Lung Cancer

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Seamus Grundy, Rachael Barton, Anne Campbell, Michael Cowen, and Michael Lind

Aetiology and Epidemiology

Lung cancer accounts for more than 90% of primary lung malignancies and is a leading cause of cancer mortality in men and women. Ninety percent of cases are caused by smoking, with 965,500 lung cancer deaths attributable to smoking worldwide in 2010. Changes in lung cancer incidence and mortality have paralleled past trends in cigarette smoking. Whilst tobacco had been widely used throughout the world for centuries, the marked increase in incidence and mortality observed in the twentieth century followed the introduction of manufactured cigarettes with addictive properties, which resulted in a new pattern of sustained exposure of the lung to inhaled carcinogens. Lung cancer incidence in developed countries peaked in the late 1980s/early 1990s, decreasing in men since the mid 1980s but continuing to increase amongst females through the late 1990s. The male-to-female incidence rate ratio for lung cancer overall is now 1.3 (squamous cell carcinoma 2.1, small cell carcinoma 1.2, and adenocarcinoma 1.1). Evidence suggests that the increase in adenocarcinoma relative to other subtypes of lung cancer since the 1960s has resulted from changes in the design and composition of cigarettes since the 1950s, such as ventilated filters and increased levels of tobacco-specific nitrosamines. The risk of lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day (in one study men aged 60–69 who smoked 20 cigarettes per day for 30 years had an age-specific mortality rate of 224.3, whereas if they smoked for 40 years, this increased to 486.8) and progressively declines following smoking cessation so that after 15 years the relative risk reduces to 1.6.

The risks from passive smoking have been increasingly recognised in recent years, with a relative risk of 1.25 (equivalent to smoking one cigarette per day).

Other causes of lung cancer include:

Occupational Exposure The proportion of lung cancers related to occupational exposure differs

S. Grundy (✉)
Thoracic Medicine, University Hospital Aintree, Liverpool, UK
e-mail: Seamus.grundy@nhs.net

R. Barton
Queen's Centre for Oncology and Haematology, Hull and East Yorkshire Hospitals NHS Trust, Castle Hill Hospital, Cottingham, UK

A. Campbell
Cellular Pathology, Hull and East Yorkshire Hospitals NHS Trust, Hull Royal Infirmary, Hull, UK

M. Cowen
Cardiothoracic Surgery Department, Hull and East Yorkshire Hospitals NHS Trust, Castle Hill Hospital, Cottingham, UK

M. Lind
Queen's Centre for Oncology and Haematology, Hull York Medical School, Castle Hill Hospital, Cottingham, UK

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between populations, but on average is around 10%. Occupational exposure occurs to carcinogens such as radon (mining), arsenic (glass, metals, and pesticides), asbestos (insulation, filters, textiles), chromates (pigments, metal industry, chrome plating), chloromethyl ethers (chemical intermediates), nickel (metallurgy, alloy, catalyst), and polycyclic aromatic hydrocarbons.

Environmental Radon Radon is an inert gas that is produced naturally from radium in the decay series of uranium. It is naturally occurring in soil and rocks. The highest levels in the UK are in Cornwall. Once inhaled, radon continues to decay and emit alpha particles. Environmental radon accounts for approximately 1000 premature deaths per year in the UK (compared with 28,000 for smokers). Occupations with a slight increase in risk include air crew and nuclear fuel plant and power station workers.

Outdoor and Indoor Air Pollution In developed countries the two indoor pollutants that most strongly increase the risk of lung cancer are passive smoking and radon. In developing countries the greatest risk is from the use of unprocessed solid fuels for cooking and space heating.

Underlying Chronic Lung Disease and Infections Pulmonary fibrosis, chronic obstructive pulmonary disease, tuberculosis, and HIV are all associated with an increased risk of developing lung cancer.

Family History A positive family history of lung cancer is a clinically useful risk factor.

Smoking interacts with many of these risk factors in an additive or synergistic fashion. For example, heavily exposed asbestos workers have a fivefold and smokers an 11-fold increase in risk, whereas asbestos workers who are also smokers have a 53-fold increase.

Pathology

Lung Cancer Carcinogenesis

The properties of a malignant neoplasm such as excessive growth, local invasiveness, and ability to form metastases are acquired in a stepwise fashion corresponding at the molecular level due to accumulation of genetic lesions. The actions of a carcinogenic substance may be either direct or indirect via the induction of chronic inflammation, hyperplasia and metaplasia (Fig. 6.1a, b). Cigarette smoke is a powerful mutagen and contains at least 43 known carcinogens. Some, such as polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, and polonium 210, are organ-specific. Carcinogenic metals present within cigarette smoke include arsenic, nickel, cadmium, and chromium. Acetaldehyde and phenol are potential promoters. Chemicals such as nitrogen dioxide and formaldehyde act as irritants, and hydrogen cyanide is toxic to cilia.

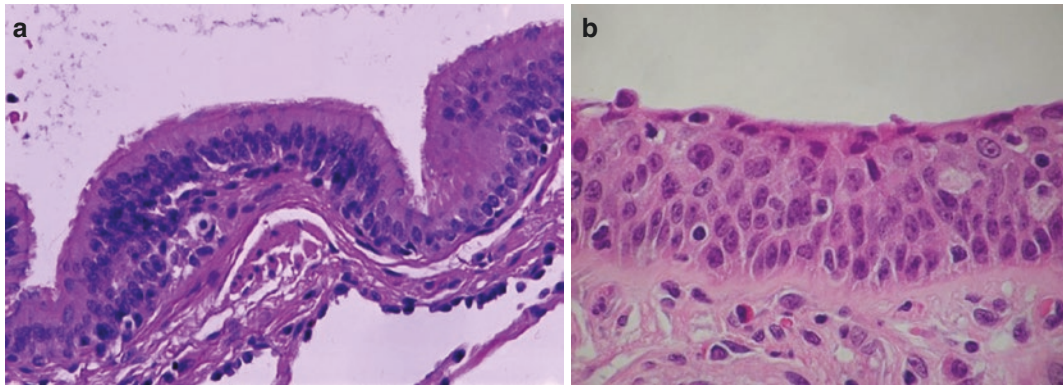

Fig. 6.1 (**a**, **b**) Comparing native respiratory pseudostratified columnar ciliated epithelium (**a**) with squamous metaplasia (**b**). Normal respiratory epithelium is replaced by squamous cells but the changes are considered reversible and are distinct from premalignant dysplasias

Carcinomas of the lung contain many genetic abnormalities but only some ("driver mutations") are essential for tumour cell survival. Whilst many genetic abnormalities are common to all lung cancer subtypes, there are also significant differences between them.

Adenocarcinoma

Driver gene alterations in adenocarcinoma include EGFR, ALK, KRAS, BRAF, ERBB2/HER2, ROS1, RET, NTRK1, and NRG1. EGFR mutations (commoner in women and non-smokers) are mutually exclusive, with the other major lung cancer driver genes such as KRAS (commoner in smokers) presumably because these all converge on the same intracellular signalling pathways. EGFR and ALK are the most clinically relevant of these gene alterations, as targeted drugs are available for those patients whose tumours have these genetic abnormalities. Drugs targeting other mutations including KRAS, ROS1, RET, and HER2 are currently being studied in lung cancer.

Squamous Cell Carcinoma

Squamous cell carcinoma is strongly associated with smoking and has 3–10 times more mutations per megabase than other common cancers. The most frequent gene mutation is TP53.

Small Cell Carcinoma

Small cell carcinoma is driven by inactivating mutations in the TP53 and RB1 genes. These high-grade tumours contain the characteristic tobacco carcinogen associated molecular signature common to all lung cancers, but inactivating RB1 mutations are a hallmark of small cell carcinoma.

Cytological and Histological Diagnosis

Traditionally the histological classification of carcinoma of the lung has been divided into small cell carcinoma (SCC) and non-small cell carcinoma (NSCLC). Within NSCLC, squamous carcinomas have become less common and adenocarcinomas are now the commonest subtype. The most recent UK data [1] apportions histological subtypes as follows: small cell (11%) and carcinoid (1%); and of the remaining 88% NSCLCs adenocarcinoma (36%), squamous (22%), other including large cell, sarcomatoid carcinoma, and some tumours not otherwise specified (11%); and no histological diagnosis in 31%. With the advent of modern oncological treatments, subtyping of NSCLC and molecular testing have become crucial for deciding the most appropriate treatment for individual patients.

Cytological diagnosis entails looking at preparations of individual cells obtained by brushing, washing/lavage or fine-needle aspiration (FNA) at bronchoscopy and endoscopic or endobronchial ultrasound (EUS and EBUS respectively). Diagnoses of lung cancer may also be made from other specimens such as pleural effusions or FNA of skin nodules or cervical lymph nodes. Diagnosis is based on recognising malignant characteristics of the tumour cells such as loss of cell cohesion, high nuclear-cytoplasmic ratios, nuclear pleomorphism (variation in shape and size), and hyperchromasia and mitotic activity. Features such as keratinisation or gland formation and/or presence of intracytoplasmic vacuoles may indicate the tumour sub-type (squamous cell carcinoma and adenocarcinoma respectively). Crucially, tissue architecture cannot be assessed by cytology.

Histological diagnosis entails microscopic examination of thin tissue sections prepared from specimens taken at procedures including bronchoscopy, image-guided biopsy, and surgery. Because architectural features of the tissue can be assessed, information can be gained not simply of tumour type, but also of factors important for staging such as lymphovascular invasion, lymph node involvement, tumour size, and extent of tumour spread.

Histological (and to a lesser extent cytological) diagnosis and subtyping of lung cancer is currently made using a combination of morphological and immunohistochemical features as summarised in Table 6.1.

Table 6.1 Morphological and immunohistochemical characteristics of the commonest histological types of lung cancer

Tumour type	Morphological features	Positive immunohistochemical markers
Adenocarcinoma	Gland formation and/or mucin production	TTF-1
Squamous cell carcinoma	Keratinisation, intercellular bridges	P40 (or P63, or CK5/6)
Small cell carcinoma	Small to intermediate sized cells with scanty cytoplasm, hyperchromatic nuclei and finely granular or glassy nuclear chromatin	CD56, TTF-1, Chromogranin A, synaptophysin

Following histological diagnosis, biopsy or cytology specimens may be sent for molecular testing, e.g. in adenocarcinoma the biopsy or cytology specimen can be tested for EGFR mutations and ALK gene rearrangements using techniques such as immunohistochemistry, PCR and Fluorescent In Situ Hybridisation (FISH). Expression of PD-L1 is also performed using immunohistochemistry to evaluate suitability for immunotherapy. As more genetically targeted drugs become available, and with the introduction of immunotherapy, the list of required tests is increasing.

Diagnosis and Staging

Presentation

In primary care the frequent presenting symptoms which trigger an urgent referral to rule out lung cancer include haemoptysis, cough (lasting longer than 6 weeks), breathlessness, weight loss, and pain. Most patients referred for assessment for possible lung cancer have multiple symptoms. However, the symptoms with which lung cancer presents are non-specific and are commonly associated with other lung diseases.

Haemoptysis Coughing up blood is the only presenting symptom which is statistically associated with a cancer diagnosis in those referred for assessment for possible lung cancer [2]. Haemoptysis can vary from streaks of blood mixed in with sputum through to expectorating clots. Rarely, lung cancer can present with massive haemoptysis.

Cough Differentiating cough caused by malignancy from cough caused by the myriad other aetiologies is very difficult. There are no specific cough features which accurately suggest malignancy. Smokers with a persistent cough, or where the nature of their cough has changed, particularly if associated with other red flag symptoms, require further evaluation, initially with a chest X-ray.

Breathlessness Breathlessness is another non-specific symptom which can be caused by lung cancer. Small peripheral tumours do not cause breathlessness. In order to cause dyspnoea the tumour needs to narrow an airway, cause atelectasis, or be associated with a pleural effusion.

Weight Loss Weight loss is commonly reported by patients as a presenting symptom associated with lung cancer. However, it is rarely the only symptom, and is non-specific. Significant weight loss commonly triggers the initial interaction with healthcare professionals, as the public recognise unexplained weight loss as a serious symptom.

Pain Pain caused by lung cancer is due to either local invasion into the parietal pleura or chest wall, bulky mediastinal nodal involvement, or due to metastatic disease, in particular bone metastases. Liver metastases can also cause pain as a presenting symptom.

Lethargy Symptoms of malaise and lack of energy are common but non-specific.

Symptoms Associated with Metastatic Disease Unfortunately, presentation with symptoms from metastatic disease is common. The commonest sites of metastatic disease which lead to presentation are bone (pain, pathological fracture, hypercalcaemia, spinal cord compression),

brain (headache, seizures, focal neurological signs/symptoms), and liver (capsule pain, jaundice, nausea). Rarely, lung cancer can present with adrenal insufficiency due to bilateral adrenal metastases [3].

Aside from unexplained haemoptysis, the common symptoms with which lung cancer first presents are all non-specific, and frequently associated with other smoking related diseases such as COPD. Furthermore, symptoms become increasingly common with more advanced lung cancer. Indeed, many early stage lung cancers are incidental findings rather than "classical" presentations. Paraneoplastic syndromes are not uncommonly due to lung cancer and can present to the endocrinologist, neurologist, or general physician. Some of the commoner presentations are shown below.

Syndrome	Comment
Clubbing, hypertrophic osteoarthropathy (HPOA)	HPOA usually associated with NSCLC
Inappropriate ADH secretion	SCLC usually
Cushing's syndrome	Ectopic ACTH secretion. Biochemical abnormalities (hypokalaemic alkalosis, hypercortisolaemia) rather than clinical CS
Humoral hypercalcaemia	Parathyroid hormone-related peptide secreted by tumour (usually squamous)
Thrombophilia	Venous thromboembolism, may be in unusual site
Subacute sensory neuropathy	Commonest neurological syndrome
Polymyositis/ Dermatomyositis	Gottron's papules, periorbital rash and oedematous eyelids
Eaton-Lambert myasthenic syndrome	Weak legs, autonomic dysfunction, ocular movements preserved. Anti-voltage-gated calcium channel antibody
Cerebellar degeneration	Anti-Yo and anti-Hu antibodies
Limbic encephalitis	Anti-Hu antibody
Glomerulopathy	Usually membranous

Physical signs on examination in patients with lung cancer can include finger clubbing, supraclavicular/cervical lymphadenopathy, hoarse voice due to vocal cord palsy, fixed monophonic wheeze, signs consistent with pleural effusion or lobar atelectasis and, rarely, hypertrophic pulmonary osteoarthropathy.

A chest X-ray should be the first investigation of choice in patients presenting with symptoms suggesting the possibility of lung cancer [4]. However, chest X-ray is significantly less sensitive at detecting lung cancer than CT scanning [5] and so a normal chest X-ray should not be considered entirely reassuring as a method of excluding a diagnosis of lung cancer.

Emergency Presentations

Emergency presentation of lung cancer warrants specific focus, as it is a major challenge for those diagnosing and treating lung cancer, and is associated with significantly worse outcomes compared to patients who are referred as outpatients [6]. In the United Kingdom approximately 35% of lung cancers are diagnosed during an emergency presentation. These patients frequently are older, have later stage disease, and worse performance status. However, even when these factors are corrected for, emergency presentation is associated with a 51% higher 12-month mortality [7]. The factors driving such high rates of emergency presentation are complex, and include cultural factors, the non-specific nature of early symptoms associated with lung cancer, and the fact that most patients with lung cancer have significant co-morbidities. The UK continues to have worse outcomes for lung cancer compared to many other countries in the European Union [8].

NICE Recommendations for Investigation and Referral of Patients with Suspicion of Lung Cancer [4]

Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) for lung cancer if they:
• Have chest X-ray findings that suggest lung cancer *or*
• Are aged 40 and over with unexplained haemoptysis

Offer an urgent chest X-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over if they have two or more of the following unexplained symptoms, *or* if they have ever smoked and have one or more of the following unexplained symptoms
• Cough
• Fatigue
• Shortness of breath
• Chest pain
• Weight loss
• Appetite loss

Consider an urgent chest X-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following

- Persistent or recurrent chest infection
- Finger clubbing
- Supraclavicular lymphadenopathy or persistent cervical lymphadenopathy
- Chest signs consistent with lung cancer

Approach to Diagnostic Testing

When assessing a patient with suspected lung cancer, the clinician must take a systematic approach to first confirm or refute the diagnosis, and then to stage and gain histology. The aim should be to achieve diagnosis and staging with the least possible tests in the shortest feasible time. Firstly ask: Which test(s) can best confirm or rule out lung cancer? Then, if after initial testing lung cancer is either confirmed or still suspected, ask a further two questions in parallel:

1. What is the best way to get a histological diagnosis?
2. Which tests will most accurately stage the cancer?

It is also essential that the clinicians ask themselves "Are these tests going to offer valuable information which will alter the patient's treatment options?". In patients with poor performance status for whom treatment will be limited to best supportive care, it is not necessary to fully stage and tissue type cancers.

Staging CT Scan

For all patients with either a chest X-ray suspicious for lung cancer or a normal chest X-ray and ongoing clinical concern for cancer, a contrast-enhanced CT scan of the thorax and upper abdomen, including the liver and adrenal glands, should be performed. The sensitivity and specificity of CT scan to detect lung cancer are 94% and 73% respectively [5].

The staging CT scan gives initial information about both the presence of lung cancer and its stage, and should guide further diagnostic decision-making with the aim of performing a single diagnostic test to give both pathological diagnosis and TNM staging.

Specifically, the CT scan gives important information about mediastinal staging. The most commonly accepted definition of pathological lymphadenopathy on CT criteria is lymph nodes with a short axis diameter of $\geq$1 cm. However, CT scanning in isolation carries significant false positive and negative rates, with a sensitivity of 55% and specificity of 84% for detecting malignant mediastinal lymph nodes [9].

Investigations Beyond the Staging CT Scan

Following CT further tests to accurately diagnose and stage lung cancer may include positron-emitting tomography combined with CT (PET-CT), bronchoscopy, EBUS, EUS, CT-guided biopsy, and image-guided sampling of extra-thoracic disease such as liver metastases or supraclavicular lymph nodes.

PET-CT

PET-CT combines a PET scan after administration of the radio-labelled glucose analogue fluoro-2-deoxy-d-glucose (FDG) with a non-contrast enhanced CT. Malignant cells demonstrate high uptake of glucose (and its analogues) and so FDG accumulates within malignant tissue. This is then detected by a PET scan. The PET scan images are overlaid onto a CT scan to give more detailed anatomical information.

PET-CT more accurately stages lung cancer compared to CT scanning alone. It detects previously unrecognised distant metastases in between 6% and 37% of cases and has better sensitivity and specificity for detecting malignant mediastinal lymph nodes (80% and 88% respectively) [9]. However, it is by no means a perfect test. Non-malignant tissue, particularly inflammatory processes such as infection or granulomatous disease, display increased PET avidity, and certain tumours such as slow growing well-differentiated adenocarcinoma (particularly of lepidic-predominant type) and typical carcinoid can frequently display normal PET avidity. The investigation of innocent incidental findings, such as within the bowel, may cause a delay in decision-making [10].

EBUS

EBUS has partly replaced surgical mediastinoscopy as a diagnostic/staging investigation in recent years. There are two types of EBUS: convex probe EBUS, which is used to image and sample mediastinal lymph nodes and central parenchymal lesions; and radial probe EBUS, which can sample peripheral lung lesions that are either inaccessible or high risk for CT-guided biopsy, but it is not widely available.

EBUS can access mediastinal lymph node stations 2, 4, 7, 10, and 11 (Fig. 6.2). In experienced hands, EBUS has sensitivity of 89% for detecting malignant mediastinal lymph nodes and a negative predictive value of 91% [9]. For patients with radiologically suspected malignant mediastinal lymph nodes but negative EBUS, surgical mediastinoscopy prior to resection should be considered. Using PET avidity and ultrasonographic heterogeneity, a risk stratification model can be used to determine the need for further staging procedures prior to resection with a negative predictive value of 98% [11].

EBUS can provide both accurate mediastinal staging and a tissue diagnosis in a single procedure, and should be performed as the first test if mediastinal staging is required.

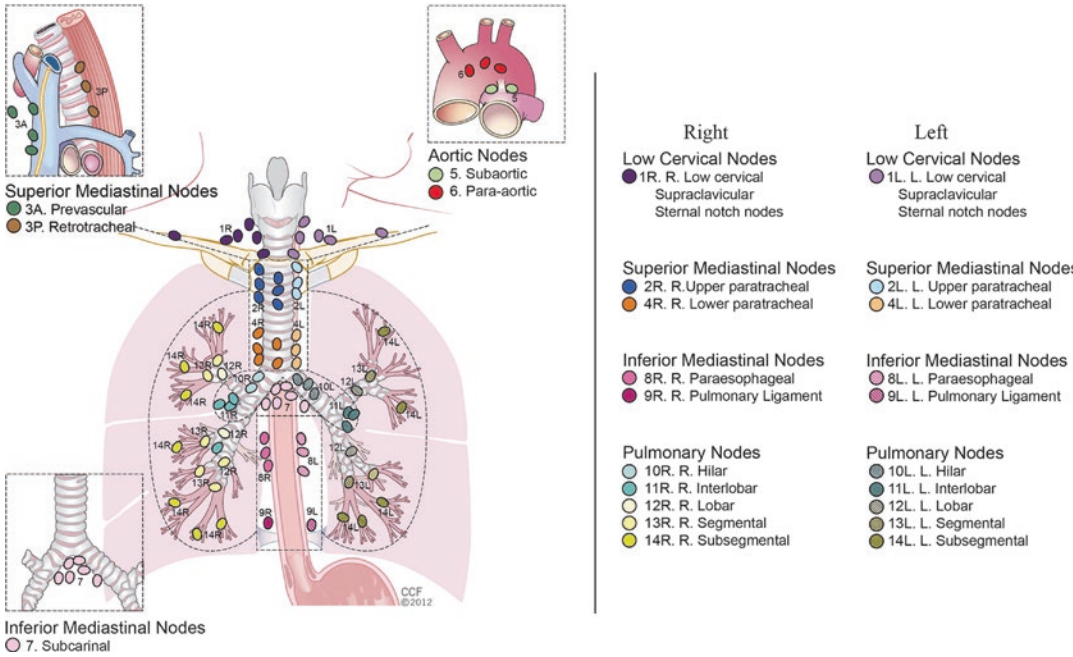

Fig. 6.2 International Association for the Study of Lung Cancer (IASLC) lymph node map. From El-Sherief AH, Lau CT, Wu CC, et al. International Association for the Study of Lung Cancer (IASLC) lymph node map: Radiologic review with CT illustration. RadioGraphics 2014;34:1680–91. With permission from RSNA—Radiological Society of North America

EUS

Endoscopic ultrasound guided needle aspiration is similar in principal to EBUS but involves intubating the oesophagus rather than the trachea. EUS can access the left-sided paratracheal nodes (2L, 4L), station 7, and stations below the diaphragm (station 8 and 9). It can also be used to sample possible adrenal metastases. Technically, it is easier to access 4L using EUS than EBUS. In cases with a pathological appearance on PET-CT or CT, EUS has a sensitivity of 89% and negative predictive value of 86% [9].

Combining EBUS with EUS at the same sitting allows access to almost the entire mediastinum. This approach offers a sensitivity of 91% and negative predictive value of 96% [9].

Image-Guided Trans-Thoracic Lung Biopsy

Most centres in the UK utilise CT for image-guided lung biopsy but fluoroscopy, ultrasound, and electromagnetic navigation can also be used. This technique is useful for peripheral lung lesions for which a histological diagnosis is required and in whom mediastinal staging is not required to guide management. This includes patients with metastatic disease for whom only a tissue diagnosis is required, and patients with peripheral tumours with no evidence of mediastinal or metastatic disease on CT and PET-CT. This procedure carries a risk of approximately 15% for pneumothorax and 1% significant haemorrhage.

Surgical Mediastinoscopy

Mediastinoscopy is a surgical procedure performed under general anaesthetic. A mediastinoscope is inserted through an incision above the suprasternal notch. Mediastinoscopy is historically the gold standard technique for pre-operative staging of the mediastinum. It is possible to access stations 2 and 4 on both sides, station 3 anterior to vessels, and not accessible by EBUS, and anterior station 7. Mediastinoscopy has a sensitivity of 78% for detecting mediastinal malignant nodes and negative predictive value of 91% [9]. This relatively low sensitivity is primarily due to some stations not being easily accessible. The decision regarding whether to proceed to surgical mediastinal staging if EBUS/EUS is negative depends on the level of suspicion of malignancy stratified according to PET findings and EBUS evidence of ultrasonographic heterogeneity.

Supraclavicular Ultrasound-Guided FNA

Lung cancer frequently metastasises to the supraclavicular lymph nodes. In patients with supraclavicular lymph nodes larger than 5 mm, ultrasound-guided assessment and fine-needle aspiration of suspicious nodes has been shown to detect malignancy in 45% of cases [12]. However, this study did not include PET-CT analysis. Current standard would be to perform ultrasound guided FNA for all neck/supraclavicular nodes which are $\geq$1 cm in diameter or display significant PET avidity.

Which Investigations to Choose Based on CT Findings

Based on the findings of the initial staging CT scan, patients can be broadly divided into five groups. The approach to diagnosis and staging of each of these groups is different.

Group 1: Peripheral Tumour with Normal Mediastinal Lymph Nodes

The most important next test for this group of patients is PET-CT, whilst simultaneously assessing fitness for radical treatment. Initially this is with full pulmonary function tests and consideration of co-morbidities. In the absence of mediastinal lymphadenopathy on CT and PET-CT, and no evidence of distant metastases, the false negative rate for this group of patients is 4% [13, 14]. This is deemed an acceptable level to make mediastinal staging unnecessary.

Group 2: Lung Tumour with Discrete Enlarged Mediastinal Lymph Nodes

These patients require PET-CT and mediastinal staging. The preferred method for mediastinal staging is dependent on local expertise/resource and the anatomical location of lymphadenopathy, but in general this would be EBUS ± EUS. When using EBUS there are two possible approaches to lymph node sampling, either systematic sampling of all stations from N3 to N2 to N1 or targeted sampling of the pathological stations based on radiology. A pragmatic approach is to perform targetted sampling in patients with N3 disease and multi-station N2 disease, but to perform systematic nodal sampling in patients with N1 disease and single station N2 disease according to radiology. These patients can potentially be treated radically.

Group 3: Lung Tumour Directly Invading the Mediastinum Without Metastases

These patients are not operable, and so gaining a tissue diagnosis is the priority. Choice of method between bronchoscopy, EBUS, or image-guided biopsy is dependent on the test most likely to give a positive diagnosis, availability of investigations, and patient choice. PET-CT should also be performed in these patients in order to detect distant metastatic disease not detected by CT scan if radical treatment is being considered.

Group 4: Central Tumour or N1 Disease

These patients all require a PET-CT acknowledging that the false negative rate for N2 may be as high as 25% [9]. EBUS can sample the most stations accurately with good sensitivity as described above. There is no published literature focusing specifically on the role of combined EBUS/EUS for this group. The question of whether to proceed to surgical mediastinoscopy if EBUS is negative depends on local availability of surgical mediastinoscopy, thoroughness of EBUS sampling, and awareness of local false negative rates.

Group 5: Lung Tumour with Metastatic Disease

These patients generally only require a histological diagnosis. Biopsy by the safest and most readily available technique is appropriate if the patient is fit enough for chemotherapy. In frail patients where no oncological treatment is planned, and where survival is likely to be only a few weeks, then histology is unnecessary. PET-CT should be reserved for patients with oligometastatic disease in whom radical treatment might be considered.

Lung Cancer Staging

There are two complementary staging systems for lung cancer; tumour, node, metastasis (TNM) as per the International Association for the Study of Lung Cancer, and Group stage [15]. The individual T, N, and M definitions are based on the fact that each descriptor has prognostic significance (Table 6.2).

The tumour (T) descriptor is based on both the size of the primary tumour and whether it is invading surrounding structures. The node (N) descriptor is based on the anatomical location of pathological nodes in respect to the primary tumour with increasing N status with more distant spread. The metastases (M) descriptor is based on the presence and distribution of metastases. The most recent (Eighth Edition) Lung Cancer Stage Classification was adopted in the UK in January 2018.

Group Staging and Survival

Group staging combines different TNM stages which have similar prognoses and are treated similarly (Fig. 6.3).

Lung cancer survival is critically dependent on staging, and many patients present late with stage 3 or 4 disease. Overall, 1- and 5-year survival in the UK is approximately 38% and 9% respectively [1]. By stage, 5-year survival is 35% (stage 1), 21% (stage 2), 6% (stage 3), and negligible for stage 4. These figures are significantly worse than the 5-year survival figures from a global database, shown in Table 6.3. The cause of

Table 6.2 International Association for the Study of Lung Cancer TNM staging criteria

Descriptor	Definition
T	*Primary tumour*
T0	No primary tumour
T1	Tumour ≤3 cm
T1a	Tumour ≤1 cm
T1b	Tumour >1 cm but ≤2 cm
T1c	Tumour >2 cm, but ≤3 cm
T2	Tumour >3 cm but ≤5 cm or tumour with any of the following: • Involves main bronchus but not carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis extending to the hilar region
T2a	Tumour >3 cm but ≤4 cm
T2b	Tumour >4 cm but ≤5 cm
T3	Tumour >5 cm but ≤7 cm or any of the following: • Directly invading chest wall, phrenic nerve, or parietal pericardium, • Separate tumour nodules in same lobe
T4	Tumour >7 cm or any size with • Invasion of diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina. • Tumour nodules in different ipsilateral lobe
N	*Regional lymph nodes*
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial, ipsilateral hilar and intrapulmonary nodes
N2	Metastasis in ipsilateral mediastinal and/or subcarinal nodes
N3	Matastasis in contralateral mediastinal, contralateral hilar, any scalene or supraclavicular nodes
M	*Distant metastasis*
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumour nodule(s) in contralateral lobe, tumour with pleural or pericardial nodules, malignant pleural or pericardial effusion
M1b	Single extrathoracic metastasis in a single organ
M1c	Multiple extrathoracic metastases in one or several organs

From: Peter Goldstraw, Kari Chansky, Johnn Crowley, Ramon Rami-Porta, Hisao Asamura, Wilfired EE Eberhardt, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thoracic Oncol. 2016; 39–51. With permission of Elsevier

this discrepancy is multifactorial and complex, but the UK data set is considered robust and more closely reflects everyday clinical practice.

Small cell lung cancer is staged as limited or extensive stage. Limited stage lung cancer is disease which is unilateral and can be encompassed in a radiation field. Extensive stage small cell lung cancer is defined by metastasis to contralateral lung or lymph nodes or distant metastasis.

Performance Status

The performance status scale was developed by researchers from the Eastern Cooperative Oncology Group (ECOG) to take into account a patient's level of functioning when planning trials of cancer treatments. It is often used in clinical practice when considering if a patient is fit enough for treatment such as radiotherapy or chemotherapy.

T/M	Label	N0	N1	N2	N3
T1	T1a ≤*1*	IA1	IIB	IIIA	IIIB
	T1b >*1-2*	IA2	IIB	IIIA	IIIB
	T1c >*2-3*	IA3	IIB	IIIA	IIIB
T2	T2a *Cent, Visc Pl*	IB	IIB	IIIA	IIIB
	T2a >*3-4*	IB	IIB	IIIA	IIIB
	T2b >*4-5*	IIA	IIB	IIIA	IIIB
T3	T3 >*5-7*	IIB	IIIA	IIIB	IIIC
	T3 *Inv*	IIB	IIIA	IIIB	IIIC
	T3 *Satell*	IIB	IIIA	IIIB	IIIC
T4	T4 >*7*	IIIA	IIIA	IIIB	IIIC
	T4 *Inv*	IIIA	IIIA	IIIB	IIIC
	T4 *Ipsi Nod*	IIIA	IIIA	IIIB	IIIC
M1	M1a *Contr Nod*	IVA	IVA	IVA	IVA
	M1a *Pl Dissem*	IVA	IVA	IVA	IVA
	M1b *Single*	IVA	IVA	IVA	IVA
	M1c *Multi*	IVB	IVB	IVB	IVB

Fig. 6.3 Group staging of lung cancer. See Table 6.2 for explanation of abbreviations

Table 6.3 Survival of patients from the International Association for the Study of Lung Cancer database diagnosed between 1999 and 2010

Clinical stage	5-year survival (%)
1A[a]	83
1B	68
2A	60
2B	53
3A	36
3B	26
4A	10
4B	0

[a]Stage IA refers to patients with 1–2 cm tumours. Survival figures for tumours <1 cm and 2–3 cm are 92% and 77% respectively [16]

Grade	Activity
0	Fully active, able to carry out all pre-disease activities without restriction
1	Restricted in physically strenuous activity but capable of light work
2	Ambulatory, capable of selfcare but unable to carry out any work. Up and about >50% of waking hours
3	Limited selfcare, confined to bed or chair >50% of waking hours
4	Completely disabled. Incapable of any selfcare. Confined to bed or chair

Lung Cancer Screening

Lung cancer frequently presents with advanced disease. The prognosis of stage 3 and 4 disease is poor, and treatment options are limited, with little impact on overall survival rates over the last two decades despite multidisciplinary working, thoracoscopic surgery, and more aggressive chemoradiotherapy regimes.

The aim of lung cancer screening is to detect lung cancer in high-risk individuals before it has reached the advanced stages and would allow radical treatments with improvement in mortality. Historically chest X-ray and sputum cytology have been studied as means of screening, but they were shown to be ineffective [17]. The development of CT technology has allowed high quality images to be obtained with excellent sensitivity for detecting lung cancer using low dose protocols. A low-dose CT (LDCT) protocol exposes the patient to approximately one-fifth of the radiation of a standard CT scan, equivalent to approximately 6 months' background radiation. Initial studies evaluating the efficacy of LDCT in screening high-risk, asymptomatic individuals showed that LDCT detects more cancers than

chest X-ray and that the cancers detected were frequently stage 1. The U.S. National Lung Cancer Screening Trial recruited 53,454 individuals, either current smokers or ex-smokers within 15 years, with at least 30 pack years history, aged between 55 and 74 years. They were randomized to annual LDCT or CXR for 3 years, with further clinical follow-up for the next 3.5 years. Throughout the study period, 1060 lung cancers were detected in the LDCT group and 941 in the CXR group. Significantly higher numbers of detected cancers were stage 1 in the LDCT group. The trial reported a 20% relative risk reduction of lung cancer-related mortality in the group undergoing LDCT (absolute numbers of cancer related deaths 356 and 443 respectively) [18]. These results have led to the recommendation that lung cancer screening should be offered to high-risk individuals between the ages of 55 and 80 years in the USA.

There remain unanswered questions about the applicability of this to a European population/health care service. Important research questions include:

1. What is the optimal interval between scans?
2. What age range should be screened?
3. How best to engage high-risk, hard-to-engage populations?
4. Are there biomarkers which can help define high-risk individuals for CT screening?

Another issue is the false positive rate of LDCT because of detection of indeterminate lung nodules. The vast majority of these are benign, but a small proportion turn out to be malignant [19]. Consequently, they require ongoing CT follow-up, leading to anxiety, expense, and radiation exposure to individuals which otherwise would not have occurred. The psychosocial impact of this needs studying carefully to inform on the potential negative impacts of a lung cancer screening programme [20].

The cumulative radiation risk is negatively associated with age, and higher for females than males due to the risk of breast cancer. It is estimated that lung cancer screening will cause one to three cancers per 10,000 individuals screened [21].

Management of Lung Cancer

Management of Complications

Airways Compromise

Lung cancer commonly affects the central airways and can cause significant dyspnoea due to endobronchial disease or airway compression. As well as standard therapies such as chemotherapy and radiotherapy, endobronchial therapies can be useful in symptom relief or as a bridge to allow time for systemic treatments to work. For endobronchial disease which requires debulking there are a number of options including Nd:YAG laser, cryotherapy, or endobronchial stents. There is no evidence supporting these interventions as anything other than palliative.

Superior Vena Cava Obstuction

Thoracic malignancies can cause direct compression and symptomatic obstruction of the superior vena cava (SVC). The SVC syndrome occurs in 4% of non-small cell lung cancers and 10% of small cell lung cancers. It presents with signs of raised venous pressure, including facial and upper limb oedema, and congested chest wall veins. Oedema of the larynx can cause dyspnoea, cough, and rarely stridor.

Initial treatment with oral steroids and possibly diuretics is common practice, but not evidence-based. With severe symptoms, intravascular stenting of the SVC should be considered, which leads to rapid relief of symptoms. If the symptoms are not severe, time can be taken to treat the underlying disease.

Paraneoplastic Syndromes

Paraneoplastic syndromes present with signs and symptoms in association with the presence of lung cancer, but not caused directly by the physical effects of the tumour. They are present in approximately 10% of cases of lung cancer [22]. Paraneoplastic syndromes can cause endocrine, neurological, dermatological, and rheumatological effects. The specific neoplastic syndromes tend to associate with certain types of lung cancer with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) being most

commonly associated with small cell lung cancer, and humoral hypercalcaemia of malignancy being most commonly associated with squamous cell cancer. In general, the approach to managing paraneoplastic syndromes should focus on treatment of the underlying malignancy where possible. However, paraneoplastic syndromes can be refractory to treatment. Specific treatments are available, including demeclocycline or oral vaspressin antagonists for SIADH which is refractory to fluid restriction, and intravenous bisphosponates for symptomatic hypercalcaemia.

Surgery

Introduction

Until the development of radical radiotherapy, surgery offered the only chance of cure for non-small cell lung cancer. Radical surgery with curative intent is recommended for most early-stage disease and can be considered for higher staged tumours.

The Role of the Surgeon

The role of the thoracic surgeon in cancer management has evolved to include diagnosis, staging, and palliative care, as well as surgical resection. Rigid bronchoscopy for diagnosis is used when patients cannot tolerate fiberoptic bronchoscopy under sedation, or in patients with suspected carcinoid tumours at risk of bleeding. For peripheral tumours where biopsy has failed or is not safe a surgical biopsy, excision biopsy or frozen section can be performed at open thoracotomy or VAT (video-assisted thoracoscopy). There also remains a growing group of patients where the diagnosis is not known prior to resection and the diagnosis is only made post-operatively (up to 15% of cases of VATS resections reported from some units).

Cervical mediastinoscopy and video-assisted mediastinoscopy remain the gold standard for pre-operative mediastinal staging. Stations 2, 3, 4, and 10 (hilar nodes) can be accessed. Stations 5 and 6 are more routinely accessed by left anterior mediastinotomy. VATS can access most of the stations in the mediastinum but is rarely used as a staging procedure.

Surgical excision can be the only treatment for some cancers, and for many patients is the most important treatment giving the best chance of cure. A successful resection requires removal of the entire tumour with a clear resection margin leaving no residual disease (R0). This must be achieved safely without significantly compromising organ function or quality of life. As such, radical intention to treat with surgery is defined as treatment to significantly improve survival. When considering radical treatment with surgery, the patient needs to be assessed for resectability (the ability to achieve a R0 resection) and operability (that the patient is medically fit to undergo the lung resection surgery and will not be left disabled after the surgery because of the lung resection).

Radical surgery can be considered for all patients with early-stage disease (T1-3 N0-1) dependent on medical fitness. Surgery can also be considered in selected patients with T4 N0-1 disease where the tumour invades the carina, great vessels, and mediastinum. Surgery for N2 disease remains controversial. Single station N2 disease can be considered for radical resection, with a reported survival of up to 30% [23]. Survival is poor in multi-station N2 disease and should not be considered for radical surgery outside of a multi-modality clinical trial [24].

Fitness for Surgery

Patients with lung cancer are highly likely to suffer from other smoking-related cardio-respiratory diseases. Assessment is made using a tripartite risk assessment outlined in the BTS Guidelines on the Radical Management of Patients with Lung Cancer [24]. Other resources include NICE guidance [25] and the American College of Chest Physicians (ACCP) guidelines for assessing pre-operative patients with lung comorbidities [26]. A careful assessment of the patient's fitness is made to judge the degree of risk to the patient and

assess whether surgery should be performed. Risk-scoring models are advised to assess perioperative mortality, including the Thoracoscore model, [27] a logistic regression-derived model utilising nine variables. Although extensively used in Europe, there is evidence it may not be accurate in real world practice [28].

The risk of cardiac death or non-fatal myocardial infarction is 1–5% during lung resection. Cardiac risk factors include atrial fibrillation, hypertension, valvular disease, and a history of heart failure or ischaemic heart disease. Guidelines advise avoidance of surgery within 30 days of a myocardial infarction. It is safe to proceed with surgery if the patient has two or less cardiac risk factors and good functional cardiac capacity. However, if patients have an active cardiac condition, three or more cardiac risk factors, or poor cardiac functional capacity, they should be referred for a cardiological opinion. Other factors which need to be considered because of their effect on perioperative morbidity and mortality are the presence of cerebrovascular disease, diabetes requiring insulin therapy, and a raised serum creatinine level.

Anti-ischaemic medication should be continued in the peri-operative period. Where patients have stable chronic angina or other conventional indications for revascularisation, this should be considered before lung resection. If a patient has a coronary stent, antiplatelet therapy should be discussed with a cardiologist prior to surgery.

The risk of post-operative dyspnoea is calculated pre-operatively. Standard spirometry and gas transfer with segment counting can be used to estimate predicted postoperative (PPO) lung function. A PPO FEV1 and DLCO >60% predict a low risk of postoperative breathlessness, whereas a PPO FEV1 and DLCO <30% predict a high risk.

Further assessment measuring maximal oxygen uptake (VO2 max) with a cardio-pulmonary exercise test (CPET) is useful for borderline cases: VO2max of 10–15 ml/kg/min indicates an increased surgical risk, whereas a VO2max <10 ml/kg/min predicts a high risk of perioperative death.

Radical Surgery

Surgical procedures for curative resection include wedge resection, segmentectomy, lobectomy, bilobectomy, and pneumonectomy. Since the findings of the Lung Cancer Study Group in 1995, [29] lobectomy has been the gold standard operation for lung cancer confined to a lobe. Lobectomy had better outcomes than segmentectomy and wedge resection for all tumours over 1 cm in size. However, there is increasing interest in lung conservation, and segmentectomy can be indicated for tumours up to 2 cm provided there can be a good margin to the resection and the tumour is staged accurately with an appropriate lymph node dissection. Pneumonectomy is a major operation carrying increased operative risk and causing major physiological disturbance, especially in the older patient (>80 years). There has consequently been a significant decline in the number of pneumonectomies performed because of the wider utilization of sleeve resection.

Over the past 25 years VATS has had an increased role, especially in the treatment of early-stage lung cancer, with now over 30% of resections in many units performed by VATS. Non-randomised trials have shown the procedure to be safe and may allow as complete a cancer-clearing operation as at thoracotomy with lymph node sampling/resection. VATS appears to be associated with less post-operative pain, fewer complications, shorter post-operative stay, and faster recovery, factors which may well increase the uptake of adjuvant chemotherapy in a timely fashion. Overall, the reported series show survival is at least equivalent to open surgery [30]. Early results from robotic surgery are encouraging, with reports of considerable lower pain scores and quicker recovery.

Surgery may be considered for locally advanced T4 tumours or advanced oligometastatic disease where the metastasis can be treated radically. Evidence is confined mainly to small reported series, and surgery should only be considered offered following full discussion at the MDT and accurate disclosure to the patient.

Outcomes for Surgery

Despite the increasing resection rate, including higher risk patients, peri-operative 30-day mortality remains relatively constant at 2–2.5% for lobectomy and 5.8% for pneumonectomy [1]. There is further attrition, particularly in patients with more advanced tumours, with a 90-day mortality, which is double the 30-day mortality [31]. Adjuvant (post-operative) chemotherapy was found to be detrimental in stage 1a disease, but offers benefit in higher stage disease.

Radiotherapy for Lung Cancer

Radical and Palliative Treatment for Lung Cancer

The current gold-standard radical treatment for non-small cell lung cancer (NSCLC) is complete surgical resection with adjuvant chemotherapy for those at high risk of recurrence. However, the majority of patients with NSCLC present with disease which is too advanced for surgical resection. Patients with small-cell lung cancer (SCLC) rarely undergo radical resection, as their disease is usually locally advanced within the thorax and frequently overtly metastatic at the time of presentation. Most lung cancers managed with radical intent therefore undergo non-surgical treatment, comprising radiotherapy alone or a combination of radiotherapy and chemotherapy. Recently, advances have allowed the development of radical stereotactic radiotherapy techniques for patients with early-stage, non-small cell lung cancer who are medically unfit for surgical resection.

Palliative treatment for lung cancer is aimed at improving the symptoms of incurable disease and where possible, extending life expectancy. So far only palliative chemotherapy has been shown to improve length of life, but there is good evidence to support the use of radiotherapy in the palliative setting for symptomatic benefit.

Principles of Radiotherapy

Radiotherapy (RT) uses ionising radiation to treat cancers and is usually given as high-energy photons produced in a linear accelerator. Less commonly, RT is given as electron treatment for superficially situated cancers, and more rarely, as proton beam therapy. A fraction of radiotherapy refers to the dose of radiation, expressed in Grays (Gy), given at a single exposure, which is usually delivered once each day on consecutive working days. Fractions of RT can be given more often than once per day (hyperfractionation) or less frequently than once per day (hypofractionation), and can be given as a single exposure in the palliative setting. A course of RT refers to the sum of the fractions delivered, and is expressed as the total dose of radiation delivered in a given number of fractions over a specified period of time.

Radical RT can eradicate localised cancers if given in a way which maximises damage to malignant cells while allowing repair mechanisms to operate and restore the function of normal cell populations. Radiotherapy causes damage to DNA, in particular double strand breaks which are difficult to repair accurately. In normal dividing cell populations, DNA repair mechanisms and cell cycle controls are intact, DNA damage from RT is detected, and the cell cycle is halted until repair is complete or a terminally damaged cell is diverted along a cell death pathway. In malignant cells, mutations are frequent and can occur in genes which code for cell cycle control mechanisms and DNA repair enzymes. Damage to DNA by radiotherapy may therefore fail to induce the normal damage repair mechanisms, resulting in continuation of the cell cycle and abnormal mitosis with death of the daughter cells. It must be remembered that an inherent limitation of radiotherapy, and indeed chemotherapy, stems from the fact that a cancer consists of many varied populations of cells which have accumulated mutations and hence have different phenotypes, including their susceptibility to anti-cancer treatments. Conventional radical RT exploits the difference in the potential

of malignant and normal populations of cells to repair radiation damage by splitting the total dose of RT into many small fractions delivered over several weeks. A typical radical dose for non-small cell lung cancer would deliver 66 Gy in 33 fractions over 6½ weeks. This allows time between fractions for normal cells to undergo more recovery than the malignant population. The difference in survival of the normal and malignant cells is manifest as the RT course continues, although as there is damage to both populations, cure can only be achieved if the malignant cells can be eradicated without irreparable damage to normal cells. To maximise this therapeutic differential and avoid dose-limiting normal tissue toxicity, it is important to deliver a high dose of RT to the cancer while minimising the dose to surrounding normal tissues. This is achieved by conforming the radiotherapy beams to the shape of the cancer mass, and by using accurate imaging to ensure that the target is covered by the beam at each fraction. These techniques are described below.

Risks of Radiotherapy

Toxicity from radiotherapy is usually divided into "early" and "late" with an arbitrary cut-off at 6 months after completion of RT. Early reacting tissues are those with a rapid turnover of cells such as the bone marrow, skin, and mucosal surfaces. These lose integrity because of radiation damage during the course of RT, and this may continue for several weeks after the end of treatment. Recovery from acute side effects occurs gradually over the weeks after RT is complete, and the severity of the toxicity depends more on the total dose delivered than the dose per fraction. Late reacting tissues are usually those with a slow turnover of cells, such as fibrous tissue, muscle, bone, glia, and blood vessels. Late damage usually causes changes such as fibrosis, necrosis, and telangiectasia, and may cause complications many years after the RT has finished. In general, late reacting tissues are more sensitive to the dose per fraction than the total dose. Thus in the development of dose and fractionation regimens, it is important to balance the chances of cure of the cancer with the risks of both early and late side effects. Palliative RT uses the same photon energies and delivery mechanisms as radical RT, but as the aim is not cure but relief of symptoms, dose and fractionation regimens are designed to achieve maximal symptomatic benefit while minimising toxicity.

In the treatment of lung cancers with radiotherapy, the organs most at risk of damage—and therefore those which limit treatment dose and volume—are the lungs, oesophagus, heart, and spinal cord. Care must be taken when planning RT to the chest, as the length of oesophagus taken to high dose is linked to the severity of the acute radiation toxicity or late fibrosis and stricture. In the acute phase of radiation oesophagitis, patients may struggle to maintain their hydration and nutrition, and this should be anticipated and actively managed with help from dieticians and with the liberal use of analgesics. Oesophageal stricture is rare, and recurrent cancer should be ruled out in patients with a previously treated lung cancer who present with dysphagia. Endoscopic dilatation may be required and often needs to be repeated. The spinal cord is outlined during the planning process and the beams are carefully arranged to avoid overdose, which can lead to the late effect of radiation myelitis. If the cancer lies too close to the spine, particularly if the vertebral body is invaded, radical treatment may not be possible.

The lungs are also carefully delineated, and the percentage volume of lung outside the high-dose region which receives more than 20 Gy must be kept below a maximum of 35%. As many patients with lung cancer have co-existing chronic obstructive pulmonary disease, full lung function tests, including transfer factor, may be required to ensure that patents with poor respiratory reserve can be safely treated. Acute radiation damage ("radiation pneumonitis") usually presents as breathlessness and cough, which may be accompanied by a fever. It is difficult to distinguish from infection, and management usually comprises symptomatic measures plus steroids and antibiotics. Radiation pneumonitis is usually self-limiting, but the late side effect of radiation

fibrosis may affect lung function if the volume is large, and therefore stringent pre-treatment assessment and careful radiotherapy planning are essential.

Planning and Delivery of Radiotherapy for Lung Cancer

In its early days, radical RT was delivered essentially as a "box" encompassing the lung cancer and surrounding tissues as defined by the available imaging. With more recent advances in radiotherapy and radiology, it has been possible to conform the radiotherapy volume to the shape of the cancer to be treated, excluding as much normal tissue as possible while still treating the cancer to high dose.

The planning of conventional three-dimensional conformal radiotherapy (3D CRT) for both non-small cell and small-cell lung cancer involves the careful delineation of the cancer and involved lymph nodes, usually with the help of CT or PET/CT images. The patient undergoes a radiotherapy planning CT scan, usually performed without contrast, lying supine on a flat bed with their arms supported above the head to allow for beam entry through the lateral chest wall (Fig. 6.4). Patients who are too breathless to lie in this way cannot, realistically, undergo radical RT unless their breathing can be improved by other interventions. Technology is available to allow RT planning using a PET/CT scan, and some UK departments are moving to adopt this for lung cancer, which should speed up the RT planning process, avoid an additional visit to hospital, and improve the ability of the clinical oncologist to define the target tissues. The planning CT scan is carried out after careful alignment of the patient with orthogonal lasers in the CT suite which are replicated in the treatment rooms. Small tattoos made on the skin along the laser lines ensure that the position of the patient during RT planning can be reproduced on each treatment day. The planning CT scan is viewed by the clinical oncologist using RT planning software, and the cancer and involved nodes are outlined in three dimensions with a margin added to take the uncertainties

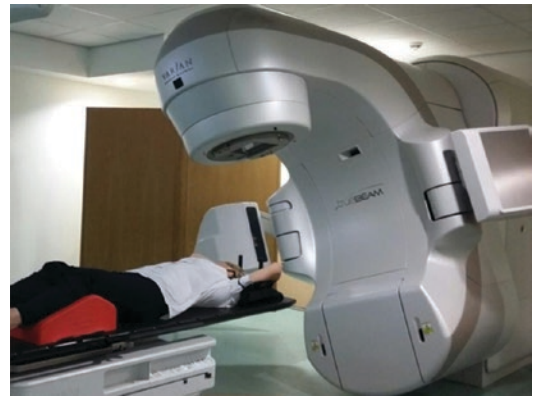

Fig. 6.4 Demonstration of the treatment position required for radical radiotherapy to the chest. The linear accelerator has side arms to allow cone-beam CT imaging

of microscopic spread, tumour movement, and patient positioning into account. RT beams are arranged by a team of specialist dosimetrists and physicists using RT planning computer software to maximise the dose to the cancer and minimise the dose to normal structures. The planning process takes 10–14 days and at each stage, stringent checks are put in place to ensure that the planned treatment volume is accurate and safe to deliver. Once treatment begins, the patient and their skin tattoos are aligned with the treatment room lasers on each day, and treatment is delivered with imaging checks for positioning as described below. The treatment should continue as prescribed without any unplanned breaks, although treatment is not given at the weekends in conventionally fractionated RT. Occasionally weekend treatments or an additional fraction at the end of the RT course may be required to account for planned departmental holidays, and occasionally for unscheduled interruptions, such as machine breakdown or patient illness.

Palliative RT is planned in a similar way, but the patient usually does not need to lie with their arms above their head unless the area to be treated lies laterally in the chest. Patient positioning can be more flexible according to the site to be treated, to take into account bony pain or breathlessness. Any available imaging, e.g. PET/CT, MRI, or isotope bone scan, can be used to assist in the definition of the treatment volume, which

includes the area to be treated plus an adequate margin. This is usually covered by a single field or two opposing fields to provide a simple arrangement. Dose constraints to normal tissues are not usually of concern in palliative treatments unless there has been high-dose treatment in the same area in the past. Palliative treatments are usually carried out over fewer days than radical RT, typically in one to five fractions.

Methods of Improving the Delivery of RT to Lung Cancers

Intensity-Modulated Radiotherapy

In order to deliver high doses of RT to a lung cancer while avoiding dose-limiting toxicity to surrounding normal structures, it is important to be able to conform the high-dose volume as closely as possible to the structure to be treated. Intensity-modulated radiotherapy (IMRT) describes a method of radiotherapy planning using sophisticated "inverse treatment planning" computer algorithms to achieve this [32]. Whereas standard RT planning for 3D CRT uses established field arrangements for localised lung cancers, adjusting the parameters of the field size, shape, angle, and weighting to generate a "best fit," IMRT uses clinician-defined high-dose regions in conjunction with dose constraints to organs at risk of toxicity (OARs). Planning algorithms generate a conformal RT "dose map" with each beam varying not only in shape, but also in intensity across the beam. For example, it is possible using IMRT to treat a high-dose volume close to the spinal cord, without exceeding the strict dose constraints required to avoid late toxicity to the spine (Fig. 6.5). IMRT is delivered using the same photon energies and the same linear accelerators as conventional 3D CRT, though recent developments have allowed the use of "arc" therapy. This involves the linear accelerator head moving axially around the patient while delivering IMRT, the shape and intensity of the beam being modulated as it travels to deliver a more uniform dose than previously possible. Technological developments are continuing with the aim of further improving the accuracy and specificity of RT delivery, maximising the chance of local control while minimising toxicity to surrounding structures. RT departments in the UK are rapidly moving towards the adoption of IMRT as the standard for radical RT treatment of non-small cell lung cancer.

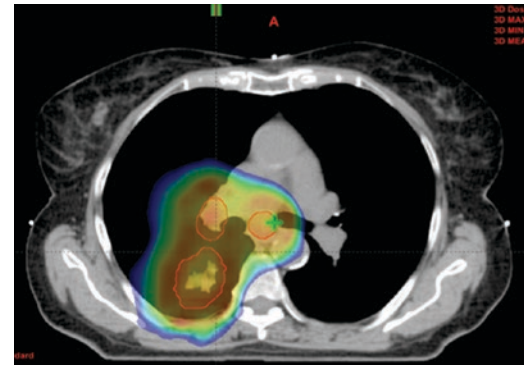

Fig. 6.5 A patient with a T2N2 non-small cell cancer of the right lower lobe was treated with radical radiotherapy using IMRT. The high-dose volume can be seen to conform to the volume containing the cancer and nodes while avoiding the spinal cord

The Clinical Application of RT for Lung Cancer

Radiotherapy Alone for NSCLC

Several factors limit the ability of radical radiotherapy alone to effect a cure for stage I–III non-small cell lung cancer: (1) the presence of metastatic disease, which is undetectable by current techniques; (2) the inherent radio-resistance of a proportion of the cancer cells; and (3) the propensity of malignant cells to repopulate at an increased rate once cell death is induced. Repopulation may in part be overcome by shortening the overall duration of a course of radiotherapy, thus reducing the time available for the cells to repopulate. Taking this to its maximal extent, the regimen of continuous hyperfractionated accelerated radiotherapy (CHART) was developed. The results of CHART compared to conventional RT have been encouraging, with a 9% absolute improvement in 2-year survival, from 20% to 29%, with a 14% improvement seen in patients with squamous cell lung cancer [33]. However, CHART remains difficult for many

departments to implement, owing to the limitations of staffing. In addition, criticism of the CHART study has highlighted the dose of RT in the standard arm which, at 60 Gy, would be considered lower than the currently recommended dose of 66 Gy.

Radiotherapy in Combination with Chemotherapy

For patients with non-small cell lung cancer and involved mediastinal nodes, the results of radiotherapy alone are poor in terms of local control and long-term survival. Chemotherapy can be combined with radiotherapy to improve the measured outcomes, and may be given either sequentially (chemotherapy followed by RT to the residual mass) or concurrently with RT. The use of concurrent chemotherapy probably has a dual effect as a local radiosensitiser and also through its ability to target distant metastatic disease. In clinical trials, the benefits of concurrent treatment over sequential are clearly seen, with an absolute survival benefit of 8% at 2 years and an improvement in overall survival at 5 years of 4.5% (15.1% vs 10.6%) [34, 35] making concurrent chemoradiotherapy the gold-standard. However, normal tissue constraints may make sequential treatment preferable if the cancer is large, as concurrent treatment is more toxic in the acute phase than sequential, with a higher rate of neutropenia and radiation-induced grade 3–4 oesophagitis (18% vs 4%). Radiotherapy is planned and delivered in the same way as described above, a typical combination comprising two cycles of platinum doublet chemotherapy administered concurrently with the radical radiotherapy, and a further two cycles given in the adjuvant setting once RT is complete.

Stereotactic Ablative Body Radiotherapy

Stereotactic ablative body radiotherapy (SABR) is a method of administering high doses of radical RT to an accurately defined, small, extracranial volume, and is named to distinguish it from stereotactic radiotherapy or radiosurgery used to treat lesions in the brain. It has been developed as an alternative to surgical resection for patients with T1-T2a node negative tumours who are not fit for surgery for medical reasons, including poor lung function or cardiac co-morbidities. SABR uses either multiple fixed beams or arc therapy to deliver ablative doses of RT well above those used for radical RT given by 3D-CRT or IMRT. SABR is planned using the same techniques as IMRT with a 4D-CT scan, PET/CT imaging, and inverse planning algorithms (Figs. 6.6 and 6.7). The margins around the cancer are small and cone-beam CT images taken before treatment and, if necessary, during and after each fraction, are critical to ensure that the target lies in the high-dose volume and that doses to surrounding normal structures are limited. Owing to the very high doses used, normal tissue constraints are strict: the high-dose volume cannot lie within 2 cm of the proximal bronchial tree or distal trachea; treatable cancers are limited to 5 cm diameter; and if the high-dose volume includes the chest wall, a smaller dose per fraction is used to reduce the late side effect of rib necrosis, fracture, and pain.

Current use of SABR is limited to patients who cannot undergo surgery, as it has not been tested in a randomised clinical trial against surgical resection, but initial results are promising. Analysis of the first 273 patients treated in the inaugural UK SABR centre showed a median survival of 27.3 months, with an overall survival of 78, 55,

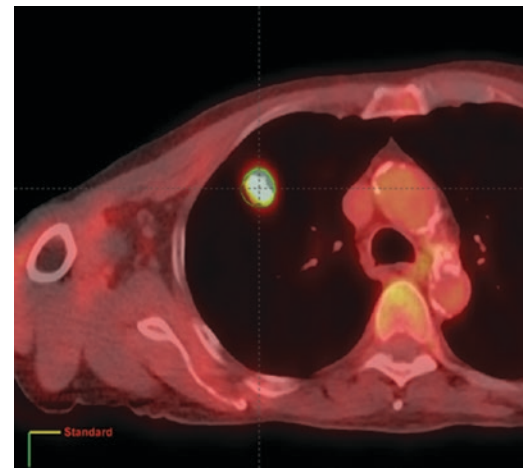

Fig. 6.6 PET-CT scan with pseudo colour. The right upper lobe T1N0 cancer is easily seen. The volume to be treated with SABR to high dose has been outlined

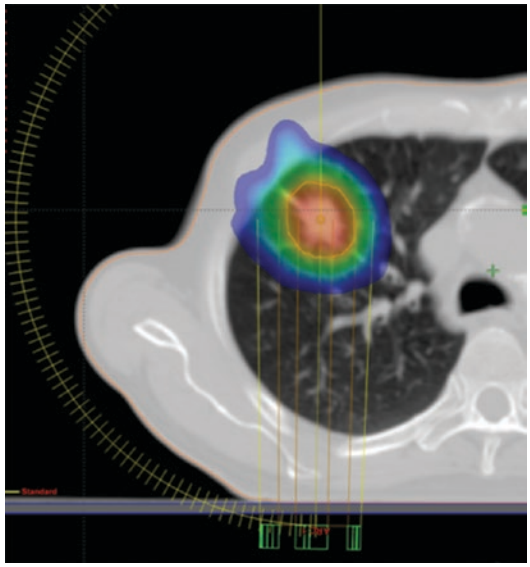

Fig. 6.7 Same patient as in Fig. 6.6. The small right upper lobe cancer is being treated with SABR to 54 Gy in three fractions. The colour overlay shows a range from 50% (dark blue) to 115% (pink) of the prescription dose. The curved hatched line around the patient's right chest represents the path of one of the two arc radiotherapy beams

and 39% at 1, 2 and 3 years, respectively [36]. Histological confirmation was obtained in only 35% of cases, reflecting the poor lung function and substantial comorbidities which precluded surgery in this medically inoperable cohort. Acute side effects were few and largely limited to grade 1–2 cough, shortness of breath, pneumonitis, chest pain, fatigue, oesophagitis, and skin reactions. Grade 3 toxicities beyond 12 weeks were rare, comprising breathlessness, fatigue, and chest pain, the latter affecting three patients at a year post-treatment. Although matched comparisons suggest that SABR provides survival results comparable to those of surgery, selection bias is unavoidable. Unfortunately, a planned randomised controlled trial comparing SABR with surgery failed to recruit adequately and was closed.

Post-operative Radiotherapy for Non-small Cell Lung Cancer

Many clinical trials have attempted, over the years, to define the role of post-operative RT (PORT) in completely resected non-small cell lung cancer. A meta-analysis, first published in 1998 and updated in 2005, showed a detrimental effect on survival equivalent to an 18% relative increase in the risk of death, reducing overall survival at 5 years by 5%, from 58% to 53% [37]. Sub-group analysis suggests that this effect is most marked in stage I and II disease (N0 and N1), whereas for stage III, N2 disease, there is no evidence of either benefit or detriment, PORT possibly contributing to local control but not affecting overall survival. The studies contributing to these meta-analyses were largely conducted in the 1960s and 1970s, before modern linear accelerators were developed, and using what would now be considered unsatisfactory techniques and large volumes, planned without CT or PET/CT staging. It is possible that the increased risk of death stemmed from greater cardiac and lung toxicity. If so, the use of more modern RT techniques could conceivably overcome this and confer a survival benefit in stage III disease. A retrospective analysis of 4483 patients with completely resected stage IIIA non-small cell lung cancer compared overall survival with and without PORT and found a slight improvement in median and 5-year overall survival with the addition of PORT to adjuvant chemotherapy, although the 95% confidence intervals overlapped [38]. In order to answer this question, a phase III study, lungART, is underway, randomising patients with completely resected non-small cell lung cancer and mediastinal nodal involvement (N2) between two arms: post-operative conformal radiotherapy vs no post-operative radiotherapy (LungART protocol) and where the primary end point is disease-free survival. Until this study reports, PORT for completely resected stage III NSCLC remains controversial.

In contrast, in spite of a paucity of evidence, PORT is recommended in most lung cancer guidelines for the treatment of patients with positive margins or macroscopic residual disease following radical surgery for NSCLC. Retrospective analyses suggest that including the positive resection margin or residual disease and treating with 3D CRT or IMRT to a dose of 50–55 Gy reduces the risk of local recurrence [39]. Recent data suggest that there may be an influence on overall survival, but confirmation will require a randomised clinical trial.

Small-Cell Lung Cancer

Small-cell lung cancer (SCLC) is an extremely chemotherapy-sensitive cancer, which tends to metastasise early in its development and frequently before a diagnosis is made. Cure rates range from 10 to 15%, with a median survival of 16–24 months in limited stage disease, which can be defined in practical terms as cancer confined to one hemithorax, including supraclavicular nodes which can be encompassed within a radical radiotherapy field.

RT for Limited-Stage SCLC

For limited-stage SCLC, the combination of systemic chemotherapy and involved-field thoracic radiotherapy, given without elective irradiation of uninvolved intrathoracic lymph nodes, results in better overall survival rates than chemotherapy alone [40]. As with NSCLC, concurrent chemoradiotherapy is superior to sequential treatment, [41] particularly if the RT commences early, with the first or second cycle of chemotherapy [42]. However, large cancers are often not treatable concurrently in view of the volume to be encompassed within the radiotherapy field, and sequential treatment may be considered safer, particularly in patients with poor performance status and suboptimal lung function. Chemotherapy usually comprises a two-drug combination of a platinum agent with etoposide delivered as four to six cycles. As carboplatin is more likely to exacerbate the toxicity of radiotherapy than cisplatin, the latter is usually given in conjunction with radiotherapy.

Prophylactic Cranial Irradiation

Brain metastases are common in small-cell lung cancer, with at least 18% of patients having brain metastases at diagnosis, with the proportion approaching 80% in patients alive 2 years later. The brain has often been considered a sanctuary site for metastatic disease, with systemic chemotherapy penetrating less well because of the blood-brain barrier, and salvage treatment with chemotherapy or radiotherapy often proving unsatisfactory. Meta-analysis has shown that the addition of prophylactic cranial irradiation (PCI) to the whole brain following a complete response to chemotherapy for limited-stage small-cell lung cancer improves overall survival. The proportion still alive 3 years from randomisation was shown to increase from 15.3% without PCI to 20.7% in the treatment group [34]. PCI decreased the risk of developing brain metastases, with an absolute reduction of 25% in the cumulative incidence at 3 years, from 58.6% in the control group to 33.3% in the treatment group. Standard management of patients with limited stage SCLC therefore includes PCI, usually given in the UK as 25 Gy in 10 fractions over 2 weeks. A study of 286 patients with extensive stage SCLC and a performance status of 0–2 who had achieved a response to chemotherapy compared either no further therapy or PCI delivered as one of several RT regimens [43]. At 1 year, the incidence of extracranial progression was similar in the two groups, but patients in the PCI arm had a median progression-free survival (PFS) of 14.7 weeks and a median overall survival (OS) of 6.7 months, compared to those in the arm receiving standard care, who had a median PFS of 12 weeks and OS of 5.4 months. Symptomatic brain metastases occurred in 16.8% of the group receiving PCI and 41.3% of the control group, corresponding to a risk of symptomatic brain metastases at 6 months of 4.4% in the PCI group and 32.0% in the control group. The main side effects of treatment were hair loss and fatigue, but there were no detectable differences in global health-related quality of life measures. PCI has therefore been adopted as standard treatment in the UK to be offered to patients with extensive stage SCLC who have achieved a response to chemotherapy and who maintain a performance status of 0–2. As the overall survival of these patients remains poor, radiotherapy regimens are usually limited to 1–2 weeks.

PCI in the acute phase may cause total, though temporary, alopecia, nausea, headache, skin erythema, and intense fatigue. Occasionally, patients will suffer a somnolence syndrome with lethargy and sleepiness, typically manifesting some weeks after RT is complete. This distressing side effect may be partially helped by ste-

roids and gradually resolves, sometimes over months. Of more concern are the historical reports of a significant decline in cognitive function seen in patients who have had radiotherapy to the whole brain.

Thoracic Radiotherapy for Extensive-Stage SCLC

Involved field thoracic radiotherapy also confers a benefit for selected patients with extensive, incurable disease. An international study randomised 498 patients of performance status 0–2 with extensive stage SCLC who had achieved any response to chemotherapy and had thoracic disease considered treatable with an acceptable radiotherapy field [44]. All patients underwent prophylactic cranial irradiation. Consolidative RT reduced intrathoracic recurrence but did not confer any survival advantage at 1 year (the primary endpoint), although post-hoc analysis of a small subgroup of 2-year survivors suggested there may be a long-term survival benefit. On the basis of these unconfirmed findings, thoracic consolidation with RT may be recommended for patients with extensive stage SCLC who respond to chemotherapy, are of adequate performance status, and who have disease which can be encompassed within an acceptable RT field.

Palliative Radiotherapy

Intra-Thoracic Disease

Palliative radiotherapy for lung cancer of both small-cell and non-small cell types aims to relieve symptoms, but there is no good evidence that it extends survival. RT is usually given to local disease within the chest for troublesome symptoms such as cough, pain, haemoptysis, and breathlessness. Fourteen randomised clinical trials of 19 different radiotherapy regimens for symptomatic non-small cell lung cancer were analysed by meta-analysis [45]. A lack of consensus on criteria for reporting a response to RT means that useful comparison between trials is probably not meaningful. All the studies showed that palliative RT improved local chest symptoms, though there was great variation between studies in the extent, duration, and speed of onset of symptom relief. Commonly quoted rates of symptom improvement are 50% for cough and 75% for chest pain and haemoptysis. RT regimens used frequently in the UK include 36 Gy in 12 fractions, 20 Gy in 5 fractions (Fig. 6.8), 16–17 Gy in 2 fractions delivered a week apart, and a 10 Gy single fraction. The shorter courses tend to be prescribed for patients with a poor performance, and there is good evidence that a single fraction of 10 Gy can provide good, rapid relief of symptoms without the disruption of a longer course of treatment.

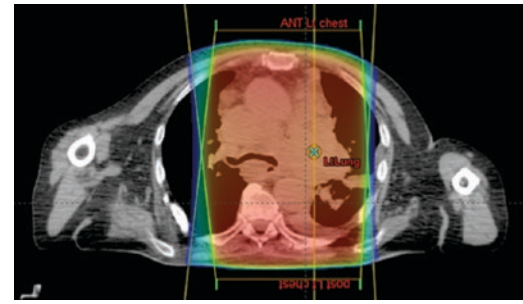

Fig. 6.8 A patient with locally advanced small-cell lung cancer and large airways narrowing treated with palliative intent using a large field to the mediastinum and 20 Gy in five fractions over a week

Endobronchial RT is occasionally used to palliate obstructive symptoms of lung cancer. A meta-analysis of the small number of available trials has suggested that endobronchial radiotherapy is less effective that external beam RT in palliating symptoms [46]. There may be a role for endobronchial treatment in selected patients where prior external beam RT precludes further treatment by this modality.

Extra-Thoracic Sites

Bony metastases are common in lung cancer. A meta-analysis concluded that a single fraction of RT is as effective as multiple fractions in the

treatment of painful bony metastases [47]. Dose-finding studies support a dose of 8 Gy as the optimal dose for a single fraction [48]. The caveat to this conclusion is that patients treated with a single fraction of RT seem to have a higher rate of retreatment than those treated with multiple fractions, although the time to recurrence of pain is not any shorter. This suggests that it may be the clinician's reluctance to treat a second time after a higher initial dose which leads to this finding. In the UK, the majority of uncomplicated bone metastases should be treated with a single fraction of RT. Metastases in long bones, especially the femur, are at particular risk of fracture and may require either prophylactic pinning or surgical fixation. Stratification of this risk is conveniently made using the Mirels score (see Table 6.4 below) where a score of 9 or greater is regarded as high risk and prophylactic fixation usually recommended. Most centres in the UK offer post-operatively RT in an attempt to prevent progression of the metastasis and failure at the surgical site, although there is no evidence to support this practice.

Other extra-thoracic metastatic sites commonly seen in patients with lung cancer include the liver, adrenal glands, and brain. Radiotherapy is rarely used in the treatment of metastatic disease to the adrenal glands unless they are very large and causing pain; toxicity from RT to the liver far outweighs any potential benefit, even if the metastasis is solitary.

Brain metastases are very common in both small-cell and non-small cell lung cancer. Brain metastases from SCLC are usually a marker of widespread disease, and although they are often sensitive to systemic chemotherapy and whole brain radiotherapy, results are disappointing, with patients having only a short life expectancy. For a patient with NSCLC, solitary metastases occurring in patients with a good performance status and limited extracranial disease will often be resected or treated with stereotactic RT (STRT). Several regional centres within the UK are now commissioned to deliver STRT to brain metastases using a technique similar to SABR, although the metastases are usually treated with a single large fraction. Until recently, whole brain RT (WBRT) was considered standard treatment for patients with multiple brain metastases from non-small cell lung cancer. In the QUARTZ trial, 538 patients with NSCLC and brain metastases which were not considered suitable for either surgical resection or stereotactic RT were randomised to receive whole brain radiotherapy to a dose of 20 Gy in 5 fractions or no radiotherapy [49]. Analysis of the results has shown no significant difference in the primary endpoint of quality adjusted life years, taking both survival and patient-rated quality of life into account. In addition, no significant difference was demonstrated in the secondary endpoint of overall survival. Median survival was 9.4 weeks (95% CI 7.7–11.0) in the group receiving steroids plus RT, and 8.1 weeks (95% CI 7.6–9.0) in the arm receiving steroids alone, underlining the poor prognosis of patients with unresectable brain metastases from NSCLC. Although no benefit from WBRT was seen in the QUARTZ trial, neither was there any evidence of detriment. Stereotactic radiotherapy or surgical excision is well established in the treatment of low-volume brain metastases in patients with NSCLC and a good performance status. Similarly, patients with small-volume extracranial metastatic disease limited to no more than three sites (termed oligometastatic disease) can be considered to have a better prognosis than most patients with metastatic non-small cell lung cancer. There are case reports and case series of patients who have had a prolonged survival following surgery or SABR to residual metastatic disease following a good response to systemic therapy, but randomised clinical trials are needed to define the potential benefit and selection criteria for treatment.

Table 6.4 Mirels score for stratifying fracture risk in patients with long bone metastases

Score	1	2	3
Site	Upper limb	Lower limb	Peritrochanteric
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size (amount of cortex)	<1/3	1/3–2/3	>2/3

Chemotherapy

Whilst in the management of lung cancer, surgery and radiotherapy can successfully control local disease, many lung cancer deaths are due to metastatic disease. Hence systemic anti-cancer therapy (SACT) has been frequently used with varying degrees of success to treat this condition. Conventional cytotoxic agents have been the mainstay of SACT treatments for the last three decades, but are often limited by toxicity and relative lack of effectiveness. The increase in our understanding of the biology of lung cancer has led to the development of targeted treatments which may well supplant conventional cytotoxic chemotherapy in the future. SACT is used in the following stages and indications for lung cancer.

Palliative

- Stage IIIb and IV non-small cell lung cancer (NSCLC)
- Most small-cell lung cancer patients (SCLC)

Adjuvant

- Stage I and II resected NSCLC with tumours >4 cm or N1 disease
- Resected SCLC

Combined with Radiotherapy (Usually Concomitant)

- Stage IIIa and some IIIb NSCLC
- Limited SCLC patients of good performance status (0–2)

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy with or without radiotherapy has been used to downstage patients with N2 disease so they can be operated on. However, a recent meta-analysis of over 1000 patients has shown no survival benefit with this approach [50].

The Role of Chemotherapy as Palliative Treatment for Advanced Lung Cancer

Given the very poor prognosis of NSCLC patients, many have reasonably questioned the utility of subjecting patients to toxic chemotherapy. Early studies generally demonstrated a small survival advantage for platinum-based chemotherapy in advanced non-small cell lung cancer, and that this benefit was confined to patients with a performance status (PS) of 0–2 [51]. These findings have been confirmed by a large meta-analysis [52]. Furthermore, there does not appear to be any adverse effect on quality of life with such treatment. Over 50% of lung cancer patients are over the age of 70 years, and the usefulness of cytotoxic chemotherapy in elderly patients with advanced non-small cell lung cancer is debated. Early studies utilizing single-agent vinorelbine versus best supportive care demonstrated a survival advantage. A recent Cochrane systematic review has shown the elderly may benefit from platinum-based combination chemotherapy over single-agent therapy, but at the expense of higher toxicity, and so non-platinum-based chemotherapy for elderly patients with co-morbidities was recommended, although further studies are needed. For small-cell lung cancer not amenable to treatment with curative intent, platinum-based chemotherapy remains the best form of palliation.

The Role of Cytotoxic Chemotherapy in the Adjuvant Treatment of Resected Lung Cancer

Although surgery remains the best modality to cure patients with early stage lung cancer, nearly 50% will die from recurrent disease, and many of those will have distant metastases. A meta-analysis in 1995 suggested a non-significant improvement in survival by the addition of chemotherapy to surgery [53]. Since that time, a number of large

randomised trials have demonstrated varying degrees of survival advantage to the use of platinum doublet chemotherapy post-operatively in non-small cell lung cancer. The LACE meta-analysis confirmed the efficacy of this approach except in Stage IA patients. A subgroup analysis suggested that the benefit of adjuvant chemotherapy in stage Ib patients was confined to tumours >4 cm.

Whilst patients with small-cell lung cancer rarely present with operable disease, if they do they should be offered surgery followed by adjuvant chemotherapy/radiotherapy.

Conventional Cytotoxic Treatment

Non-small Cell Lung Cancer

Single Agent Versus Doublet Chemotherapy

A number of single agents have been demonstrated to have activity in NSCLC, but cisplatin has been shown to be the most active agent. Subsequently it was shown that cisplatin/etoposide was superior to single-agent cisplatin and since that time, platinum doublets have become the norm in treatment of this condition. In the late 1990s several randomised trials were performed comparing cisplatin doublets with etoposide and vinorelbine with platinum doublets with docetaxel, paclitaxel, and gemcitabine. These results tend to show the third-generation doublets do slightly better, but that there are no real differences between individual third generation doublets [54]. Adding a third drug to a platinum doublet improves response rates, but not survival, and increases the toxicity. A recent meta-analysis of four randomised trials comparing six cycles of platinum doublet chemotherapy with fewer cycles showed there was no advantage to giving more than three or four cycles.

Cell-Type Specific Chemotherapy

It has been well known for many years that as well as pathological differences existing between squamous and non-squamous cancer, there are biological and clinical differences. A subset analysis of a large phase III trial comparing cisplatin/gemcitabine versus cisplatin/pemetrexed revealed the superiority of cisplatin/pemetrexed in non-squamous histologies.

Maintenance Therapy

Maintenance therapy is defined as continuation of usually a single drug to maintain remission following induction by a platinum doublet. This may be by a drug already used in the induction doublet (continuous maintenance) or a different drug (switch maintenance). A meta-analysis indicated that patients with adenocarcinoma (but not squamous cancer) and those with good PS (0–1) appear to derive most benefit from maintenance chemotherapy [55]. Long-term analysis of data from the PARAMOUNT study shows pemetrexed is well tolerated, with no adverse effects on quality of life, barring low-grade impairment of renal function and anaemia.

Second-Line Treatment with Cytotoxic Chemotherapy

Following relapse and/or progression with first-line chemotherapy, the life expectancy can generally be measured in weeks to months, and the maintenance of quality of life for these patients is paramount. Two drugs (docetaxel and pemetrexed) have been shown to improve survival by a very short amount. Comparison of docetaxel with pemetrexed as second-line treatment shows the two drugs were equivalent in terms of efficacy, but pemetrexed was less toxic.

Chemotherapy for Small-Cell Lung Cancer

Platinum (either cisplatin or carboplatin) and etoposide remain the mainstay for chemotherapy for this disease. Despite the inherent chemosensitivity of this disease, the vast majority of these patients relapse and die of their disease. Patients who have a reasonable disease-free interval following initial therapy may respond to rechallenge with the same chemotherapy regimen. The topoisomerase I inhibitor, topotecan, is the only drug to show meaningful second-line activity in this disease.

Targeted Treatments in Lung Cancer

Over the past 30 years conventional cytotoxic chemotherapy has resulted in modest gains in survival for patients with lung cancer. Greater understanding of the molecular events involved in the pathogenesis of this disease has resulted in the development of targeted therapies that appear to be more efficacious and less toxic, and can be tailored to the specific genetic makeup of a patient's tumour that may be amenable to therapeutic inhibition either by monoclonal antibodies or small molecule inhibitors. Three therapeutic areas appear promising:

- tyrosine kinase inhibitors
- anti-angiogenic agents
- immune checkpoint inhibitors

Tyrosine Kinase Inhibitors

Cellular functions such as proliferation and survival are controlled by extracellular growth factors which bind and activate cell surface receptors leading to phosphorylation of tyrosine residues on the intracellular domain of the receptor. This activates intracellular signalling pathways, resulting in transcription of genes involved in cell proliferation and survival. In cancer cells these processes are deranged, allowing cells to escape normal controls of proliferation and programmed cell death (apoptosis). One such system is the epidermal growth factor receptor (EGFR) pathway.

Two different classes of EGFR inhibitors are used clinically:

1. Monoclonal antibody–Cetuximab.
2. Receptor tyrosine kinase inhibitors (RTKI):
   - Gefitinib
   - Erlotinib
   - Afatanib

Initial studies in advanced non-small cell lung cancer—either in a first-line setting combined with chemotherapy or as a single agent in a second- and third-line setting—were disappointing, with no survival advantage with the RTKI. However, a subsequent trial of erlotinib versus best supportive care in the second- and third-line setting did show a small survival advantage. Analysis of the tumours of those patients who responded well to gefitinib in previous trials demonstrated that patients who harboured mutations consisting of deletions of exon 19 or a point mutation in exon 21 (L858R) responded very well to these agents. Such patients tended to be never smokers, of Asian descent, or have adenocarcinoma histology. A secondary acquired mutation at residue 790 of the EGFR resulting in a substitution of a methionine for a threonine (T790M) is thought to be an important mechanism by which NSCLC becomes resistant to RTKIs.

A number of prospective randomised studies have shown that response rates, progression-free survival, and toxicity favour the use of an RTKI as first-line therapy for NSCLCs that have EGFR-sensitising mutations. Overall survival does not seem to be prolonged with RTKI, probably due to patients on the chemotherapy arms being subsequently crossed over to RTKIs.

RTKIs can cause rash, diarrhoea, elevated liver enzymes, sore throat, hair and nail changes, and interstitial lung disease. There may be slight difference in the toxicity profiles between the different agents, with afatinib (an irreversible EGFR inhibitor) causing more skin rash and gefitinib more interstitial lung disease. RTKIs are therefore the standard of care for first-line treatment for advanced non-small cell lung cancer harbouring an EGFR-sensitizing mutation. TKIs have also been studied in patients without a sensitizing mutation ("wild type"). The TAILOR study comparing erlotinib with docetaxel with erlotinib in a second-line setting and showed that wild type patients did better on chemotherapy [56]. As a result of this and other studies, it is generally felt there is little clinical utility in using these agents in wild type EGFR patients.

All patients treated with RTKIs will eventually develop resistance to these agents. In over half of these patients, the mechanism of resistance to current agents is by the T790M second-

ary mutation. A number of third generation TKIs active in T790M have now been evaluated, and osimertinib has now been approved for use in those with progressive disease who have developed this mutation after a first-line TKI. Rociletinib has also been shown to be active in these patients, but awaits fuller evaluation.

Patients who may have developed resistance to first- or second-line TKIs will require a further biopsy to confirm the presence of a treatable mutation. Obtaining tissue for the second time might not be safe or feasible, but there is now the possibility of identifying circulating tumour DNA (ctDNA) from plasma samples, so-called *liquid biopsy*. The technical aspects of this technique are evolving, but at present the available testing is specific but relatively insensitive.

Humanised Monoclonal Antibodies Against EGFR in NSCLC

An initial study of cetuximab combined with cisplatin/vinorelbine against cisplatin/vinorelbine alone showed superior efficacy for the cetuximab combination, but at the expense of greater toxicity. Subsequently a second trial of chemotherapy with or without cetuximab failed to show any such advantages. A second-generation antibody necitumumab appeared to improve survival in squamous cell cancers, but not adenocarcinomas, and has not been recommended by NICE because of cost and low efficacy.

ALK Inhibitors

The anaplastic lymphoma kinase (ALK) gene on chromosome 2 codes for a receptor tyrosine kinase ALK protein, which is a member of the insulin receptor kinase family. In approximately 5% of non-small cell lung cancer, a rearrangement occurs in chromosome 2 resulting in the EML4 (echinoderm microtubule-associated protein-like 4) gene being transposed next to the ALK gene. This results in a fusion protein where the kinase function is constitutively activated. ALK gene rearrangements occur mainly in adenocarcinoma and never smoker patients, and tend not to occur in patients with EGFR mutations.

Currently there are four methods of detecting ALK rearrangements: immunohistochemistry (IHC), fluorescent in situ hybridisation (FISH), reverse transcription polymerase chain reaction (RT-PCR) and direct sequencing. All of these have different pros and cons, sensitivities and specificities [57].

At this time, there are four small molecule ALK inhibitors in varying stages of clinical development: crizotinib, ceterinib, alectinib, and brigatinib. Crizotinib was the first inhibitor to enter clinical practice. An initial study demonstrated a 57% response rate in ALK-positive NSCLC who had progressed on prior systemic therapy. A subsequent study in ALK-positive NSCLC previously treated with a platinum doublet randomised between crizotinib and docetaxel or pemetrexed demonstrated improved progression free survival, overall response rate, and lung cancer-related symptoms for crizotinib. More recently a randomised study of this agent confirmed the superiority of this agent versus standard chemotherapy, with an improvement in quality of life for crizotinib treated patients. The main toxicities of crizotinib are visual disturbances, nausea, diarrhea, vomiting, oedema, elevated transaminases, constipation, and fatigue. The second-generation ALK inhibitor ceritinib has been shown to be active in ALK-positive patients who have progressed on crizotinib, and has been approved for use in the UK. Side effects include gastrointestinal upset, hyperglycaemia, abnormal liver enzymes, Q Tc prolongation, and pneumonitis. Both alectinib and brigatinib have useful activity in patients who have progressed on crizotinib, and have been approved for use in the United States.

Inhibitors of Tumour Angiogenesis

Tumour angiogenesis is central to the progression, invasion, and metastasis of all solid tumours. Even small tumours have the ability to attract in new blood vessels mediated by the secretion of

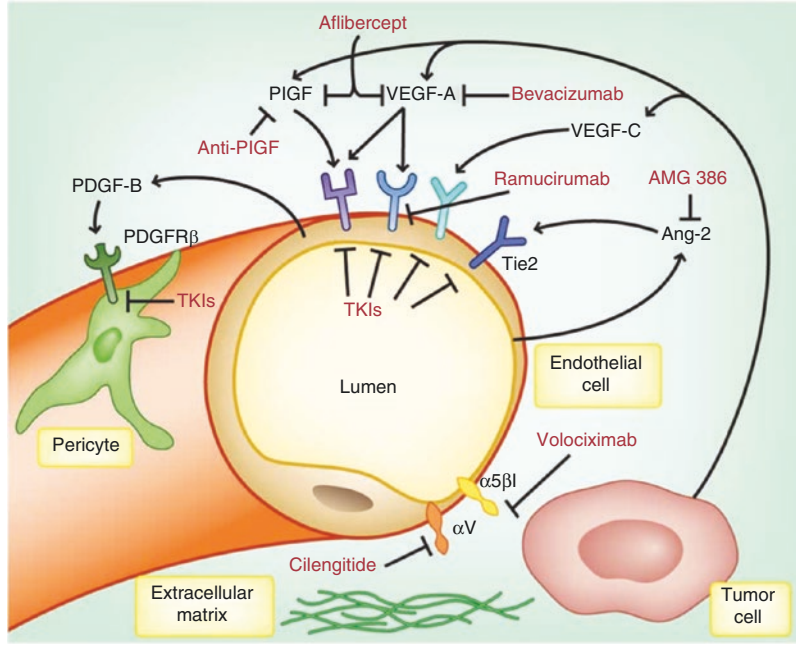

Fig. 6.9 VEGF pathways. Reprinted by permission from: Springer Nature, Nature Biotechnology. Modeling and predicting clinical efficacy for drugs targeting the tumor milieu. Mallika Singh, Napoleone Ferrara. © 2012

several pro-angiogenic factors (the angiogenic "switch"). The most notable of these is vascular endothelial growth factor (VEGF) (Fig. 6.9). As such, VEGF has been the target of several anti-angiogenic drugs.

Angiogenesis inhibitors come as either monoclonal antibodies or small-molecule tyrosine kinase inhibitors. Two monoclonal antibodies, bevacizumab and ramucirumab, have been used in non-small cell lung cancer. Bevacizumab works by inhibiting the binding of VEGF to receptors VEGFR-1 and VEGFR-2. Ramucirumab works by targeting the extracellular domain of VEGFR-2. The benefits of adding these agents to conventional chemotherapy would appear small. Of the small-molecule anti-angiogenic inhibitors, nintedanib, a triple angiokinase inhibitor, has shown an improvement in overall survival when combined with docetaxel versus docetaxel alone, especially in patients relapsing/progressing within 9 months of platinum-based chemotherapy.

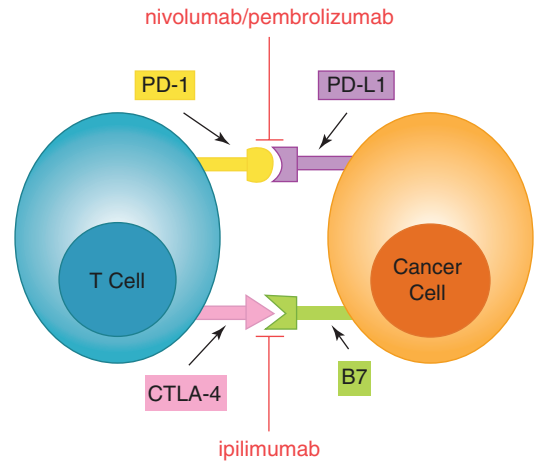

Fig. 6.10 Immune checkpoints in cancer and corresponding inhibitor therapies. T cells express the immune-checkpoint receptors PD-1 and CTLA-4. Binding and activation of these immune checkpoint receptors to their cognate ligands (PD-L1 and B7) expressed on cancer cells results in T cell inhibition. Monoclonal antibodies inhibit PD-1 signalling or CTLA-4 activation, resulting in survival and activation of T cells. Figure provided by Bethany Marshall

Immune Checkpoint Inhibitors

It is well known that the immune system is crucial in the development and progression of human cancers. It is also known that tumours can evade the immune system (Fig. 6.10).

Killer T cells primed by interacting with tumour antigen-presenting cells will normally destroy

tumour cells. However, tumour cells are able to destroy killer T cells by interaction through the PD-L1/PD1 system. Antibodies to PD1 or PD-L1 can inhibit this process, thus restoring immunocompetence. Currently there are four monoclonal antibodies that inhibit this system in lung cancer: two PD-1 inhibitors (nivolumab and pembrolizumab) and two PD-L1 inhibitors (atezolizumab and tremelimumab). There have been two pivotal studies of nivolumab in non-small cell lung cancer. In the first, Checkmate 017 [58], patients with squamous histology who had failed platinum-based chemotherapy were randomised to nivolumab or docetaxel. Nivolumab improved overall survival by just over 3 months. One-year progression-free survival was 42% with nivolumab versus 24% with docetaxel, and many of these responses seem durable. The overall response rate was 20% for the nivolumab arm as opposed to 9% for docetaxel. Serious toxicity was much lower in the nivolumab arm than in the docetaxel arm. A second and similar study in non-squamous cancers, Checkmate 057 [59], again showed overall survival and response rates favoured nivolumab over docetaxel, and the response rates were better in those whose tumours expressed higher levels of PD-L1. In the Keynote-010 study, patients with both squamous and non-squamous histologies who had relapsed following platinum-based chemotherapy were randomised to docetaxel or one of two differing doses of pembrolizumab [60]. Again, the results favoured the PD-1 inhibitor, but the effect was greater in the non-squamous cell carcinoma patients. Whilst these agents are less toxic than conventional chemotherapy, they do have serious and potentially fatal side effects such as pneumonitis, hepatitis, hypophysititis, and colitis. The two PD-L1 inhibitors are still undergoing clinical trials, but atezolizumab had only a weak survival advantage compared to docetaxel, and is considered too costly.

Lastly, there is considerable confusion and conflicting data about the role of tumour PD1 and/or PD-L1 expression as a predictive biomarker. This is compounded by the fact that the pharmaceutical companies are each using different diagnostic antibodies and different cut-off points for positivity. In Checkmate 017, PD-L1 status did not appear to predict responsiveness to nivolumab, but this was not the case for pembrolizumab, where increased responsiveness was found in patients whose tumours had PD-L1 expression>50%. In the KEYNOTE-024 study, pembrolizumab led to improved response rates and short-term survival compared with chemotherapy in the first-line setting in patients whose tumors expressed ≥50% PD-L1 with less toxicity [61]. Nivolumab is now approved for use in advanced or metastatic NSCLC after progressing on chemotherapy, and pembrolizumab for untreated NSCLC if >50% of tumour cells express PD-L1.

Ongoing studies are evaluating combination immunotherapy targeting PD-L1 and CTLA4, and also combined immunotherapy with conventional chemotherapy in advanced lung cancer.

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