrent chemotherapy (Milano et al., 2007, Schultheiss et al., 1995, van Baardwijk et al., 2008a, van Baardwijk et al., 2008b). The risk of developing radiotherapy-induced lung toxicity can be estimated by calculating the dose-volume histogram of the lungs, including V_{20} and mean lung dose (MLD) (Graham et al., 1999, Kwa et al., 1998). (Lim et al., 2010)

The greatest limitation of thoracic radiotherapy is radiotherapy induced lung toxicity (Graham et al., 1999, Kwa et al., 1998, Roach et al., 1995, Gandara et al., 2003). Radiotherapy planning parameters such as V_{20} and MLD are effective tools for predicting radiation pneumonitis (Graham et al., 1999, Kwa et al., 1998). (Lim et al., 2010)

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 T_{LCO}) for radical radiotherapy have not been established (Lim et al., 2010). (SIGN, 2014)

According to the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) lung-specific paper (Marks et al., 2010) it is prudent to limit V_{20} to ≤30–35% and mean lung dose to ≤20–23 Gy (with conventional fractionation) if one wants to limit the risk of radiation pneumonitis to ≤20% in definitively treated patients with non–small cell lung cancer.

Cole et al. (2014) investigated the potential dosimetric and clinical benefits predicted by using four-dimensional computed tomography (4DCT) compared with 3DCT in the planning of radical radiotherapy for non-small cell lung cancer.

Twenty patients were planned using free breathing 4DCT then retrospectively delineated on three-dimensional helical scan sets (3DCT). Beam arrangement and total dose (55 Gy in 20 fractions) were matched for 3D and 4D plans. Plans were compared for differences in planning target volume (PTV) geometrics and NTCP for organs at risk using dose volume histograms. Tumour control probability and NTCP were modelled using the Lyman–Kutcher–Burman (LKB) model. This was compared with a predictive clinical algorithm (Maastro), which is based on patient characteristics, including: age, performance status, smoking history, lung function, tumour staging and concomitant chemotherapy, to predict survival and toxicity outcomes. Potential therapeutic gains were investigated by applying isotoxic dose escalation to both plans using constraints for MLD (18 Gy), oesophageal maximum (70 Gy) and spinal cord maximum (48 Gy). (Cole et al., 2014)

In addition to oesophageal dosimetry, the use of concurrent delivery of chemotherapy has been shown to increase toxicity rates (Belderbos et al., 2005, Auperin et al., 2010). (Cole et al., 2014)

Radiation pneumonitis is an important consideration for patients with lung cancer, particularly for those with already compromised respiratory function (Wang et al., 2002). This potentially life-threatening complication is generally experienced in the first months after treatment. Established theoretical models to predict the risk of pneumonitis include MLD or the volume of lung receiving more than a threshold dose (e.g. V_{20}) (Kwa et al., 1998, Fay et al., 2005). Predicted rates for lung toxicity in this group were 22% less for the 4D group. When specific tumour and patient characteristics were combined with dosimetric parameters, this apparent improvement was not seen. This suggests that despite close attention to dose constraints and dose volume histogram (DVH) characteristics, clinical factors may have a larger impact on pneumonitis risks and outweigh any improvements that 4DCT may convey on an individual basis. (Cole et al., 2014)

Treatment with 4DCT/IMRT was at least as good as that with 3DCRT in terms of the rates of freedom from locoregional progression (LRP) and distant metastasis (DM). There was a significant reduction in toxicity and a significant improvement in OS (Liao et al., 2010).

Recommendation 2.7.3.1	**Grade**
Perform three-dimensional treatment planning in patients undergoing radical thoracic radiotherapy. 4DCT should be performed where available.	**B**

Recommendation 2.7.3.2	**Grade**
The dose volume parameters for the organs at risk (e.g. oesophagus, lung) need to be taken into account. It is prudent to limit V_{20} to ≤30–35% and mean lung dose to ≤20–23 Gy (with conventional fractionation) if one wants to limit the risk of radiation pneumonitis to ≤20% in definitively treated patients with NSCLC.	**B**

Good practice point
Pre-radical radiotherapy pulmonary function tests are recommended.

Good practice point
A clinical oncologist specialising in lung oncology should determine suitability for radical radiotherapy, taking into account performance status, comorbidities and tumour volume.

Clinical question 2.7.4

In patients with NSCLC post surgery, which groups should receive postoperative radiotherapy (PORT) or adjuvant RT?

a) pN2 R0

b) any pN, R1, R2 resection

Evidence summary

A clinical guideline (Lim et al., 2010) and a meta-analysis (PORT meta-analysis Trialist Group, 1998) addressed this clinical question.

a) pN2 R0

The role of postoperative radiotherapy in treatment of patients with completely resected NSCLC remains unclear. The PORT Meta-analysis Trialists Group undertook a systematic review and meta-analysis of the available evidence from randomised trials.

Updated data were obtained on individual patients from all available randomised trials of postoperative radiotherapy versus surgery alone. Data on 2128 patients from nine randomised trials (published and unpublished) were analysed by intention to treat. Median follow-up was 3.9 years (2.3–9.8 for individual trials) for surviving patients. The results show a significant adverse effect of postoperative radiotherapy on survival (HR 1.21 [95% CI 1.08–1.34]). Subgroup analyses suggest that this adverse effect was greatest for patients with stage I/II, N0–N1 disease, whereas for those with stage III, N2 disease there was no clear evidence of an adverse effect. The authors concluded that postoperative radiotherapy is detrimental to patients with early-stage completely resected NSCLC and should not be used routinely for such patients. The role of postoperative radiotherapy in the treatment of N2 tumours is not clear and may warrant further research. (PORT Meta-analysis Trialists Group, 1998)

b) Any pN, R1, R2 resection

The role of PORT in patients with a positive resection margin (R1 resection) is unknown as there are no randomised trials examining the role of radiotherapy in this group of patients (Wind et al., 2007, Jassem, 2007). PORT is often given in routine practice if pathological examination shows tumour at the resection margin on the basis of retrospective series showing a reduction in the local recurrence rates following PORT (Massard et al., 2000, Kimura and Yamaguchi, 1994, Ghiribelli et al., 1999, Gebitekin et al., 1994, Heikkila et al., 1986) or an excess of local recurrence rates without PORT (Snijder et al., 1998). However, some retrospective series have shown high local recurrence rates despite the use of PORT (Gebitekin et al., 1994, Snijder et al., 1998). It should also be noted that a retrospective study showed an adverse impact of radiotherapy on survival in patients irradiated for positive margins (Massard et al., 2000). (Lim et al., 2010)

A literature review on this topic suggested that patients with stage I and II disease and positive margins are more likely to benefit from PORT than patients with stage III disease (Wind et al., 2007). Indeed, survival of patients with stage I and II non-small cell lung cancer and an R1 resection of the bronchial resection margin is significantly worse compared with the stage corrected survival after radical surgery (Liewald et al., 1992). The potential benefit of this treatment in terms of reduction of the risk of local recurrence rate has to be weighed carefully against the risk of morbidity and mortality related to PORT. (Lim et al., 2010)

The optimal dose/fractionation for PORT is not known, but modern studies suggest that a dose in the range of 50-55 Gy using conventional fractionation should be used (Trodella et al., 2002, Bogart and Aronowitz, 2005). There are few randomised data investigating the benefit of PORT and its optimal sequencing in the context of adjuvant chemotherapy. In adjuvant chemotherapy trials allowing the use of PORT, the radiotherapy was delivered after completion of adjuvant chemotherapy and did not seem

to offset the beneficial effect of adjuvant chemotherapy (Douillard et al., 2006, Arriagada et al., 2004, Scagliotti et al., 2003). (Lim et al., 2010)

Recommendation 2.7.4.1	**Grade**
In patients with R1 resection, regardless of N status, postoperative radiotherapy (PORT) should be proposed sequentially delivering a radical dose of 60 Gy in 30 fractions.	**B**

Recommendation 2.7.4.2	**Grade**
In patients with a pN2 stage and a complete resection there is no consensus to the benefit of PORT. If considered, PORT should be delivered at a dose of 50 Gy standard fractionation.	**B**

Recommendation 2.7.4.3	**Grade**
PORT is **not** indicated in patients with a complete resection R0 and N0 disease.	**B**

Clinical question 2.7.5

In patients with small-cell lung cancer (SCLC), what is the evidence supporting the role of radiotherapy (including technical parameters)

a) **Limited-stage prophylactic cranial irradiation (PCI)**
b) **Limited-stage thoracic radiotherapy**
c) **Extensive-stage PCI**
d) **Extensive-stage thoracic radiotherapy**

Evidence summary

A meta-analysis (Pignon et al., 1992), three randomised controlled trials (Le Pechoux et al., 2009, Slotman et al., 2007, Slotman et al., 2015) and a retrospective study (Patel et al., 2009) addressed this clinical question.

a) Limited-stage prophylactic cranial irradiation (PCI)

A large retrospective analysis evaluating the effects of PCI on overall survival and cause-specific survival (Patel et al., 2009) found overall survival at 2 years, 5 years, and 10 years was 23%, 11%, and 6%, respectively, in patients who did not receive PCI. In patients who received PCI, the 2-year, 5-year, and 10-year overall survival rates were 42%, 19%, and 9%, respectively ($p<0.001$). The cause-specific survival rate at 2 years, 5 years, and 10 years was 28%, 15%, 11%, respectively, in patients who did not receive PCI and 45%, 24%, 17%, respectively, in patients who did receive PCI ($p<0.001$). On multivariate analysis of cause-specific and overall survival, age at diagnosis, sex, grade, extent of primary disease, size of disease, extent of lymph node involvement, and PCI were found to be significant ($p<0.001$). Significantly improved overall and cause-specific survival was observed in patients treated with prophylactic cranial irradiation on unadjusted and adjusted analyses. This study concurs with the previously published European experience. PCI should be considered for patients with limited-stage small cell lung cancer.

The optimum dose of prophylactic cranial irradiation (PCI) for limited-stage small-cell lung cancer (SCLC) is unknown. A randomised clinical trial (Le Pechoux et al., 2009) compared the effect of standard versus higher PCI doses on the incidence of brain metastases. Seven hundred and twenty patients with limited-stage SCLC in complete remission after chemotherapy and thoracic radiotherapy from 157 centres in 22 countries were randomly assigned to a standard (n=360, 25 Gy in 10 daily fractions of 2.5 Gy) or higher PCI total dose (n=360, 36 Gy) delivered using either conventional (18 daily fractions of 2 Gy) or accelerated hyperfractionated (24 fractions in 16 days with two daily sessions of 1.5 Gy separated by a minimum interval of 6 h) radiotherapy. After a median follow-up of 39 months (range 0–89 months), 145 patients had brain metastases; 82 in the standard-dose group and 63 in the higher-dose group.

There was no significant difference in the 2-year incidence of brain metastases between the standard PCI dose group and the higher-dose group, at 29% (95% CI 24–35) and 23% (18–29), respectively (HR 0.80 [95% CI 0.57–1.11], p=0.18). Two hundred and twenty six patients in the standard-dose group and 252 in the higher-dose group died; 2-year overall survival was 42% (95% CI 37–48) in the standard-dose group and 37% (32–42) in the higher-dose group (HR 1.20 [1.00–1.44]; p=0.05). The authors concluded that no significant reduction in the total incidence of brain metastases was observed after higher-dose PCI, but there was a significant increase in mortality. PCI at 25 Gy should remain the standard of care in limited-stage SCLC. (Le Pechoux et al., 2009)

b) Limited-stage thoracic radiotherapy

Pignon et al. (1992) performed a meta-analysis of thoracic RT for SCLC. It included 13 trials comparing chemotherapy alone to chemotherapy and thoracic RT totalling 2,140 patients, of which 433 were excluded as they had extensive disease. 1,862 of the 2,103 patients who could be evaluated died; the median follow-up of the surviving patients was 43 months. The relative risk of death in the combined therapy group compared to the chemotherapy group was 0.86 (95% CI 0.78-0.94; p=0.001). There was

a 5.4% benefit in terms of overall survival at three years for the combined therapy group. The authors concluded that thoracic RT moderately improves survival in patients with limited SCLC who are treated with combination chemotherapy.

There is controversy regarding the optimal timing of thoracic radiotherapy, with some meta-analysis suggesting a small OS benefit of early delivery concomitantly to chemotherapy. However, this is associated with an increase in treatment related toxicity (Lu et al., 2014, Spiro et al., 2006, Pijls-Johannesma et al., 2005, Huncharek and McGarry, 2004, Fried et al., 2004).

c) Extensive-stage PCI

Slotman et al., (2007) conducted a randomised trial (European Organisation for Research and Treatment of Cancer 08993-22993) of PCI in patients with extensive-stage small-cell lung cancer who had had any degree of response to chemotherapy. Patients were randomly assigned to undergo PCI or to receive no further therapy. The primary end point was the time to symptomatic brain metastases. CT scanning or MRI of the brain was performed when any predefined key symptom suggestive of brain metastases was present, but was not done routinely prior to PCI. The two groups (each with 143 patients) were well balanced regarding baseline characteristics. The cumulative risk of brain metastases within 1 year was 14.6% in the PCI group and 40.4% in the control group (HR 0.27; p<0.001). PCI was associated with an increase in median overall survival from 5.4 to 6.7 months after randomisation. The 1-year survival rate was 27.1% in the PCI group and 13.3% in the control group (p=0.003). PCI had side effects but did not have a clinically significant effect on global health status. The largest mean difference between the two arms was observed in fatigue and hair loss, which were greater in those who received PCI (Slotman et al., 2009). PCI reduced the incidence of symptomatic brain metastases and prolonged overall survival in patients with extensive-stage small-cell lung cancer (Slotman et al., 2007).

d) Extensive-stage thoracic radiotherapy

Most patients with extensive-stage small-cell lung cancer who undergo chemotherapy, and prophylactic cranial irradiation, have persistent intrathoracic disease. Slotman et al. (2015) assessed thoracic radiotherapy for treatment of this patient group.

A phase III randomised controlled trial at 42 hospitals: 16 in Netherlands, 22 in the UK, three in Norway, and one in Belgium, enrolled patients with WHO performance score 0–2 and confirmed extensive-stage small-cell lung cancer who responded to chemotherapy. Four hundred and ninety-eight patients were randomly assigned (1:1) to receive either thoracic radiotherapy (30 Gy in ten fractions) or no thoracic radiotherapy. All underwent prophylactic cranial irradiation. Three withdrew informed consent, leaving 247 patients in the thoracic radiotherapy group and 248 in the control group.

Mean interval between diagnosis and randomisation was 17 weeks. Median follow-up was 24 months. Overall survival at 1 year was not significantly different between groups: 33% (95% CI 27–39) for the thoracic radiotherapy group versus 28% (95% CI 22–34) for the control group (HR 0.84, 95% CI 0.69–1.01; p=0.066). However, in a secondary analysis, 2-year overall survival was 13% (95% CI 9–19) versus 3% (95% CI 2–8; p=0.004). Progression was less likely in the thoracic radiotherapy group than in the control group (HR 0.73, 95% CI 0.61–0.87; p=0.001). At 6 months, progression-free survival was 24% (95% CI 19–30) versus 7% (95% CI 4–11; p=0.001). No severe toxic effects were recorded. The most common grade 3 or higher toxic effects were fatigue (11 vs 9) and dyspnoea (three vs four). (Slotman et al., 2015)

The authors concluded that thoracic radiotherapy in addition to prophylactic cranial irradiation should be considered for all patients with extensive-stage small-cell lung cancer who respond to chemotherapy. (Slotman et al., 2015)

This is supported by a recent meta-analysis (Palma et al., 2016) that combined the RCT detailed above (Slotman et al., 2015) with an older RCT (Jeremic et al., 1999). Palma et al. (2016) examined the role of thoracic radiotherapy (TRT) in patients receiving platinum-based chemotherapy for extensive-stage small-cell lung cancer. Overall, the delivery of TRT was associated with improved overall survival (HR 0.81; 95% confidence interval, 0.69-0.96; p=.014) and progression-free survival (HR 0.74; 95% confidence interval, 0.64-0.87, p<.001). Bronchopulmonary toxicity (grade 3 or higher) was similar in both groups (≤2%). Oesophageal toxicity (grade 3 or higher) was 6.6% in the TRT arm and 0% in the non-TRT arm (p<.001). The study concluded that TRT improves overall survival and progression-free survival in patients with extensive-stage small-cell lung cancer, with a small incremental risk of oesophageal toxicity. Future randomised trials to identify possible survival benefits of TRT dose escalation in patients with extensive-stage small-cell lung cancer would assist clinicians in selecting the optimal dose while minimising oesophageal toxicity.

Recommendation 2.7.5.1	**Grade**
Consolidation prophylactic cranial irradiation (PCI) is recommended in patients with limited-stage small-cell lung cancer (SCLC) having a response to chemoradiotherapy.	**A**

Recommendation 2.7.5.2	**Grade**
In combined modality care, thoracic radiotherapy is recommended in patients with limited-stage SCLC and should be initiated as early as possible.	**A**

Recommendation 2.7.5.3	**Grade**
Consolidation PCI is recommended in patients with extensive-stage SCLC having a response to chemotherapy.	**A**

Recommendation 2.7.5.4	**Grade**
Consolidation thoracic radiotherapy may be considered in patients with extensive-stage SCLC having a response to chemotherapy.	**A**

2.8 Palliative Care

Responsibility for the implementation of palliative care recommendations
While the CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the recommendations in this National Clinical Guideline, each member of the multidisciplinary team is responsible for the implementation of the individual guideline recommendations relevant to their discipline.

The literature used in the development of this guideline was based on the 7th edition of the Lung Cancer TNM staging system. The 8th edition of the TNM staging system was published in December 2016 (Brierley et al., 2016), this may lead to changes in recommendations over time, which should be taken into consideration at multidisciplinary team meetings.

Clinical question 2.8.1

Does the involvement of specialist palliative care result in better quality of life for patient or family, symptom control, or improved cost effectiveness compared with standard care alone (no involvement from specialist palliative care)?

Evidence summary

An ASCO provisional clinical opinion (Smith et al., 2012) addressed this clinical question.

Based on strong evidence from a phase III RCT (Temel et al., 2010), patients with metastatic NSCLC should be offered concurrent palliative care and standard oncologic care at initial diagnosis. Patients assigned to early palliative care had a better quality of life than patients assigned to standard care (mean score on the FACT-L scale [in which scores range from 0 to 136, with higher scores indicating better quality of life], 98.0 vs. 91.5; p=0.03). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs. 38%, p=0.01). Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care (33% vs. 54%, p=0.05), median survival was longer among patients receiving early palliative care (11.6 months vs. 8.9 months, p=0.02). While a survival benefit from early involvement of palliative care has not yet been demonstrated in other oncology settings, substantial evidence demonstrates that palliative care when combined with standard cancer care or as the main focus of care leads to better patient and caregiver outcomes. These include improvement in symptoms, QOL, and patient satisfaction, with reduced caregiver burden. Earlier involvement of palliative care also leads to more appropriate referral to and use of hospice, and reduced use of futile intensive care. While evidence clarifying optimal delivery of palliative care to improve patient outcomes is evolving, no trials to date have demonstrated harm to patients and caregivers, or excessive costs, from early involvement of palliative care. (Smith et al., 2012)

Recommendation 2.8.1.1	**Grade**
Patients with stage IV non-small cell lung cancer (NSCLC) should be offered concurrent specialist palliative care and standard oncological care at initial diagnosis.	**B**

Good practice point

All patients with advanced stage lung cancer should have their palliative care needs assessed.

Clinical question 2.8.2

Who should comprise the palliative care multidisciplinary team?

Evidence summary

A report from the National Advisory Committee on Palliative Care (DoH, 2001) addressed the clinical question.

Better outcomes tend to be observed where teams are categorised as 'specialist' and consist of multidisciplinary trained staff. There is no strong evidence to support a particular team composition in each setting, and no research evidence on the level of specialisation required for team members. There is no evidence on the number of team members from each profession required to enable provision of an effective and efficient service.

According to the Report of the National Advisory Committee on Palliative Care (DoH, 2001) all specialist palliative care services should have at least one consultant in palliative medicine, with a support team of non-consultant hospital doctors (NCHDs).

Specialist palliative care services should have nursing staff with a skill mix to meet the requirements of the service.

Specialist services should also have the following staff available full-time, part-time or with regular sessions:

- Physiotherapist(s)
- Occupational therapist(s)
- Social worker(s)
- Staff specifically trained to meet the psychosocial needs of the patient, family and carers
- Suitably trained and experienced members of staff who will be responsible for bereavement services
- Co-ordinator of spiritual care
- Speech and language therapist
- Dietitian/clinical nutritionist
- Pharmacist
- Complementary therapist(s). (DoH, 2001)

Good practice point

A specialist palliative care multidisciplinary team meeting should be available to provide, physical, psychological, social and spiritual care to patients with lung cancer and their carers.

3 Development of this National Clinical Guideline

3.1 Clinical and financial impact of lung cancer

The diagnosis, staging, and treatment of patients with lung cancer requires multidisciplinary care in an acute hospital setting. The majority of patients will require diagnostic tests (radiology, pathology) and depending on the treatment plan may require surgery, radiotherapy and chemotherapy.

A population-based cost analysis (Luengo-Fernandez et al., 2013) illustrated the economic burden of cancer on the European Union (EU). In 2009, cancer is estimated to have cost the EU €126 billion, with healthcare costs accounting for €51 billion (40%). They found that lung cancer had the highest economic cost (€18.8 billion, 15% of overall cancer costs), followed by breast cancer (€15.0 billion, 12%), colorectal cancer (€13.1 billion, 10%), and prostate cancer (€8.43 billion, 7%).

Inpatient care was the major component of health-care costs in lung cancer (€2.87 billion, 68%). The highest productivity losses attributable to mortality were identified for lung cancer (€9.92 billion; 23% of the €42.6 billion in productivity losses because of all cancers). The costs of informal care were also highest for patients with lung cancer (€3.82 billion; 16% of the €23.2 billion total informal care provided). With lung cancer incidence expected to increase by 136% in females (Nordpred model) and 52% in males (NCRI, 2014), there could be a significant increase seen in healthcare costs per person in Ireland.

Most of the recommendations in this guideline represent current standard practice and are therefore cost neutral. However, the GDG have identified areas that require change in practice to ensure full implementation of the guideline. The potential resource implications of applying these recommendations have been considered (Appendix 6: Budget Impact Assessment). However, it is important to note that the cost effectiveness analysis and the budget impact analysis are carried out separately from the generation of clinical recommendations. The methodology applied is documented in Section 3.8 Methodology and literature review. For areas where additional resources are required to implement the guideline the resources required will be sought through the HSE service planning process.

3.2 Rationale for this National Clinical Guideline

The National Cancer Strategy (DoHC, 2006) recommended that national site-specific multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care. The principal objective of developing these guidelines is to improve the quality of care received by patients. Other objectives include:

- Improvement in patient outcomes,
- Potential for reduction in morbidity and mortality,
- Improvement in quality of life,
- Promotion of interventions of proven benefit and discouragement of ineffective ones,
- Improvements in the consistency and standard of care.

The National Cancer Strategy 2017-2026 (DoH, 2017) recommends: *The NCCP will develop further guidelines for cancer care in line with National Clinical Effectiveness Committee (NCEC) standards*.

3.3 Aim and objectives

The overall objectives of the NCCP's National Clinical Guideline 'Diagnosis, staging and treatment of patients with lung cancer' are:

- To improve the quality of clinical care,
- To reduce variation in practice,
- To address areas of clinical care with new and emerging evidence.

The guideline is based on the best research evidence in conjunction with clinical expertise, and developed using a clear evidence-based internationally used methodology.

3.4 Guideline scope

This National Clinical Guideline was developed to improve the standard and consistency of clinical practice in line with the best and most recent scientific evidence available.

This guideline focuses on the diagnosis, staging, and treatment of patients with lung cancer. This guideline does not include recommendations covering every detail of diagnosis, staging, and treatment. Instead this guideline focuses on areas of clinical practice:

(i) known to be controversial or uncertain,
(ii) where there is identifiable practice variation,
(iii) where there is new or emerging evidence,
(iv) where guidelines have potential to have the most impact.

This guideline focuses solely on the clinical management of patients with lung cancer. The NCCP has developed general practitioner (GP) referral guidelines, standardised GP referral forms, and GP electronic referral for patients with lung cancer. The NCCP in partnership with the Irish Cancer Society has commenced a cancer survivorship programme. The main goal for the NCCP Survivorship Programme is to empower patients to achieve their best possible health while living with and beyond a diagnosis of cancer. This involves providing information, guidance and support to survivors and their families and healthcare professionals in relation to healthy lifestyle, disease prevention and control. It aims to promote a good quality of life and prolonged survival for people who experience cancer.

The NCCP has also a Lung National Clinical Leads Network with defined terms of reference. The output of this network includes the following:

- Development and agreement of Key Performance Indicators (KPIs),
- Organising annual multidisciplinary Cancer Quality and Audit Fora,
- Focus on cancer specific issues such as the development of information resources for patients and health professionals.

Patient information booklets/leaflets covering various aspects of the cancer journey are available on the NCCP website.

3.5 Conflict of interest statement

A conflict of interest form (see 'NCCP Methodology Manual') was signed by all GDG members and reviewers. The GDG was managed by the Chair to promote the highest professional standard in the development of this guideline. Where a conflict arises a GDG member absents themselves from discussion pertaining to their area of conflict.

3.6 Sources of funding

The guideline was commissioned and funded by the NCCP; however, the guideline content was not influenced by the NCCP or any other funding body. This process is fully independent of lobbying powers. All recommendations were based on the best research evidence integrated with clinical expertise.

3.7 Methodology and literature review

The methodology for the development of the guideline was designed by a research methodologist and is based on the principles of Evidence-Based Practice (EBP) (Sackett et al., 2000). The methodology is described in detail in the NCCP Methodology Manual for guideline development.

3.7.1 Step 1: Develop clinical questions

The first step in guideline development was to identify areas of new and emerging evidence, areas with identifiable variation in practice, or areas with potential to impact on patients care. These questions then formed the basis for the types of evidence being gathered, the search strategy, and the inclusion and exclusion criteria.

To formulate the clinical questions they were broken down into their component parts using the PICO(T) framework:

- Participant/Population
- Intervention/Exposure
- Control/Comparison
- Outcome
- Time

This process was carried out by discipline specific sub-groups. The GDG signed off the entire list of clinical questions to ensure a comprehensive guideline. The resulting 44 clinical questions are listed in Appendix 2: Clinical Questions in PICO format.

3.7.2 Step 2: Search for the evidence

The clinical questions formulated in step one were used to conduct literature searches of the primary literature. The systematic literature review protocol was developed for the guideline development process by the HSE librarians in conjunction with the NCCP (Appendix 4: Literature review protocol). The following bibliographic databases were searched in the order specified below using keywords implicit in the PICO(T) question and any identified subject headings:

- Cochrane Library
- Point-of-Care Reference Tools
- Medline
- Embase (where available)
- Other bibliographic databases such as PsycINFO, CINAHL, as appropriate.

The literature was searched based on the hierarchy of evidence. The literature was updated prior to publication. This necessitated a complete review and rewrite of the medical oncology section in July 2016. This is a live document, updates and reviews are carried out at three year intervals.

A literature search for the budget impact assessment was performed using the SIGN economic filter (Table 11. Economic literature review protocol). Full details of this search strategy are available in Appendix 6: Budget Impact Assessment.

3.7.3 Step 3: Appraise the literature for validity and applicability

International guidelines were appraised using the international, validated tool the AGREE II instrument (Brouwers et al., 2010). Primary papers were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (SIGN).

Economic papers included in the Budget Impact Assessment (Appendix 6: Budget Impact Assessment) were appraised by a health economist using validated economic checklists developed by SIGN.

There were three main points considered when appraising all the research evidence:

- Are the results valid? (internal validity)
- What are the results? (statistical and clinical significance)
- Are the results applicable/generalisable to the patient/population of this guideline? (external validity)

3.8 Formulation and grading of recommendations

The evidence which addressed each clinical question, both from international guidelines and primary literature, was extracted into evidence tables. Recommendations were formulated through a formal structured process. A 'considered judgment form' (adapted from SIGN) was completed for each clinical question.

The following items were considered and documented:

- What evidence is available to answer the clinical question?
- What is the quality of the evidence?
  - Is the evidence consistent?
  - Is the evidence generalisable to the Irish population?
  - Is the evidence applicable in the Irish context?
- What is the potential impact on the health system?
- What is the potential benefit versus harm to the patient?
- Are there resource implications?

The evidence summaries and recommendations were then written. Each recommendation was assigned a grade by the GDG. The grade reflected the level of evidence upon which the recommendations were based, the directness of the evidence, and whether further research is likely to change the recommendation. The levels of evidence tables and grading systems used are documented in Appendix 10: Levels of Evidence & Grading Systems.

Good practice points were based on the clinical expertise of the GDG. For the economic literature, key messages are presented in boxes entitled 'relevance to the guideline recommendations'.

3.9 Consultation summary

3.9.1 Patient Advocacy

A collaborative approach is used in the development of the NCCP patient information, clinical guidelines and other national projects. All NCCP booklets are submitted to the National Adult Literacy Agency (NALA) (www.nala.ie) for the Plain English Award. This is to ensure comprehension and readability are in line with health literacy best practice standards. Service user testing is a key part of the process, and includes liaising with the HSE Patient Forum, online surveys, and engaging with other relevant patient groups e.g. Irish Cancer Society, Marie Keating Foundation.

The views and preferences of the target population were sought by inviting patient advocacy groups (HSE Patient Forum, Irish Cancer Society, Cancer Care West, Marie Keating Foundation, Gary Kelly Cancer Support Centre and Bray Cancer Support Centre) to engage in the National Stakeholder Review process (Appendix 5: Details of consultation process).

3.9.2 National Stakeholder review

The draft guideline was signed off by the entire GDG, and the NCCP Guideline Steering Group before going to National Stakeholder Review. It was circulated to relevant organisations and individuals for comment between June 12th – July 24th 2014. A full list of those invited to review this guideline is available in Appendix 5: Details of consultation process.

Stakeholders were asked to comment on the comprehensiveness of evidence used to form the recommendations. Stakeholders were required to submit feedback with supporting evidence on a form provided (see 'NCCP Methodology Manual') along with a completed conflict of interest form. A time-period of six weeks was allocated to submit comments.

All feedback and supporting evidence received was reviewed by the GDG. All modifications were documented.

3.10 External review

The amended draft guideline was then submitted for international expert review. The GDG nominated three international reviewers to provide feedback on the draft guideline. These reviewers were chosen based on their in-depth knowledge of the subject area and guideline development processes. The review followed the same procedure as the National Stakeholder Review. The guideline was circulated for comment between the 19th May 2016 and the 4th of July 2016. A log was recorded of all submissions and amendments from the national stakeholder review and international expert review process and is available on request from the GDG.

3.11 Implementation

This National Clinical Guideline should be reviewed by the multidisciplinary team and senior management in the hospital to plan the implementation of the recommendations.

The CEO, General Manager and the Clinical Director of the hospital have corporate responsibility for the implementation of the National Clinical Guideline and to ensure that all relevant staff are appropriately supported to implement the guideline. A Cancer Network Manager from the NCCP meets with each cancer centre on a quarterly basis for performance monitoring and service planning.

All medical staff with responsibility for the care of patients with lung cancer are required to:

- Comply with this National Clinical Guideline and any related procedures or protocols.
- Adhere to their code of conduct and professional scope of practice guidelines as appropriate to their role and responsibilities.
- Maintain their competency for the management and treatment of patients with lung cancer.

The implementation plan is based on the COM-B theory of behaviour change (Michie et al., 2011), as outlined in the NCCP Methodology Manual. The implementation plan outlines facilitators and barriers to implementation (Appendix 7: Implementation Plan).

This National Clinical Guideline will be circulated and disseminated through the professional networks who participated in developing and reviewing this document. The guideline will also be available on the NCEC and NCCP websites.

A multidisciplinary team (MDT) is responsible for the implementation of the guideline recommendations.

A summary of tools to assist in the implementation of this National Clinical Guideline are available in Appendix 3: Summary of the tools to assist in the implementation of the National Clinical Guideline.

3.12 Monitoring and evaluation

The National Cancer Control Programme engages regularly with the individual cancer centres and with Hospital Group structures. Discussion of performance data, improvement plans, resources including manpower, service planning and development takes place at regular review meetings between the NCCP and senior management at cancer centre and Hospital Group level.

3.13 Procedure to update this National Clinical Guideline

This guideline, published in 2017, will be considered for review by the NCCP in three years. Surveillance of the literature base will be carried out periodically by the NCCP. Any updates to the guideline in the interim period or as a result of three year review will be subject to the NCEC approval process and noted in the guidelines section of the NCCP and NCEC websites.

4 Appendices

Appendix 3: Summary of the tools to assist in the implementation of this National Clinical Guideline

NCCP. National Clinical Guidelines for Cancer – Methodology Manual.
National Cancer Control Programme, 2014.

NCCP Website: Information for Health Professionals

NCCP Website: Patient Information

Health Information and Quality Authority (HIQA). National Standards for Safer Better Healthcare

Centre for Evidence Based Medicine

Improving Health: Changing Behaviour - NHS Health Trainer Handbook

UCL Centre for Behaviour Change

Michie, S; Atkins, L; West, R; (2014) The Behaviour Change Wheel: A Guide to Designing Interventions. (1st ed.). Silverback Publishing: London.

Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ; 337.

Medical Research Council. (2008). Developing and evaluating complex
interventions: new guidance. Available from: www.mrc.ac.uk/complexinterventionsguidance.

Guide for health professionals
30 Second Stop Smoking Advice, NCCP

Patient information booklets/leaflets
Rapid Access Lung Clinic - A Guide for Patients, NCCP

Quit smoking to reduce your cancer risk - NCCP cancer prevention factsheet, NCCP

Appendix 9: Glossary and abbreviations

Glossary

Definitions within the context of this document

Case Control Study	The observational epidemiologic study of persons with the disease (or other outcome variable) of interest and a suitable control (comparison, reference) group of persons without the disease. The relationship of an attribute to the disease is examined by comparing the diseased and nondiseased with regard to how frequently the attribute is present or, if quantitative, the levels of the attribute, in each of the groups. (CEBM website)
Case Series	A group or series of case reports involving patients who were given similar treatment. Reports of case series usually contain detailed information about the individual patients. This includes demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment. (CEBM website)
Cohort study	The analytic method of epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature of cohort study is observation of large numbers over a long period (commonly years) with comparison of incidence rates in groups that differ in exposure levels. (CEBM website)
Validity	The extent to which a variable or intervention measures what it is supposed to measure or accomplishes what it is supposed to accomplish. The internal validity of a study refers to the integrity of the experimental design. The external validity of a study refers to the appropriateness by which its results can be applied to non-study patients or populations. (CEBM website)
Meta-analysis	A systematic review may or may not include a meta-analysis, which is a quantitative summary of the results. (CEBM website)
Randomised trial	An epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, maneuver, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. (CEBM website)
Systematic review	The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic. Systematic reviews focus on peer-reviewed publications about a specific health problem and use rigorous, standardised methods for selecting and assessing articles. A systematic review may or may not include a meta-analysis, which is a quantitative summary of the results. (CEBM website)

Abbreviations

The following abbreviations are used in this document:

3DCRT	Three-Dimensional Conformal Radiotherapy
4DCT	Four-Dimensional Computed Tomography
AE	Adverse Event
AAH	Adenomatous Alveolar Hyperplasia
AGREE II	Appraisal of Guidelines for Research and Evaluation II
ALK	Anaplastic Lymphoma Kinase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AUC	Area Under the Curve
BAC	Bronchioloalveolar Carcinoma
BED	Biologically Effective Dose
BH	Beaumont Hospital
BSC	Best Supportive Care
BTS	British Thoracic Society
CAV	Cyclophosphamide, Doxorubicin and Vincristine
CB	Core Needle Biopsy
CDR	Clinical Decision Rule
CEA	Cost-Effectiveness Analysis
CEBM	Centre for Evidence-Based Medicine
CEO	Chief Executive Officer
CFRT	Conventionally Fractionated Radiotherapy
CHART	Continuous Hyperfractionated Accelerated Radiation Therapy
CI	Confidence Interval
CISH	Chromogenic In Situ Hybridisation
CK5	Cytokeratin 5
CK6	Cytokeratin 6
CNS	Central Nervous System
COM-B	Capability; Opportunity; Motivation; Behaviour
COPD	Chronic Obstructive Pulmonary Disease
CQ	Clinical Question
CrI	Credible Interval
CRT	Chemoradiotherapy
CSO	Central Statistics Office
CT	Computed Tomography
CUH	Cork University Hospital
CXR	Chest X-ray
D_{LCO}	Diffusing Capacity of the Lung for Carbon Monoxide
DM	Distant Metastasis
DoH	Department of Health
DOR	Duration of Response
DP	Docetaxel, Cisplatin
DVH	Dose Volume Histogram
EBP	Evidence Based Practice
EBUS	Endobronchial Ultrasound
EBUS FNA	Endobronchial Ultrasound Fine Needle Aspiration

EBUS ROSE	Endobronchial Ultrasound Rapid On Site Evaluation
EBUS TBNA	Endobronchial Ultrasound Transbronchial Needle Aspiration
ECOG	Eastern Cooperative Oncology Group
ED	Extensive Disease
EGFR	Epidermal Growth Factor Receptor
EGFRM	Epidermal Growth Factor Receptor Mutation
ENB	Electromagnetic Navigation Bronchoscopy
ESMO	European Society for Medical Oncology
EU	European Union
EUS	Endoscopic Ultrasound
EUS-FNA	Endoscopic Ultrasound – Fine Needle Aspiration
FACT-L	Functional Assessment of Cancer Therapy-Lung
FEV_1	Forced Expiratory Volume in 1 Second
FDG-PET	Fludeoxyglucose Positron Emission Tomography
FISH	Fluorescence In Situ Hybridisation
FN	False Negative
FNA	Fine Needle Aspiration
FP	False Positive
GBP	Great British Pound
GDG	Guideline Development Group
GGO	Ground Glass Opacity
GI	Gastrointestinal
GP	General Practioner
GUH	Galway University Hospital
HART	Hyperfractionated Accelerated Radiotherapy
HIQA	Health Information and Quality Authority
HR	Hazard Ratio
HSE	Health Service Executive
HTA	Health Technology Assessment
IANO	Irish Association for Nurses in Oncology
IASLC	International Association for the Study of Lung Cancer
ICERs	Incremental Cost Effectiveness Ratios
ICGP	Irish College of General Practitioners
ICU	Intensive Care Unit
IHC	Immunohistochemistry
IMRT	Intensity-Modulated Radiation Therapy
IPHA	Irish Pharmaceutical Healthcare Association
IQR	Intra-Quartile Range
IRC	Independent Review Committee
ISMO	Irish Society for Medical Oncologists
IV	Intravenous
KPI	Key Performance Indicator
LD	Limited Disease
LKB	Lyman–Kutcher–Burman
IRC	Independent Review Committee
LRP	Locoregional Progression
LRR	Locoregional Recurrence

LYG	Life Years Gained
MDM	Multidisciplinary Meeting
MDT	Multidisciplinary Team
MFLC	Multifocal Lung Cancer
MLD	Mean Lung Dose
MLND	Mediastinal Lymph Node Dissection
MMUH	Mater Misericordiae University Hospital
MPH	Mater Private Hospital
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MTC	Mixed Treatment Comparison
NALA	National Adult Literacy Agency
NB	Navigational Broncoscopy
NCCN	National Comprehensive Cancer Network
NCCP	National Cancer Control Programme
NCHD	Non-Consultant Hospital Doctor
NCPE	National Centre for Pharmacoeconomics
NCRI	National Cancer Registry Ireland
NE	Non-Estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOS	Not Otherwise Specified
NPV	Negative Predictive Value
NSCLC	Non-Small Cell Lung Cancer
NTCP	Normal Tissue Complication Probability
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PCI	Prophylactic Cranial Irradiation
PET	Positron Emission Tomography
PET-CT	Positron Emission Tomography-Computed Tomography
PFS	Progression-Free Survival
PICO	Population/Patient; Intervention; Comparison/Control; Outcome
PLT	Posterolateral Thoracotomy
PORT	Postoperative Radiotherapy
ppo	Postoperative Predictive
PPP	Purchasing Power Parity
PPV	Positive Predictive Value
PS	Performance Status
PSM	Propensity Score Matching
PTV	Planning Target Volume
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
QUANTEC	Quantitative Analyses of Normal Tissue Effects in the Clinic
QUB	Queens University Belfast
RCPath	The Royal College of Pathologists
RCSI	Royal College of Surgeons in Ireland

RCT	Randomised Controlled Trial
R-EBUS	Radial Endobronchial Ultrasound
RECIST	Response Evaluation Criteria In Solid Tumours
RFA	Radiofrequency Ablation
ROC	Receiver Operating Characteristic
ROSE	Rapid On Site Evaluation
RR	Response Rate
RT	Radiation Therapy
SABR	Stereotactic Ablative Radiotherapy
SACT	Systemic Anticancer Therapy
SBRT	Stereotactic Ablative Radiation Therapy
SCLC	Small-Cell Lung Cancer
SFH	St. Francis Hospice
SIGN	Scottish Intercollegiate Guideline Network
SJH	St. James' Hospital
SPECT	Single-Photon Emission Computed Tomography
SUV	Standardised Uptake Volume
SVUH	St. Vincent's University Hospital
TBNA	Transbronchial Needle Aspiration
TCD	Trinity College Dublin
TCP	Tumour Control Probability
TKI	Tyrosine Kinase Inhibitor
TL	Thoracoscopy
TLCO	Transfer Factor of Carbon Monoxide
TRT	Thoracic Radiotherapy
TTF-1	Thyroid Transcription Factor-1
TTNA	Transthoracic Needle Aspiration
TTNB	Transthoracic Needle Biopsy
UICC	Union for International Cancer Control
UHL	University Hospital Limerick
VATS	Video-Assisted Thoracoscopic Surgery
VB	Virtual Bronchoscopy
VO_2 max	Maximal Oxygen Consumption
WHO	World Health Organisation

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Section 1: Background

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