18.19 Malignant diseases 4338 18.19.1 Lung cancer

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CONTENTS 18.19.1 Lung cancer 4338 S.G. Spiro and N. Navani 18.19.2 Pulmonary metastases 4360 S.G. Spiro 18.19.3 Pleural tumours 4361 Y.C. Gary Lee 18.19.4 Mediastinal tumours and cysts 4368 Y.C. Gary Lee and Helen E. Davies 18.19.1 Lung cancer S.G. Spiro and N. Navani ESSENTIALS Lung cancer remains the commonest killing cancer in both men and women in the developed world, and is increasingly common in developing countries, although as a result of decreased tobacco consumption in Western countries there has been a considerable reduction in the incidence among men over the last 20 years, and a slowing down in incidence in women over the last few years. Nevertheless, lung cancer is a greater cause of mortality in women than breast cancer in Western countries. There are several important industrial associations with lung cancer, in particular asbestos, but tobacco remains by far the most important cause. Pathology—there are four main cell types of lung cancer, of which adeno-, squamous, and large-cell varieties comprise non-small cell lung cancer, with the more aggressive type—small cell—being regarded as a separate entity from the point of view of treatment and prognosis. Clinical features—there are no particular presenting features that strongly suggest a new lung cancer, hence it is a disease that often presents late and with metastatic disease. Symptoms and signs can be subdivided into (1) intrapulmonary symptoms—cough (most com- monly), haemoptysis (most dramatically), wheeze, chest discomfort, and breathlessness (rare as a presenting feature); (2) extrapulmonary, intrathoracic symptoms and signs—Horner’s syndrome, vocal cord paralysis, superior vena caval obstruction, dysphagia, cardiac tam- ponade, arrhythmias; (3) extrathoracic, metastatic manifestations— 30% of patients present with symptoms due to distant metastases, the most common sites being bones, liver, adrenal glands, brain and spinal cord, lymph nodes, and skin; and (4) paramalignant

syndromes—syndrome of inappropriate secretion of antidiuretic hor- mone, ectopic ACTH syndrome, hypercalcaemia, neuromyopathies, finger clubbing, and hypertrophic pulmonary osteoarthropathy. Incidental findings and screening—about 5% of lung cancers are found by chance on a chest radiograph or CT scan performed for reasons other than suspicion of cancer, and these tend to have a better prognosis. Screening of high-risk groups for lung cancer with low-dose CT scanning of the thorax is being implemented and ran- domized trials are beginning to be reported. The very large National Lung Screening Trial of 53 000 individuals in the United States has shown a 20% reduction in mortality from lung cancer with three an- nual CT screens compared to a control group, and a 6.7% reduction in all-cause mortality. Clinical staging—accurate clinical staging is paramount for treat- ment decisions, especially for non-small cell lung cancer, which may be resectable. Following a chest radiograph, a CT of the neck, thorax, and upper abdomen should be performed. Biopsy of the primary tumour (via a bronchoscope for centrally situated lesions or by per- cutaneous image-guided needle, depending on best access) or of a metastasis (often mediastinal lymph nodes by endobronchial ultra- sound systems) is required. The latter provides a diagnosis and in- formation on disease stage at the same time. PET scanning, which depends on the uptake of a glucose analogue (fluorodeoxyglucose, FDG) by active tumour and its metastases, is recommended as a sta- ging test in those patients where resection or another curative treat- ment is contemplated. Integrated PET-CT changes the clinical stage in about 20% of apparently resectable cases, but has low resolution for detecting brain metastases, hence further imaging of the brain by MRI or CT may be required before embarking on surgical resection. Prognosis and management—(1) non-small cell lung cancer— ‘cura- tive’ treatment by surgical resection can be applied to 15–20% of all cases, of whom about 60% survive at 5 years. Radical radiotherapy cures very few with locally advanced disease, although better re- sults are obtained with the addition of concurrent chemotherapy. Newer techniques such as stereotactic radiotherapy, with tighter focus on the tumour, may increase the cure rate. In patients with advanced non-small cell lung cancer and good performance status, survival at 1 year is 15–20% with supportive care alone, and 50% with 18.19 Malignant diseases

18.19.1 Lung cancer 4339 chemotherapy tailored to the non-small cell lung cancer phenotype. Emerging evidence of mutations within tumours has led to better identification of those who may respond to targeted therapy (e.g. with tyrosine kinase inhibitors, rather than cytotoxic chemotherapy in patients whose tumour harbours an epidermal growth factor re- ceptor mutation). Immunotherapy has been an importance advance in treatment of advanced disease and is likely to play an increasing role in the future. (2) Small-cell tumours—life expectancy of those with untreated disease is about 3.5 months for limited disease and 6 weeks for extensive disease. Chemotherapy remains the cornerstone of treatment: modern regimens would be expected to achieve a com- plete response rate (i.e. disappearance of all measurable disease) in 40 to 50% of cases and a partial response rate (>50% reduction in tu- mour bulk) in a further 40%. Patients achieving a complete response after chemotherapy should have prophylactic cranial irradiation, and consolidation thoracic radiotherapy in some cases. Median survival is around 18 months for limited disease and 9 months for extensive stage disease. Management of complications—some complications of lung cancer require specific measures to alleviate symptoms: (1) vocal cord par- alysis may be helped by injection of Teflon into the affected cord; (2) obstruction of the upper airway causing stridor, or of the lower major airways, is usually treated initially with radiotherapy; (3) ma- lignant pleural effusion is treated with talc pleurodesis or indwelling pleural catheter; (4) dexamethasone may control the symptoms of brain metastasis and, if so, this may be

consolidated with whole brain radiotherapy, and (5) intravenous stenting can cause dramatic relief from superior vena caval obstruction. The multidisciplinary team—the importance of the combined support to the patient and the family given by the lung cancer nurse specialist family doctor, palliative care medical and nursing staff, and hospice or- ganizations, and the hospital team cannot be overemphasized. Epidemiology Lung cancer is the most common cause of death with malignant dis- ease in the Western world. It has shown the greatest relative and absolute rise in mortality of any tumour this century in England and Wales, and particularly in Scotland. It causes 35 000 deaths per year in England and Wales, with 70% of these occurring in men. In the European Union there are 1.35 million deaths per year in men (the highest death rate from any tumour), and in women in 1995 it accounted for 24% of all female cancer deaths. In the United States of America it has been increasing in incidence by up to 10% per year since the 1930s, but over the last decade this trend has levelled off, particularly in men. Nevertheless, about 120 000 American men die of lung cancer each year, the figure for women being 34 000, similar to that for breast cancer. However, whereas the age-adjusted incidence in women increased by 4.1% per year between 1973 and 1994, between 1990 and 1994 the annual incidence rose by only 0.2%. The increasing incidence in women means that lung cancer is now the fourth commonest cancer in women worldwide and the second commonest cause of cancer death. Age-standardized mortality rates for cancer show that in Europe lung cancer in men was by far the commonest cause of death. Hungary has the highest mortality (109.5 deaths per 100 000 population) with Poland (104.5) second, and Estonia third with 91.5 deaths per 100 000. For women, Denmark has the highest incidence (49.5), with Hungary (39.8) second and the United Kingdom (38.7) third. Within the United Kingdom there are much higher rates in Scotland and the North of England, reflecting smoking patterns. Perhaps the worst epidemic is in China, where 0.8 million men died in the year 2000 from smoking-related diseases. Of all deaths attrib- uted to tobacco in China, 15% were due to lung cancer. Aetiological factors Tobacco In every country, the increase in mortality from lung cancer has ap- peared to coincide with an increase in tobacco usage, particularly cigarette smoking, after what seemed to be an appropriate latent interval. Prospective studies, among which the long-term study of British doctors was particularly informative, confirmed the in- creased risk of death from lung cancer from any tobacco use, but most specifically that of cigarettes. There was a strong dose–response relationship with the number of cigarettes smoked, illustrated in Table 18.19.1.1. The most important variable in smoking inten- sity is the number of cigarettes smoked, but other variables include the depth of inhalation, number of puffs, butt length, use of a filter, and the type of tobacco smoked. Further evidence that the relation- ship was causal came from a study which documented reduction in mortality after stopping smoking: 15 years after cessation the risk of death fell from 15.8 times to twice that in nonsmokers, equiva- lent to 11% of that pertaining in those who continued to smoke. Stopping smoking before the age of 40 years greatly reduces the risk of developing smoking-related diseases. Globally, there has been a huge change in cigarette consumption. Between 1970 and 1985 the overall world consumption rose by 7% while there was a drop of 25% and 9% in consumption in the United Kingdom and the United States of America, respectively. This is due to huge increases in Asia (22%), Latin America (24%), and Africa (42%). The current epidemic of smoking in China lags be- hind Western society by 20 years. Thus, in China in 1996 the average Table 18.19.1.1 Death rate from lung cancer in males by smoking habits when last asked (British doctors' study) Tobacco use category Death rate (age-standardized per 100 000) Nonsmokers 10 Ex-smokers 43 Continuing smokers Any tobacco 104 Pipe and/or cigar only 58 Mixed 82 Cigarette smokers only 140 Number smoked per day 1–14 78 15–24 127 25 or more 251

section 18 Respiratory disorders 4340 number of cigarettes smoked per adult male was 11 per day, a figure that that peaked in the West at 10 a day in 1980. Nearly one-third of the world's smokers reside in China, who reported 1.3 million new cases of lung cancer in 2003. Another disturbing trend is the increasing incidence among women. More women in developed nations will die of lung cancer than breast cancer. Due to historical smoking patterns the incidence rates of lung cancer in women are not declining, because smoking rates have not yet started to decline, as they have in men. Currently far more men than women are dying of this disease, but the gap is re- lentlessly closing. With regard to socioeconomic status, lung cancer is likelier to occur in the poor and less educated, which is a wide- spread pattern around the world. Primary prevention and smoking cessation must be directed at these groups. Passive smoking Evidence that passive smoking predisposes to lung cancer is far from certain. Approximately 15% of lung cancers occur in nonsmokers, and 5% of these have been attributed to passive smoking. However, the perceived risk to those working in smoke-filled environments has led to a ban on smoking in public places in an increasing number of countries. Occupation People who develop lung cancer as a result of their occupation are a small but important group. The association with asbestos is now firmly established, various studies having identified that those ex- posed are at 4.9 to 7.3 times greater risk than those who are not. This risk is much enhanced if the asbestos industry worker smokes cigarettes; one study estimating this at 93 times higher than for nonsmokers not exposed to asbestos. Exposure to radioactive isotopes, mainly radon daughters, is as- sociated with a higher risk of lung cancer and occurs among various groups of miners, particularly those involved in extraction of pitch- blende and uranium. Polycyclic aromatic hydrocarbons are believed to be responsible for the increased risk in workers in gas and coke ovens and in foundry workers. Workers in nickel refining, chromate manufacture, and the arsenical industry are also exposed to a higher risk of lung cancer. Diesel engine exhaust is a major cause of lung cancer in truck drivers and railway workers (See http://www.iarc.fr/ en/media-centre/pr/2012/pdfs/pr213_E.pdf). The amount of lung cancer caused by occupational exposure may well have been underestimated in the past, and a summary of the important industrial products and processes involved is shown in Box 18.19.1.1. Air pollution The decline in male mortality is occurring earlier than would be ex- pected from changes in smoking habits. The high mortality figures in the United Kingdom and Germany compared with France and Italy, for example, seem likely to be due in part to heavy industry and coal burning. Analysis by county in the United States of America shows an association between lung cancer deaths and counties with chem- ical, petroleum, ship-building, and paper industries. Legislation for cleaner air has caused both environmental and occupational pollu- tion to fall dramatically in the past 30 years, and this has preceded changes in smoking habits. Pathology A detailed understanding of the natural history, pathology, and pathogenesis of lung cancer is becoming increasingly important as the assessment, management, and prognosis of the disease depends largely upon the tumour phenotype, genotype, and the presence or absence of metastases at the time of presentation. It has been esti- mated that about seven-eighths of a tumour's life will have passed when it is diagnosed, and that the vast majority will have dissemin- ated at the time of diagnosis, even though most metastases may be too small to detect. Squamous cell carcinomas seem to arise most commonly in seg- mental and subsegmental bronchi in response to repetitive carcino- genic stimuli or inflammation and irritation. The mucosal lining is most susceptible to injury at the bifurcation of bronchial structures. Dysplasia progresses to carcinoma in situ, when the entire thick- ness of the mucosa may be replaced by proliferating neoplastic cells. These changes may be strictly localized or multicentric, and are thought to be a field cancerization effect, sometimes causing syn- chronous primary tumours. Tumour infiltration

follows loss of the basal membrane. The precise origins of small-cell carcinomas re- main an enigma, while evidence is emerging that adenocarcinomas arise in areas of alveolar adenomatous hyperplasia. A significant number of lung tumours arise in the periphery of the lung, perhaps three-quarters of adenocarcinomas and large-cell anaplastic malig- nancies, one-third of squamous (or epidermoid) carcinomas, and one-fifth of small-cell carcinomas. Adenocarcinoma has become the commonest cell type; it is more prevalent in eastern Asia and the United States of America where approximately 50% of new lung cancers are adenocarcinomas. Squamous cell lung cancer still accounts for up to one-half of new cases in Europe, although this is changing as adenocarcinomas seem to be becoming commoner throughout the world. There has been a slow decline in the prevalence of small-cell lung cancers to 15–20% of new diagnoses, with 10–15% of the less easily differentiable large- cell tumours comprising the rest. Adeno-, squamous-, and large-cell tumours are grouped as nonsmall-cell lung cancers (NSCLC) as their staging and treatment is similar. From studies of growth rates of radiologically measurable primary tumours, adenocarcinomas have Box 18.19.1.1 Industrial products and processes known to cause or suspected of causing lung cancer • Fibre exposure (asbestos) • Nickel refining • Aluminium industry • Arsenic and arsenic compounds • Benzoyl chloride • Beryllium • Cadmium • Chloromethyl ether • Chromates • The electronics industry • Irradiation • Soots, tar, oils • Mustard gas • Diesel engine exhaust

 a volume-doubling time of 90–120 days, squamous cell 60 days, and small-cell 30 days, making this last cell type extremely aggressive. Squamous (epidermoid) carcinoma These tumours are composed predominantly of flattened to polyg- onal neoplastic cells that tend to stratify, form intercellular bridges, and elaborate keratin. About 60% present as obstructive lesions in lobar and main-stem bronchi. The tumours tend to be bulky and produce intraluminar granular or polypoid masses, hence distal pneumonia and abscess formation are common, and cavitation is seen in about 10%. The cells are usually well differentiated, but in some cases differentiation is poor and the appearances are those of predominantly anaplastic cells, frequently arranged in the classical pattern of stratifying sheets. Small-cell anaplastic carcinoma This is now recognized as a pathologically and clinically distinct form of lung cancer. The tumour is composed of neoplastic cells with dark oval to round spindled nuclei and scanty, indistinct cytoplasm arranged in ribbons, nests, and sheets. The cells tend to crush easily on biopsy, and extensive areas may be necrotic. This type of tumour presents as a proximal lesion in 75% of cases and may arise anywhere in the tracheobronchial tree and rapidly in- vade vessels and lymph nodes, disseminating widely even before symptoms arise from the primary tumour. It is invariably associ- ated with smoking, and over 50% of patients have extensive, ad- vanced disease at presentation. The cells secrete peptides which cause clinical syndromes in 10% of cases. Adenocarcinoma This tumour forms acinar or glandular structures, having prom- inent papillary processes, and may be mucin-provoking. About 70% appear to originate peripherally in the lung and they are frequently fairly circumscribed. The initial presentation is a pleural effusion in about 10% of cases. If related to bronchi, they tend to cuff and stenose the lumen. Adenocarcinomas occasionally arise in old tuberculous scars and are the predominant tumour type in patients with lung cancer related to asbestos, or in patients who have never smoked. Approximately 80% of lung adenocarcinomas express thyroid tran- scription factor-1 (TTF-1), which is a helpful diagnostic tool. Several subtypes of adenocarcinoma are recognized (http://www.ncbi.nlm.nih.gov/pubmed/21252716). The confusing term bronchoalveolar carcinoma has been replaced with the morpho- logically more accurate term adenocarcinoma in situ to describe

lung cancer arising in distal bronchioles or alveoli with a lepidic growth check lepidic pattern. Invasive adenocarcinoma is divided into acinar, papillary, micropapillary, solid, and mucinous subtypes. Mutation in the epidermal growth factor receptor (which sensitizes the patient's tumour to tyrosine kinase inhibitors) rarely occurs in the mucinous adenocarcinoma subtype, but is present in 10–15% of all lung adenocarcinomas. Large-cell carcinoma These tumours, which have been described as an unclassified category, include all tumours that show no evidence of maturation or differentiation. They are composed of pleomorphic cells with variable enlarged nuclei, prominent nucleoli and nuclear inclu- sions, and abundant cytoplasm, and they are mucin-producing in many instances. The tumours tend to be bulky and are often nec- rotic. They are frequently peripheral, invade locally, and disseminate widely, with about one-half of patients having disseminated disease on presentation. Although these tumours are highly malignant and undifferentiated, the cure rate after surgery is surprisingly high, but radiotherapy is ineffective in controlling the disease. Large-cell car- cinoma is a smoking-related disease in more than 90% of patients. Tumour heterogeneity It is increasingly apparent that lung cancer subtypes do not exist in a single patient in isolation. Resected small cell lung cancers com- monly contain areas of NSCLC differentiation. Adenosquamous carcinomas are also well recognized. Larger biopsy specimens and sampling from different metastatic sites have demonstrated tumour heterogeneity to be an important clinical issue. Carcinoid tumours Carcinoid tumours are described in Chapter 15.9.2. Genetics and biology Genetic influences may play a role in the development of lung can- cers, particularly in patients under 50. In one study, lung cancers were attributable to a mendelian dominant inheritance pattern in 27% of patients under 50, but only 9% of those over 70. Oncogenes and tumour suppressor genes The ras family of oncogenes (H, K, and N) was the first to be de- scribed in association with lung cancer. Mutations of ras genes occur in 20–40% of NSCLC, especially adenocarcinomas, and the presence of K-ras mutations is linked with significantly shortened survival and resistance to tyrosine kinase inhibitors. Lung cancer cells not only show mutations that activate dominant cellular proto-oncogenes, but also genetic mechanisms that inacti- vate recessive tumour suppressors. The commonest abnormality is a deletion in the short arm of chromosome 3, which is found in over 90% of small-cell lung cancer and 50% of NSCLC patients. Other sites of loss of heterozygosity include 11p, 13q, and 17p. Tumour suppressor genes have been identified in inherited cancers, mainly in studies of familial retinoblastoma. Mutations in TP53 occur in 75% of small-cell lung cancer and 50% of NSCLC. The gene is lo- cated on the short arm of chromosome 13q14, and it is thought that it may normally protect cells against accumulation of mutations. Depletions and mutations of TP53 are linked with metastatic dis- ease. Alterations of p53 protein have been found in early bronchial neoplasia, and may be a useful marker for the early detection of lung cancer. Other markers, including heterogenous nuclear ribonuclear protein A2/B1 overexpression in sputum, may allow earlier detec- tion of tumours. Lung-cancer-associated antigens Several monoclonal antibodies have been generated against lung- cancer-associated antigens. Thirty-six monoclonal antibodies raised against small-cell lung cancer have been grouped into eight clus- ters. No antigen is specific for small-cell lung cancer. Antibodies belonging to the major cluster (cluster 1) are directed against the neural-cell adhesion molecule (NCAM), but the nature of the other

 antigens remains unclear. Studies of both small-cell and NSCLC cell lines show that NCAM secretion is associated with a neuroendo- crine phenotype irrespective of the histological type of lung cancer. Monoclonal antibodies may have a therapeutic value when coupled with a radionuclide or a toxin. Radiolabelled antibodies can be used to detect

minimal disease in bone marrow aspirates or biopsy specimens. Epidermal growth factor receptor tyrosine kinase The expression of epidermal growth factor receptor (EGFR) tyro- sine kinase is up-regulated in 70% of squamous cell cancers and 50% of adenocarcinomas, and the discovery of a mutation in the EGFR receptor in some patients with lung cancer was a significant break- through. This led to highly successful trials with the small-molecule tyrosine kinase inhibitors gefitinib, erlotinib, and Afatanib. The re- sponses to these targeted treatments in those with the EGFR muta-tion is striking, and has led to pathologists examining all diagnostic biopsies for their presence. Targeted therapy is now the first-line treatment for EGFR positive individuals, who commonly are Asian, women, and nonsmokers with an adenocarcinoma. Other molecular aberrations NSCLC harbours other 'driver' mutations, which if 'turned off' can be a highly effective antitumour therapy. These are found in mul- tiple genes, particularly adenocarcinomas, including (in addition to EGFR) HER2, KRAS, BRAF, PIK3CA, ATK1, MEK1, ROS1 and, ALK. Mutations within individual genes can be associated with pri- mary drug resistance, primary drug sensitivity, or secondary drug resistance. The distinct tumour mutation profile of many Asian women has become a target for treatment (see next) as 90% of them may contain one of EGFR, HER2, ALK, ROS1, and KRAS, of which EGFR, HER2, ROS1, and ALK are treatable with kinase inhibitors. It is estimated that 70% of adenocarcinomas have a currently iden- tifiable oncogenic driver, which may be the tumour's Achilles heel. The roll out of next generation genetic sequencing technologies has meant that it is now possible to genotype a patient's lung cancer to provide the most appropriate treatment. Clinical features Lung cancers present late in their natural history. In general, death will occur when a tumour load reaches 1 kg, which is equivalent to 40 volume-doubling times, yet halfway through the lifespan of a lung cancer—20 volume doublings—it is only 1 mm in diameter (Fig. 18.19.1.1). It becomes visible on a chest radiograph at about 1 cm and the typical size at presentation with symptoms or signs is 3–4 cm. CT and PET-CT will identify lesions as nodules when they are considerably smaller, but up to 98% of incidentally discovered nodules are benign, making radiological investigations problematic. The clinical features of lung cancer are very variable: they can be respiratory, but all too often they are constitutional and attrib- utable to metastatic disease. In one series of 678 consecutive pa- tients only 27% presented with symptoms related to the primary tumour. Most had either nonspecific symptoms, including anorexia, weight loss, and fatigue (27%), or specific symptoms of metastatic disease (32%). However, in about 5% of patients the presentation is a radiographic abnormality found by chance on routine examin- ation (Fig. 18.19.1.2). These patients tend to have a better prognosis (20–70% 5-year survival) than those with symptoms related to the primary tumour (12–35% 5-year survival). There is usually a considerable time delay between the patient noticing a symptom and presenting to a primary care physician, which varies in different studies from 4 months to 2 years, with the specific exception of haemoptysis, when the mean delay from first symptom to first visit is much shorter at about 43 days (range 0–256 days). There may also be a delay between first presentation to a physician and the realization that there may be a lung cancer present. One study identified a delay of 56 days (range 0–477 days). This is understandable in the context that an average primary care physician (in the United Kingdom) sees a new lung cancer only every 102 104 106 108 1010 1012 Tumour size Number of tumour cells Number of doublings 40 10 30 20 1mm 5mm 1cm 3cm 10cm 1014 CT/PET Chest radiograph Average size at presentation Fig. 18.19.1.1 The lung cancer growth curve and ability to detect a tumour during its natural history. Fig. 18.19.1.2 Chest radiograph showing a chance finding of a right upper lobe mass (arrow) with a bulky right hilum.

18.19.1 Lung cancer 4343 12 months or so, and in a Dutch study of patients presenting with cough (11 092 separate patient encounters), lung cancer was not listed as a specific entity among the 20 most common eventual causes. Clinical symptoms and signs of lung cancer can be subdivided into those arising from the lung itself; from the extrapulmonary intrathoracic structures; extrathoracic metastases; and from endo- crine, metabolic, and neurological (paramalignant) syndromes (Table 18.19.1.2). Intrapulmonary symptoms Cough is the most common initial presenting symptom, but be- cause it is a symptom of so many respiratory disorders, the possi- bility of tumour may be overlooked and cough may be attributed to some other cause, particularly in smokers who have had chronic bronchitis for many years. Patients with a persistent cough should have a chest radiograph, particularly if they are smokers over 40 years of age (Figs. 18.19.1.3–18.19.1.7). A change in the cough habit, or a cough lasting more than 3 weeks, is significant and also requires investigation. If the trachea or main bronchi are involved, the cough may be harsh in character and may be accompanied by wheezing or stridor. If cough is manifestly ineffective, with its explosive ability lost, in- volvement of the recurrent laryngeal nerve should be suspected, especially if there is accompanying hoarseness. A recent awareness campaign which for three months in summer 2013 asked those in a UK region with a cough lasting more than three weeks to see their GP, resulted in 700 more primary lung cancers being found than in the corresponding period two years earlier. Expectoration of sputum may be due to irritation of the tumour in a major airway or to infection occurring distal to partial bronchial obstruction, although this is more common in chronic obstructive pulmonary disease (COPD). The value of sputum cytology in diag- nosis is described next. Haemoptysis, which is the sole presenting symptom in about 5% of cases and occurs at some stage in the disease in 50% of patients, is a symptom not easily ignored by patient or physician. The degree varies from streaking of the sputum with blood to larger amounts, but massive haemoptysis (>200 ml) is rare, except as a terminal event when the tumour may erode a large pulmonary blood vessel. The Table 18.19.1.2 The presentation of lung cancer (frequency (%) of commoner symptoms/signs indicated) Chest symptoms Mediastinal involvement Chest radiographic abnormalities Paramalignant syndromes Extrathoracic metastases Haemoptysis (6–35) Superior vena caval obstruction (0–4) Peripheral nodule Hypercalcaemia (0–10) Bone pain (6–25) Cough (8–75) Left recurrent laryngeal nerve palsy (0–10) Lobar/lung collapse SIADH (0–50) Neurological Wheeze (0–10) Diaphragmatic palsy (0–5) Cavitating mass SIACTH (0–5) Jaundice Stridor (0–2) Pericardial effusion Abnormal hilum HPOA/clubbing (0–20) Skin nodules Pain (20–50) Dysphagia Pleural effusion Lambert–Eaton syndrome (0–3) Lymphadenopathy Dyspnoea (3–60) Lymphangitis Cerebellar dysfunction Weight loss (0–68) Bone lesion Neuropathies Lethargy (0–10) Wide mediastinum SIACTH, syndrome of inappropriate ACTH; SIADH, syndrome of inappropriate antidiuretic hormone; HPOA, hypertrophic pulmonary osteoarthropathy. Fig. 18.19.1.3 Cavitating squamous cell lung cancer. Fig. 18.19.1.4 Chest radiograph showing a tumour in the right lower lobe behind the heart causing a double shadow for right heart border.

section 18 Respiratory disorders 4344 most significant description given by patients is that of coughing up blood, or with streaks in their sputum, every morning for several days in succession. Wheeze may be observed in a few patients. Localized persistent wheeze, often volunteered to come from one side of the chest, even after coughing, is a significant observation indicating obstruction of a larger or central airway (Fig. 18.19.1.7). Stridor is a feature that is poorly recognized and often confused with wheeze. It is due to narrowing of the glottis, trachea, or major bronchi, and is best heard after the patient coughs and then breathes in deeply with the mouth open. Dyspnoea is a presenting symptom in only a few patients. As the disease progresses

dyspnoea is inevitable, being proportional to the amount of lung involved, either directly by tumour replace- ment or indirectly by endobronchial disease causing airway nar- rowing or obstruction. Progressive breathlessness is also a feature of malignant pleural and, rarely, pericardial effusion, superior vena caval obstruction, and lymphangitis carcinomatosis. Chest discomfort is a common symptom, occurring in up to 40% of patients at diagnosis. The discomfort is often of an ill- defined nature and may be described in terms of intermittent aching somewhere in the chest. Definite pleural pain may occur in the presence of infection, but invasion of the pleura by tumour may be painless. However, invasion of the ribs or vertebrae causes continuous, gnawing, localized pain (Fig. 18.19.1.8). A tumour in the superior pulmonary sulcus (Pancoast tumour) can cause progressive constant pain in the shoulder, upper anterior chest, or interscapular region, soon spreading to the arm once the bra- chial plexus is invaded. Other symptoms of this type of tumour in- clude weakness and atrophy of the muscles of the hand, Horner's syndrome, hoarseness, and spinal cord compression at levels D1 and D2. Fever, chills, and night sweats may occur due to chest infection, but fever may very rarely be present in rapidly progressive tumours without evidence of infection, particularly if there are hepatic metastases. Extrapulmonary, intrathoracic symptoms Invasion of adjacent, mainly mediastinal, structures can give rise to certain specific clinical features. Involvement of the last cervical and first thoracic segment of the sympathetic trunk by cancer produces Horner's syndrome. Malignant infiltration of the recurrent laryngeal nerve—almost always the left branch because of its course adjacent to the left hilum—gives rise to vocal cord paralysis. The right recur- rent laryngeal nerve is occasionally affected in the base of the neck. Recurrent aspiration pneumonias may follow vocal cord paralysis. Extension of the tumour with invasion or compression of the superior vena cava or by paratracheal lymphadenopathy results
Fig. 18.19.1.5 Chest radiograph showing a collapsed left upper lobe due to proximal tumour.
Fig. 18.19.1.6 (a) Chest radiograph showing an ill-defined parenchymal mass (arrow) in the left upper lobe; (b): CT scan of the chest of the same patient as in (a), confirming a large central mass (arrow) encasing the left upper lobe bronchus.

 in the characteristic features of superior vena caval obstruction—awareness of tightness of the collar, fullness of the head, and suf- fusion of the face (particularly after bending down), blackouts, breathlessness, and engorgement of veins with a downward venous flow in the neck, the upper half of the thorax, and arms, often accom- panied by oedema of the face. Dysphagia is due to compression of the mid-oesophagus from without by tumour metastases in subcarinal lymph nodes and only rarely to direct invasion. Cardiac and pericardial metastases usually occur late in the disease and are manifested clinically by tachycardia, arrhythmias, pericardial effusion, and breathlessness. Invasion of the phrenic nerve results in elevation and paralysis of a hemidiaphragm, with increased dyspnoea in those with pre-existing lung disease (e.g. COPD). Involvement of the ribs, spine, and pleura are extrathoracic manifestations. Very rarely bronchogenic carcinoma causes spon- taneous pneumothorax. It must not be forgotten that spread of tu- mour to the other lung may occur, or that synchronous primaries may coexist. Extrathoracic metastatic symptoms About 30% of patients present with symptoms due to distant metas- tases, the most common sites being bones, liver, adrenal glands, brain Fig. 18.19.1.7 (a) Chest radiograph showing a right upper lobe tumour causing wheeze with bulky right paratracheal nodes (arrow); (b) CT scan of the chest of the same patient as in (a), showing grossly enlarged mediastinal pretracheal lymph nodes (arrow); (c) chest radiograph of the same patient as in (a), showing complete response after two courses of chemotherapy.

section 18 Respiratory disorders 4346 and spinal cord, lymph nodes, and skin (Figs. 18.19.1.8–18.19.1.11). Metastases to nodes are frequent and should be sought with great care, particularly those in the scalene area, which are usually the first to be involved. The best position for examination for these is from behind with the patient seated relaxed in a chair. The side affected usually corresponds to the side of the lung lesion, the exception being that tumours from the left lower lobe may metastasize to the nodes in the right scalene area. Involvement of the nodes in the floor of the supraclavicular fossa is equally common. Bony metastases are common, particularly in small-cell tumours, and occur predominantly in the skull, ribs, vertebrae, humeri, and femora. They cause pain as a presenting symptom in up to 25% of patients. Early involvement may be detected by a rise in al- kaline phosphatase of bony origin, isotope scanning, or biopsy. Conventional skeletal surveys are often unhelpful and misleading. Bone lesions are usually confirmed when a PET-CT scan is done for staging purposes, and isotope scans are now rarely performed. Liver secondaries are common and may be silent, although a rise in liver enzymes, particularly alkaline phosphatase of liver origin, may be an early sign. CT scans and ultrasonography may detect involvement in a liver which is not clinically enlarged, but as the metastases develop the liver may become grossly enlarged with an irregular margin. Metastases to the brain may be the presenting symptom in lung cancer in 4% of patients and may be encountered at some time in the illness in 30% (Fig. 18.19.1.10). The symptoms simulate those of any expanding brain tumour. The adrenal glands are involved in 15 to 20% of patients, rarely producing symptoms and found on a staging CT. The skin should be examined for the presence of the typical, slightly bluish, umbilicated lesions of tumour spread. Subcutaneous metastases may be found at almost any site (Fig. 18.19.1.11). Organ-specific scans are rarely required with the use of PET-CT, and these are only conducted in patients with organ-specific symp- toms, or with general symptoms such as weight loss or malaise. Lack of energy and, more particularly, loss of interest in normal pursuits are symptoms of great importance; a sense of vague ill health com- monly occurs.
Paramalignant syndromes Endocrine and metabolic manifestations Many of the unusual manifestations of malignant disease are the result of endocrine and metabolic manifestations of the cancer itself. Cancer cells appear to be able to synthesize polypeptides that mimic virtually all the hormones produced by conventional endocrine organs—hence the term ‘ectopic hormones’. From time to time the clinical features resulting from ectopic hormone se- cretion precede those of the pulmonary tumour, emphasizing the importance of a high index of suspicion in such circumstances.
Fig. 18.19.1.8 Chest radiograph showing a large left upper lobe mass with a right rib metastasis (arrow) causing pain, which was the reason for presentation in this case.
Fig. 18.19.1.9 CT scan of the upper abdomen revealing a large necrotic liver metastasis (arrow).
Fig. 18.19.1.10 CT scan of the brain in patient presenting with vagueness. Note marked cerebral oedema around metastases (arrows), and midline shift.

Ectopic hormone measurement cannot, however, be used for screening purposes. These syndromes can occur in up to 10% of patients with lung cancer.
Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) The continued secretion of vasopressin (ADH) in excess of the body’s needs for control of blood tonicity leads to retention of water in both the intracellular and extracellular compartments. The cerebral oedema resulting from water intoxication can cause drowsiness, lethargy, irritability, mental confusion, and disorientation, with fits and coma being the most profound fea- tures. The patient is usually asymptomatic until the sodium falls below 120 mmol/litre, when the hyponatraemia is dilutional in type with a low serum osmolality. Urine

osmolality usually ex- ceeds 300 mosmol/kg. The commonest cancer causing this syn- drome is small-cell lung cancer, where it is clinically obvious in 1 to 5% of cases, with subclinical involvement detectable by a water-loading test in more than 50%. Restriction of fluid to a daily intake of 700–1000 ml may redress the hyponatraemia, and demethylchlortetracycline (demeclocycline) 600–1200 mg daily is often highly effective, making water restriction unnecessary. Tolvaptan, a selective competitive vasopressin receptor antagonist, has also been shown to be effective in this scenario. The syndrome resolves promptly (within 3 weeks) with combination cytotoxic chemotherapy in most patients with small-cell lung cancer, but commonly recurs at, or predicts, relapse. Ectopic ACTH syndrome Secretion of an adrenocorticotrophic substance by a small-cell car- cinoma or bronchial carcinoid leads to bilateral adrenal hyperplasia and to secretion of large amounts of cortisol. The onset of symptoms may be so acute that death may occur within a few weeks, when the typical features of Cushing's syndrome do not have time to develop. However, it is a common paramalignant syndrome and increased levels of adrenocorticotropic hormone (ACTH) may be detectable in up to 50% of patients with small-cell lung cancer, with Cushing's it- self described in 1 to 5% of these patients. The chief clinical features are thirst and polyuria, oedema, pigmentation, and hypokalaemia. Hypertension and profound myopathy may also be present. Serum cortisol is often grossly elevated, with loss of the normal diurnal rhythm; the level is not suppressed by dexamethasone; and hypo- kalaemic alkalosis can be severe, with plasma potassium less than 3.0 mmol/litre and bicarbonate more than 30 mmol/litre. Drugs which block adrenocortical steroid biosynthesis may produce partial and re- versible medical adrenalectomy, and metyrapone in doses from 250 mg three times daily to 1 g four times daily may cause temporary relief of symptoms. Removal of the tumour, if practicable, will cause remission, particularly if the cause is a carcinoid tumour. Small-cell lung cancers with this syndrome seem to respond poorly to chemotherapy. Hypercalcaemia Hypercalcaemia may be associated with ectopic secretion of para- thormone by squamous cell cancers but is more commonly due directly to the presence of multiple bone metastases. The primary tumour may also produce a cAMP-stimulating factor or a prosta- glandin causing hypercalcaemia. A protein with parathormone- like activity has been purified from lung cancer cell lines. Increased bone resorption as the explanation for hypercalcaemia has been attributed to the parathormone-like protein released from cancer cells. The incidence in patients with lung cancer ranges from 2 to 6% at presentation, to 8 to 12% during the course of the disease. Hypercalcaemia is unlikely to cause symptoms unless the serum cal- cium exceeds 2.8 mmol/litre, and levels much higher than this are sometimes encountered. Endogenous serum parathyroid hormone levels are usually completely supressed. The main clinical features are nausea, vomiting, abdominal pain, and constipation, polyuria, thirst, and dehydration, muscular weakness, psychosis, drowsiness, and eventually coma. Immediate treatment is to relieve fluid deple- tion, and large volumes of intravenous 0.9% saline (up to 5 litres in 24 h) may be required. Intravenous bisphosphonates followed by oral maintenance therapy is now the treatment of choice. Gynaecomastia Swelling of the breasts, which may be painful, occurs mainly in the subareolar area, and there may be atrophy of the testes. The associ- ation is chiefly with large-cell carcinomas. Increased gonadotropin production is the cause.
Fig. 18.19.1.11 CT (A) and PET (B) scan of the abdomen showing a solitary mass in the right anterior abdominal wall (arrows) in a patient with a lung tumour. The mass is PET positive.

 Other endocrine manifestations Hyperthyroidism is a rare feature, but neither goitre nor eye signs are prominent. Spontaneous hypoglycaemia, the masculinizing syndrome in young women, and hyperglycaemia are very rarely encountered.

Pigmentation associated with α- and β-melanocyte- stimulating hormone may occur. Neuromyopathies A variety of poorly understood neurological syndromes can occur with lung cancer. The diagnosis of a paramalignant neurological syn- drome should only be made once other causes including electrolyte imbalance, metastatic disease, cerebral and spinal vascular disease, infection, and toxicity from associated treatment have been elimin- ated. The main neurological syndromes include the Lambert–Eaton myasthenic syndrome (LEMS), limbic encephalopathy, polyneur- opathy, cerebellar degeneration, retinopathy, and autonomic neur- opathy. LEMS is the most widely recognized of these disorders and presents with gradual onset of proximal limb weakness, more notice- able in the legs than the arms. Difficulty in swallowing and dryness of the mouth are common, although diplopia is rare. The symptoms may be worse in the mornings and improve as the day progresses. Physical examination will confirm weakness and loss of tendon jerks, but the latter can be restored for a few minutes by performing tasks of repetitive forced contractions (post-tetanic potentiation). Neurological paramalignancies are associated almost exclusively with small-cell lung cancers, affecting up to 4% of cases. Recent studies of consecutive new patients with small-cell lung cancer re- ported LEMS in 1.6%, polyneuropathy in less than 1%, subacute cerebellar degeneration in less than 1%, and limbic encephalitis in less than 1%. The severity of the syndromes is not related to tumour bulk and seems to occur more frequently in patients with limited disease; in some a primary tumour is not detected before death, despite disabling symptoms. Nearly all the neurological paramalignant syndromes are asso- ciated with the presence of type 1 antineuronal nuclear antibodies (ANNA-1), also known as anti-Hu antibodies. Small-cell lung can- cers express Hu antigen and up to 20% of these patients have detect- able circulating levels of anti-Hu antibodies, although not all will develop paramalignant disorders. The response of these syndromes to effective chemotherapy of the underlying tumour is variable. Improvement is uncommon with motor or sensory neuropathies, or with cerebellar degeneration. However, LEMS can be associated with a better overall prognosis, and the condition responds to specific therapy with 4-aminopyridine which appears to potentiate the release of acetylcholine at the nerve receptor end plate. Finger clubbing and hypertrophic pulmonary osteoarthropathy Finger clubbing accompanies a variety of intrathoracic disorders. Gross clubbing is readily recognizable; its early presence may best be demonstrated by the ability to rock the nail on its abnormally spongy bed; the nail fold angle will become obliterated as increased transverse curvature of the nail develops. Clubbing of the toes can be present but is less pronounced. Hypertrophic pulmonary osteoarthropathy (HPOA), which is a systemic disorder, may be preceded by finger clubbing alone. It con- sists of a painful symmetrical arthropathy, usually of the ankles, knees, and wrists, and periosteal new bone formation in the distal limb long bones. Associated finger clubbing can be gross. Clubbing and HPOA can be associated with any cell type of lung cancer, but mostly with squamous and adenocarcinoma, and very rarely with small cell types. The typical radiographic appearances are shown in Fig. 18.19.1.12. The affected areas are hot and painful and sometimes oedematous, making walking difficult. Removal of the tumour is followed by im- mediate regression, but symptoms recur if the tumour recurs. Clubbing is much more common than HPOA, occurring in up to 25% of patients presenting with lung cancer. It seems to be com- moner in women than men, and in NSCLC compared to small-cell, while HPOA is seen in less than 5% of patients with NSCLC. Miscellaneous The haematological effects of lung cancer are normally nonspecific. Normocytic normochromic anaemia is the most common finding. Leucoerythroblastic anaemia denotes bone marrow infiltration and is particularly likely in small-cell lung cancer. Venous thrombosis and thrombophlebitis due to hypercoagulability are common complica- tions of malignancy and may precede the detection of the underlying cancer; recurrent migratory phlebitis

resistant to anticoagulation is an ominous feature. Marantic endocarditis is extremely rare, as are skin rashes such as acanthosis nigricans, dermatomyositis, hypertrichosis languinosa, and erythema gyratum repens. Rarely, the nephrotic syn- drome due to membranous glomerulonephritis is encountered. Investigations The investigations used to make the diagnosis and assess the stage of lung cancer will vary according to the presentation, the cell type, the age, and general condition of the patient. The rapid doubling time of small-cell lung cancer causes it to dis- seminate widely, and at diagnosis it is very rarely considered oper- able. However, the slower doubling times for squamous cell cancers and adenocarcinomas, together with the relatively lesser tendency for Fig. 18.19.1.12 Radiograph of the ankle showing new periosteal growth due to hypertrophic pulmonary osteopathy.

 the former to disseminate, makes surgery the best option whenever possible for the NSCLCs. A precise anatomical staging classification was first applied to lung cancer in 1973 and immediately demon- strated that the prognosis of NSCLC depended strongly on the extent (or stage) of the disease, and the introduction of the TNM staging system (T describing the primary tumour, N the extent of regional lymph node involvement, and M the absence or presence of metas- tases) encouraged an ordered assessment of investigations and selec- tion of cases for surgery. Based on this experience, the system was modified in 1997 and again in 2009 using a much more extensive data set from centres around the world, and survival data is now based on more than 100 000 cases (Table 18.19.1.3 and Table 18.19.1.4). The following investigations form the basis for the diagnosis and staging of patients with lung cancer. Chest radiography The value of the chest radiograph in the diagnosis and management of pulmonary neoplasm needs no emphasis Table 18.19.1.3 International Association for the Study of Lung Cancer staging project: TNM classification T: Primary tumour Tx Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy T0 No evidence of primary tumour Tis Carcinoma in situ T1 Tumour ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)a T1a(mi) Minimally invasive adenocarcinomab T1a Tumour ≤1 cm in greatest dimensiona T1b Tumour >1 cm but ≤2 cm in greatest dimensiona T1c Tumour >2 cm but ≤3 cm in greatest dimensiona T2 Tumour >3 cm but ≤5 cm or tumour with any of the following featuresc: – Involves main bronchus regardless of distance from the carina but without involvement of the carina – Invades visceral pleura – Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung T2a Tumour >3 cm but ≤4 cm in greatest dimension T2b Tumour >4 cm but ≤5 cm in greatest dimension T3 Tumour >5 cm but ≤7 cm in greatest dimension or associated with separate tumour nodule(s) in the same lobe as the primary tumour or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumours), phrenic nerve, parietal pericardium T4 Tumour >7 cm in greatest dimension or associated with separate tumour nodule(s) in a different ipsilateral lobe than that of the primary tumour or invades any of the following structures: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina N: Regional lymph node involvement Nx Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene, or supraclavicular lymph node(s) M: Distant metastasis M0 No distant

metastasis M1 Distant metastasis present M1a Separate tumour nodule(s) in a contralateral lobe; tumour with pleural nodules or malignant pleural (or pericardial) effusiond M1b Single extrathoracic metastasise M1c Multiple extrathoracic metastases in one or more organs a The uncommon superficial spreading tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a. b Solitary adenocarcinoma, ≤3 cm with a predominately lepidic pattern and ≤5 mm invasion in any one focus. c T2 tumours with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension. d Most pleural (pericardial) effusions with lung cancer are due to tumour. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumour and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging descriptor. e This includes involvement of a single distant (nonregional) lymph node. Goldstraw P., Chansky K., Crowley J., 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, Journal of Thoracic Oncology, Vol 11. No 1 (January 2016) reproduced with permission from Elsevier.

section 18 Respiratory disorders 4350 (see Figs. 18.19.1.2–18.19.1.8). Anything suspicious should lead to the radiologist suggesting a CT scan of the neck, thorax, and upper abdomen (including particularly the liver and adrenals) when faced with the likelihood of a new lung cancer. The finding of a normal radiograph of the chest does not exclude lung cancer, as patients presenting with haemoptysis and a normal chest radiograph are sometimes found to have a central tumour on bronchoscopy. The rounded or ovoid shadow of a peripheral tumour is described in greater detail as follows; these are sometimes cavitated. The common appearance of a tumour arising from the main central airways (70% of all cases) is enlargement of one or other hilum. Even experienced observers sometimes have difficulty in deciding whether or not a hilar shadow is enlarged, and if there is any suspicion, investi- gation by CT and/or bronchoscopy—ideally with endobronchial ultra- sound to examine the lymph nodes—should be pursued. Consolidation and collapse distal to the tumour may have occurred by the time that the patient presents, with the tumour itself often being obscured in the process. Collapse of the left lower lobe is often hard to identify, as is a tumour situated behind the heart (see Fig. 18.19.1.4). Apically lo- cated masses or superior sulcus tumours (Pancoast tumours) may be misdiagnosed as pleural caps, and often have a history of several months of pain in the distribution of the brachial nerve roots. Loss of the head of the first, second, or third rib is not unusual. The mediastinum may be widened by enlarged nodes. Involve ment of the phrenic nerve may lead to paralysis and elevation of the hemidiaphragm, which then moves paradoxically on sniffing. Tumour spreading to the pleura causes effusion, but such an abnormality may also be secondary to infection beyond obstruction caused by a central tumour. The ribs and spine should be carefully examined for the pres- ence of metastasis (see Fig. 18.19.1.8). Spread of tumour from medi- astinal nodes peripherally along the lymphatics gives the appearance characteristic of lymphangitis carcinomatosa—bilateral hilar enlarge- ment with streaky shadows fanning out into the lung fields on either side. Rarely, localized obstructive emphysema may be observed. Sputum cytology Cytological examination of sputum is a noninvasive test for the diag- nosis of malignant pulmonary disease. The positive incidence on a single sample is 40% with tumours less than 2 cm in diameter and 60% with larger masses. Central tumours yield more positive results than peripheral lesions. The yield increases according to the number of spe- cimens examined, and three consecutive morning specimens should be submitted in the first instance. The

yield rose to 85% with four samples in a study of those in whom a diagnosis of lung cancer was eventually made. However, given current emphasis on detailing tumour phenotype and genotype, sputum cytology is no longer recommended for patients who are well enough and agree to minimally invasive tissue sampling. CT scanning Although it is recommended that patients suspected of having lung cancer should be referred for a chest X-ray, we know from screening studies that CT is about four times better at identifying new lung can- cers than the conventional chest radiograph. CT imaging is extremely important in the staging of lung cancer. It can identify the site, size, and extension of the primary tumour far more clearly than a conventional chest radiograph. CT imaging is extremely important in the staging of lung cancer. It can identify the site, size, and extension of the primary tu- mour far more clearly than a conventional chest radiograph. It also fre- quently identifies mediastinal lymphadenopathy when posteroanterior and lateral chest radiographs fail to show any abnormality. It will also identify silent metastatic disease in the supraclavicular lymph nodes, liver, adrenal glands, and in abdominal lymph nodes. It is recommended that a CT is performed prior to considering bronchoscopy as the primary lesion may be shown to be poorly ac- cessible to the bronchoscope and may be easier to sample by CT guided transthoracic biopsy. The CT scan may also identify medias- tinal involvement which can be directly sampled by bronchoscopic or ultrasound-guided techniques, or direct sampling towards an ab- dominal metastasis. These would both provide a diagnosis and also help stage the disease from a single procedure. Mediastinal lymphadenopathy on CT is arbitrarily taken to be pathological if a gland is more than 10 mm in short axis. However, pre- vious infective conditions such as tuberculosis or an associated distal pneumonia can cause appearances indistinguishable from malignant enlargement. Positive CT scans of the mediastinum must therefore be confirmed by mediastinal lymph node biopsy to confirm tumour involvement. This is important because nearly 40% of lymph nodes deemed enlarged on CT criteria are found not to contain cancer when they are sampled, either by biopsy or at the time of surgery. PET-CT Table 18.19.1.4 International Association for the Study of Lung Cancer staging project: stage grouping Occult carcinoma TX N0 M0 Stage 0 Tis N0 M0 Stage IA1 T1a(mi) N0 M0 T1a N0 M0 Stage IA2 T1b N0 M0 Stage IA3 T1c N0 M0 Stage IB T2a N0 M0 Stage IIA T2b N0 M0 Stage IIB T1a-c N1 M0 T2a N0 M0 T2b N0 M0 T3 N0 M0 Stage IIIA T1a–c N2 M0 T2a-b N2 M0 T3 N1 M0 T4 N0 M0 T4 N1 M0 Stage IIIB T1a–c N3 M0 T2a–b N3 M0 T3 N2 M0 T4 N2 M0 Stage IIIC T3 N3 M0 T4 N3 M0 Stage IVA Any T Any N M1a Any T Any N M1b Stage IVB Any T Any N M1c TNM, tumour, node, metastasis; Tis, carcinoma in situ; T1a(mi), minimally invasive adenocarcinoma. Goldstraw P., Chansky K., Crowley J., 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, Journal of Thoracic Oncology, Vol 11. No 1 (January 2016) reproduced with permission from Elsevier.

 scanning (see next section) is often performed before a lymph node is biopsied: this will confirm abnormality by an increased uptake (SUV) and/or it may identify an occult metastasis that might be more access- ible to biopsy and upstage the patient, thus changing management. Another advantage of CT is its ability to detect tumour invasion of the surrounding pleura and chest wall, although its ability to assess invasion of the mediastinum itself is poor and should not be used as a criterion of unresectability. Bronchoscopy Bronchoscopy, which is described in detail in Chapter 18.3.3, is a common diagnostic method in lung cancer. About 50% of all lung cancers arise in a main bronchus, lobar, first-, or second-generation airways, and will be visible and within biopsy or cytological brush range. Histological confirmation is now obtainable in 85–90% of bronchoscopically visible lesions, and with five or more biopsies of a visible

endobronchial lesion should approach 95% sensitivity. Bronchoscopy allows blind mediastinal lymph node sampling using dedicated transbronchial aspiration needles, which can pro- vide critical staging information, but this technique has been super- seded by endobronchial ultrasound-guided transbronchial needle aspiration (see next section). In addition to diagnostic information, bronchoscopy also yields valuable information regarding suitability for surgical resection. Attempts to resect are ill advised if the main carina is obviously in- volved, or where there is involvement of the trachea, unless confined to the right lateral wall. Endobronchial ultrasound-guided transbronchial
needle aspiration (EBUS-TBNA) and endoscopic ultrasound needle aspiration biopsy (EUS-FNA) Historically the mediastinum has been staged and malignant involve- ment of mediastinal nodes has been confirmed by surgical sampling by mediastinoscopy (for right paratracheal and subcarinal nodes) and/or anterior mediastinotomy for left-sided nodes. These tech- niques are being increasingly replaced by minimally invasive tech- niques including endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), where fine needle aspiration is per- formed with a needle placed within the working channel of a bron- choscope which harbours an ultrasound probe integrated into the tip. Endoscopic ultrasound needle aspiration or core-biopsy (EUS-FNA) allows access to posterior and left-sided mediastinal lymph nodes via a similar needle placed within an echoendoscope in the oesophagus. EBUS-TBNA and EUS-FNA are reported to be highly sensitive and specific in diagnosing metastases to mediastinal and hilar lymph nodes. EBUS-TBNA allows minimally invasive sampling of paratracheal, subcarinal and hilar lymph nodes, and meta-analyses of diagnostic accuracy have demonstrated a sensitivity of 90% in accessible lymph nodes. Sampling mediastinal lymph nodes via EBUS-TBNA provides diagnostic tissue suitable for sequencing, as well as an accurate nodal staging, in a single investigation. A recent trial has shown that routine use of EBUS-TBNA can speed up the diagnostic pathway and provide more accurate staging, which resulted in a survival benefit for patients (http://www.ncbi.nlm.nih.gov/pubmed/25660225). Percutaneous transthoracic needle biopsy Percutaneous needle biopsy of an intrapulmonary mass may be carried out using a variety of cutting needles to obtain a core of tissue for histo- logical analysis. The procedure can be performed under fluoroscopic, CT, or ultrasound control, but is best avoided in patients with poor respiratory function, bullae adjacent to the tumour or with bleeding di- atheses. Positive yields as high as 90% have been reported, with biopsy samples having a higher and more specific yield than cytological aspir- ates. It is a useful diagnostic method in patients for whom exploratory thoracotomy may be hazardous, or in attempts to determine whether a solid mass is a primary, secondary, or benign tumour. Pneumothorax occurs following about 25% of procedures, with some 2–4% requiring a chest drain. Small haemoptyses are a common complication. Thoracoscopy Visualization of the parietal and visceral pleura plays an important part in the diagnosis of effusions and pleural tumours. Biopsy of le- sions can be carried out under direct vision, and absence of pleural tumour is important in decisions about resectability of a lung tu- mour. Thoracoscopy is inadvisable in the absence of effusion or pneumothorax, and is unsatisfactory in the presence of empyema or gross haemothorax. However, in otherwise operable tumours with a pleural effusion that is not bloodstained and without positive cy- tology or pleural biopsy, thoracoscopy may be a useful next step in determining operability. Video-assisted thoracoscopy (VATS) has extended this technique and will also permit inspection and sam- pling of suspicious intrathoracic lymph nodes. Positron emission tomography (PET) scanning Integrated PET-CT scanning, which depends on the uptake of a glucose analogue (fluorodeoxyglucose, FDG) by active tumour and its metas- tases, has gained wide acceptance as a test with much better character- istics than CT, especially for

systemic staging. It is now recommended in those where resection or another curative treatment is contemplated. Because uptake of the PET isotope in malignant structures is based on tumour activity and not (as with CT) just lesion size, its routine use as a preoperative staging tool has been shown to save about 20% of all thoracotomies, which (if proceeded with) would have been futile and noncurative. However, PET scanning has a 40% false-positive rate, due to coexisting infection or inflammation, and a positive area of uptake should always be confirmed by sampling if that abnormal area would directly affect a management decision. A new generation of combined MRI/PET scanners are currently under evaluation. Lung function testing The ability to climb one flight of stairs without breathlessness has been claimed to be a very good indication of fitness for resection, but formal evaluation of lung function is essential in all patients being considered for treatment with curative intent. Spirometry, lung volumes and transfer factor are required prior to offering sur- gery or radiotherapy with curative intent. This allows assessment of peri-operative risk but also physiological reserve after treatment. Differential lung function needs assessing using a ventilation perfu- sion scan to calculate the quality of performance of the lung tissues likely to remain after a planned resection. Simple formulae are avail- able to predict the postoperative lung function from these scans with reasonable accuracy. However, if the predictions are borderline for the resection intended, then an exercise test should be performed to calculate the maximum oxygen uptake and surgery only performed if this is more than 15 ml/kg per min. In general, the risks are greater for a pneumonectomy and worse for a right-sided operation, and much greater than for a lobectomy. The surgeon needs to be given clear advice as to how extensive a resection an individual patient can tolerate safely, without significant respiratory compromise as a result of a curative pulmonary resection.

 Other investigations In general, the ability to identify small metastatic deposits is as unsatisfac- tory for lung carcinomas as for other solid tumours. The available tech- niques are relatively crude, and this partially explains the high extrathoracic relapse rate following so-called ‘curative’ resections for NSCLC. In patients with no symptoms other than those caused by their pri- mary tumour, imaging scans of brain, liver, and bones are unhelpful if there is no clinical evidence of neurological, hepatic, or bony disease, and normal biochemistry. Such scans have been superseded by PET-CT. CT scan of the upper abdomen identifies abnormalities of one or both adrenal glands in up to 10% of patients considered for surgery, and fine needle aspiration of the adrenal gland should be performed if this remains the only contraindication to pulmonary resection. Bone scans have a high false-positive rate due to Paget’s disease, active arth- ritis, healing fractures, renal disease, and hyperparathyroidism. PET- CT scans have a similar sensitivity to bone scans but a significantly higher specificity, only rarely being positive in nonmalignant bone conditions. Recent data suggest that MRI scans of the brain may de- tect asymptomatic brain metastases in 5% of patients undergoing lung surgery, with higher rates in upper lobe adenocarcinomas, tumours more than 3 cm, and when there is nodal involvement, MRI brain with contrast is now routinely recommended by NICE for patients with stage III being considered for treatment with curative intent. Biopsy or cytological aspiration of enlarged lymph nodes and skin metastases should be carried out whenever indicated. If an iso- lated hepatic or bony lesion identified with PET-CT or CT scanning appears to be the only contraindication to surgery, then this should be biopsied under radiological control. Staging The staging algorithm investigations for NSCLC are summarized in Fig. 18.19.1.13. The final procedure before thoracotomy, or other lo- calized treatment such as radical radiotherapy, is assessment of the mediastinum, since this may be involved in up to 50% of patients with a peripheral, poorly

differentiated tumour, and in a much greater per- centage of those with central lesions. If CT shows no other obvious site of disease and a PET scan only confirms uptake in the primary tumour and at no other distant site, then the surgeon can proceed directly to thoracotomy. If the CT and/or PET scan is abnormal at a distant site, this should be assessed and biopsied. If a CT is abnormal in the medias- tinum and PET is not available, then mediastinal exploration should be performed by whatever technique is applicable. Increasingly this is by EBUS-TBNA or EUS, proceeding to mediastinoscopy only if biopsies of suspicious areas are not confirmed by these techniques. Similarly, isolated suspicious lesions in the liver, adrenal glands, and other organs should be biopsied as they both stage as inoperable and provide the pathological diagnosis. However, most patients with extrathoracic me- tastases will have abnormal nodes within their mediastinum. Treatment and prognosis of NSCLC Surgery Surgery remains the single modality most likely to be curative in NSCLC. Before surgery, the patient should have been carefully staged (Fig. 18.19.1.13), and the chances of long-term survival will be greatly influenced by this. All patients with stage IIIB disease (Table 18.19.1.4) should not undergo thoracotomy, but those with stage I, II, and some with IIIA disease can be considered for resection. In general, patients with squamous cell carcinomas have higher 5- and 10-year survival rates than those with adenocarcinoma and large-cell carcinomas, and the more differentiated the tumour the better is the prognosis. Clearly, small peripheral lesions with no nodal disease (stage IA) fare best (up to 70% survival at 5 years), but the survival rate decreases with both size of tumour and increasing involvement of hilar and mediastinal nodes. The 5-year survival curves for a series of 3 211 patients from Norway, operated upon between 1993 and 2002, are shown in Fig. 18.19.1.14 for survival by pathological stage and for extent of resection. Essentially the survival data is similar to that for a decade previously, as used by Mountain in the setting of the updated TNM classification, although this may change with the 2009. About 20% of all patients who present with NSCLC eventually come to surgery. Most of the others are excluded almost immedi- ately because of clinically evident metastatic disease, radiological or bronchoscopic evidence of inoperability, general frailty and/or sig- nificant associated other illnesses, or inadequate lung function. Of those having a ‘curative’ resection, the overall survival rate at 5 years is approximately 50% and at 10 years it is 16–18%. Death from local or distant recurrence of the tumour is equally probable, highlighting the inadequacies of current staging techniques. However, the careful application of the TNM system and the advent of more sophisticated scanning equipment such as PET-CT may lead to improvement. NEW PRESENTATION Chest radiograph, CT Scan Bronchoscopy and Biopsy (TBNA/EUS) Guided Biopsy Stage/Cell Type Small Cell (usually chemotherapy) Metastatic NSCLC Nonsurgical Management NSCLC- potentially resectable Assess Patient (age, co-morbidity, lung function) PET scan Primary Only Avid Distant Sites Avid Biopsy Resect Negative Unfit Fit Positive Fig. 18.19.1.13 Staging algorithm for non-small-cell lung cancer.

 Advanced age is not a contraindication to surgery. About 45% of new patients with lung cancer are over 70 years of age and these in- dividuals appear to tolerate lobectomy as well as younger patients, although the mortality for pneumonectomy (8–10%) is double that of those under 70. There is no evidence that tumours grow more slowly in elderly people, hence the disease is as likely to be the ter- minal event in older as in younger patients and resection should be encouraged in patients who are fit. Smokers should be persuaded to stop smoking before thoracotomy because continued smoking increases perioperative complications. Video-assisted thoracoscopic resection of peripheral masses was ini- tially reserved for those with inadequate lung function for lobectomy, as hilar and mediastinal node evaluation and dissection is

not always possible. However, as experience has developed, it is being used more and more for lobectomy, as well as exploration of the draining hilar and mediastinal nodes. Advantages may include less postoperative pain and shorter inpatient stays. The survival data shows no differences between a VATS lobectomy and a lobectomy by thoracotomy and clinical trials are ongoing. However, a wedge resection may confer a worse 5-year survival than anatomical segmentectomy. These lung sparing procedures may be more suitable for elderly subjects. Radiotherapy Patients who are excluded from surgery because of adverse prognostic factors, advanced stage of tumour, or other coincidental disease con- stitute the largest group treated with radiotherapy. Although the usual aim of radiotherapy will be palliative, there will be a small group of patients in whom more aggressive therapy will be used in the hope of cure, or at least long-term survival, particularly in those who have refused surgery. Radiotherapy for lung cancer is limited by the com- parative radiosensitivity of three critical normal tissues likely to be in- cluded in the radiation beam: normal lung, spinal cord, and the heart, each of which has a specific tolerance dose. Increased radiation dose leads to greater killing of tumour cells but may produce unwanted damage to normal cells. Radiation dose must be expressed not only in terms of total dose but also numbers of fractions and overall time. Standard of care is to use stereotactic ablative radiotherapy (SABR) to allow accurate radiation delivery. If conventionally fractionated rad- ical radiotherapy is used the typical regimen are 55 Gy in 20 fractions over four weeks, or 60-66 Gy in 30-33 fractions over 6-6 1/2 weeks. Alternative to surgery In some patients with a technically resectable tumour there may be medical contraindications for resection or the patient may refuse sur- gery. In general, the results of radical radiotherapy in these patients are inferior to the 5-year survival following surgery. The best result for radiotherapy was a 5-year survival rate of 22% for peripheral squa- mous cell cancers, but other series record a 5-year survival rate of 6%. Stereotactic ablative body radiotherapy (SABR) is a new treat- ment which is seen as a meaningful alternative to surgery for per- ipheral stage 1 (<3 cm) lung cancers. It allows very high (ablative) doses of radiotherapy to be given to precise areas of the lung and therefore minimizes damage to uninvolved lung parenchyma. This means that patients with poor lung function who would not tolerate 1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0 Years 0 1 2 3 4 5 6 7 8 9 10 Pneumonectomy Bilobectomy Lobectomy 11 Survival probability Sublobar resection 0 24 48 72 Months 0% 20% 40% 60% 80% 100% Proposed Events/N MST 24 Month 60 Month IA1 IA2 IA3 IB IIA IIB IIIA 2052/3200 IIIB 1551/2140 68/781 NR 97% 92% 505/3105 NR 94% 83% 546/2417 NR 90% 77% 560/1928 NR 87% 68% 215/585 NR 79% 60% 605/1453 66.0 72% 53% 29.3 55% 36% 19.0 44% 26% IIIC 831/986 12.6 24% 13% IVA 336/484 11.5 23% 10% IVB 328/398 6.0 10% 0% Fig. 18.19.1.14 Left panel: Kaplan–Meier survival curves according to surgical procedure for patients resected for lung cancer diagnosed between 1993 and 2002 in Norway. Right panel: same population showing survival by stage. Goldstraw P., Chansky K., Crowley J., 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, Journal of Thoracic Oncology, Vol 11. No 1 (January 2016) reproduced with permission from Elsevier.

 thoracic surgical resection, can have SABR with similar 5 year lung cancer specific survival rates. Preoperative and/or postoperative radiotherapy Preoperative radiotherapy has been given in a few uncontrolled studies, but there is no evidence that this approach improves survival in patients who have a complete resection. Two recent meta-analyses have shown no benefit from postoperative radiotherapy for stage I and II disease, and it is not clear whether or not it has any value in stage IIIA disease with nodal involvement, but benefit is likely to be small and it is not currently recommended. Where a surgical resec- tion is not complete

(e.g. there is microscopic pleural or bronchial margin involvement of tumour), many centres employ postoperative radiotherapy to the involved margin. Radical radiotherapy for locally advanced, inoperable disease In otherwise fit patients with small-volume intrathoracic disease which is not resectable, usually because of mediastinal involvement, it is common practice to attempt to cure with radiotherapy. Results with daily single fractions are disappointing, even with doses of up to 60 Gy, with 5-year survival rates ranging from 5 to 17%. In 1997 continuous hyperfractionated accelerated radiotherapy (CHART), with a fraction every 8 h for 12 consecutive days to a total of 54 Gy, was compared to conventional daily radiotherapy in NSCLC. CHART gave an absolute improvement in 2-year survival from 20% to 29%, with the greatest benefit (14% absolute improve- ment) in squamous cell cancers. This appears a real advance in the provision of radiotherapy for locally advanced, inoperable tumours, but it has not proved to be a feasible technique for busy radiotherapy departments. A similar approach with no treatment at week-ends (CHARTWELL) may be as useful and seems to be effective. Studies of combining radiotherapy with concurrent or sequential courses of chemotherapy have been compared to radiotherapy alone and shown a survival benefit. It also appears that concurrent chemo- therapy may be better than the two treatment modalities given con- secutively, although the toxicity for the concurrent approach is higher. Concurrent chemoradiotherapy is now regarded as the approach of choice for locally advanced, inoperable NSCLC. Very recent data have also demonstrated the benefit of adding immunotherapy with Durvalumab to concurrent chemo-radiotherapy to inoperable stage III disease (https://www.nejm.org/doi/full/10.1056/NEJMoa1809697). Palliation Radiotherapy can provide excellent palliation for many symptoms, with two of the most distressing, haemoptysis and cough, controlled in up to 80% of cases. Administration of two fractions (each of 8.5 Gy, 1 week apart) appears adequate. Dyspnoea from bronchial obstruction and dysphagia are relieved in most cases. The syndrome of superior vena caval obstruction is relieved in about 80% of suf- ferers, but usually requires a more conventional course of five to ten fractions of radiotherapy. Pain from bone secondaries can be re- lieved in more than 50% by a single fraction of 8 Gy, often given at the same time as a clinic visit. Brain metastases generally respond poorly to radiotherapy. A 48- h trial of dexamethasone, 4 mg orally four times daily or 8 mg twice daily, is recommended as initial management. If a worthwhile re- sponse follows the resolution of the oedema surrounding the metas- tases, then radiotherapy will consolidate this gain, after which steroids should be rapidly withdrawn. A UK randomized trial has called into question the role of whole brain radiotherapy for patients with brain metastases from lung cancer. Selected patients may benefit from stereotatic radiosurgery to the brain when there are a limited number of metastases. Spinal cord compression is a relatively common occurrence as- sociated with vertebral body metastatic disease. Pain and bony ten- derness often precede it and may be helpful in localizing the lesion. Responses to radiotherapy are usually incomplete and disappointing, often because of interruption of the vascular supply to the spinal cord by the tumour. Systemic anti-cancer therapy Conventional chemotherapy Several cytotoxic agents show activity against NSCLC, but much less frequently or dramatically than with small-cell tumours. However, combination chemotherapy can achieve impressive response rates; par- tial responses in 50% of patients with locally advanced disease and in 35% of those with advanced extrathoracic disease have been reported. Chemotherapy became a routine treatment for inoperable NSCLC about 20 years ago after a meta-analysis of 53 randomized controlled studies in which patients did or did not receive chemotherapy in add- ition to surgery, radiotherapy, or to best supportive care. This sug- gested a 5% advantage for the addition of chemotherapy to surgery (confidence intervals—1 to 7%), a smaller nonsignificant advantage for the addition of chemotherapy to radiotherapy, and—in those with advanced disease—a 10%

improvement in survival at 1 year for the addition of chemotherapy to best supportive care. The agents used in these early trials were more toxic than the newer, currently available agents, and the associated deleterious effects on quality of life have dramatically improved. Also it has emerged that different combin- ations of drugs are more effective for different cell types of NSCLC. The optimal initial chemotherapy for squamous cell NSCLC is carboplatin or cisplatin, plus gemcitabine. A large study of these agents compared to cisplatin and pemetrexed, showing superior survival for the latter doublet for adenocarcinomas and large-cell carcinomas, and this had become the initial treatment of choice. However, the routine assessment for EGFR mutation and other genetic changes as well as bio- markers for response to immunotherapy has changed this (see next). In patients with adenocarcinoma and stable disease after first- line chemotherapy, maintenance chemotherapy with pemetrexed is often considered. In the United Kingdom, only 20% of patients receive second line chemotherapy after progression of disease with initial treatment. The use of chemotherapy as an adjuvant following successful sur- gery has shown a 5.2% increase in the 5-year post-surgery survival for patients with at least Stage IIA disease, and this should be offered to those who have recovered well and within 60 days of their surgery. In advanced disease, which will include up to 75% of all cases of NSCLC, chemotherapy confers an important survival advantage compared to best supportive care alone. In general, studies of pal- liative chemotherapy have shown a quality of life benefit, at least over the first few months after treatment is complete. There is no particular regimen that stands out, but chemotherapy in advanced disease, chosen on their cell type, for patients with a good perform- ance status will increase the median survival by 4 to 6 months and the 1-year survival from 18% untreated to 35 to 50%. More recent clinical trials have shown a differential effect of chemotherapy in that adenocarcinomas have a higher response rate and survival with

 pemetrexed plus a second agent, while squamous cell tumours re- spond better to platinum containing doublets. Hence the import- ance of establishing the cell type in NSCLC prior to planning therapy. Targeted therapies The rapid evolution of molecular biology and the ability to identify the presence of mutations in small biopsy tissue samples has led to a drive for targeted therapy based on inhibition of the ‘driver’ mutant gene. The first important mutation discovered—and now routinely sought for— was EGFR, and mutation of EGFR in NSCLC has made it a target for treatment. Several oral inhibitors of EGFR, including gefitinib, erlotinib, afatinib and osimertinib are in current use. Patients who harbour EGFR mutations have approximately a 70% better response rate and pro- longed progression-free survival and improved quality of life on an EGFR tyrosine kinase inhibitor (TKI) than with conventional chemo- therapy. Conversely, patients whose tumours are wild-type for EGFR display minimal responses to EGFR TKI, and may do better with first- line chemotherapy. With this approach the overall survival of patients with EGFR mutant tumours treated first line with TKIs is about 27– 30 months. By comparison, the overall survival of patients with meta- static unselected NSCLC on first-line chemotherapy is 10–12 months. Similar observations have been made for patients with tumours harbouring ALK fusions, which can now be treated with the ALK TKI crizotinib, which is also used for non-squamous NSCLC that has rearrangements in the receptor tyrosine kinase, ROS1. Other targeted therapies are in preparation, and this approach is likely to become of increasing importance in the future. Immunotherapy Immune checkpoint inhibition has emerged as a key advance in the management of advanced lung cancer. Immunotherapy has demon- strated significant clinical utility in patients with advanced NSCLC, and several anti PD-1 and anti PD-L1 monoclonal antibodies have been approved as first or second-line therapies. These agents interfere with both costimulatory and co-inhibitory pathways

regulating the antigen specific T-cell response. PD-1 is a cell-receptor involved in pro- grammed cell death. The PD-1 receptor binds to the ligands PD-L1 and PD-L2 and results in downregulation of anti-tumour cytolytic T-cell activity, inducing T cell exhaustion and immune tolerance. Immune checkpoint inhibitors therefore allow the host's immune system to rec- ognise tumour cells and exert anti-tumour activity. This group of medi- cations are genereally well tolerated but due to their mechanism of action may result in autoimmune disorders. Pembroluzimab together with chemotherapy is currently approved for the first line treatment of advanced NSCLC and has been shown to be superior to chemotherapy alone (https://www.ncbi.nlm.nih.gov/pubmed/29658856). It has been approved by NICE as the first line systemic therapy for advanced NSCLC. In patients who have high levels of expression of PD-L1 (>50% of cells) pembroluzimab alone is licensed for use (https://www. ncbi.nlm.nih.gov/pubmed/27718847). Immunotherapy is commonly also used a second line treatment and is currently being investigated in the adjuvant and neo-adjuvant settings for earlier stage disease. Treatment and prognosis of small-cell lung cancer Small-cell lung cancer is separated from the other types of lung cancer because of its very different biological and clinical features. It has an ex- plosive growth pattern, and careful staging puts most patients into the inoperable category. However, simple staging has some prognostic im- pact and those with limited disease (tumour confined to one hemithorax and the ipsilateral supraclavicular fossa) fare better than those with ex- tensive disease (involvement of any site outside the hemithorax). The life expectancy of those with untreated small-cell lung cancer is about 3.5 months for limited disease and 6 weeks for extensive disease. Prognostic factors Multivariate analyses of large patient populations show that routine biochemical values such as serum sodium, albumin, and alkaline phosphatase allow separation of prognostic subgroups. In addition, performance status and extent of disease are important influences. For instance, a good performance status and normal biochemical values (i.e. a good prognostic category) has a 2-year survival rate of 20%, yet a correspondingly low performance status with one or more abnormal biochemical parameters (poor prognosis) has virtually no 2-year sur- vivors (Fig. 18.19.1.15). Women tend to do better than men and those under 60, better than those over 60 years of age. These factors are helpful both for stratification within clinical studies and for identifying those patients likely to do well with chemotherapy and those for whom intensive potentially toxic chemotherapy would appear inappropriate. Survival beyond 5 years (cure) is achieved in 4 to 12% of patients with limited disease and in hardly anyone with extensive disease at diag- nosis. Most studies of long-term survival report late deaths due to other cancers, including NSCLCs in up to 30% of these long-term survivors. Surgery Very occasionally patient with small-cell lung cancer can be surgi- cally cured, usually those presenting with a peripheral tumour and no evidence of local spread or metastasis despite extensive staging investigations. These patients are rare, but nevertheless have a 5-year survival rate in the region of 30 to 40% when surgery is combined with adjuvant chemotherapy. Radiotherapy Radiotherapy has an important role in palliation of symptoms that may develop after relapse following chemotherapy. Chest irradiation also significantly decreases the rate of recurrence at the primary tumour site 100 90 80 70 60 50 40 Cumulative % surviving 30 20 10 9 18 27 36 45 Months P I G E L Fig. 18.19.1.15 Survival in small-cell lung cancer by prognostic factors (G, good; Im, intermediate; P, poor) compared to full staging (L, limited; E, extensive disease).

 and in the mediastinum. A total dose of 40 to 50 Gy is usually given. Two meta-analyses on the value of adding radiotherapy to chemotherapy have shown a 5% advantage at 3 years for the addition of radiotherapy. The optimal timing of radiotherapy in relation to chemotherapy has been the subject of much debate. The 2019 NICE

guidelines recom- mend offering twice-daily radiotherapy concurrently with the first or second cycle of chemotherapy to patients with limited-stage disease and good performance status, if their disease can be encompassed within a radical thoracic radiotherapy volume. If patients are not well enough for concurrent chemoradiotherapy but respond well to chemotherapy, then radiotherapy can be offered after chemotherapy is completed. Cranial irradiation Cranial metastases are common, with 10% of patients in remission developing them as their first site of relapse. Prophylactic cranial ir- radiation given at the end of chemotherapy will delay the presenta- tion of cerebral metastases and also reduce their overall incidence. This is important, as the development of cerebral disease is associ- ated with severe morbidity, often making it difficult for the sufferer to live at home. A meta-analysis looking at the effects of prophylactic cranial irradiation on survival showed that the cumulative incidence of brain relapse was halved and the risk of death reduced by 16%, with this survival benefit being maintained after 6 years, hence it is now recommended that patients achieving a complete response after chemotherapy should have prophylactic cranial irradiation. Chemotherapy Small-cell lung cancer is much more sensitive to cytotoxic chemo- therapy than the NSCLC tumours, with a much higher response rate for several cytotoxic drugs. In the late 1970s there was a very rapid improvement in median survival, and subsequent studies using combinations of three and four drugs brought longer re- sponse times, but responses have subsequently reached a plateau. Nevertheless, with modern combination cytotoxic treatment, which is usually given as an outpatient procedure every 3 weeks, the median survival has been extended to 14 to 18 months for limited disease and to 9–12 months for extensive disease. There is no outstanding regimen, although etoposide and carboplatin is favoured by most. Modern regimens would be expected to achieve a complete response rate (i.e. disappearance of all measurable disease) in 40–50% of cases and a partial response rate (>50% reduction in tumour bulk) in a further 40%, giving a total response rate of 80– 85%. All these regimens have side effects: most patients will experi- ence some nausea and vomiting, and life-threatening septicaemia occurs in 1 to 4%, but treatment-related deaths are uncommon. There is no established second line treatment at relapse, although if remission has been achieved for a year or longer, restarting the same chemotherapy regimen can be effective in some cases. Much effort has been applied during the last 25 years to improve the median and long-term survival of patients with small-cell lung cancer. Recently, the addition of immunotherapy has been shown to improve survival in patients with extensive small cell lung cancer (https://www.ncbi.nlm.nih.gov/pubmed/30280641). In general, those patients likely to do better are those who present with limited disease and a good performance status. Patients with extensive disease tend to have a uni- versally bad prognosis and very few survive beyond 2 years. However, some metastatic sites (bone and bone marrow) are not as sinister as others (brain or liver), and the occasional patient with extensive dis- ease does well with chemotherapy, but in general treatment is offered in this circumstance for palliation and not in the hope of cure. Studies assessing the quality of life in patients presenting with small-cell lung cancer have shown that over 70% have important symptoms such as weight loss, malaise, bone pain, dyspnoea, and haemoptysis. Most of these patients have extensive disease, but after 3 months of chemotherapy symptoms can be relieved in 60 to 70% of sufferers, making chemotherapy worthwhile, with symptomatic benefits far outweighing the potential side effects. Ten per cent of small-cell lung cancer patients present with superior vena caval obstruction: this re- sponds as well as any presentation to chemotherapy. Intensity of treatment Intensifying the dosage or the frequency of administration of cyto- toxic agents has been thoroughly explored without real benefit on median survival. Small advantages are occasionally seen, but these have to be balanced by the increased toxicity resulting from a

more aggressive approach. Attempts to overcome or delay the emergence of cell resistance to chemotherapy have involved alternating com- binations of drugs, but these more complicated regimens have not been rewarding either. Similarly, the use of colony growth stimula- tion factors to allow higher or more frequent doses of drugs has not added to survival. Other studies with very high dose schedules and bone marrow harvesting and reinfusion have been unsuccessful. Duration of treatment Toxicity of chemotherapy increases with the number of courses given. It is now apparent that most of the tumour response to chemotherapy occurs within the first two or three cycles. Studies attempting to minimize the duration of chemotherapy without ad- versely affecting survival have shown that six courses of combin- ation chemotherapy is optimal (with a course every 3 weeks), with no benefit from maintenance regimens in this setting. General management of patients with lung cancer There is increasing emphasis on pre-habilitation, optimsing co-morbidities prior to anti-cancer treatment, improving nutrition and treating nicotine addiction in patients with lung cancer. There are also certain complications which require specific measures to al- leviate symptoms. Vocal cord paralysis Patients who seem likely to survive for 6 months or more and who have vocal cord paralysis are considerably helped by an injection of PTFE (Teflon) into the affected cord, which restores voice produc- tion in a high percentage of cases and reduces the risk of aspiration. Airway obstruction Obstruction of the upper airway causing stridor, or of the lower major airways, is usually treated initially with radiotherapy. Should this complication recur or be unsuitable for radiotherapy, then endobronchial tumour can be debulked using laser photocoagulation or cryoextraction, administered either via a video bronchoscope or under general anaesthetic via a rigid instrument. This is most suit- able as a palliative treatment in central tumours occluding large air- ways: removal of considerable quantities of tumour can be achieved in a single treatment session with the rigid instrument. Trials are in pro- gress assessing the additional benefits of endobronchial radiotherapy

 (brachytherapy) using iridium or caesium wires delivered via the video bronchoscope. This procedure irradiates endobronchial tu- mour to a circumferential depth of about 1 cm, and will often produce a further remission. It is used where further external-beam radio-therapy cannot be given because of the risk of exceeding normal tissue tolerance. Infection distal to tumour requires antibiotic therapy and, where appropriate, oxygen therapy and bronchodilators. Severe, re- current haemoptysis may be controlled by radiotherapy or laser. Pleural effusion Malignant pleural effusion recurs after aspiration unless the pleural space is obliterated. Chemical pleurodesis can be induced by intrapleural instillation of several agents, or by the more invasive procedure of talc pleurodesis. However, the increasing availability of VATS makes a talc pleurodesis preferable in all reasonably fit pa- tients who can undergo a general anaesthetic (see Chapter 18.17). In general a pleurodesis is recommended early in management, before embarking on chemotherapy in NSCLC. Indwelling pleural catheters are an important option for patients with malignant pleural effusions. In small-cell lung cancer it is worthwhile to give chemotherapy first as it is likely to gain control. Other issues Dexamethasone, 4 to 16 mg orally daily, may control the symptoms of brain metastasis and, if so, this should be consolidated with radio- therapy to prevent severe steroid-induced myopathy, especially in pa- tients who show a good symptomatic response to the steroids. Prednisolone, 20 mg orally daily, is often used to improve the sense of well-being, as are blood transfusion or hyperalimentation. Steroids are often helpful for the control of pain from liver metas- tases involving the liver capsule. Pain and hypercalcaemia from bone metastases can be particu- larly challenging to control. Bisphosphonates are commonly used for palliation in this setting. Denosumab, a human monoclonal anti- body that targets bone remodelling, has also been

approved by NICE for use in patients with lung cancer and bone metastases. Early evi- dence may suggest that it may have anticancer effects and offer some survival benefit over bisphosphonates in this setting (http://www. ncbi.nlm.nih.gov/pubmed/23154554). Palliative care is described in Section 7, but the importance of the combined support to the patient and the family given by the family doctor, palliative care medical and nursing staff, hospice or- ganizations, and the hospital team cannot be overemphasized. Prevention and screening Smoking cessation Lung cancer is a preventable disease which in 80% of cases is due to smoking, particularly of cigarettes. Strenuous efforts must be made to persuade people not to start smoking, to establish more effective methods of enabling people to stop, and to promote further research into effective health education. The promotion of cigarettes with low tar, nicotine, and carbon monoxide contents may have made a small contribution to prevention, but low-tar cigarettes are not a substitute for giving up smoking. Penal taxation by governments may help, as will smoke-free public places. The use of electronic nicotine delivery systems is booming, with US$3bn spent on these globally in 2013 and sales forecast to increase by a factor of 17 by 2030 (http://apps.who.int/gb/fctc/PDF/cop6/FCTC_COP6_10-en.pdf?ua = 1). While such systems may be a pathway to the reduction of tobacco smoking, they may also be viewed as products that could undermine efforts to denormalize to- bacco use and encourage uptake in younger people. The role of elec- tronic nicotine delivery systems in tobacco control is currently the subject of intense debate. Occupational measures The identification of occupational hazards and implementation of appropriate measures to safeguard the health of employees are clearly important preventive measures, even although the number at risk is very small. Population screening Screening of normal but high-risk populations with chest radiog- raphy and/or sputum cytology has been shown to have no effect on the mortality from lung cancer, even though more cancers are discovered. However, new studies of various populations using low- dose spiral CT have identified lung cancers in 1.4–2.7% of subjects in prevalence screens, the great majority having stage I disease, which is about four to six times what one would pick up by chest radi- ography. The older the subjects screened, the greater the smoking history and the presence of airways obstruction, the higher the inci- dence of occult lung cancers. A large study of 53 454 individuals has been published. The National Lung Screening Trial (NLST) randomized current and ex-smokers to three annual low-dose CT scans in the screened group, whereas the control group had a chest radiograph. The trial has shown a 20% re- duction in mortality for the CT-screened arm, with 247 deaths from lung cancer per 100 000 person-years in the screened arm versus 309 in the controls. This represents an overall reduction in all-cause death rate of 6.7%. A study of this magnitude is unlikely to ever be repeated and its impact will seriously affect thinking regarding screening for lung cancer, although there is data to suggest that the high-risk in- dividual for lung cancer is elderly, poorly educated and risk averse, and unlikely to participate in a screening trial. However, other ran- domized trials, smaller than NLST, are in progress and will report soon, and although low-dose CT may become an important method of identifying lung cancers early, it has its problems and limitations. Small-cell cancers grow too rapidly to be found by screening and will present with symptoms. Depending on where in the world the study is performed, many subjects will be found to have benign nodules that require follow-up according to radiological algorithms which may re- quire repeated scans. The incidence of nodules varies from 15 to 40%, which is a potentially huge burden for imaging departments. Despite these caveats, CT screening for lung cancer began in the United States in 2014. Cost-effectiveness data from the NLST is now available and suggests a cost per QALY of $81 000, but with wide con- fidence intervals (http://www.ncbi.nlm.nih.gov/pubmed/25372087). Refining the population that undergoes CT screening for lung cancer may improve cost-

effectiveness and is of key importance if imple- mentation of CT screening is to take place universally. Various tools can be used to select individuals according to their lung cancer risk in a more nuanced approach than simply smoking history (http://www. ncbi.nlm.nih.gov/pubmed/23863051). Application of these risk pre- diction tools to individuals, combined with smoking cessation, may make CT screening more palatable to healthcare systems if they can maximize cost-effectiveness.

section 18 Respiratory disorders 4358 Other primary lung tumours The slow-growing intrabronchial lesions previously grouped under the heading of bronchial adenoma have now been re- classified into bronchial carcinoids, adenoid cystic tumours, and mucoepidermoid tumours. They are not related to cigarette smoking, and tend to be diagnosed at a younger age than car- cinoma of the bronchus. Bronchial adenomas True bronchial adenomas derived from bronchial glands are rare. These tumours were once thought to be benign, but they are po- tentially and often frankly malignant, being capable not only of destructive local growth but also of metastasis to regional lymph nodes in about one-third of patients, and to distant organs, par- ticularly liver and brain, in about 10%. They are occasionally lo- cated in the trachea. Bronchial carcinoids The most common symptoms of bronchial carcinoids are cough, haemoptysis, and recurrent pneumonia, although not infrequently the lesion is discovered on routine radiographic examination be- fore symptoms develop. In the few cases that have extensive liver secondaries, there may be the classical symptom pattern of inter- mittent cyanotic flushings, intestinal cramps and diarrhoea, bronchoconstriction, and cardiovascular lesions. The radiographic appearances are those of a solitary nodule, pulmonary collapse, or obstructive hyperinflation. As most of the tumours occur in main stem or proximal portions of lobar bronchi, bronchoscopy is usually the definitive diagnostic measure. The tumour appears as a white or pink polypoid or lobulated mass, with the bronchial mucosa ap- pearing to be intact. Biopsy should be carried out with caution as it may be followed by brisk haemoptysis. Surgical resection is the treatment of choice. In the absence of regional spread or distant metastases 5-year survival prospects are excellent, but if there is involvement of regional nodes, survival rates fall to 70%. Some aggressive carcinoid tumours carry a much worse prognosis. The mechanism and management of the general symptoms of the carcinoid syndrome are described in Chapter 15.9.2. FURTHER READING Ahrendt SA, et al. (1999). Molecular detection of tumor cells in bronchoalveolar lavage fluid from patients with early stage lung cancer. J Natl Cancer Inst, 91, 332–9. Albain KS, et al. (2009). Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet, 374, 379–86. American Thoracic Society and European Respiratory Society (1997). Pretreatment evaluation of non-small-cell lung cancer. Am J Respir Crit Care Med, 156, 320–32. Annema JT, et al. (2010). Mediastinoscopy vs endosonography for me- diastinal nodal staging of lung cancer: a randomized trial. JAMA, 304, 2245–52. Arbour KC, Riely GJ (2019). Systemic Therapy for Locally Advanced and Metastatic Non-Small Cell Lung Cancer: A Review. JAMA, 322, 764–74. Auperin A, et al. (1999). Prophylactic cranial irradiation for patients with small cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med, 341, 476–84. Beckles MA, et al. (2003). The physiological evaluation of patients with lung cancer being considered for surgery. Chest, 123, 105–14S. British Thoracic Society, Society of Cardiothoracic Surgeons of GB, Ireland Working Party (2001). Guidelines on the selection of pa- tients with lung cancer for surgery. Thorax, 56, 89–106. Brown JS, et al. (1996). Age and the treatment of lung cancer. Thorax, 51, 564–8. Bruske-Hohlfeld I, et al. (2000). Occupational lung cancer risk for men in Germany: results from a proband case-control study. Am J Epidemiol, 151,

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