

Guidelines for the diagnosis and treatment of Lung Cancer

Irish Thoracic Society Lung Cancer Sub-committee
All Ireland Lung Cancer Working Group

Third edition 2009

Foreword

For too long lung cancer in Ireland has been overlooked, belying its importance as the country's biggest cancer killer and the most common type of cancer in both sexes.

On behalf of the Irish Thoracic Society Lung Cancer Sub-committee I wish to thank Professor Tom Keane and his team for recognising and acting on this by choosing to develop lung cancer care services as part of the National Cancer Control Programme (NCCP).

The publication of the Guidelines for the Diagnosis and Treatment of Lung Cancer 3rd Edition marks an important milestone in this process. It provides a blueprint for the provision of timely and appropriate multidisciplinary care for patients with lung cancer. This will lead to earlier diagnosis and improved outcomes for patients. It will also provide standards against which the delivery of care can be measured.

These guidelines would not have been possible without the contributions of a number of people. Great credit is due to the 'All Ireland Lung Cancer Working Group', for their work on editions one and two, providing a strong basis for this the 3rd edition. I wish to pay particular thanks to the Irish Thoracic Society Lung Cancer Sub-committee. This group was established out of concern and frustration at deficiencies in lung cancer care services over many years and is representative of medical professionals from all stages of lung cancer care, different hospital types and regional spread. Its members have given generously of their time and expertise, resulting in what we believe is a very robust and comprehensive document.

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Contents

1 Introduction and Background Information

2 Aims of the Guidelines

3 Access to diagnostic services

- Rapid Access clinics
- Multidisciplinary teams
- indications for urgent CXR

4 Diagnosis:

Assessment of patients with suspected lung cancer

4.1 *Clinical Assessment: Performance status and co-morbidities*

4.2 *Physiological Assessment: Pulmonary function*

4.3 *Radiological Assessment: CT scan*

4.4 *Pathological Assessment: Bronchoscopy and tissue diagnosis*

5 Staging

5.1 *staging of non-small cell lung cancer*

5.2 *staging of small cell lung cancer*

5.3 *staging assessment*

6 Treatment

6.1 *Treatment of Non-Small Cell Carcinoma*

6.1.1 *General Overview*

6.1.2 *Principles of Radiation in the Management of Lung Cancer*

6.1.3 *Principles of surgery for lung cancer*

6.1.4 *Chemotherapy in NSCLC*

6.1.5 *Treatments by stage*

6.2 *Treatment of Small Cell Carcinoma*

7 Palliative therapies

8 Management of Superior Vena Cava Syndrome

9 The Solitary Pulmonary Nodule

10 Health promotion and lung cancer prevention

11 Bibliography

12 Appendix I – Tables

13 Appendix II – Pulmonary Function guidelines for assessment of operability

1

Introduction and background information

- Lung cancer is the leading cause of cancer mortality in Ireland representing approximately 20% of all deaths due to cancer
- Lung cancer kills more Irish people every year than breast and colon cancer combined
- 2474 new cases per year - 933 female, 1541 male*
- 2286 deaths per year - 862 female, 1424 male*
- The incidence of lung cancer is projected to increase by 141% in women and 61% in men between 2010 and 2030**.
- In women - *3rd most common cancer site, 2nd most common cause of cancer death, 9.7% of new cancer cases, 16.5% of cancer deaths*
- In men - *2nd most common cancer site, Most common cause of cancer death, 15.9% of new cancer cases, 24.4% of cancer deaths*
- Compared to other EU countries, incidence rates for men are below average but for women are almost twice the EU average.
- 5-year survival figures for Ireland are only 8% for men and 10% for women. These compare to rates of 13% and 16% in France and 15% and 18.5% for the United States[^].
- <1% of cases occur before age 40, rates rise steeply after age 40 and peak at 65-75.
- The incidence of lung cancer in women has been rising steadily over past three decades.
- Currently >75% of patients present with locally advanced or disseminated disease.
- Over 90% of lung cancer in Ireland may be attributed to smoking tobacco and is therefore theoretically preventable.
- Other known risk factors are exposure to radon, asbestos and other occupational carcinogens
- The prevalence of smoking in Ireland remains over 23%, with peak prevalence of 31% in the 25-34 year old age group.
- The success rate for smoking cessation among established smokers is around 20% with pharmacological therapy. The vast majority of people taking up smoking will fail in attempts to quit. This and the long lag time between beginning smoking and the development of lung cancer mean that lung cancer will continue to be a major cause of cancer mortality for the foreseeable future.
- Unfortunately efforts to detect lung cancer earlier by screening have so far failed to show a conclusive mortality benefit.
- However, earlier diagnosis, efficient and correct diagnosis and staging, and modern multidisciplinary management lead to improved short and long term survival with good quality of life.
- Improvements in the delivery of care are necessary through earlier diagnosis, rapid access to diagnostic and staging procedures, and provision of co-ordinated multidisciplinary treatment.

Data from:

*All-Ireland cancer statistics, second report, 1998-2000, a joint report on incidence and mortality for the island of Ireland, NI Cancer Registry and National Cancer Registry Ireland.**Patterns of Care and survival of cancer patients in Ireland 1994 to 2004, National Cancer Registry Ireland 2008. ^ SEER database, accessed at www.seer.cancer.gov, August 2009.

2

Aims of the guidelines

To raise awareness of lung cancer among health care professionals, health care providers, patients and the general public.

To assist in the provision of timely and appropriate multidisciplinary care for patients with lung cancer thereby leading to earlier diagnosis and improved outcomes.

To provide standards against which the delivery of lung cancer care can be compared.

3

Access to diagnostic services

- Patients with lung cancer often delay in presenting to their GP after first experiencing symptoms such as cough, because these symptoms are common among smokers and patients with chronic lung disease.
- When patients present to their GP, a prompt and effective referral process to a respiratory physician should be in place.
- Rapid Access Clinics which provide a bundle of initial investigations to patients with suspected lung cancer within their first visit or on the next day should be supported. This will reduce multiple hospital visits and patient anxiety and shorten the time period to diagnosis.
- Patients should be assessed in a rapid access clinic by a respiratory physician within 2 weeks of receipt of request from GP or Emergency Department for assessment.
- While it is anticipated that the majority of patients with lung cancer will be referred to a Rapid Access Clinic, it is acknowledged that a smaller proportion of such patients will be diagnosed through other referral streams (acute hospital admission, referral to respiratory physicians etc.). Such patients should be discussed and their management planned at lung cancer MDTs.

Who should be referred to Rapid Access Clinic

Where CXR or CT scan suggests lung cancer

Patients with haemoptysis, particularly if they are current or ex-smokers.

Multidisciplinary teams (MDT):

Multidisciplinary care improves outcome in lung cancer.

All patients with a working diagnosis of lung cancer should be discussed at a lung cancer MDT meeting

Members of a lung cancer MDT are outlined in table 8

The overall care pathway of the lung cancer patient is shown in Figure 2. Ideally, diagnosis, staging and multidisciplinary assessment should be completed, and a decision made on appropriate primary therapy, within 4 weeks of initial referral.

CT with contrast

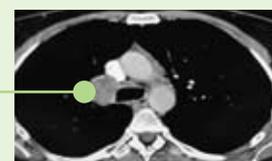
Figure 1. Chest X-ray and CT thorax



CT with contrast



Lung mass



Enlarged mediastinal lymph node

4

Diagnosis

Assessment performed at rapid access clinics

In order to manage lung cancer appropriately, the following information is required

- Initial Clinical Assessment: Performance status and co-morbidities
Are further investigations appropriate?
- Physiological Assessment: Pulmonary function tests
Will pulmonary function support invasive tests and/or radical treatment?
- Radiological Assessment: contrast enhanced CT scan of thorax and upper abdomen to level of adrenals
Provides the clinical stage of the cancer
- Airway Assessment: Bronchoscopy
Provides staging information and route for diagnosis
- Tissue Diagnosis: Biopsy, needle aspiration
often obtained at bronchoscopy (central masses) or by transthoracic needle aspiration/ core biopsy (peripheral lesions) but may be confirmed by cytology/histology from other sites such as lymph glands, skin nodules or pleural fluid

The key components of the initial assessment at are shown in Table 2

4.1 Clinical Assessment

Performance status, Co-morbidity and Weight loss

General medical condition should be assessed in detail and should be formally assessed according to the ECOG scoring system (Table 4). Weight loss should be estimated at initial assessment and actual weight documented at each clinic visit. As most patients with lung cancer are smokers, smoking-related co-morbidity is prevalent. Other co-morbidity must also be taken into account, particularly in patients under consideration for surgery, chemotherapy or radical radiotherapy. Conditions which tend to dictate against these therapies include –

cachexia

severe ischaemic heart disease eg) unstable angina or heart failure poorly responsive to medical therapy

severe COPD (see pulmonary function below)

severe other co-morbidity which carries increased risk for surgery/chemotherapy/radical RT or has profound implications for quality of life, cognitive function etc.

4.2 Physiological assessment:

Pulmonary Function

Pulmonary function is essential for patients under consideration for surgery, chemotherapy or radical radiotherapy.

For patients undergoing surgery:

No level of pulmonary function impairment should necessarily be considered prohibitive for treatment and no patient with a potentially curable cancer should be denied an opinion from a thoracic surgeon on the basis of pulmonary function tests. However, a number of useful guidelines exist to inform the multidisciplinary team. These are outlined in Appendix II which includes an algorithm for the assessment of (cardio)pulmonary reserve and operability.

Patients undergoing radiotherapy:

- The effect of modern thoracic irradiation on lung function appears to be small and in most cases subclinical but can be augmented by concurrent chemotherapy and smoking.
- Some patients with central obstructing tumours can develop an improvement in lung function after irradiation.

Arterial Blood Gases

- Hypoxaemia is not a contraindication to surgery and may improve after surgery where there is poor local ventilation due to collapse/atelectasis.
- Hypercapnia has traditionally been considered to increase risk significantly, and while this has not been proven and some studies suggest otherwise, severe hypercapnia should be considered a significant risk factor.

4.3 Radiological Assessment:

CT thorax and upper abdomen (all patients)

All patients should have CT of thorax and upper abdomen as far as the adrenal glands. This provides the most important clinical staging information and the report should include detailed description of the primary lesion, satellite lesions if present, nodal enlargement and metastases (Table 7). CT scans should be reported by a radiologist with special interest in lung cancer.

4.4 Bronchoscopy and Tissue diagnosis

Bronchoscopy will usually provide tissue diagnosis and will also provide information essential for staging. The following diagnostic procedures may be carried out during bronchoscopy-

Primary lesion (T) –

Visible lesions -	lavage brushings (particularly diffuse lesions transbronchial needle aspirate (TBNA)endobronchial biopsies
Peripheral lesions -	lavage ± transbronchial biopsies ± transbronchial needle aspirate (TBNA)
Central lesions not visible	transbronchial/transtracheal needle

Mediastinal lymph nodes (N) –

Where CT shows mediastinal glands ≥ 1 cm, adjacent to trachea or main bronchi, transbronchial/transtracheal needle sampling may also be carried out during bronchoscopy (see below under staging). This may provide essential staging information and may provide the tissue diagnosis where the primary lesion is not visible within the airway. The TBNA should be done as the first procedure to minimize the risk of a false positive finding. Rapid On-Site Cytology Evaluation (ROSE) may improve diagnostic yield of TBNA. Image guidance with endobronchial ultrasound (EBUS) or endoscopic ultrasound (EUS) allows real-time nodal sampling and increases the diagnostic yield.

Diagnostic techniques include:

Image-guided (usually CT) percutaneous aspirate/ core biopsy of –

primary lung lesion

satellite lung lesions

mediastinal lymph nodes

Endobronchial ultrasound guided TBNA

Endoscopic ultrasound guided FNA of mediastinal nodes or left adrenal

Mediastinoscopy

Mediastinotomy

Thoracoscopy/Thoracotomy and biopsy

In the setting of clinical apparent metastatic disease (M) diagnosis and confirmation of stage may be provided by

Fine needle aspirate (FNA)/ core biopsy of palpable lymph glands

FNA/ core biopsy of skin nodules

Image-guided FNA of liver or bone lesions

Pleural aspirate (\pm biopsy)

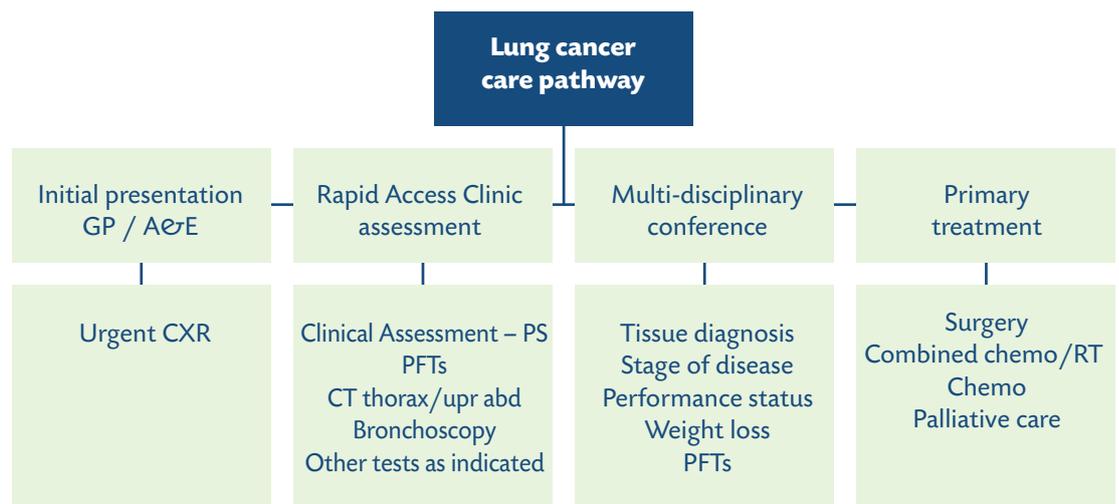
Histological Diagnosis

80-85% of lung cancers are non-small cell in type.

Occasional difficulties arise in differentiating pleural based adenocarcinoma from mesothelioma and primary from secondary adenocarcinomas. In these cases a panel of immunohistochemistry markers may be helpful.

- Mesothelioma: Calretinin, CK 5/6 and Wilm's tumour antigen positive
- Adenocarcinoma: TTF-1, CK 7 and CEA positive
- Secondary Adeno e.g. bowel: TTF-1, CK 7 negative, CK 20 positive

Figure 2. Lung cancer care pathway



5

Staging

Non-small cell lung cancer is staged according to the TNM Classification system (Table 5). The 7th edition has recently been published and contains a number of changes. Small cell lung cancer is staged as limited or extensive stage (Table 6).

Changes in 7th edition TNM for NSCLC which came into effect on the 1st August 2009 include:

T stage

There are new size cut-offs of 2,3,5 and 7cm

T1 is divided into T1a (<2cm) and T1b (2-3cm)

T2 is divided into T2a (3-5cm) and T2b (5-7cm)

Satellite nodules located in the same lobe as the primary are reclassified at T3 (from T4 in 6th Edition)

Metastatic nodules located in a different lobe of same lung are reclassified as T4 (were M)

Malignant pleural and pericardial effusion are now M1 (from T4)

N stage

No change to N status in new edition

M stage

M1a - separate tumour nodule in contralateral lung or malignant pleural or pericardial effusion

M1b – distant metastases

Staging Assessment

- The management of lung cancer is increasingly determined by accurate definition of the stage. If there are no distant metastases, the status of the mediastinal lymph nodes is critical.

Although imaging studies can provide some guidance, in many situations sampling to confirm stage is warranted, in particular if patient is considered for radical treatment

Clinical assessment (all patients)

Specific features on clinical evaluation may suggest metastatic disease :

- hoarseness may indicate recurrent laryngeal nerve palsy
- Weight loss >10%
- Horner's syndrome usually indicates nerve involvement
- superior mediastinal obstruction (SVC syndrome) indicates N2/3 and/or T4 disease
- Supraclavicular lymphadenopathy usually indicates N3 disease (easily sampled by FNA)
- skin nodules may be metastatic M1 disease (easily sampled by FNA)
- hepatomegaly (will be evaluated by CT)
- bone pain (will require isotope bone scan / plain films / PET scan)
- neurological symptoms (require further evaluation)
- paraneoplastic syndromes (Table 3) do NOT imply metastasis or inoperability
- anemia, elevated LFTs, hypercalcemia

Bronchoscopy (all patients)

In addition to tissue diagnosis, bronchoscopy will provide staging information –

- differentiate T4/T3/T2 in the airway, i.e. main carina/main bronchus/more peripheral
- rule out second airway lesion(s) undetected by CXR/CT
- sampling of N2 glands by TBNA helpful when positive BUT insensitive – unhelpful when negative

Positron Emission Tomography (PET)

FDG-PET scanning may be performed in the following situations:

- 1) patients under consideration for radical treatment (resection and high dose chemoradiation)
 - Lung cancer cells typically have a high avidity for fluoro-deoxy-glucose (FDG) used for PET scanning. Experience to date suggests that PET leads to a significant change in stage in over 10% of cases, principally by uncovering metastatic disease. FDG-PET also has greater sensitivity and specificity than CT for mediastinal lymph node involvement.
 - Where CT suggests resectability and surgery is intended and the PET is negative for mediastinal or metastatic disease, resection should proceed.
 - If PET is positive the findings should be confirmed by sampling. Where histology of nodes is ultimately negative, resection should be offered. If the nodes are proven to be involved, induction chemotherapy may be considered followed by restaging for possible resection. Alternatively a combined chemoradiation approach is appropriate.
- 2) Characterization of pulmonary nodules (selected cases)

Mediastinal lymph node staging

Where radical therapy is a consideration and CT shows mediastinal lymph node enlargement (>1cm), sampling is required to differentiate malignant from benign reactive nodes. Even large nodes can be reactive and small nodes can harbour disease.

Sampling techniques and reach are displayed in figure 5.

Methods:

- “blind” TBNA – Transbronchial needle aspiration of paratracheal and subcarinal nodes may be attempted at initial diagnostic bronchoscopy. When positive, this will preclude the need for further invasive testing, but the technique is insensitive and negative results are unreliable.
- EBUS-TBNA - Endobronchial ultrasound improves localisation and diagnostic yield when sampling mediastinal or hilar lymph nodes and paratracheal masses. Radial probe EBUS which has higher resolution than the linear-array EBUS bronchoscope used in EBUS-TBNA has good sensitivity for detecting airway wall invasion by tumours abutting the central airway
- EUS-FNA – transoesophageal ultrasound may facilitate sampling of posterior mediastinal, subcarinal and aortopulmonary window nodes
- Mediastinoscopy allows access to the upper mediastinal (1, 2R, 2L, 3) and right lower

paratracheal (4R) lymph node stations.

- Left anterior mediastinotomy may allow access to the aortopulmonary window (station 5) and supra-aortic (station 6) lymph nodes.

Pleural aspiration cytology

Where pleural effusion is present, aspiration is essential to try to differentiate malignant from benign reactive effusion. When the effusion is clinically apparent, this may easily be carried out at the same time as initial clinical assessment. Closed pleural biopsy may also be considered. For smaller effusions, localisation may be improved by radiological guidance with ultrasound or CT. In approximately 1/3 of malignant effusions it is not possible to make a diagnosis despite multiple aspirations and Thoracoscopy has a very high yield in these patients.

CT brain (selected patients)

CT detects brain metastases in 3% of asymptomatic patients and therefore should not be carried out routinely BUT should be carried out –

- if headache or other unexplained neurological symptoms/signs are present
- for adenocarcinoma of higher stage than T1N1 where surgery is under consideration
- For all patients with small cell lung cancer

MRI brain (selected patients)

MRI is more sensitive than CT for early metastases and should be carried out – when CT brain is negative but symptoms/signs suggest possible cerebral metastases

MRI thorax (selected patients)

MRI is better than CT for detection of direct invasion and may be useful in selected patients –

- where surgery is under consideration and CT suggests possible direct invasion by primary tumour of adjacent structures such as –
 - chest wall*
 - diaphragm*
 - root of the neck*
 - mediastinal structures*

MRI upper abdomen (selected patients)

MRI is superior to CT in differentiating small adrenal metastases from benign adrenal adenomas and may be considered where CT demonstrates adrenal enlargement which is not obviously metastatic, in particular if PET is not available.

Ultrasound of Abdomen (selected patients)

Ultrasound should be carried out -

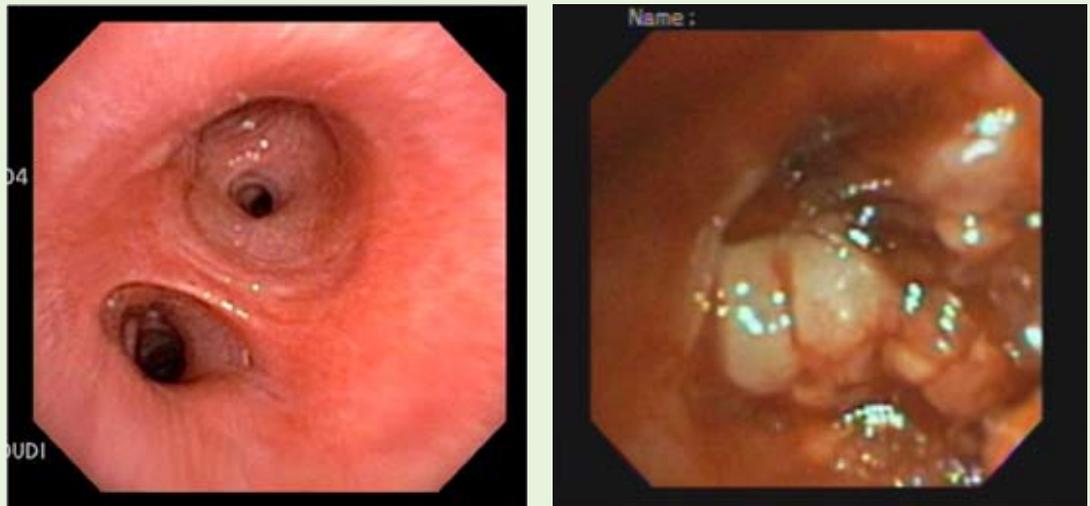
where CT shows single hepatic or renal lesions which are probably benign and better characterised by ultrasound

Isotope bone scan (selected patients)

Isotope bone scan is almost always negative when there is no bone pain and the bone chemistry is normal. It may be carried out

- if bone pain is present
- if bone chemistry is abnormal

Figure 3. Bronchoscopic image of normal airway (left) and occlusion from lung tumour



6

Treatment

General approach

Appropriate management of lung cancer requires the following information –

- 1 Tissue diagnosis**
- 2 Clinical stage**
- 3 Assessment of general medical condition (performance status), co-morbidity and weight loss**
- 4 Pulmonary function, particularly where surgery, radical radiotherapy or chemotherapy under consideration**

All patients should be discussed at a multidisciplinary forum with access to a full lung cancer team so that appropriate primary treatment and follow-up can be arranged efficiently and effectively (Table 8).

Patients who have lung cancer suitable for radical treatment (surgery, radiotherapy or chemotherapy alone or in combination), should be treated without undue delay.

Patients who cannot be offered curative treatment, can be either observed until symptoms arise or treated with immediate palliative intent. Radiotherapy is often the cornerstone of palliative management, and may need to be instituted urgently

6.1 Treatment of Non-Small Cell Carcinoma

6.1.1 General Overview

Appropriate primary treatment for NSCLC is determined predominantly by stage of disease, but also by performance status, co-morbidity and weight loss (Table 9). Where performance status is good with minimal co-morbidity and weight loss, surgery, with intention to cure, is appropriate for stage I, II and some IIIA patients. Radical RT or combined chemo/RT should be considered for locally advanced inoperable stage IIIA or IIIB disease. Palliative chemotherapy should be considered for patients with locally advanced disease not suitable for radical treatment and for patients with metastatic stage IV disease. These “aggressive” therapies may not be possible where performance status is poor, pulmonary function is inadequate, or there is severe co-morbidity or weight loss. Treatment will then largely be palliative with palliative RT where indicated for symptoms. Obviously each patient must be considered individually.

For a small number of patients with stage I disease, where surgery is not advisable because of medical co-morbidity or inadequate pulmonary function (“medically inoperable disease”), radical RT may be considered, with intention to cure.

6.1.2 Principles of Radiation in the Management of Lung Cancer

All patients with Lung Cancer should be treated with access to modern radiation therapy (RT). RT may be administered with curative or palliative intent. It may be used as the primary option (e.g. medically inoperable patients), combined with chemotherapy, or as an adjunct to surgery. It plays a critical role in palliative management. Modern techniques including CT simulation, CT/PET imaging, 3D Conformal Radiation, IMRT, Stereotactic Radiosurgery, Brachytherapy, all may have a role in the management patients with Lung Cancer. See below for further details.

6.1.3 Principles of surgery for lung cancer

Surgical resection should include adequate mediastinal lymph node dissection or sampling as defined by the removal of at least lymph node stations. There is some evidence to suggest that nodal dissection may have survival advantages especially in right sided tumours. Resection should aim to conserve lung where possible through bronchoplastic procedures (sleeve lobectomy rather than pneumonectomy). Anatomical segmentectomy or non-anatomical (wedge) resections are inferior to lobectomy but may be necessary where lobectomy is inadvisable because of inadequate pulmonary function or general medical condition. Close margins and residual disease should be marked at surgery and specimens should be reported on according to a standard template (Table 10). Findings at surgery and on pathology of the resected specimen will determine further action, both at the time of surgery and post-operatively with regard to adjuvant therapy (see below).

6.1.4 Chemotherapy in NSCLC

Performance status (PS) is the most important factor in the selection of patients for systemic chemotherapy which is offered with the intention of symptom relief, improved disease control, better quality of life (QoL) and increased survival. Chemotherapy should be offered to patients with stage III or IV NSCLC and good performance status (WHO 0,1 or a Karnofsky score of 80–100) and may be used in number of different settings:

Neo-adjuvant chemotherapy (chemotherapy prior to surgery). Remains controversial and should preferably be undertaken in the context of a clinical trial

- initial 1-2 cycles and assess response if regression (or no progression) consider surgery or radical RT if re-staging suggests all disease can be ablated. Otherwise, continue to 4 cycles or until progression as tolerated

Adjuvant chemotherapy should be offered to patients with pStage IB disease or higher who have undergone curative resection, after full discussion of the issues involved. An overall survival benefit of 5% at 5 years has been demonstrated in several large RCT.

Combined chemoradiotherapy combine with RT for locally advanced inoperable stage IIIA (and some IIIB). Concurrent treatment with XRT has been shown to be more effective than sequential therapy. (BC04 0 -1)

Palliative chemotherapy for good performance patients, with acceptable co-morbidity and inoperable disease

- initial 1-2 cycles and assess response
- continue for 4-6 cycles based on response and tolerability
- maintenance chemotherapy remains investigational at the present time
- in poor responders, consider alternative regime or alternative therapies such as EGFR/tyrosine kinase inhibitor in selected patients
- The use of newer therapies should await licensing approval, pharma-economic evaluation and funding.
- Participation in clinical trials should continue to be encouraged

6.1.5 Treatments by stage

A) NSCLC with good performance status, minimal co-morbidity and adequate pulmonary function -

Stage IA (T1N0), IB (T2N0), IIA (T1N1), IIB (T2N1)	Surgical resection –	<ul style="list-style-type: none"> Findings at surgery and on pathology of the resected specimen will determine further action, both at the time of surgery and post-operatively – Where pathology shows N2 disease, adjuvant RT may be considered. . Where pathological pStage is N0 or N1, adjuvant RT should not be offered. Where there are positive surgical margins or adverse pathological features (Table 11), post-operative chemotherapy or radiotherapy may be appropriate for selected patients. For all patients with completely resected pStage II – IV disease, adjuvant chemotherapy should be offered as standard care. 	
Stage IIB (T3N0) and IIIA (T3N1)	Superior sulcus	resectable	RT+chemo then surgery
		unresectable	RT+chemo then re-evaluate for resectability
	Chest wall or Proximal airway or Mediastinum	resectable	Margins negative - adjuvant chemo Margins positive - Re-resect or RT+chemo
		unresectable	RT+chemo then re-evaluate for resectability
Stage IIIA (T1-3N2)	Chemo/RT or radical RT	Concurrent chemoradiotherapy has been demonstrated to be more effective than sequential chemotherapy/chemoradiotherapy although it is recognised that treatment volumes may initially preclude a concurrent combined modality approach. Induction (neo-adjuvant) chemotherapy followed by resection may be considered in selected patients	
Stage IIIB (T1-3N3)	Consider chemo/RT as for IIIA		

Stage IIIB (T4N0-1)	Resectable satellite lesion	surgery	adjuvant chemo
	Resectable local invasion	surgery	adjuvant chemo
	Unresectable	chemo/RT as for IIIA	
Stage IIIB (T4N2-3)	Consider chemo/RT as for IIIA		
Pleural effusion	Local therapy if necessary – pleural drainage ± pleurodesis – this should be considered early rather than as an “end-stage” procedure. A number of options including pleurodesis through chest tube, via thoracoscopy or use of an indwelling pleural catheter may be offered. Treatment otherwise is for stage IV disseminated disease.		
Stage IV (M1 solitary site)	Consider palliative chemo as for Stage IV M1 disseminated (see below), or Best supportive care. In selected cases if primary tumour is otherwise resectable (by T and N stage) resection and definitive treatment of metastasis may be considered.		
Stage IV (M1 disseminated)	Best supportive care or Consider palliative chemo x 2 cycles- <ul style="list-style-type: none"> • response or stable disease and well tolerated - continue to 4-6 cycles • no response or poorly tolerated - best supportive care or consider alternative regime 		

B) NSCLC with poor performance status, significant co-morbidity or inadequate pulmonary function -

Stage I-II Medically Inoperable	Consider radical RT or
	Best supportive care with palliative RT where indicated
Stage III-IV	Best supportive care with palliative RT where indicated

Post-operative surveillance

Smoking cessation

every 3 months year 1 then

every 6 months year 2-3 then

annually to 5 years.

- clinical evaluation
- CXR

6.2 Treatment of Small Cell Carcinoma

General Principles

Appropriate primary treatment for SCLC is determined predominantly by stage of disease, but also by performance status, co-morbidity and weight loss (Table 12). Where performance status is good with minimal co-morbidity and weight loss, combined chemo/RT should be considered for patients with limited stage disease. RT should be administered early in the chemotherapy schedule. Prophylactic cranial irradiation (PCI) is considered in limited stage disease attaining a complete or near complete response to primary therapy, and will usually be administered following its completion. This allows completion of chemotherapy, and assessment of the response status. PCI may also be considered earlier in the treatment (i.e. concurrent with thoracic RT), but patients will be receiving concurrent chemotherapy at that time, and the response status (i.e. complete response, partial response and no response) will not yet be known at that time. Where performance status is poor or co-morbidity severe, treatment may largely be palliative. Obviously each patient must be considered individually.

SCLC with moderate-good performance status and mild-moderate co-morbidity -

Limited stage

Chemo and concurrent thoracic RT (which is best given early in the chemo schedule)

If apparent partial or complete remission, arrange CT brain and prophylactic cranial irradiation (PCI).

Extensive stage

Chemotherapy is the mainstay of treatment.

Cranial RT should be used for radiologically-proven cranial metastases, and considered for the palliation of other metastatic lesions requiring symptom relief.

Recent evidence supports the use of PCI in patients achieving a partial response or better (survival benefit).

Further management of SCLC based on outcome of primary treatment -

Complete remission lasting 3 months

- Long-term OPD follow up.
- Consider further chemotherapy for relapse

Incomplete remission or apparent complete remission lasting < 3 months

- Good performance status *consider alternative regime*
- Poor performance status *palliative care*

Surveillance of SCLC

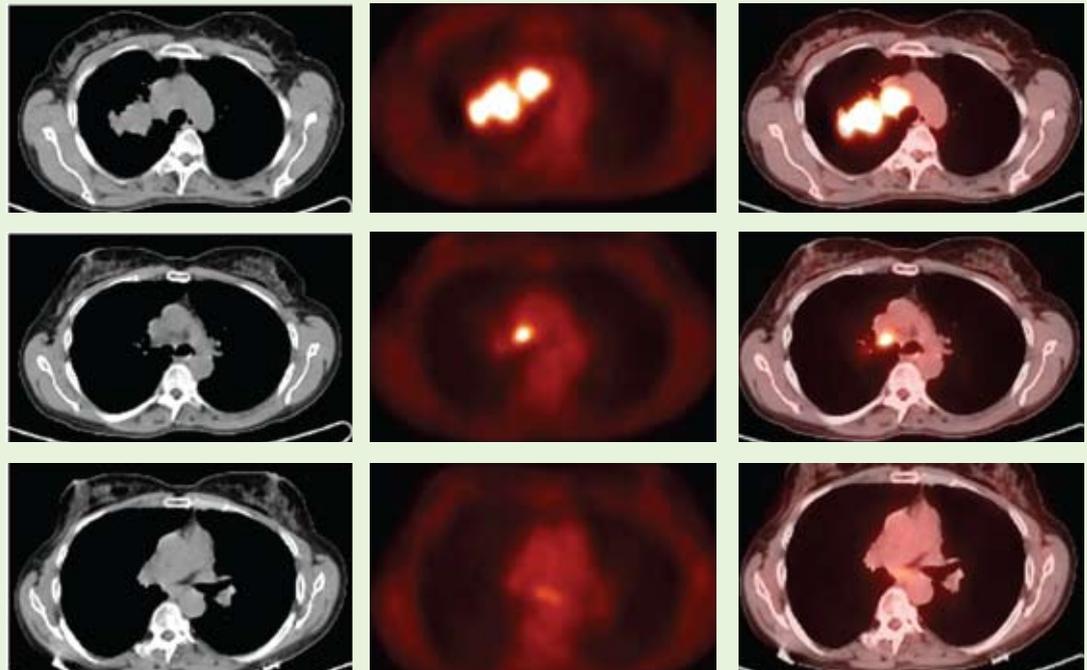
Smoking cessation

every 2 months for year 1 then

every 3 months for year 2 then

every 6 months

- clinical evaluation
- FBC, biochemistry
- CXR
- other imaging to assess sites of previous involvement as indicated

Figure 4. PET-CT fusion images

7

Palliative Therapies

Where disease is considered incurable or primary treatment is unsuccessful, the following palliative therapies may be indicated -

Palliative RT

Indications include -

- Bone pain
- Cranial metastases
- Spinal disease
- Major pulmonary collapse/atelectasis
- Haemoptysis
- Superior mediastinal obstruction (superior vena cava syndrome)

Invasive Approaches to Palliation: Endobronchial therapy

Central airway obstruction can occur as a result of tumour growth inside the airway lumen. In these patients distal lung atelectasis and post-obstructive pneumonia further contribute to morbidity. External beam radiotherapy can reduce tumour size but effect is delayed and overall results are poor in central airway obstruction. Palliative bronchoscopy can play a major role in relief of haemoptysis and dyspnoea in this setting.

Bronchoscopic therapies include bronchoscopic debulking of intraluminal tumor, balloon dilatation, laser therapy, electrocautery, cryotherapy, argon plasma coagulation (APC), endobronchial irradiation (brachytherapy), and airway stent insertion. Often a combination of techniques is required.

Oesophageal Stenting for dysphagia due to oesophageal compression or invasion by nodal disease or direct involvement.

Teflon or Surgical medialisation of the left vocal cord for recurrent laryngeal nerve palsy where there is severe hoarseness or recurrent aspiration.

Pleurodesis for symptomatic pleural effusion

Palliative care will ultimately become the principal focus of care for many patients with lung cancer. Consultation with palliative care services should be arranged in timely fashion and transfer to palliative care should occur as seamlessly as possible.



Management of Superior Vena Cava Obstruction

SVC obstruction (SVCO), although very distressing to the patient, is rarely fatal. Patients presenting with clinical features of SVCO should undergo –

- immediate CT of thorax and upper abdomen
- urgent tissue diagnosis
- urgent treatment to relieve SVCO.

CT of thorax and upper abdomen –

- will confirm the presence of SVCO
- will indicate the extent and stage of disease
- will help to indicate the most appropriate procedure for histological diagnosis

Urgent tissue diagnosis may be obtained by various procedures –

- Where CT suggests lung cancer with endobronchial tumour, bronchoscopy is usually the procedure of choice.
- Where CT suggests mediastinal tumour without intrapulmonary lesion, mediastinoscopy is usually the procedure of choice, though bronchoscopy with transtracheal or transbronchial needle aspiration may provide the diagnosis less invasively.
- Clinical examination +/- ultrasound of supraclavicular fossa may provide easy access to rapid cytological diagnosis in approximately 40% of patients.
- If possible, Rapid On-Site Cytological Evaluation should be available where SVCO is present.

Treatment of the underlying condition should commence as early as possible after tissue diagnosis –

- NSCLC –
*SVC stenting provides immediate relief where symptoms are severe
concurrent chemoRT*
- SCLC –
*chemoRT for limited stage disease
chemo for extensive stage disease*
- lymphoma –
appropriate therapy depending on type

Dexamethasone is commonly used for symptom relief in patients with SVCO. Where clinical and radiological evaluation suggests that lymphoma is likely, dexamethasone therapy should be deferred until definitive diagnostic material has been obtained.

Figure 5. Mediastinal lymph node map showing sampling techniques and their diagnostic reach

Mediastinal (N2) Nodes

Superior mediastinal nodes

- 1. Highest mediastinal
- 2. Upper paratracheal
- 4. Lower paratracheal

Aortic nodes

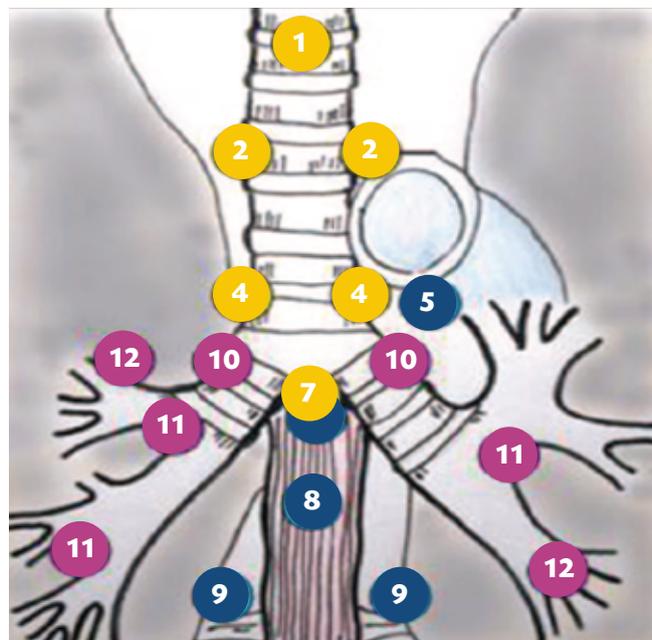
- 5. Aortopulmonary window

Inferior mediastinal nodes

- 7. Subcarinal
- 8. Paraoesophageal (below carina)
- 9. Pulmonary ligament

Bronchopulmonary (N1) Nodes

- 10. Hilar
- 11. InterLobar
- 12. Lobar



(From Yasufuku, Chest 2006)

9

Pulmonary Nodules

Solitary pulmonary nodules (SPN) are frequently discovered incidentally on thoracic imaging and may represent primary lung cancer. Previous CXR and CT's should be reviewed in all cases. In general, If the SPN is stable for at least 2 years, no additional diagnostic evaluation is necessary.

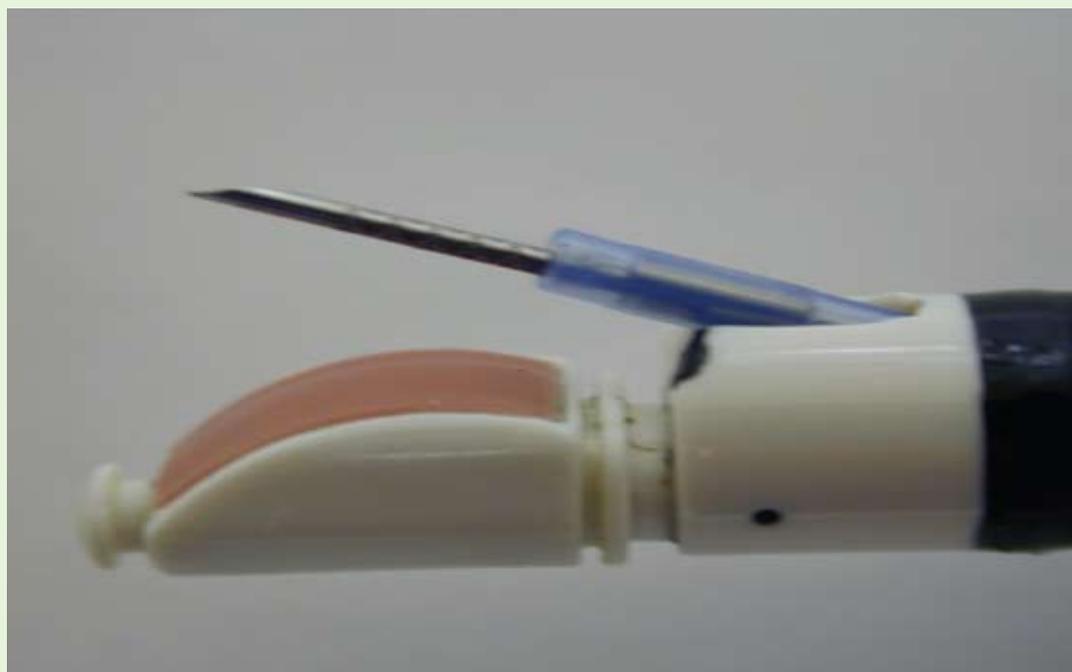
The prevalence of malignancy in patients with nodules varies with size (0 to 1% for nodules <5mm, 6-28% for nodules 5-10mm) as well as shape, being higher with irregular, lobulated or spiculated borders. Pure ground glass opacities (GGO's) are a type of pulmonary nodule that is associated with higher rates of malignancy but these may be slow growing.

The sensitivity of FDG-PET for identifying a malignant SPN is high, but specificity is low, particularly for nodules that are <10mm.

Observation with serial CT scanning (e.g. at 3,6,12 and 24 months) to ensure stability over 2 years is an acceptable management strategy in patients who would be candidates for resection and where the clinical probability of malignancy is low.

Where there is evidence of growth during follow-up, tissue diagnosis should be obtained. In general transthoracic needle biopsy is the first choice as SPNs are normally not accessible by bronchoscopy. When the clinical probability of malignancy is high and/or the nodule is hypermetabolic by FDG-PET surgical resection should be considered. If surgical biopsy is performed by wedge resection, frozen section should be obtained and completion of an anatomic resection considered if cancer confirmed.

Figure 6. Head of endobronchial ultrasound (EBUS) scope with sampling needle protruding



10 Health promotion and lung cancer prevention

In Ireland, 95% of lung cancer may be attributed to cigarette smoking. Any strategy for lung cancer must therefore be a smoking prevention, smoking cessation, no smoking and anti smoking strategy -

- the policies in relation to smoking must be implemented in full and maintained in all hospitals.
- all smoking patients, with smoking related and unrelated illnesses, must be encouraged to stop smoking at every opportunity, by all staff involved in their care. This should be done in a supportive fashion.
- smoking cessation support groups should be available in all hospitals. These may be run jointly between the respiratory and cardiology nurse specialists and as an integral part of a pulmonary or cardiopulmonary rehab programme.
- Pharmacotherapy/nicotine replacement should be available as needed/indicated.

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List of abbreviations used

ACTH	Adrenocorticotrophic hormone
A+E	Accident and emergency
ATS	American thoracic society
Chemo	Chemotherapy
CIS	Carcinoma in situ
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
CXR	Chest x-ray
EBUS	Endobronchial ultrasound
ECOG	Eastern cooperative oncology group
EGFR	Epidermal growth factor receptor
EU	European union
EUS	Endoscopic ultrasound
FBC	Full blood count
FEV1	Forced expiratory volume in one second
FNA	Fine needle aspirate
GP	General practitioner
HPOA	Hypertrophic pulmonary osteoarthropathy
LDH	Lactate dehydrogenase
NSCLC	Non-small cell lung cancer
OPD	Out-patients department
PCI	Prophylactic cranial irradiation
PET	Positron emission tomography
PTH	Parathyroid hormone
RT	Radiotherapy
SCLC	Small cell lung cancer
SIADH	Syndrome of inappropriate antidiuretic hormone
SVC	Superior vena cava
SVCO	Superior vena cava obstruction
TNM	Tumour node metastasis
US	Ultrasound

Appendix 1

Tables

- 1 Indications for urgent Chest X-ray
- 2 Initial assessment at respiratory OPD
- 3 Paraneoplastic syndromes which may be associated with lung cancer
- 4 ECOG performance status
- 5 Staging of non-small cell lung cancer (TNM classification, 7th edition)
- 6 Staging of small cell lung cancer
- 7 Template for reporting of CT thorax and upper abdomen in lung cancer
- 8 The multidisciplinary lung cancer team
- 9 Approach to treatment of NSCLC
- 10 Template for histopathology of surgical resection specimens
- 11 NSCLC – adverse pathological features
- 12 Approach to treatment of SCLC

Table 1. Indications for Urgent Chest X-ray

Symptoms –

- Haemoptysis
- New onset unexplained or persistent cough (>3 weeks)
- Alteration in character/severity of chronic cough
- Unexplained chest pain or dyspnoea
- Unexplained weight loss/cachexia
- Unexplained bone pain/neurological symptoms

Signs –

- Clubbing
- Lymphadenopathy
- Focal chest signs
- Hepatomegaly

Table 2. Initial Clinical Assessment

Full clinical evaluation including specific assessment of -

- performance status/general medical condition
- co-morbidity
- weight loss
- bone pain
- hoarseness
- pleural effusion
- superior mediastinal obstruction (superior vena cava syndrome)
- neurological symptoms, brachial neuritis, Horner's syndrome
- lymphadenopathy, especially cervical
- skin nodules
- hepatomegaly
- paraneoplastic syndromes (Table 3)

Review CXR film

ECG

Blood tests

- FBC
- Coagulation screen
- biochemistry (renal, liver and bone)

Pulmonary function tests

Investigations required for tissue diagnosis and staging –

- CT thorax/upper abdomen (with contrast)
- bronchoscopy
- other targetted investigations based on clinical evaluation
- Aspirate of enlarged neck nodes
- Pleural fluid aspiration

Table 3. Paraneoplastic syndromes which may be associated with lung cancer

Malaise, anorexia, weight loss, cachexia

Anaemia

Digital clubbing

Hypertrophic pulmonary osteoarthropathy (HPOA)

Endocrine syndromes –

- syndrome of inappropriate antidiuresis (SIADH)
- Cushing's syndrome (ACTH)
- Hypercalcaemia (PTH) – may also be due to bony metastases

Neuromyopathies –

- peripheral neuropathy
- cerebellar syndrome
- encephalopathy
- proximal myopathy
- polymyositis
- dermatomyositis
- Eaton-Lambert syndrome

Vascular –

- Thrombophlebitis migrans
- non-bacterial endocarditis

Table 4. ECOG Performance status

- 0 No symptoms. Able to carry out all normal activities without restriction
- 1 Symptoms. Restricted in physically strenuous activity but ambulatory and able to carry out light work
- 2 Ambulatory and capable of all self-care but unable to carry out any work
Up and about more than 50% of waking hours
- 3 Capable of only limited self-care
Confined to bed or chair more than 50% of waking hours
- 4 Completely disabled and unable to carry on any self-care
Completely confined to bed or chair

Table 5. Staging of Non-Small Cell Lung Cancer (TNM classification, 7th edition)

Primary Tumour T		
TX	malignant cells in sputum or bronchial washings but no tumour on imaging or bronchoscopy	
T0	no evidence of primary	
Tis	CIS	
T1	3cm or less in max diameter	T1a <2 cm T1b >2 cm but ≤ 3 cm
	no invasion of visceral pleura	
T2	no invasion proximal to a lobar bronchus	
	>3cm and ≤ 7cm in max diameter	T2a >3 cm but ≤5 cm T2b >5 cm but ≤7 cm
	involvement of mainstem bronchus >2cm from main carina	
	invasion of visceral pleura	
T3	atelectasis/obstructive pneumonitis extending to hilum but not entire lung	
	Tumour >7 cm or invasion of chest wall, diaphragm, mediastinal pleura, parietal pericardium	
	mainstem bronchus <2cm from main carina, but not involving main carina	
	atelectasis/obstructive pneumonitis of entire lung	
T4	satellite nodules within same lobe as primary tumour	
	Tumour of any size that invades mediastinum, heart, great vessels, trachea, oesophagus, recurrent laryngeal nerve, vertebra, main carina	
	separate tumour nodule(s) in a different ipsilateral lobe	

Lymph Nodes N		
N0	no nodal involvement	
N1	ipsilateral peribronchial, intrapulmonary and/or hilar nodes by direct invasion or metastasis	
N2	ipsilateral mediastinal and/or subcarinal nodes	
N3	contralateral hilar or mediastinal nodes ipsilateral or contralateral scalene or supraclavicular nodes	

Distant Metastasis M	
M0	no distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in a contralateral lobe malignant pleural or pericardial effusion
M1b	Distant metastasis

Overall Stage Groupings.

T/M	N0	N1	N2	N3
T1a	IA	IIA	IIIA	IIIB
T1b	IA	IIA	IIIA	IIIB
T2a	IB	IIA	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIA	IIIB
T4	IIIA	IIIA	IIIB	IIIB
M1a	IV	IV	IV	IV
M1b	IV	IV	IV	IV

(See diagram pg 180 S, ACCP Guidelines, TNM Staging of Lung Cancer)

Table 6. Staging of Small Cell Lung Cancer**Limited Stage - confined to a single radiotherapy port**

- one hemithorax
- mediastinum
- ipsilateral supraclavicular nodes
- no pleural effusion
- (equivalent to Stages Ia to IIIa/b NSCLC)

Extensive Stage –

- disease beyond limited stage
- (equivalent to Stage IIIb/IV NSCLC)

Table 7. Template for reporting of CT Thorax and Upper Abdomen in Lung Cancer Patients

- Primary Lesion
- dimensions
- location - lung(s), lobe(s), segment(s)
- involvement of visceral pleura and fissures
- invasion of mediastinum, chest wall, diaphragm
- for main stem lesions, proximity to, or involvement of, main carina
- atelectasis
- Satellite Lesions
- within same lobe
- within same lung
- contralateral lung
- Nodal Involvement
- report ATS nodal stations (see map – Figure 2)
- size of involved nodes (<1cm usually reactive, >2cm usually pathologically involved)
- Metastases
- liver
- adrenals
- contralateral lung
- bones, skin etc

Table 8. The Multidisciplinary Lung Cancer Team

Appropriate team members –

- nurse coordinator/specialist
- respiratory physician
- radiologist
- pathologist
- thoracic surgeon
- radiation oncologist
- medical oncologist
- palliative care physician

The extended team should also include or have close working links with –

- nutritionist/dietitian
- pharmacist
- psychologist/psychiatrist
- medical social worker
- pastoral care
- full palliative care team
- general practitioner/primary care team

Table 9 Approach to Treatment of NSCLC

Stage	Performance status Co-morbidity Weight loss Pulmonary function	good min-mild min-mild adequate	poor severe severe inadequate
I		Surgery	Palliative care Palliative RT where indicated
II		Surgery	Palliative care Palliative RT where indicated
III		Surgery ± Surgery (T3N1) ± Chemo	Palliative care Palliative RT where indicated
IV		± Chemo	Palliative care Palliative RT where indicated

Table 10. Lung Cancer Resection template

A minimum cancer dataset for lung cancer is currently under development by the Faculty of Pathology and will be released on the Faculty pages of the RCPI website later in the year.

<http://www.rcpi.ie/Faculties/Pages/FacultyofPathology.aspx>

Table 11. NSCLC – Adverse Pathological Features

- inadequate mediastinal lymph node dissection
- multiple positive hilar nodes or any positive mediastinal nodes
- close or positive margins
- extracapsular spread
- lymphovascular or perineural invasion
- high histological grade/poor differentiation

Table 12. Approach to Treatment of SCLC

Stage	Performance status Co-morbidity Weight loss	mod-good min-mild min-mild	poor severe severe
Limited		Chemo + RT PCI	Palliative care Palliative RT where indicated
Extensive		Chemo ± PCI	Palliative care Palliative RT where indicated

Appendix 2

1. General Pulmonary Function guidelines for surgical intervention.

- Pre-operative post-bronchodilator FEV1 > 2l or >80% predicted suggests suitability for resection including pneumonectomy.
- Pre-operative FEV1 > 1.5L should be suitable for lobectomy
- Predicted post-op FEV1 can be calculated based on the pre-op value and the fractional functional contribution of the lung to be resected. This can be estimated with quantitative perfusion lung scanning or from the following equation -
- Post-op FEV1 = Pre-op FEV1 x [A - (B - C)]/A where

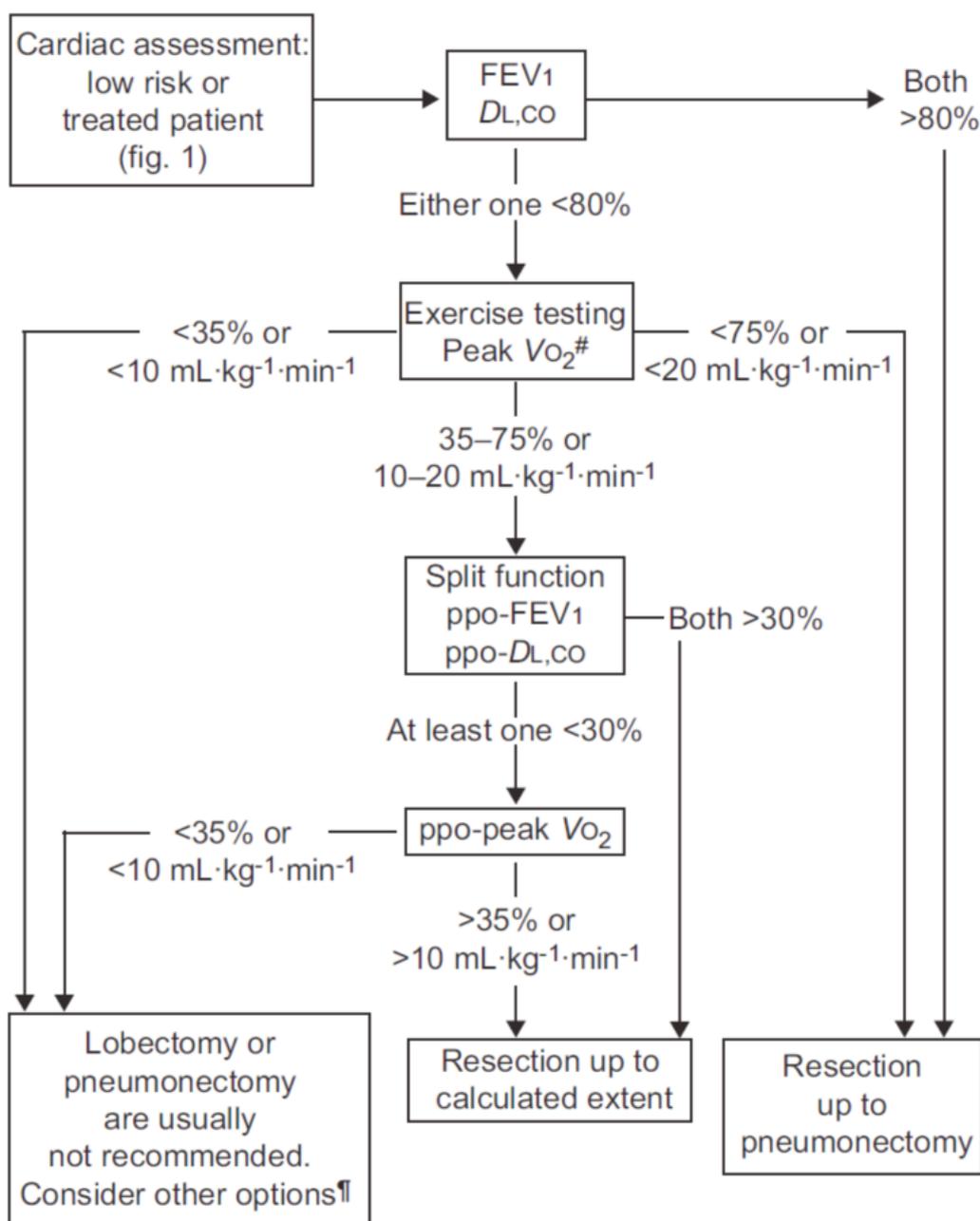
A = no of bronchopulmonary segments present pre-op (19 unless patient had previous surgery)

B = no of bronchopulmonary segments to be resected

C = no of bronchopulmonary segments to be resected which are non-functional

- Predicted post-op FEV1 > 40% normal or > 800 ml favours surgery especially when gas transfer is normal. Surgery will be less well tolerated when gas transfer is impaired.
- For borderline cases who do not fulfil above criteria, cardiopulmonary exercise testing may be considered. VO2 max > 15 ml/kg favours surgery.
- The occasional patient with lung cancer in an area of upper lobe emphysema and low FEV1 may be suitable for combined resection and lung volume reduction surgery so long as gas transfer is adequate.

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