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John D. Firth
Christopher P. Conlon
Timothy M. Cox

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18.19

Malignant diseases

CONTENTS

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 commonly), 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 tamponade, 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 hormone, 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 randomized 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 annual CT screens compared to a control group, and a 6.7% reduction in all-cause mortality.

Clinical staging—accurate clinical staging is paramount for treatment 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 percutaneous image-guided needle, depending on best access) or of a metastasis (often mediastinal lymph nodes by endobronchial ultrasound systems) is required. The latter provides a diagnosis and information 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 staging test in those patients where resection or another curative treatment 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—'curative' 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 results 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

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 receptor 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 complete response rate (i.e. disappearance of all measurable disease) in 40 to 50% of cases and a partial response rate (>50% reduction in tumour 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 paralysis 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) malignant 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 organizations, and the hospital team cannot be overemphasized.

Epidemiology

Lung cancer is the most common cause of death with malignant disease 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 attributed to tobacco in China, 15% were due to lung cancer.

Aetiological factors

Tobacco

In every country, the increase in mortality from lung cancer has appeared 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 increased 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 intensity 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 relationship 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, equivalent 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 behind 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

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 relentlessly closing. With regard to socioeconomic status, lung cancer is likelier to occur in the poor and less educated, which is a widespread 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 exposed 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 associated with a higher risk of lung cancer and occurs among various groups of miners, particularly those involved in extraction of pitchblende 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 expected 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 chemical, petroleum, ship-building, and paper industries. Legislation for cleaner air has caused both environmental and occupational pollution to fall dramatically in the past 30 years, and this has preceded changes in smoking habits.

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

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 estimated that about seven-eighths of a tumour's life will have passed when it is diagnosed, and that the vast majority will have disseminated at the time of diagnosis, even though most metastases may be too small to detect.

Squamous cell carcinomas seem to arise most commonly in segmental and subsegmental bronchi in response to repetitive carcinogenic 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 thickness 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 synchronous primary tumours. Tumour infiltration follows loss of the basal membrane. The precise origins of small-cell carcinomas remain 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 malignancies, 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

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 polygonal 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 invade vessels and lymph nodes, disseminating widely even before symptoms arise from the primary tumour. It is invariably associated with smoking, and over 50% of patients have extensive, advanced disease at presentation. The cells secrete peptides which cause clinical syndromes in 10% of cases.

Adenocarcinoma

This tumour forms acinar or glandular structures, having prominent 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 transcription 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 morphologically 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 inclusions, and abundant cytoplasm, and they are mucin-producing in many instances. The tumours tend to be bulky and are often necrotic. 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 carcinoma 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 commonly 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 cancers, 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 described 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 inactivate 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 located 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 disease. 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 detection 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 clusters. 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 neuroendocrine 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) tyrosine 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 breakthrough. This led to highly successful trials with the small-molecule tyrosine kinase inhibitors gefitinib, erlotinib, and Afatanib. The responses to these targeted treatments in those with the EGFR mutation 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 multiple 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 primary 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 identifiable 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 attributable to metastatic disease. In one series of 678 consecutive patients 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

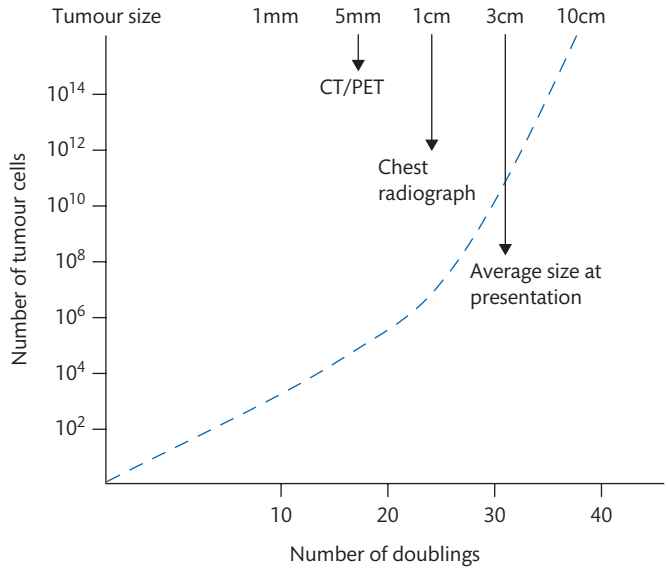


Fig. 18.19.1.1 The lung cancer growth curve and ability to detect a tumour during its natural history.

is a radiographic abnormality found by chance on routine examination (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

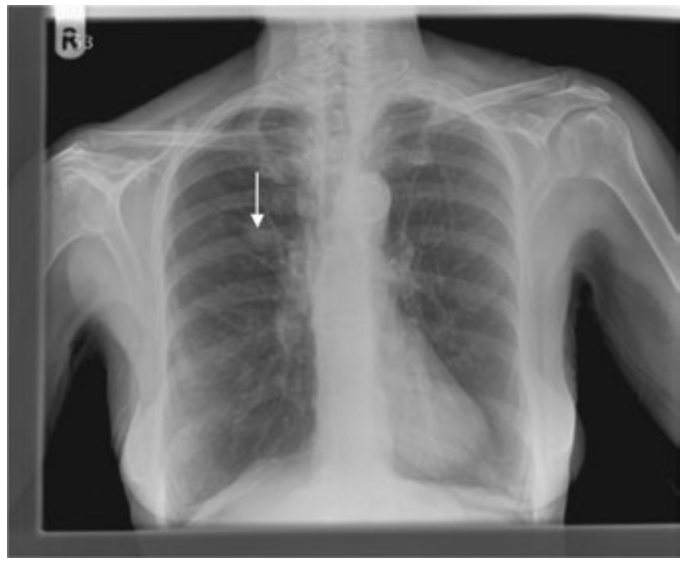


Fig. 18.19.1.2 Chest radiograph showing a chance finding of a right upper lobe mass (arrow) with a bulky right hilum.

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.

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 endocrine, metabolic, and neurological (paramalignant) syndromes (Table 18.19.1.2).

Intrapulmonary symptoms

Cough is the most common initial presenting symptom, but because it is a symptom of so many respiratory disorders, the possibility 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, involvement 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 diagnosis 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

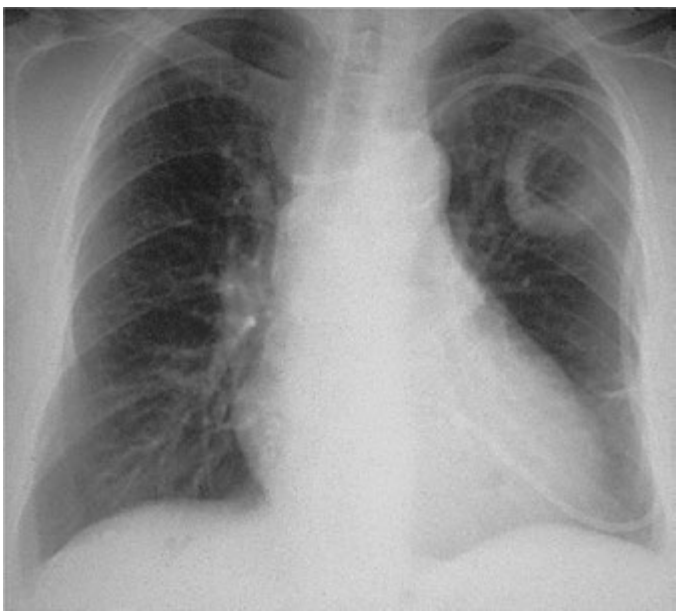


Fig. 18.19.1.3 Cavitating squamous cell lung cancer.

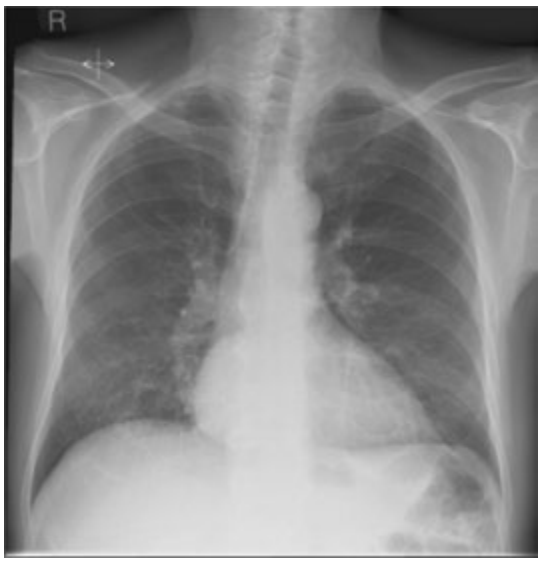


Fig. 18.19.1.4 Chest radiograph showing a tumour in the right lower lobe behind the heart causing a double shadow for right heart border.

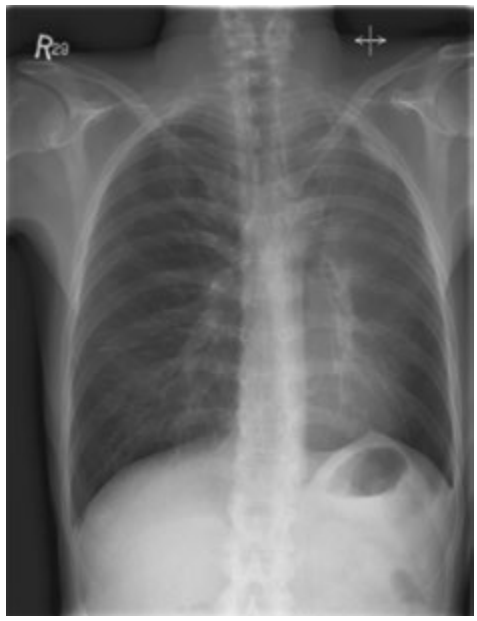


Fig. 18.19.1.5 Chest radiograph showing a collapsed left upper lobe due to proximal tumour.

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 replacement or indirectly by endobronchial disease causing airway narrowing 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 brachial plexus is invaded. Other symptoms of this type of tumour include 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

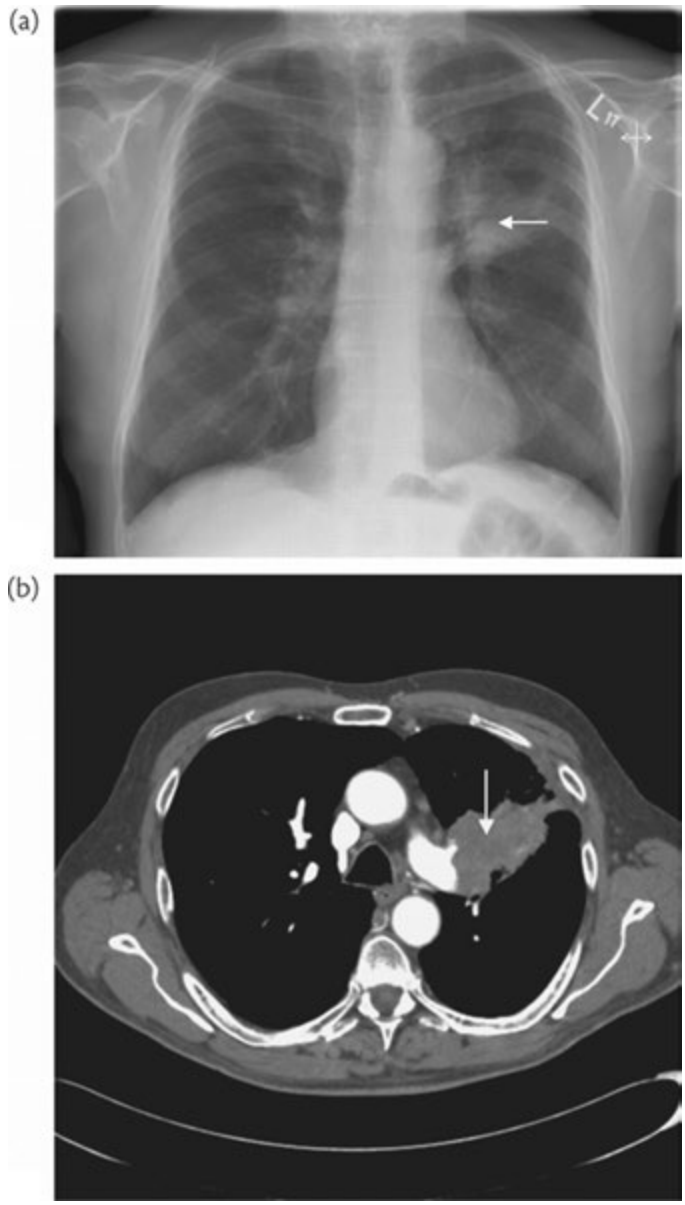


Fig. 18.19.1.6 (a) Chest radiograph showing an ill-defined parenchymal mass (arrow) in the left upper lobe; (b): CT scan of the chest of the same patient as in (a), confirming a large central mass (arrow) encasing the left upper lobe bronchus.

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 recurrent 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

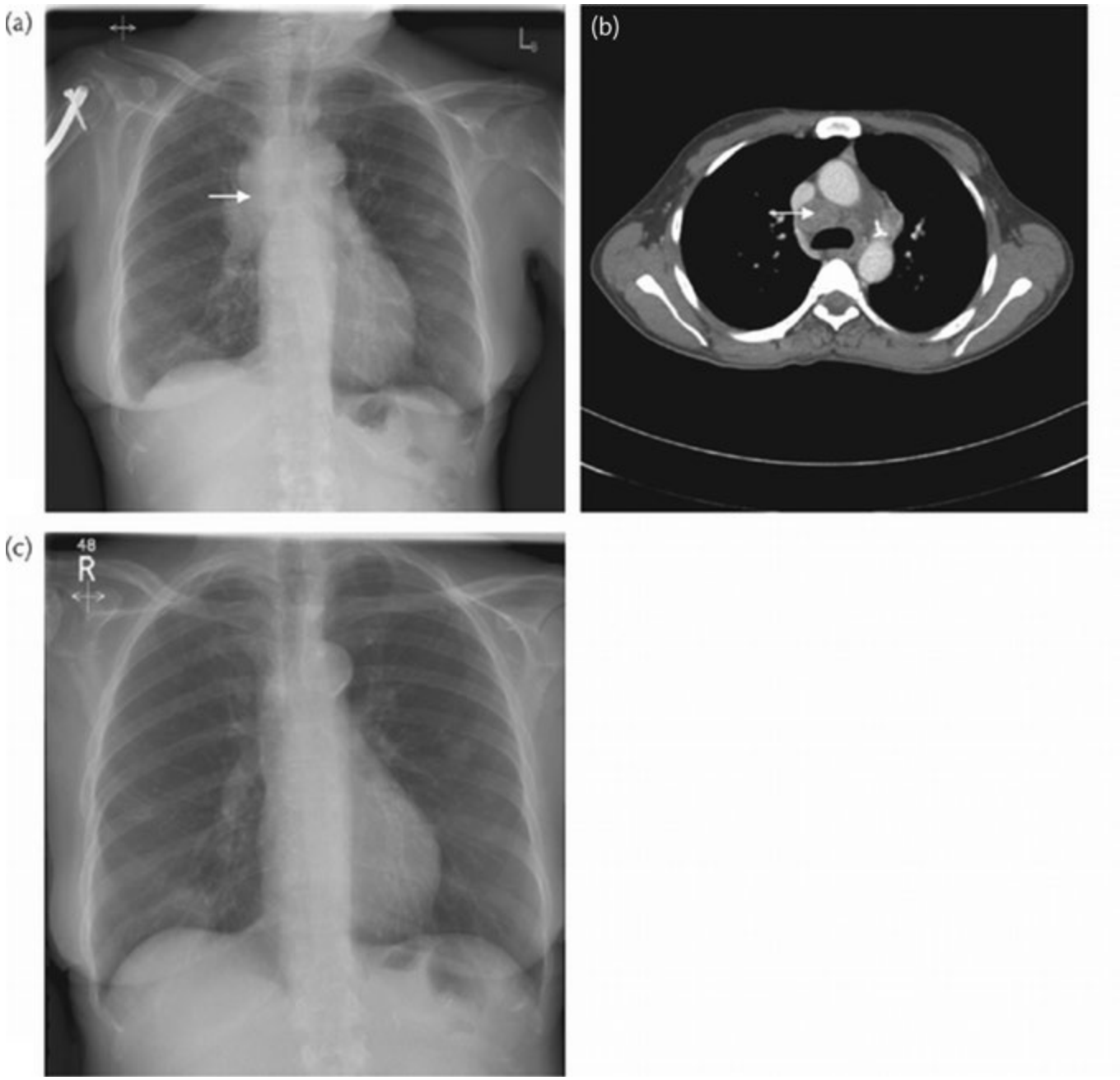


Fig. 18.19.1.7 (a) Chest radiograph showing a right upper lobe tumour causing wheeze with bulky right paratracheal nodes (arrow); (b) CT scan of the chest of the same patient as in (a), showing grossly enlarged mediastinal pretracheal lymph nodes (arrow); (c) chest radiograph of the same patient as in (a), showing complete response after two courses of chemotherapy.

in the characteristic features of superior vena caval obstruction—awareness of tightness of the collar, fullness of the head, and suffusion 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 accompanied 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 spontaneous pneumothorax. It must not be forgotten that spread of tumour 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 metastases, the most common sites being bones, liver, adrenal glands, brain

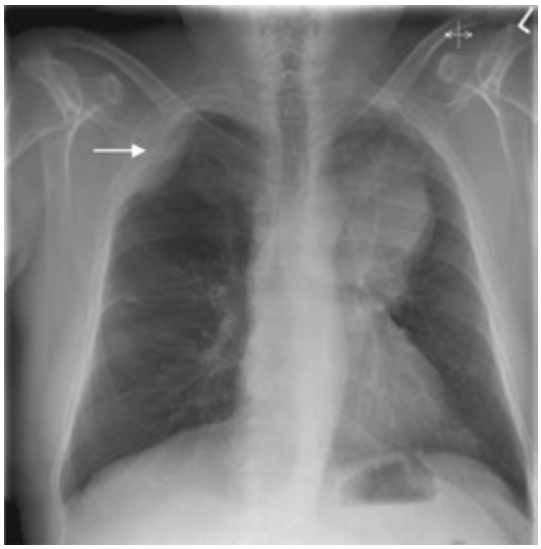


Fig. 18.19.1.8 Chest radiograph showing a large left upper lobe mass with a right rib metastasis (arrow) causing pain, which was the reason for presentation in this case.

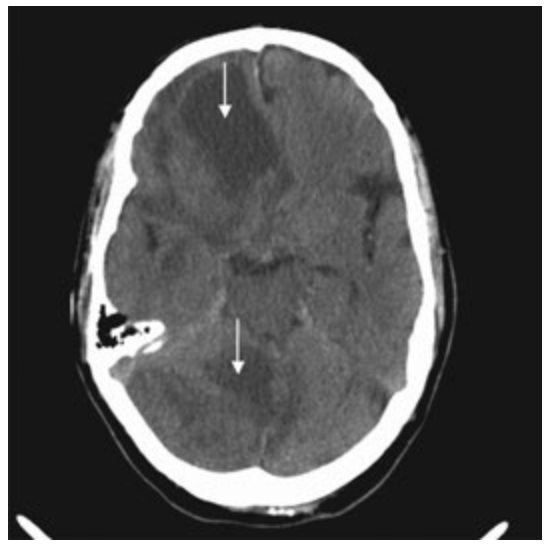


Fig. 18.19.1.10 CT scan of the brain in patient presenting with vagueness. Note marked cerebral oedema around metastases (arrows), and midline shift.

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 alkaline 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.

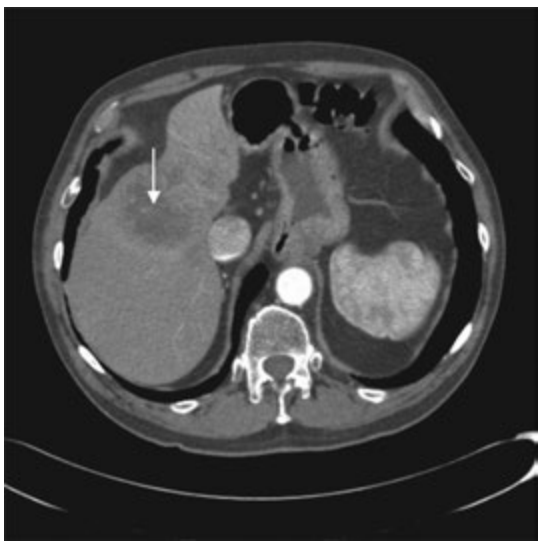


Fig. 18.19.1.9 CT scan of the upper abdomen revealing a large necrotic liver metastasis (arrow).

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 symptoms, 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 commonly 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 secretion precede those of the pulmonary tumour, emphasizing the importance of a high index of suspicion in such circumstances.

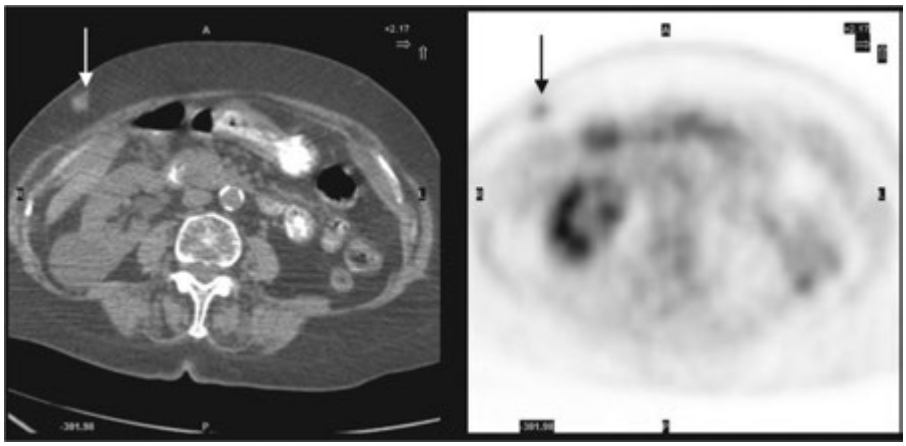


Fig. 18.19.1.11 CT (A) and PET (B) scan of the abdomen showing a solitary mass in the right anterior abdominal wall (arrows) in a patient with a lung tumour. The mass is PET positive.

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 features. 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 exceeds 300 mosmol/kg. The commonest cancer causing this syndrome 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 carcinoma 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 itself 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 hypokalaemic 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 reversible 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 parathormone 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 prostaglandin 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 calcium 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 depletion, 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 association is chiefly with large-cell carcinomas. Increased gonadotropin production is the cause.

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 syndrome 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 eliminated. The main neurological syndromes include the Lambert–Eaton myasthenic syndrome (LEMS), limbic encephalopathy, polyneuropathy, cerebellar degeneration, retinopathy, and autonomic neuropathy. LEMS is the most widely recognized of these disorders and presents with gradual onset of proximal limb weakness, more noticeable 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 reported 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 associated with the presence of type 1 antineuronal nuclear antibodies (ANNA-1), also known as anti-Hu antibodies. Small-cell lung cancers express Hu antigen and up to 20% of these patients have detectable 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 consists 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 immediate regression, but symptoms recur if the tumour recurs.

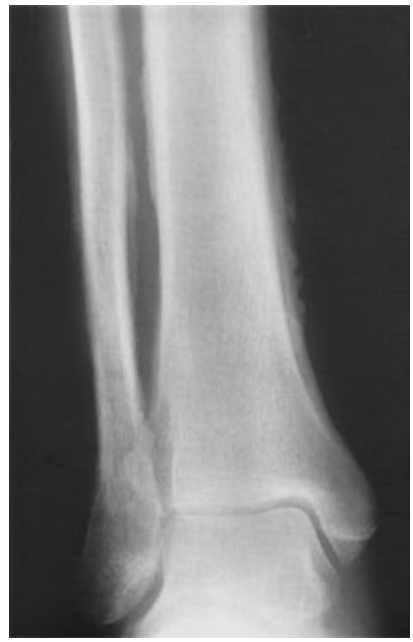


Fig. 18.19.1.12 Radiograph of the ankle showing new periosteal growth due to hypertrophic pulmonary osteopathy.

Clubbing is much more common than HPOA, occurring in up to 25% of patients presenting with lung cancer. It seems to be commoner 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 complications 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 syndrome 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 disseminate widely, and at diagnosis it is very rarely considered operable. However, the slower doubling times for squamous cell cancers and adenocarcinomas, together with the relatively lesser tendency for

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 demonstrated 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 metastases) encouraged an ordered assessment of investigations and selection 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 adenocarcinoma[b]
T1a	Tumour ≤1 cm in greatest dimension[a]
T1b	Tumour >1 cm but ≤2 cm in greatest dimension[a]
T1c	Tumour >2 cm but ≤3 cm in greatest dimension[a]
T2	Tumour >3 cm but ≤5 cm or tumour with *any* of the following features[c]:
	– 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) effusion[d]
M1b	Single extrathoracic metastasis[e]
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.

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.

(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, investigation by CT and/or bronchoscopy—ideally with endobronchial ultrasound 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 located 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. Involvement 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 presence of metastasis (see **Fig. 18.19.1.8**). Spread of tumour from mediastinal nodes peripherally along the lymphatics gives the appearance characteristic of lymphangitis carcinomatosa—bilateral hilar enlargement 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 diagnosis 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 specimens 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 cancers 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 tumour far more clearly than a conventional chest radiograph. It also frequently 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 accessible to the bronchoscope and may be easier to sample by CT guided transthoracic biopsy. The CT scan may also identify mediastinal involvement which can be directly sampled by bronchoscopic or ultrasound-guided techniques, or direct sampling towards an abdominal 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, previous 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

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 accessible 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 provide critical staging information, but this technique has been superseded 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 involved, 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 involvement 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 techniques are being increasingly replaced by minimally invasive techniques including endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), where fine needle aspiration is performed with a needle placed within the working channel of a bronchoscope 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 histological 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 diatheses. Positive yields as high as 90% have been reported, with biopsy samples having a higher and more specific yield than cytological aspirates. 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 lesions can be carried out under direct vision, and absence of pleural tumour is important in decisions about resectability of a lung tumour. 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 cytology 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 sampling 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 metastases, has gained wide acceptance as a test with much better characteristics 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 surgery 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 perfusion scan to calculate the quality of performance of the lung tissues likely to remain after a planned resection. Simple formulae are available 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 unsatisfactory for lung carcinomas as for other solid tumours. The available techniques 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 primary 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 arthritis, 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 detect 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 isolated 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 localized 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 percentage 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 mediastinum 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 metastases will have abnormal nodes within their mediastinum.

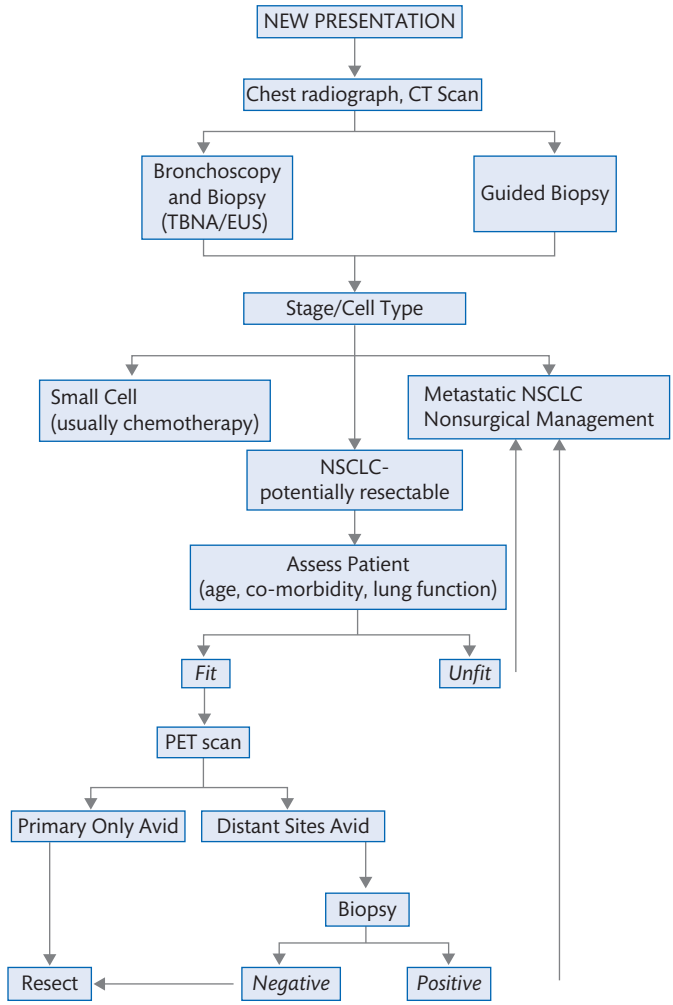


Fig. 18.19.1.13 Staging algorithm for non-small-cell lung cancer.

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 3211 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 immediately because of clinically evident metastatic disease, radiological or bronchoscopic evidence of inoperability, general frailty and/or significant 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.

Advanced age is not a contraindication to surgery. About 45% of new patients with lung cancer are over 70 years of age and these individuals 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 terminal 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 initially 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.

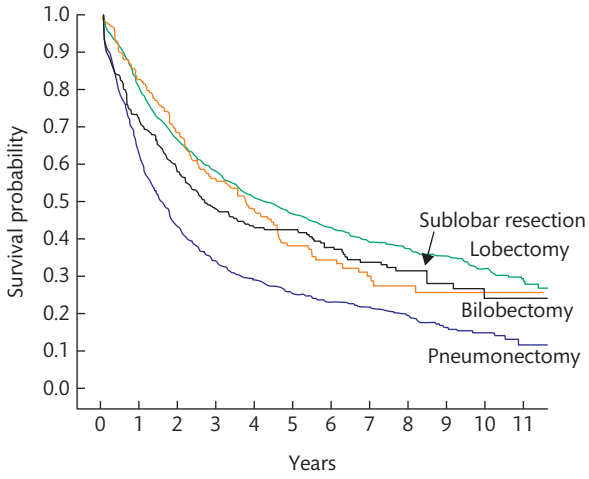
Radiotherapy

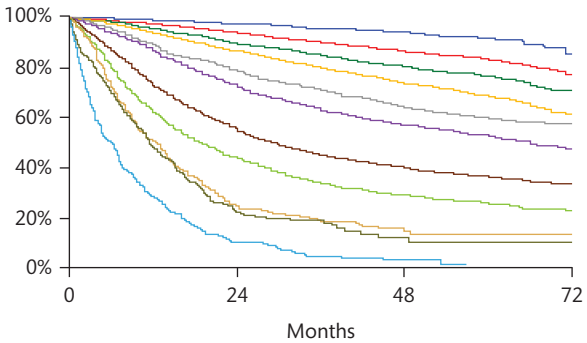
Patients who are excluded from surgery because of adverse prognostic factors, advanced stage of tumour, or other coincidental disease constitute the largest group treated with radiotherapy. Although the usual aim of radiotherapy will be palliative, there will be a small group of patients in whom more 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 comparative radiosensitivity of three critical normal tissues likely to be included 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 radical 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 surgery. 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 squamous cell cancers, but other series record a 5-year survival rate of 6%.

Stereotactic ablative body radiotherapy (SABR) is a new treatment which is seen as a meaningful alternative to surgery for peripheral 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





Proposed	Events/N	MST	24 Month	60 Month
IA1	68/781	NR	97%	92%
IA2	505/3105	NR	94%	83%
IA3	546/2417	NR	90%	77%
IB	560/1928	NR	87%	68%
IIA	215/585	NR	79%	60%
IIB	605/1453	66.0	72%	53%
IIIA	2052/3200	29.3	55%	36%
IIIB	1551/2140	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 resection 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 improvement) 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 chemotherapy may be better than the two treatment modalities given consecutively, 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 sufferers, but usually requires a more conventional course of five to ten fractions of radiotherapy. Pain from bone secondaries can be relieved 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 response follows the resolution of the oedema surrounding the metastases, 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 associated with vertebral body metastatic disease. Pain and bony tenderness 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; partial 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 addition to surgery, radiotherapy, or to best supportive care. This suggested 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 combinations 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 biomarkers 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 surgery 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 palliative 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 performance 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 respond better to platinum containing doublets. Hence the importance 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 prolonged progression-free survival and improved quality of life on an EGFR tyrosine kinase inhibitor (TKI) than with conventional chemotherapy. 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 metastatic 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 demonstrated 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 programmed 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 recognise tumour cells and exert anti-tumour activity. This group of medications 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 explosive growth pattern, and careful staging puts most patients into the inoperable category. However, simple staging has some prognostic impact and those with limited disease (tumour confined to one hemithorax and the ipsilateral supraclavicular fossa) fare better than those with extensive 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 survivors (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 diagnosis. 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 surgically 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

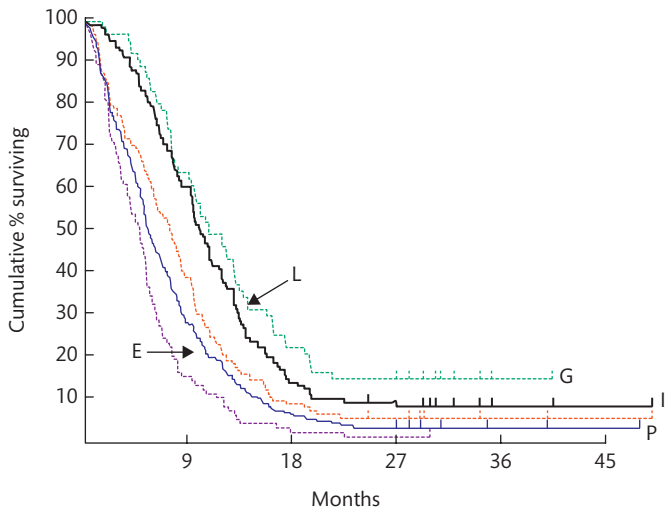


Fig. 18.19.1.15 Survival in small-cell lung cancer by prognostic factors (G, good; Im, intermediate; P, poor) compared to full staging (L, limited; E, extensive disease).

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 recommend 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 irradiation given at the end of chemotherapy will delay the presentation of cerebral metastases and also reduce their overall incidence. This is important, as the development of cerebral disease is associated 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 chemotherapy 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 response 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 experience 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 universally 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 disease 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 responds as well as any presentation to chemotherapy.

Intensity of treatment

Intensifying the dosage or the frequency of administration of cytotoxic 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 combinations of drugs, but these more complicated regimens have not been rewarding either. Similarly, the use of colony growth stimulation 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 adversely affecting survival have shown that six courses of combination 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 alleviate 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 production 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 suitable as a palliative treatment in central tumours occluding large airways: removal of considerable quantities of tumour can be achieved in a single treatment session with the rigid instrument. Trials are in progress assessing the additional benefits of endobronchial radiotherapy

(brachytherapy) using iridium or caesium wires delivered via the video bronchoscope. This procedure irradiates endobronchial tumour to a circumferential depth of about 1 cm, and will often produce a further remission. It is used where further external-beam radiotherapy 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, recurrent 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 patients 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 radiotherapy to prevent severe steroid-induced myopathy, especially in patients 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 metastases involving the liver capsule.

Pain and hypercalcaemia from bone metastases can be particularly challenging to control. Bisphosphonates are commonly used for palliation in this setting. Denosumab, a human monoclonal antibody that targets bone remodelling, has also been approved by NICE for use in patients with lung cancer and bone metastases. Early evidence 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 organizations, 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 tobacco use and encourage uptake in younger people. The role of electronic 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 radiography 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 radiography. The older the subjects screened, the greater the smoking history and the presence of airways obstruction, the higher the incidence 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% reduction 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 individual for lung cancer is elderly, poorly educated and risk averse, and unlikely to participate in a screening trial. However, other randomized 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 require 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 confidence 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 implementation 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 prediction tools to individuals, combined with smoking cessation, may make CT screening more palatable to healthcare systems if they can maximize cost-effectiveness.

Other primary lung tumours

The slow-growing intrabronchial lesions previously grouped under the heading of bronchial adenoma have now been reclassified 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 carcinoma 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 potentially 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, particularly liver and brain, in about 10%. They are occasionally located 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 before symptoms develop. In the few cases that have extensive liver secondaries, there may be the classical symptom pattern of intermittent 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 appearing 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.

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18.19.2 Pulmonary metastases

S.G. Spiro

ESSENTIALS

Malignant metastasis to the lung is common. It may present as a solitary enlarging nodule, as multiple nodules ranging enormously in size and number, and/or with diffuse lymphatic involvement. Diagnosis can usually be secured by percutaneous CT-guided biopsy and most suspicious lesions will be PET positive. Surgical excision may prolong survival or result in cure in some cases.

Introduction

Malignant metastasis to the lung is common because of the lung's rich blood supply, and may present as a solitary enlarging nodule, as multiple nodules, or with diffuse lymphatic involvement.

Surgical metastasectomy

In all patients, before resection is attempted, the patient needs to be assessed as fit for lung resection, the primary tumour site should be controlled, and all metastatic disease must be considered removable. More than one attempt at excision is possible.

Solitary metastases

About 10% of all round pulmonary lesions are metastases, but some 70% of round lesions occur in patients with a known malignancy. Colorectal cancer is reported to be the commonest tumour of origin. Diagnosis can usually be secured by percutaneous CT-guided biopsy, often preceded by a staging PET scan, where the lesion is most likely to be positive. In many cases, surgical excision may prolong survival and result in cure in some, depending on the state of the primary tumour and the likelihood of other occult metastases. Surgery is sometimes recommended after successful control of the disease with chemotherapy, or if any residual tissues become PET negative.

Routine follow-up with CT scanning has revealed an increasing number of clinically well patients deemed clear of disease at their primary site, but with distant pulmonary metastases. Usually such disease is caught at an early stage of recurrence, is of low volume, and can be resected relatively easily, usually thoracoscopically. However, if the new lesion appears solitary, the possibility of a second primary (i.e. a lung cancer), needs to be considered before resection.

Multiple metastases

Multiple metastases may range considerably in size and number, from cannon balls to multiple lesions of varying size, down to miliary shadowing, which may be accompanied by hilar lymphadenopathy or pleural effusion. Breast, colon, renal cancers, melanoma, and lung primaries are the commonest underlying tumours, but other tumours amenable to chemotherapy occur, such as testicular cancer, choriocarcinoma, and also sarcomas. Diagnosis may be achieved by cytology or histology on various samples from the pleura or lung and can occasionally be made from cytology of expectorated or induced sputum. Tumours that are suitable for chemotherapy (e.g. choriocarcinoma) or endocrine manipulation (e.g. breast) need to be recognized. Solitary or multiple Kaposi's sarcoma is a feature of AIDS and can involve the bronchi and pleura as well as lung tissue.

Table 18.19.2.1 Five-year survival following resection of pulmonary metastases according to primary tumour type

Tumour type	5-year survival (%)
Soft tissue sarcoma	25
Osteogenic sarcoma	20–40
Colon/rectal carcinoma	8–37
Renal cell carcinoma	13–50
Breast carcinoma	14–49
Head/neck carcinoma	40–50
Melanoma	25

Resection remains the treatment of choice, and good prognostic factors include the time from treatment of the primary tumour to the development of lung metastases, the fewer the number, the absence of extrapulmonary metastases, and the longer the tumour doubling time. The most favourable group are younger patients with a good performance status, with sarcomas who present with lesions a year or more after successful treatment of the primary disease. Factors including older age, male sex, and more lung metastases predict poorer survival after resection of any initial pulmonary metastases. The number of lung metastases present at a first metastasectomy and the preoperative interval predict recurrence in the lung.

Survival following surgical excision is summarized in Table 18.19.2.1. In a study of recurrent lung metastases after excision of colorectal cancer, which is the commonest type of cancer in clinical reports of surgical metastasectomy, the overall median survival from second lung metastasectomy was 70 months.

Other techniques

Other techniques to remove pulmonary metastases include radio- or microwave ablation. This can achieve high ablation rates (>70%) and is usually most effective in lesions of 3 cm diameter or less. Two year survival rates of about 75% are common. The commonest complication is pneumothorax (<10%), with a very occasional need for an intercostal drain. Pulmonary haemorrhage is also a significant risk at about 5%.

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18.19.3 Pleural tumours

Y.C. Gary Lee

ESSENTIALS

Benign tumours are rare in the pleural cavity, with solitary fibrous tumour of the pleura the most frequent of these rarities.

Malignant pleural tumours are common and can arise from the pleura (most commonly mesothelioma) or as metastases from extrapleural malignancies (especially lung and breast cancer). They typically present with breathlessness, chest pain, and a pleural effusion. Diagnosis requires histocytological confirmation of malignant cells from pleural fluid and/or pleural biopsies.

Mesothelioma—most cases are due to asbestos exposure, characteristically after a latent period of more than 20 years, with risk related to the duration and intensity of asbestos exposure and the fibre type (worst with needle-like amphiboles). The condition is incurable, with overall median survival of about 9 months. Care involves control of pain and pleural effusion, chemotherapy with pemetrexed, cisplatin and bevacizumab, and radiotherapy for symptom palliation. Recent randomized trials did not show benefits of radical resection.

Metastatic pleural malignancy—most tumours that have spread to the pleura are incurable. For tumours that are highly responsive to chemotherapy (e.g. lymphoma or small cell carcinoma) treatment may control pleural fluid re-accumulation. Definitive treatment for fluid control (e.g. talc pleurodesis) should be performed in patients with symptomatic recurrence of malignant pleural effusions. Randomized trials did not find significant differences in efficacy whether talc is delivered by thoracoscopic poudrage or as a slurry. Indwelling pleural catheters provide an effective alternative to pleurodesis or when the latter fails. Surgical pleurodesis may be considered in selected patients.

Introduction

Pleural malignancies can arise as primary tumours from the pleura (mostly mesotheliomas) or as metastases from extrapleural cancers (especially lung, breast, and ovarian carcinomas). Malignant pleural effusion affects about 660 patients per million population annually, and account for up to 50% of exudative effusions. Relatively little research has been performed on the best management for malignant effusions, and a recent worldwide survey of 859 respiratory specialists identified marked differences in clinical practice.

Benign pleural tumours

Benign tumours are relatively rare in the pleural cavity, with solitary fibrous tumour of the pleura the most frequent of these rarities. Asbestos pleural thickening (e.g. plaques and round atelectasis) are discussed elsewhere (see Chapter 18.17). Extrapleural fat can occasionally mimic malignant pleural thickening, especially in obese patients. Pleural lipoma is a rare entity of little clinical significance.

Solitary fibrous tumour of the pleura

Solitary fibrous tumour of the pleura (SFTP) accounts for less than 5% of all pleural tumours. It has also been called 'localized fibrous mesothelioma', 'benign mesothelioma' or 'pleural fibroma'. The aetiology is unknown: there is no established relationship with asbestos or tobacco exposure. It affects both sexes equally and can affect patients of all ages. The tumour arises from mesenchymal cells, usually from the visceral pleura.

Symptoms and effusions are uncommon. Cough, chest pain, or dyspnoea is relatively mild, even if present. Hypertrophic pulmonary osteoarthropathy affects around 20% of patients, and intermittent hypoglycaemia due to tumour secreted insulin-like growth factor is reported. SFTPs are often huge when discovered (>10 cm in 50% of cases in one series—**Fig. 18.19.3.1**) and can be pedunculated (more common) or sessile. CT scanning usually reveals a well-encapsulated, lobulated mass showing heterogeneous attenuation, but there are no pathognomonic findings on imaging. The condition is usually amendable to surgery.

Most SFTPs (*c.*80%) are benign with good long-term prognosis after resection. Malignant SFTPs do occur, the diagnosis usually being based on histological findings (hypercellular clusters, high mitotic activity, and infiltrations) but not on clinical or radiological findings. Recurrence after resection occurs at a rate of 2–8% in benign SFTPs, but up to 63% in malignant variants, and patients with malignant sessile SFTPs have a 30% mortality at 2 years. The role of neoadjuvant or postoperative chemotherapy has not been established.

Mesothelioma

Malignant pleural mesothelioma kills up to 3000 patients in the United Kingdom a year. An estimated 250 000 deaths from mesothelioma are expected in western Europe alone over these three decades. Asbestos mining and its global uses are still increasing, especially in developing countries where regulation is poor. A significant rise of the global incidence of mesothelioma in the coming decades has been predicted.

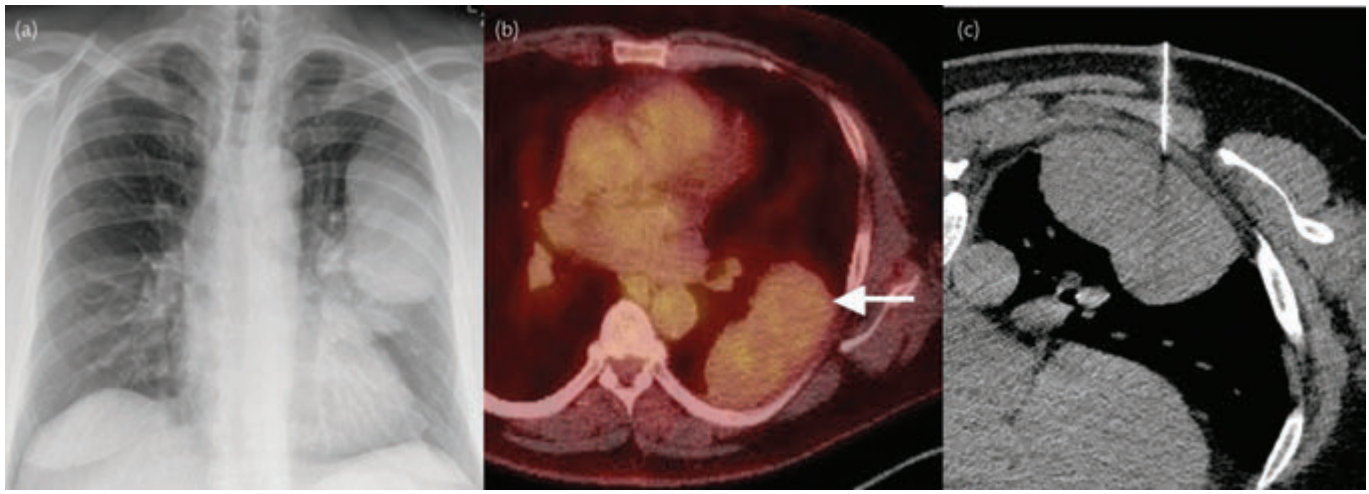

Fig. 18.19.3.1 Solitary fibrous tumour. The chest radiograph (a) of a 56-year-old man with a persistent cough shows a large lobulated opacity in the left hemithorax. Computed tomography (CT) and positron emission tomography (b) showed a 10.8 cm solid pleural-based mass (arrow) with heterogeneous low-grade fluorine-18 fluorodeoxyglucose (FDG) uptake, involving the left lower lobe and invading across the oblique fissure to involve the left upper lobe. CT-guided core biopsy of the mass (c) showed features consistent with a solitary fibrous tumour, which was subsequently resected.

Aetiology

Asbestos exposure

Most mesotheliomas are due to asbestos exposure, characteristically after a long latent period (>20 years in 96% of patients). Most (>90%) mesothelioma arises from the pleura, occasionally from the peritoneum, and rarely from the pericardium and tunica vaginalis of the testis.

The risk of mesothelioma is related to the duration and intensity of asbestos exposure and the fibre type. Workers involved in the mining and processing of asbestos, and those using end-products of asbestos for insulation (e.g. plumbers and builders), are at obvious risk of developing mesothelioma, but family members of asbestos workers are also at increased risk from asbestos fibres brought home on work clothes. Home renovation that disrupts asbestos material used in old buildings are now increasingly recognized as a common source of exposure.

The risk of developing mesothelioma depends on the physical characteristics of the inhaled asbestos fibres. Needle-like amphibole fibres—for example, crocidolite (blue asbestos), amosite (brown asbestos), anthophyllite, tremolite, and actinolite—are eliminated slowly from the lungs (half-life >7 years) and carry the highest risks. Serpentine fibres— for example, chrysotile (white asbestos)—are cleared more rapidly as they are curly, more soluble, prone to fragment, and are less oncogenic than amphiboles.

The oncogenic mechanism(s) of asbestos is poorly understood, but involves DNA damage, alteration of cell-cycle check points, chromosomal rearrangement/loss, altered expression of cytokine mediators, and dysregulation of apoptosis pathways.

There are currently no means to identify which people exposed to asbestos are likely to develop mesothelioma. Recent research efforts have concentrated on identifying screening tests for early mesothelioma, but serum levels of soluble mesothelin, the most studied biomarker for this purpose, still have inadequate sensitivity to be used as clinically as a screening tool for the asbestos-exposed population.

Other causes

Erionite, a naturally occurring mineral found mainly in Turkey, induces pleuropulmonary diseases similar to asbestos and including mesothelioma. Mesothelioma is not linked with prior thoracic irradiation (e.g. for Hodgkin's lymphoma), or with smoking. Simian virus 40 (SV40) can induce pleural, peritoneal, and pericardial mesotheliomas in experimental animals, but epidemiological studies do not support a causal link in humans. There is increasing preclinical evidence that carbon nanotubes can induce significant damage to the mesothelium and predispose to mesothelioma, although this has yet to be proven in humans.

No definite cause can be identified in up to 20% of patients with mesothelioma.

Pathology

Mesothelioma typically spreads in a diffuse sheet-like manner, beginning in the parietal pleura followed by visceral pleural involvement. The latter often results in encasement of the underlying lung (**Figs. 18.19.3.2** and **18.19.3.3**). As mesothelioma progresses it can infiltrate surrounding structures including the ipsilateral lung, chest wall, mediastinum, and later the contralateral pleural cavity and peritoneum. The gross appearance is often indistinguishable from pleural metastatic carcinoma. Spread to regional lymph nodes is common, but clinically significant distant metastases are infrequent, although at autopsy 60% of patients have extrathoracic metastases.

The common histological subtypes of malignant mesothelioma are epithelioid (60% of cases), sarcomatoid (10%), and biphasic with components of both (30%). Median survival is worse in patients with the sarcomatoid variant (<6 months) than in the epithelioid

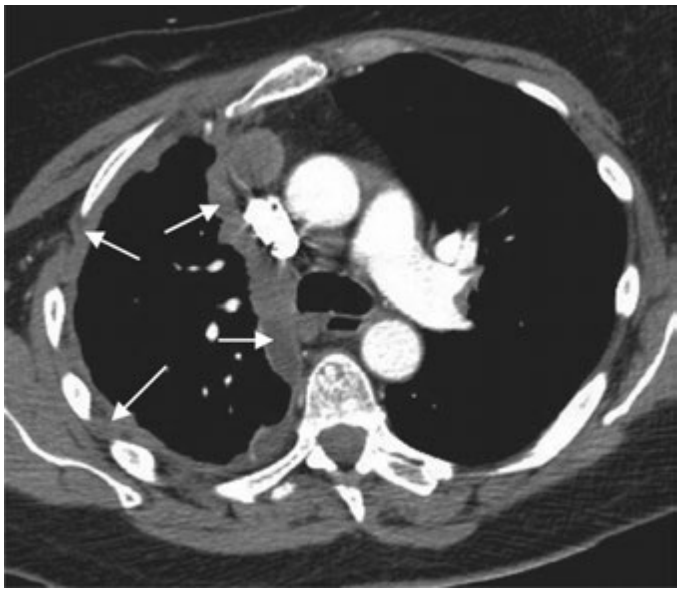

Fig. 18.19.3.2 A patient with advanced right pleural mesothelioma: CT scan showed a thick rind of tumour encasing the lung (arrows), with resultant shrinking of the ipsilateral hemithorax.

type (12 months). Desmoplastic mesothelioma is a rare (<1%) variant that histologically mimics benign fibrous tissue.

Clinical features and diagnosis

Pleural effusion and the associated dyspnoea and/or chest pain are the commonest presentations. Most (95%) patients have a pleural effusion at least sometime during their disease course.

Constitutional symptoms, especially weight loss and lethargy, are common (*c.* 30%) at presentation and increasingly so as the cancer advances. Tumour fever can occur and is difficult to distinguish from infection. Involvement of other (mainly intrathoracic) structures may result in pericardial effusion/arrhythmia, dysphagia, Horner's syndrome, spinal cord compression (**Fig. 18.19.3.4**) or superior vena cava obstruction. Distant metastases (e.g. cerebral involvement) are late events.

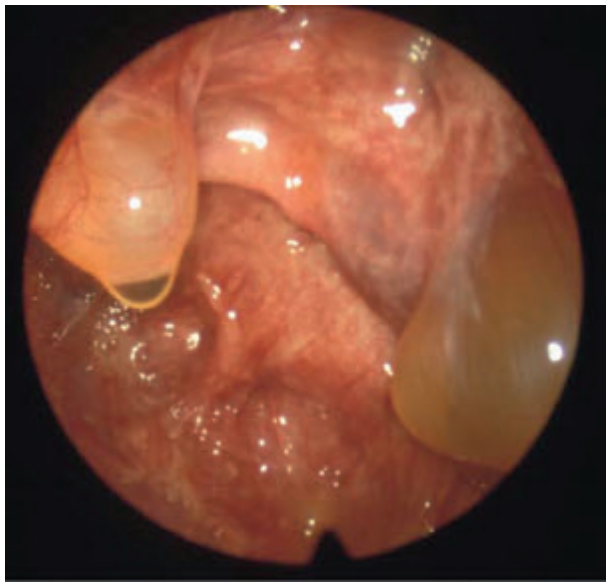

Fig. 18.19.3.3 Thoracoscopic view of pleural mesothelioma on the parietal pleural surface.

The diagnosis of pleural mesothelioma usually arises from the investigation of undiagnosed pleural effusion (see Chapter 18.17).

Biomarkers for mesothelioma

Much recent research has focused on discovering biomarkers for mesothelioma. Patients with mesothelioma have an elevated mesothelin level in their serum and pleural fluid when compared with patients with other pleural cancers or benign pleuritis. However, the sensitivity and specificity of mesothelin are insufficient to allow it as a standalone diagnostic test. In patients with equivocal histocytologic results or who are unsuitable for diagnostic interventions, an elevated mesothelin level may contribute to the clinical-radiologic-histologic diagnosis in a multidisciplinary tumour board setting. Elevated serum mesothelin can occur in occasional carcinomas, and in patients with renal failure. Conversely, sarcomatoid mesotheliomas rarely overexpress mesothelin. Other biomarkers (fibulin-3, osteopontin, megakaryocyte potentiating factor, and so on) have shown promise but their roles as biomarkers have not been as thoroughly scrutinized as mesothelin.

Prognosis

The overall median survival for malignant pleural mesothelioma is about 9 months. Good performance status and epithelioid histology are associated with better survival. Rarely isolated cases of long survivors (e.g. over 10 years) have been reported.

There are several staging systems (e.g. International Mesothelioma Interest Group classification), and early-stage disease (e.g. limited to parietal pleura) carries better prognosis. Disease response in research settings are usually monitored by the modified RECIST criteria. Total glycolytic volume measurements on PET and mesothelin levels before and after chemotherapy also have predictive values on survival.

Management

Mesothelioma is incurable despite the use of surgery, chemotherapy, radiotherapy, or their combinations. Specific antifolate/cisplatin chemotherapies are the only treatment to have shown survival benefits, albeit for about 12 weeks. Management should therefore aim to improve quality of life. The use of a multidisciplinary palliative care team experienced in mesothelioma is recommended, as the clinical course of mesothelioma differs from other solitary tumours. Patients often pursue legal claims for compensation, which can create additional stress.

Pain control

Most patients eventually experience pain and dyspnoea, and early use of opioids is required. Radiotherapy is effective for localized pain (e.g. from bone erosion) and needle tract metastases. Invasive pain control techniques with indwelling epidural catheters and spinal cordotomy are sometimes needed.

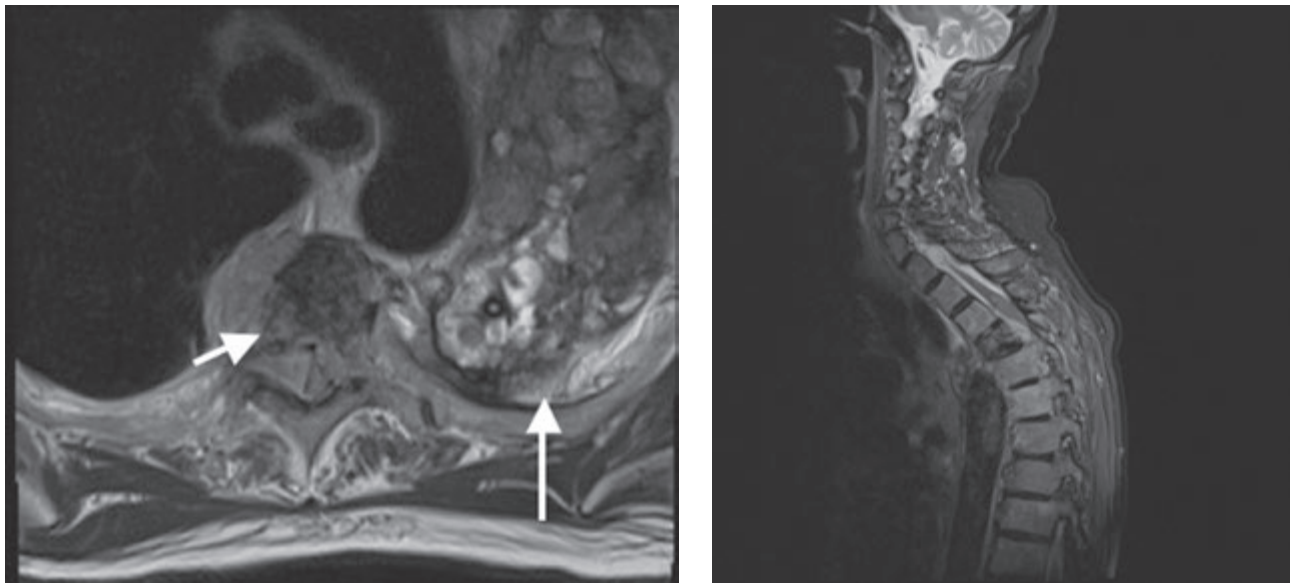

Fig. 18.19.3.4 Spinal cord compression in mesothelioma. This 80-year-old patient with known malignant pleural mesothelioma presented with back pain, paraplegia, and urinary retention. (a) Magnetic resonance imaging of the spine shows tumour (short arrow) encasing the upper thoracic spinal cord resulting in severe canal stenosis and cord compression. (b) Malignant pleural disease is demonstrated by high signal intensity on the T2-weighted image.

Pleural fluid control

Recurrent effusions (and dyspnoea) are a key problem for most patients with mesothelioma. In a series of 390 patients, 42% required further treatment to control fluid re-accumulation. Pleurodesis (either as surgical approach or talc slurry) was effective in two-third of patients and avoid further pleural intervention. However, pleurodesis is not useful when tumour has encased the visceral pleura, preventing lung expansion ('trapped lung', Fig. 18.19.3.5) and prohibiting apposition of the pleural surfaces. An indwelling pleural catheter is an increasingly used alternative and allows domiciliary pleural fluid drainage (Fig. 18.19.3.6)—see also under 'Metastatic pleural malignancy'.

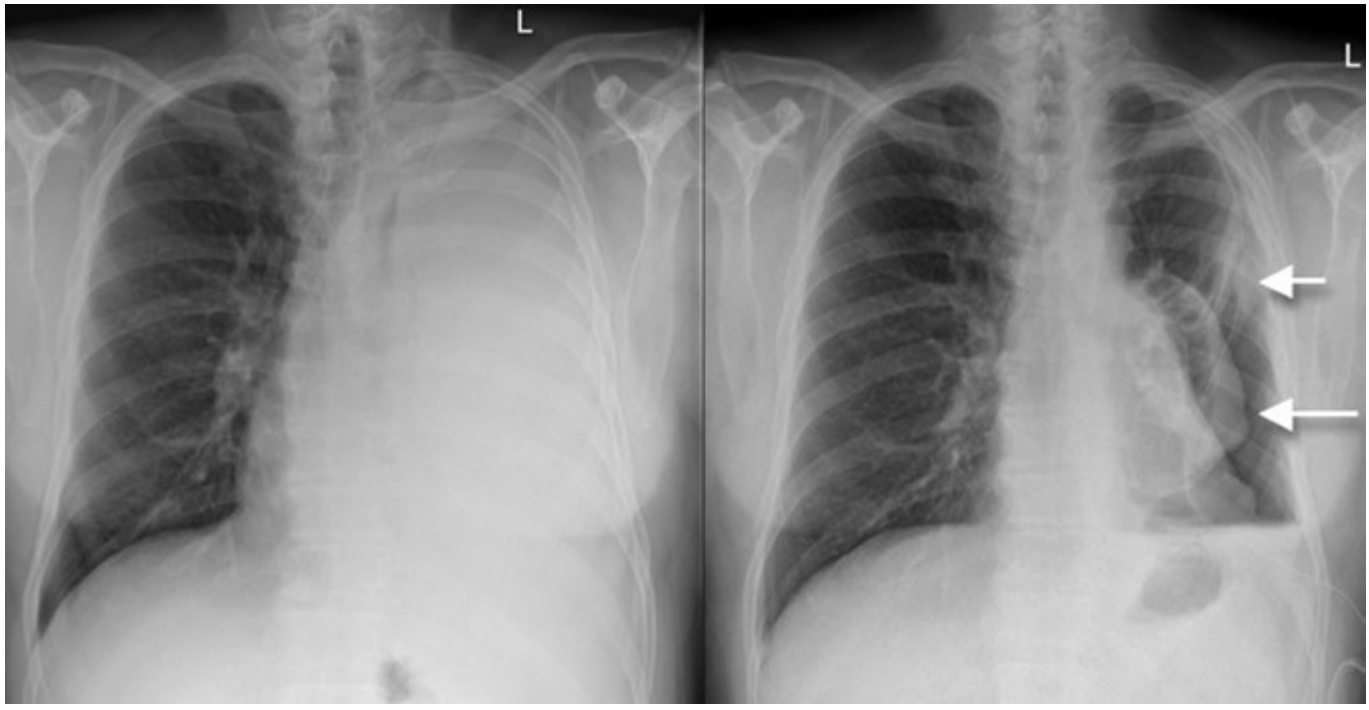

Fig. 18.19.3.5 Trapped lung. This 60-year-old man with mesothelioma underwent insertion of an indwelling pleural catheter for management of his large symptomatic malignant pleural effusion (left panel). Trapped lung was suspected prior to effusion drainage because of the absence of mediastinal shift away from the side of the large effusion. The lung failed to fully expand after fluid evacuation (right panel). The presence of visceral pleural thickening further supports the diagnosis of a trapped lung.

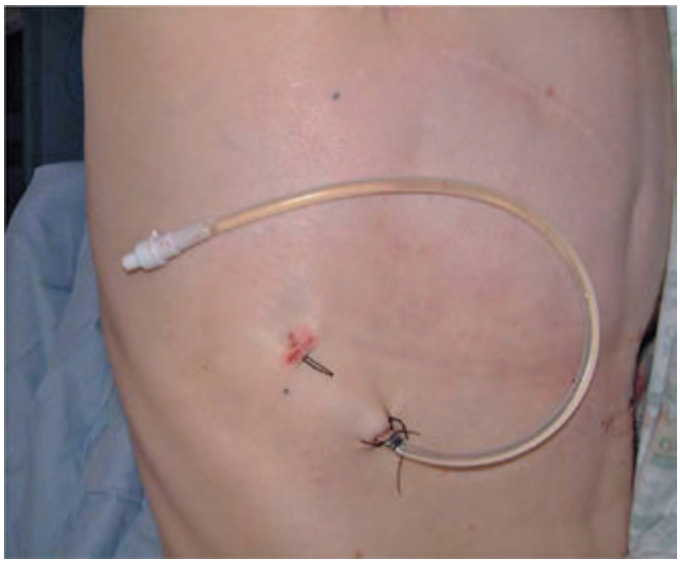

Fig. 18.19.3.6 An indwelling pleural catheter in a patient with recurrent pleural effusions.

Chemotherapy

Mesothelioma is relatively resistant to common chemotherapeutic agents and drug penetration to the pleura and underlying tissues is variable. Palliative chemotherapy using cisplatin with either pemetrexed or raltitrexed (antifolate agents) can improve symptoms and prolong median survival by 2.8 months in mesothelioma.

Radiotherapy

Radiotherapy has been tried with curative intent, but the disease area to be covered is too large and the resulting radiation toxicity (to the underlying heart, liver, and so on) unacceptable. Intensity-modulated radiotherapy is under investigation.

Radiotherapy however has an established role in symptom palliation, with about 60 to 80% of patients experiencing improvement in specific tumour-related complications, although it does not prolong survival. Radiotherapy is often used in compression of the oesophagus, superior vena cava, and spinal cord, though clinical response is variable.

Mesothelioma can invade sites of pleural procedures (Fig. 18.19.3.7), but the reported incidence varies among studies. Three (small) randomized studies on the use of prophylactic radiotherapy have shown conflicting results. Longitudinal series have revealed that the risks of needle track metastases are related to the size of the pleural procedures (with needle aspiration the lowest and thoracotomy the highest). All efforts should be taken to minimize the number of pleural procedures in patients with possible mesothelioma to minimize the frequency of unpleasant chest wall tumour invasion. A recent multicentred randomized trial did not find a role for routine prophylactic radiotherapy after large bore pleural interventions such as chest drain/thoracoscopy.

Surgery and multimodality treatment

Mesothelioma spreads along serosal surfaces and infiltrates underlying structures instead of growing as a discrete mass; hence complete surgical resection is not feasible.

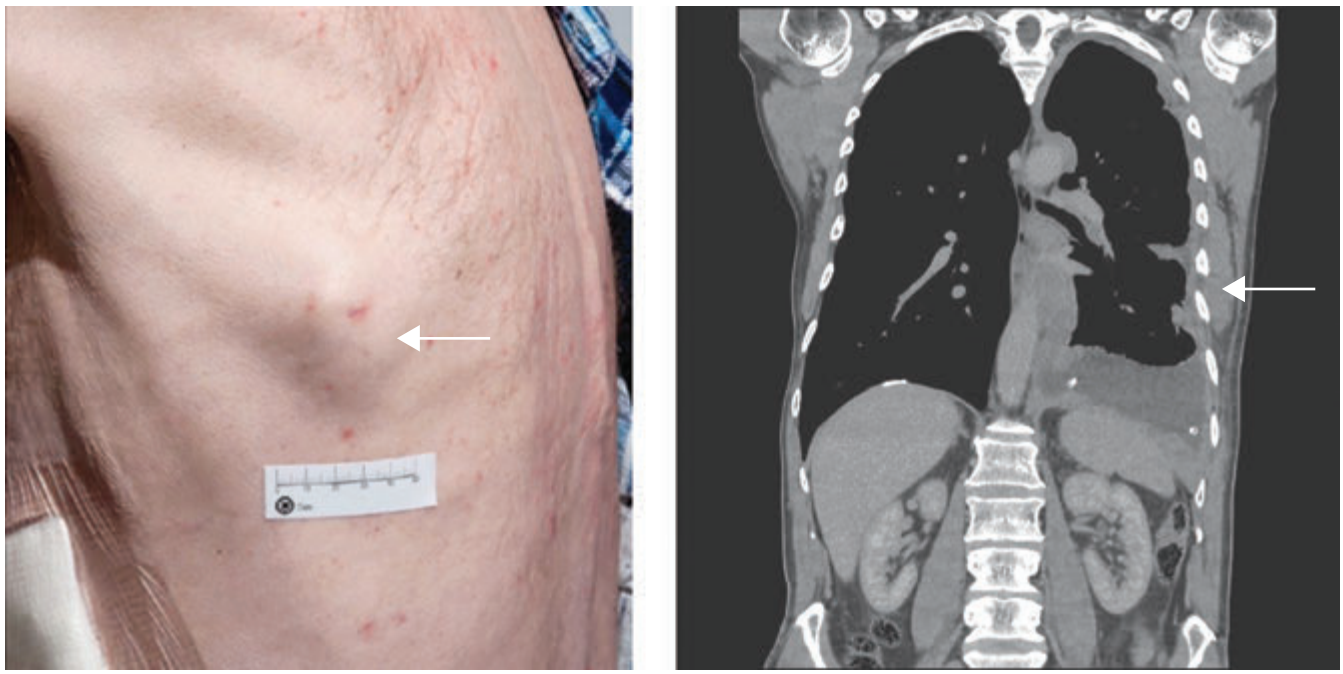

Fig. 18.19.3.7 Needle tract metastases in malignant pleural mesothelioma. This patient with mesothelioma developed a painful lump on the posterolateral chest wall (left panel, arrow) along the needle tract of a previous thoracentesis which was confirmed on CT imaging (right panel, arrow). The CT also revealed tumour involvement of the left hemidiaphragm and an indwelling pleural catheter *in situ* for management of his recurrent malignant pleural effusion.

Radical surgery to provide tumour cytoreduction has been attempted in combination with adjuvant radiotherapy and chemotherapy. Extrapleural pneumonectomy (EPP) and pleurectomy with decortication (P/D) are the two commonest approaches practised.

EPP involves removal of the entire lung, parietal pleura, pericardium, diaphragm, and mediastinal lymph nodes. EPP carries significant mortality (5–10% from surgery alone) and morbidity (>25% life-threatening complications). A randomized clinical trial has now confirmed that patients who underwent EPP had a significantly shorter median survival than those who were randomized not to have EPP (14 vs. 19 months, respectively). Two studies have shown that EPP significantly impaired quality of life.

P/D is an alternative debulking procedure which does not involve pneumonectomy. It failed to show any survival benefit in a recent multicentre, randomized trial but increased postoperative complication when compared with talc pleurodesis.

Metastatic pleural malignancy

Most cancers can spread to the pleura resulting in a pleural effusion and associated dyspnoea. Up to 30% of patients with lung and breast carcinomas (Fig. 18.19.3.8) and 10% of those with lymphoma will suffer from a malignant effusion. Ovarian and colon carcinomas as well as adenocarcinomas from unknown primary site also occur.

Metastatic malignant disease may follow direct spread or haematogenous embolization of tumour to the peripheral lung parenchyma, followed by visceral pleural invasion. The parietal pleura is assumed to be secondarily affected by shedding of malignant cells from the visceral pleura, or from tumour migration via adhesions. Pleural involvement from direct cancer invasion (e.g. from breast cancer) or haematogenous spread can also occur.

In lung cancer, the presence of malignant involvement of the pleura often denotes more advanced staging and prohibits curative surgery. The importance of pleural involvement in lung cancer has attracted strong interests. The latest TNM staging for non-small cell lung cancer included a classification of visceral pleural invasion (VPI). VPI denotes poorer prognosis in lung cancer patients who undergo resection. Also, in *c*.5% of lung cancer patients undergoing surgery, tumour cells can be detected if a pleural lavage is performed during the operation. A positive lavage predicts a higher risk of cancer recurrence and poorer prognosis (median survival 12 months, vs. 49 months for those with a negative lavage).

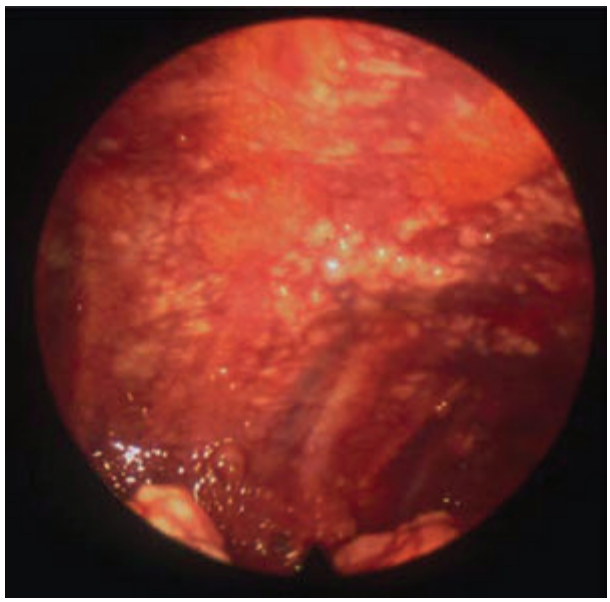

Fig. 18.19.3.8 Thoracoscopy showing scattered tumour from metastatic breast carcinoma on the parietal pleural surface.

Malignant effusions develop primarily as a result of increased vascular permeability and resulting plasma leakage. Reduced pleural fluid outflow, secondary to tumour blockage of parietal pleural stomata and/or the downstream lymphatic drainage pathways, also contributes.

Clinical features

Dyspnoea results from altered respiratory mechanics when the pleural cavity expands to accommodate the extra (often litres) volume of fluid. The weight of large effusions often everts the diaphragm and may result in its paradoxical movements. Small malignant effusions can be asymptomatic. Underlying lung disease (e.g. lymphangitis, airway obstruction, comorbid chronic obstructive pulmonary disease, or pulmonary embolus) and extrapulmonary causes (e.g. pericardial effusion or anaemia) often contributes to breathlessness and must not be overlooked.

Pleuritic pain is common and implies malignant infiltration of the parietal pleura, as the visceral pleura is devoid of pain sensation.

Diagnosis

The diagnosis of malignant pleural metastases should be made by histological or cytological assessment of pleural fluid or pleural tissue samples (see Chapter 18.17). Clinical assessment, radiological appearances (e.g. on CT or PET) or tumour marker measurements cannot provide a definitive diagnosis. Imaging can, however, guide biopsy and improve yield. It is important to obtain a histocytological diagnosis of the type of malignancy (e.g. between mesothelioma and metastatic carcinoma): this alters treatment strategies and has prognostic implications.

Management

A tumour that has spread to the pleura is incurable in most cases. Surgery and radiotherapy are unable to eradicate pleural metastases. In patients whose primary tumour is highly responsive to chemotherapy (e.g. lymphoma or small cell carcinoma), treatment may control the pleural effusion, but most cases of malignant effusion are not responsive to chemotherapy.

Indications for pleurodesis

If the patient is symptomatic from a malignant effusion, drainage is required and consideration should be given to attempts to prevent fluid re-accumulation. The conventional strategy is to create pleurodesis—the adherence of the parietal and visceral pleura—either surgically or by introducing a chemical agent. This can be achieved in about 70% of cases, although reported success rates vary markedly with the agents employed, clinical methods, and definitions of success. No clinical or biochemical markers reliably predict the outcome of pleurodesis in individual patients, but a low pleural

fluid pH (<7.20) or glucose (<1 mmol/litre) is associated with a lower pleurodesis success rate and shorter survivals.

Many breathless patients with a malignant effusion do not gain significant benefit after pleural fluid drainage: pleurodesis should be considered only in those who do. The presence of a trapped lung is a relative contraindication to pleurodesis as poor apposition of the pleural surfaces will render pleurodesis ineffective.

Pleurodesis should be reserved for patients with good short-term prognosis (arbitrarily defined as expected survival >3 months) although predicting survival in individual patients is notoriously difficult. The LENT score has been shown to help predict survival in malignant effusion patients: high pleural fluid ***L***DH, poor ***E***COG performance status, high ***N***eutrophil:Lymphocyte ratio in blood, and ***t***umour types predict prognosis.

There are no controlled studies that define the best timing of pleurodesis, with most physicians recommending the procedure when the patient has had one or more episode of fluid recurrence. An alternative approach is to attempt pleurodesis of large effusions when they first present, as the recurrence rate is high (>70%) and early pleurodesis, before trapped lung ensues, may be more successful. This strategy avoids some episodes of unpleasant dyspnoea as fluid recurs.

Pleurodesis produces adherence of the pleural surfaces by provoking acute pleural injury, which results in pleural inflammation. If the inflammatory process is sufficiently intense, chronic inflammation and fibrosis ensues, resulting in pleural adhesions and eventual obliteration of the pleural cavity (successful pleurodesis). This process is often painful, as the parietal pleura is heavily infiltrated by sensory nerves. It is probable that the more intense the induced pleural inflammation, the higher the likelihood of success, but at the expense of producing more pain and distress to the patient.

Methods of pleurodesis

Pleurodesis can be performed by various surgical means (e.g. abrasion of the pleura or pleurectomy). A thoracoscopic approach is preferred to thoracotomy. Alternatively, pleurodesis agents can be delivered intrapleurally via a chest tube when complete lung re-expansion is confirmed on radiographs following drainage of effusions.

The most commonly used agent worldwide is talc, followed by tetracycline/doxycycline/minocycline, and bleomycin, though other agents (e.g. iodopovidone, silver nitrate, and picibanil (OK432)) have also been employed. A meta-analysis of 11 studies showed that talc is superior in efficacy to tetracycline and bleomycin.

Talc can be delivered via a chest tube (as a slurry) or insufflated (as a poudrage) during thoracoscopy. Three published randomized trials have found no significant differences in their success rates. If a patient undergoes thoracoscopy for diagnostic purposes, talc poudrage can be performed at the same setting, otherwise pleurodesis can be performed by either talc slurry or poudrage, depending on availability, in patients with an established diagnosis.

Pain is the most common side effect of pleurodesis, and narcotic analgesics and/or conscious sedation (e.g. midazolam) should be used where possible. Rotation of the patient does not improve the success rates of pleurodesis. In animal studies, systemic corticosteroids and heparin can significantly reduce effective pleurodesis by inhibiting pleural inflammation and the coagulation cascade respectively; their relevance in humans is unknown.

Talc pleurodesis toxicity

Talc can induce fever and pain, which usually subsides within 72 h. Systemic absorption of talc particles and embolization to distant organs have also been reported if preparations containing small talc particles (<10 μm) is used. Marked systemic and pulmonary inflammation with resultant hypoxaemia can occur, presumably from systemic absorption of small talc particles. Talc-related adult respiratory distress syndrome (ARDS) occurred in 6% of patients and caused the death of 2.3% in a study of 484 patients. Talc-related ARDS can occur with either talc poudrage or slurry, and with doses from 2 to 10 g, but no cases of the condition were observed in a study of over 550 patients in which a graded talc preparation (with median particle size >20 μm) was used—though even in this study patients had a higher oxygen requirement after the pleurodesis.

Recurrent pleural effusions

For patients where pleurodesis fails, another attempt with a different agent, implantation of an indwelling pleural catheter (IPC), pleuroperitoneal shunting, serial therapeutic thoracentesis, or a surgical pleurodesis are possible. Repeated thoracenteses combined with narcotics and oxygen are appropriate when a very short life expectancy (<2 weeks) is likely. A pleuroperitoneal shunt is contraindicated in the presence of ascites.

Indwelling pleural catheters

IPCs are increasingly used for ambulatory drainage of recurrent (especially malignant) pleural and peritoneal effusions, allowing patients to perform fluid drainage when symptoms arise (**Fig. 18.19.3.6**). Spontaneous pleurodesis can occur in up to 50% of patients (who do not have a trapped lung) over time.

IPC is accepted as the preferred treatment in patients who failed pleurodesis or have a trapped lung. Increasingly, it is used as an alternative to talc pleurodesis as the first choice of definitive therapy for recurrent effusions. A recent randomized trial suggested that IPC provides equally good improvement in quality of life and symptomatic relief when compared with talc pleurodesis.

IPC insertion can be performed on an outpatient basis and requires significantly shorter hospital stay than pleurodesis, as shown in two randomized studies. A pilot, nonrandomized study showed that patients treated with IPC spent significantly fewer days in hospital than those pleurodesed in their remaining lifespan. This observation has recently been validated in a multicentred trial.

It is important that patients fitted with an IPC be provided with sufficient aftercare. The adverse event rates associated with IPC use are low, as shown in large longitudinal series. Infection, often the major concern from clinicians, occurs in *c*.5% of patients and is generally mild and easily controlled with antibiotics. Interestingly infection (especially from *Staphylococcus aureus*) can induce pleurodesis in a significant proportion of patients, allowing removal of the IPC. Symptomatic loculation of the effusion can occur and may response at least in the short-term to intrapleural fibrinolytics. Catheter tract metastases develop most commonly in mesothelioma patients and can be treated with radiotherapy without removing the IPC beforehand.

Future developments

Current treatments for malignant pleural effusion are crude. Compounds such as iodine and silver nitrate have been used in some countries, as alternatives to talc, and have shown effectiveness with acceptable side effect profiles. The development of novel pleurodesis agents that induce fibrosis without pleural inflammation, for example, tumour growth factor-β (TGFβ), may allow effective pleurodesis without the adverse events associated with talc use. IPC and pleurodesis are approaches with completely different pros and cons; trials are underway to combine both strategies. Instilling talc via IPC inserted has shown benefits in a randomized trial. Placement of IPC in the same setting of thoracoscopic talc poudrage has shown promise. Sclerosant-eluded IPC produced effective pleurodesis in animal studies.

Direct inhibition of pleural fluid accumulation (via manipulation of vascular permeability mediators) may become possible, and will be preferable over interventional procedures of secondary prevention of fluid recurrence.

Studies to date have mostly considered malignant effusions as a single disease entity. Work is underway to better phenotype patients with malignant effusions to identify subgroups of patients who will benefit symptomatically from fluid drainage, and to tailor available therapies to patients with different underlying cancers, staging, effusion biology (e.g. rate of recurrence) and comorbidity. Patient-reported outcome measures are increasingly adopted as key measures of treatment outcome instead of radiological determination of fluid accumulation.

Acknowledgements

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18.19.4 Mediastinal tumours and cysts

Y.C. Gary Lee and Helen E. Davies

ESSENTIALS

Mediastinal masses are most conveniently categorized by their anatomical site in the anterior, middle, or posterior mediastinum.

Most present as a radiographic abnormality alone, or in association with symptoms arising from compression of other mediastinal structures. Systemic symptoms such as fever or weight loss are more likely with malignant tumours such as lymphomas or thymomas.

Anterior mediastinal masses—commonly caused by thymic tumours (including thymic lymphoma), germ cell tumours, and thyroid masses. Thymomas are often benign, but they can be locally invasive and associated with para-neoplastic phenomena such as myasthenia gravis (in 30%).

Middle mediastinal masses—most commonly caused by lymph node enlargement (e.g. secondary to carcinoma, lymphoma, sarcoidosis, tuberculosis, or histoplasmosis), bronchogenic carcinomas and cysts arising from mediastinal structures such as the pericardium, bronchi, or oesophagus. Giant follicular lymph node hyperplasia (Castleman's disease or angiofollicular lymphoid hyperplasia) is a rare condition; patients may present with symptoms secondary to compression of local structures or with constitutional features; frank malignant transformation may arise.

Posterior mediastinal masses—neurogenic tumours account for most; if benign they tend to be asymptomatic, while pressure effects are frequently seen with malignant tumours.

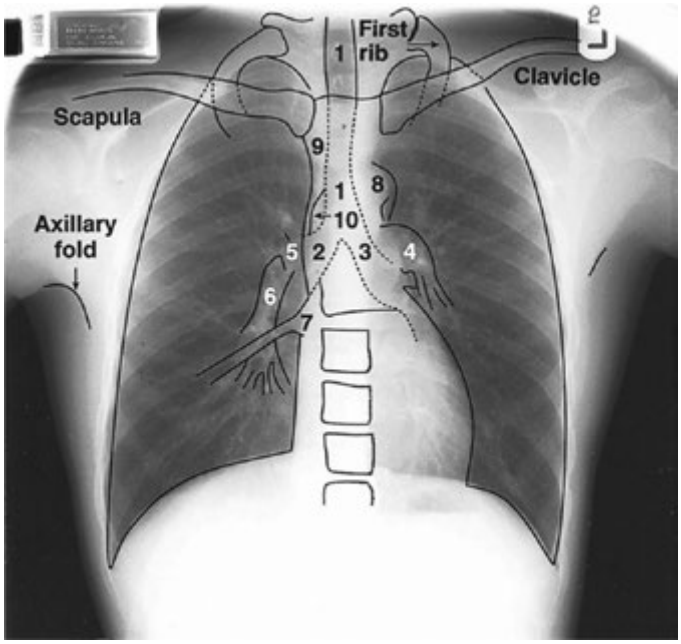

Fig. 18.19.4.1 Posteroanterior chest radiograph with diagrammatic overlay to illustrate normal mediastinal structures: (1) trachea, (2) right main bronchus, (3) left main bronchus, (4) left main pulmonary artery, (5) right upper lobe pulmonary vein, (6) right interlobular artery, (7) right lower and middle lobe vein, (8) aortic knuckle, (9) superior vena cava, (10) azygos vein.

Introduction and anatomy

The mediastinum encompasses all the intrathoracic structures with the exclusion of the lungs and pleura. It encompasses the heart, great vessels, trachea, oesophagus, thymus, nerves, thoracic duct, and lymph nodes. The superior boundary is the thoracic inlet represented by a plane at the level of the first rib. The inferior boundary is the diaphragm. The mediastinum has traditionally been subdivided into several compartments: a superior and inferior compartment, with the latter being subdivided into anterior, middle, and posterior divisions. In fact there are no true anatomical boundaries and structures in the superior mediastinum are contiguous with those inferiorly, hence a more logical subdivision is simply into anterior, middle, and posterior compartments (Figs 18.19.4.1 and 18.19.4.2). Such a division helps to compartmentalize what is complex anatomy and give some guide to the most likely pathology occurring in any particular area.

Detailed knowledge of normal mediastinal anatomy is a prerequisite to the interpretation of both normal and abnormal chest radiographs. It is not within the remit of this chapter to describe the anatomy in detail, but major structures can be identified on CT imaging.

- *Anterior mediastinum*: This is bounded anteriorly by the sternum and posteriorly by the pericardium, aorta, and brachiocephalic vessels. It contains the remnant of the thymus gland, branches of the internal mammary artery, veins, and associated lymph nodes.
- *Middle mediastinum*: This contains the heart and pericardium, ascending aorta, and aortic arch, lower half of the superior vena cava with azygos vein tributary, inferior vena cava, brachiocephalic vessels, pulmonary arteries and veins, bifurcation of the trachea and major bronchi, bronchial lymph nodes, phrenic nerves, and the vagus nerve.
- *Posterior mediastinum*: The area located behind the pericardium and in front of the vertebral bodies. It is bordered laterally by the mediastinal pleura. It contains structures in the paravertebral

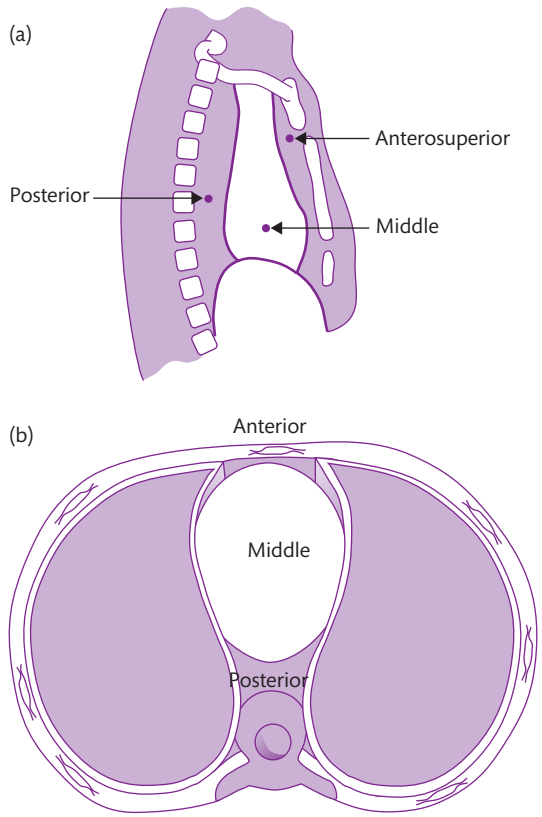

Fig. 18.19.4.2 A schematic representation of the mediastinal compartments: (a) lateral projection showing division into anterior (or anterosuperior), middle and posterior compartments; (b) cross-sectional depiction.

gutter as well as the descending thoracic aorta, oesophagus, azygos, and hemiazygos veins, thoracic duct, lymph nodes, and autonomic nerves.

Lymph nodes are present in all three compartments thereby knowledge of their anatomical relationships, together with sites of drainage, is important when interpreting radiographic mediastinal enlargement. The most important group of visceral nodes lie in the middle mediastinum and are predominantly subcarinal and paratracheal. Bronchopulmonary and hilar nodes are numerous but not visible radiographically unless pathologically enlarged.

Clinical investigation

Radiological assessment

Most mediastinal cysts and tumours are discovered incidentally following a chest radiograph. Occasionally there may be symptoms such as cough, chest pain, or breathlessness, or features resultant from compression of the numerous surrounding mediastinal structures.

CT imaging is the most appropriate subsequent investigation for any patient with a suspected mediastinal mass and frequently facilitates accurate diagnosis. It allows localization, characterization, and definition of the relationship of the mass to adjacent structures. The presence of calcification, fluid attenuation, heterogeneity, and vascularity can also be ascertained.

Radio-labelled ^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) combined with CT scanning (PET-CT) is increasingly used in the evaluation of mediastinal masses. It is a useful tool for predicting loco-regional involvement of lung or thyroid malignancies, and for detection of distant disease. False positives may result from inflammatory processes such as granulomatous disease.

MRI is more sensitive in the assessment of spinal tumours and detection of neural or vascular invasion than CT and may be favoured in some patients due to the lower adherent radiation dose.

Tissue sampling

Fine needle aspiration sampling is of limited use in assessment of mediastinal abnormalities and histological confirmation is favoured.

Anterior mediastinal lesions can be readily approached percutaneously, and while aspiration of clear fluid will supplement the radiological suspicion of a cyst, cytological examination alone may be insufficient for a pathological diagnosis. Anterior mediastinotomy will allow open biopsy of such lesions.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is increasingly used in the assessment of middle mediastinal lymph nodes. This technique has superseded conventional 'blind' transbronchial needle aspiration, affording image guided aspiration of subcarinal, pretracheal, paratracheal, and hilar nodes.

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) may be used to sample aorto-pulmonary window (AP or subaortic), subcarinal, para-oesophageal, and pulmonary ligament nodes.

Mediastinoscopy is performed through an incision in the neck and allows inspection of structures surrounding the superior vena cava and trachea as far as the carina. It is particularly useful in obtaining lymph node biopsies prior to possible surgery for lung cancer, especially in areas inaccessible to EBUS-TBNA.

Bronchoscopy alone is of limited value when evaluating mediastinal masses unless there is a suspicion of a concomitant bronchial neoplasm. Neural tumours arising in the posterior mediastinum usually require surgical resection and there is little to be gained by preceding this with fine needle aspiration.

Clinical features

It is not surprising that the diversity of anatomical structures in the mediastinum is reflected by an equally diverse range of neoplastic, developmental, and inflammatory masses (**Table 18.19.4.1**).

Table 18.19.4.1 Mediastinal masses

Anterior compartment	
Thymus	Thymoma
	Carcinoma
	Hyperplasia
	Cyst
	Lymphoma
	Ectopia
Germ cell tumours	Benign
	Malignant
Thyroid	
Lipoma, lipomatosis[a]	
Middle compartment	
Lymphadenopathy[a]	Sarcoidosis
	Infection including tuberculosis
	Malignancy: metastatic, lymphoma
Giant follicular lymph node hyperplasia (Castleman's disease)	
Mediastinal cysts	Pericardial cysts
	Bronchogenic cysts
Posterior compartment	
Oesophageal	
Enteric cysts	Oesophageal duplication
	Neurenteric cysts
Leiomyoma	
Carcinoma	
Vascular abnormalities[a]	Aneurysm
	Haemangioma
	Anomalous vessels
Neural tumours	Neurilemmoma or schwannoma
	Neurofibroma
	Malignant schwannoma
	Ganglioneuroma, ganglioneuroblastoma
	Neuroblastoma
	Phaeochromocytoma
	Ependymoma
Bochdalek diaphragmatic hernia	

[a] May be present in more than one compartment.

Although clinical symptoms and signs may give diagnostic clues, many mediastinal masses, particularly those that are benign, are asymptomatic and usually detected on routine chest radiography.

Many studies have documented the relative frequency of different causes of primary mediastinal tumours and cysts, with neurogenic tumours and thymic tumours being the commonest (approximately 20% each), followed by lymphoma, reduplication cysts, germ cell tumours, and thyroid masses. Mediastinal masses in children are more likely to be malignant than in adults.

Common symptoms are cough and chest pain, which arise as a consequence of distortion of the normal mediastinal anatomy. Non-specific constitutional symptoms such as fever or weight loss are more likely to occur with a malignant tumour (e.g. lymphoma or thymoma).

Compression of vital structures can also result in specific symptoms: tracheal or bronchial compression leads to breathlessness with stridor or wheeze; oesophageal narrowing results in dysphagia; superior vena caval compression produces the characteristic features of facial and periorbital oedema, chemosis, and distended veins; involvement of the recurrent laryngeal nerve results in hoarseness and a bovine cough (this usually results from a malignant tumour but can develop with a benign lesion such as aneurysm of the aortic arch); involvement of the sympathetic chain (also likely to be due to malignant infiltration) results in the characteristic features of Horner's syndrome with enophthalmos, miosis, ptosis, and unilateral facial anhidrosis; compression of intercostal nerves may produce neuralgia; and intraspinal extension of tumours may lead to long tract signs.

Anterior mediastinal masses

Thymus

The normal thymus is located in the superior portion of the anterior mediastinum. Its main function is the production of T lymphocytes. Radiologically, the normal thymus can only be seen in childhood and regression occurs during adolescence. Enlargement of the thymus is the commonest single cause of an anterior mediastinal mass and may be due to the development of a thymoma, thymic carcinoma, thymic hyperplasia, or a thymic cyst. The thymus can also be the site of involvement by lymphoma, particularly Hodgkin's disease.

Thymomas

These arise due to neoplastic epithelial proliferation of the thymus gland and can present at any age, peak incidence being in middle age (Fig. 18.19.4.3). They are often benign with no overt cellular atypia, but can rarely behave in a malignant fashion with invasion of adjacent structures and the occurrence of distant metastases (invasive thymoma).

Histologically, thymomas are classified into subtypes A, AB, B1, B2, and B3 according to the morphological appearance of the neoplastic epithelial cells and relative epithelial cell: lymphocyte proportions. This classification correlates closely with the Masaoka staging system, modified by Koga *et al.*, and predicts tumour behaviour:

I: Completely encapsulated
IIA: Microscopic transcapsular invasion
IIB: Transcapsular infiltration into thymus or, mediastinal soft tissue; not breaching pleura or pericardium
III: Macroscopic invasion of neighbouring organ
IVA: Pleural or pericardial dissemination
IVB: Distant metastases; lymphatic or haematogenous spread

Localized symptoms of chest pain and cough are more common with malignant disease. Systemic symptoms may arise; myasthenia gravis affects approximately 30% of patients; other rare associations include red-cell aplasia, hypogammaglobulinaemia, systemic lupus erythematosus, and polymyositis.

Surgical resection is curative in most cases. Minimally invasive operative approaches without sternotomy are favoured whenever possible. Local invasion is less common, but often precludes complete removal and recurrence is the rule. In these patients, therapy is palliative, and consists of a combination of surgical debulking, radiotherapy, and chemotherapy. Long-term follow up is advocated in all cases as delayed recurrence may occur.

Thymic carcinoma

Thymic carcinoma (or type C thymoma) is an aggressive malignancy of thymic epithelial cells exhibiting cellular atypia no longer specific to the thymus. There is a male preponderance. Patients commonly present with loco-regional metastases (e.g. lymph node and pulmonary). Treatment is with surgical resection and adjuvant chemotherapy, but the overall prognosis is poor (5 year survival approximately 30%).

Thymic hyperplasia

Thymic enlargement may be 'true' or 'follicular'. The former typically arises in childhood, peaking in adolescence; retention of normal histological and architectural features is seen. Follicular thymic hyperplasia is characterized by the presence of lymphoid follicles in the thymus regardless of its size. It occurs in approximately two-thirds of patients with myasthenia gravis. It is also known as lymphoid hyperplasia or autoimmune thymitis.

Thymic cysts

These are uncommon. They can be unilocular or multilocular and usually contain straw-coloured fluid. Most patients are asymptomatic, but since cystic change can occur in some thymomas and in Hodgkin's disease, thorough cytological examination of the cyst's contents and its wall is required to exclude malignant disease.

Thymic lymphoma

This is fairly common, particularly in patients with nodular sclerosing type Hodgkin's disease. The presence of systemic symptoms and other mediastinal and/or hilar nodes should alert the clinician to the possibility of lymphoma.

Ectopic thymus

Ectopic and accessory thymic tissue may occur anywhere along the path of embryonic thymic development as a result of failure of descent, sequestration, or involution. It is rare in adults, but may be incidentally detected in childhood. Histological examination reveals normal thymic tissue.

Germ cell tumours

Extragonadal germ cell tumours account for about 15% of all mediastinal cysts and tumours, and approximately 5–10% of all germ cell tumours are found in the mediastinum. Their exact aetiology is unknown, but they are thought to derive from abnormal migration

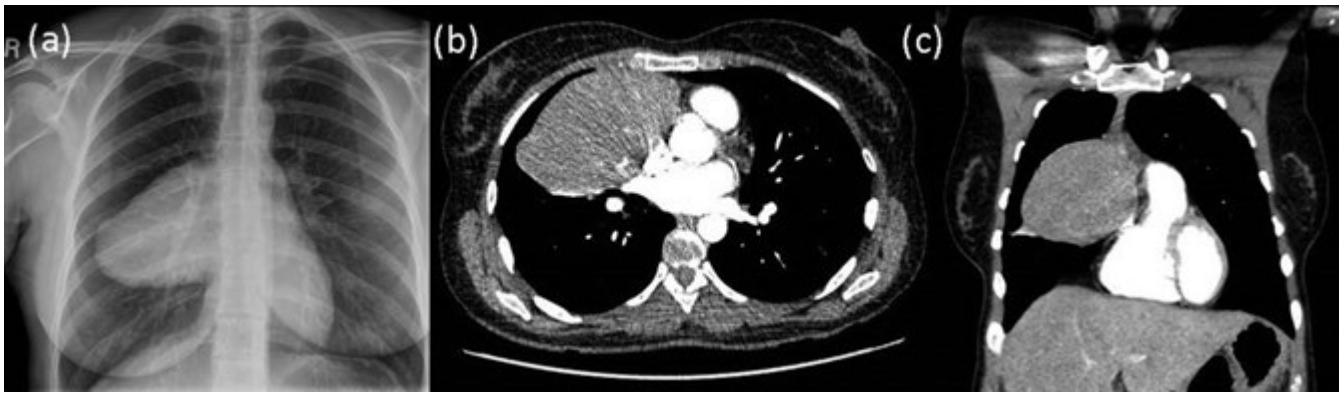

Fig. 18.19.4.3 An incidentally detected anterior mediastinal mass on the chest radiograph (panel (a)) of an asymptomatic 45-year-old woman. Computed tomography (b) axial and (c) coronal views were highly suggestive of a thymic tumour and surgical resection confirmed a type B1 thymoma.

of primitive germinal cells or developing thymic cells exhibiting germ cell potential.

Germ cell tumours may be malignant or benign (80%), the former being more common in childhood. Malignant tumours are more prevalent in men (approximately 9:1), typically in their third to fifth decades; benign tumours exhibit an equal sex differential. Elevation of serum tumour markers such as alpha-fetoprotein (α-FP) or β-human chorionic gonadotrophin (β-HCG) is present in most cases.

Benign germ cell tumours

These consist of a disorganized mixture of ectodermal, mesodermal, and endodermal tissues and may include skin, hair, cartilage, bone, epithelium, teeth, and neural tissue. Tumours include mature (benign) teratomas, teratodermoids, epidermoid cysts, and dermoid cysts. Mature teratomas account for up to 70% of mediastinal germ cell tumours, and CT appearances give a strong indication of this diagnosis. Surgical excision is the treatment of choice to minimize risk of expansion and exclude malignant change.

Malignant germ cell tumours

These are classically divided into seminomas and nonseminomatous germ cell tumours. Most nonseminomatous tumours are malignant teratomas; teratocarcinomas, choriocarcinomas, embryonal carcinomas, and yolk-sac carcinomas are less common. Histological analysis often reveals a spectrum of malignant tissue; and mixed germ cell tumours are now recognized.

Nonseminomatous germ cell tumours range from well differentiated to trophoblastic; in most patients elevated serum levels of β-human chorionic gonadotrophin (β-hCG) and α-fetoprotein (AFP) are seen, which can be used both diagnostically and to monitor treatment response. Seminomas tend to be nonsecretory.

Both types of tumour are highly malignant and invade adjacent mediastinal structures. They are not curable by surgery, although this may be needed for diagnostic purpose and utilized as part of a multimodality treatment approach, particularly for nonseminomatous tumours, following adjuvant chemotherapy. Both types are responsive to cisplatin based chemotherapy; response rates are high, although cure rates are lower than for gonadal germ cell tumours. Radiotherapy may be used in the treatment of seminomas.

Thyroid masses

Retrosternal extension of an enlarged thyroid is one the commoner causes of a mass in the superior mediastinum. Women are more frequently affected. Most are benign multinodular goitres that arise in the neck and extend into the mediastinum through the thoracic inlet. They may contain cystic areas, sometimes with haemorrhage and areas of calcification. Radiographically, they have a sharply defined and often lobulated outline. While they rarely cause symptoms, compression of the trachea at the thoracic inlet can result in respiratory distress and is an indication for surgical resection.

Thyroid cancer may also involve the mediastinum, either by direct extension or by metastasizing to intrathoracic nodes.

Lipoma, lipomatosis

Lipomata are well-circumscribed mesenchymal tumours originating from adipose tissue. Localized lipomata may arise throughout the mediastinum (more common anteriorly), or diffuse accumulations of unencapsulated adipose tissue (lipomatosis) be seen. Detection is frequently incidental, although symptoms may develop from their mass effect. The diagnosis is made radiologically, with homogeneous fat attenuation masses described.

Middle mediastinal masses

Lymphadenopathy

Enlarged lymph nodes are not confined to the middle mediastinum, although this is the commonest site of intrathoracic lymphadenopathy. Reactive changes occur in association with many pulmonary infections, but in most cases the nodes are not significantly enlarged and remain undetected on plain chest radiography. Gross lymphadenopathy is a feature of carcinoma and lymphoma, with sarcoidosis, tuberculosis, and histoplasmosis being other possibilities. Treatment depends on the underlying cause.

Giant follicular lymph node hyperplasia (Castleman's disease)

This is a rare condition of unknown aetiology characterized by nonclonal lymph node hyperplasia. It may be classified by site: localized to a single lymph node (unicentric) or involving multiple nodes (multicentric); or histologically into the more common hyaline vascular type with lymphoid follicles and penetrating capillaries, or a plasma cell type with sheets of mature plasma cells within interfollicular tissues surrounding germinal centres. Multicentric disease may be associated with human herpes virus-8 (HHV-8) positivity.

Unicentric Castleman's disease is often detected incidentally, but patients with multicentric disease frequently develop systemic symptoms with fever, anaemia, and weight loss. Hepatosplenomegaly may be evident, and an association with POEMS syndrome is recognized (POEMS is an acronym for features of the syndrome: **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal gammopathy, and **S**kin abnormalities). There are no diagnostic radiographic features (Fig. 18.19.4.4) and the diagnosis is usually made after surgical resection or biopsy.

Single site Castleman's disease is generally benign and surgical resection is curative. In patients with multicentric disease, progressive hyperplasia with generalized lymphadenopathy may develop as a consequence of malignant transformation. There is no standard treatment: corticosteroids, chemotherapy, and immunomodulation (e.g. anti-IL-6 monoclonal antibodies) may be considered. Antiviral agents may be given if HHV-8 is detected.

Mediastinal cysts

Cysts within the mediastinum are a relatively common cause of a mediastinal mass. They can arise in association with the pericardium, bronchi, gut, or thoracic duct. Most patients are asymptomatic.

Pericardial cysts

These develop embryologically in relationship to the pericardium, although direct communication with the pericardial sac is rare. Radiographically they appear as smooth, clearly demarcated densities, which can be mistaken for a pericardial fat pad or a hernia through the foramen of Morgagni. Aspiration reveals clear fluid. Surgical excision is not recommended.

Bronchogenic cysts

Bronchogenic cysts arise in association with the major airways and are thought to reflect ventral budding of the primitive foregut. They are lined by respiratory epithelium and may contain inspissated mucus. Symptoms are uncommon, but local pressure on the trachea or bronchi can result in cough or wheeze. Occasionally the cysts communicate with the trachea and trigger repeated infections. Surgical excision is the treatment of choice, particularly if there are associated symptoms (Fig. 18.19.4.5).

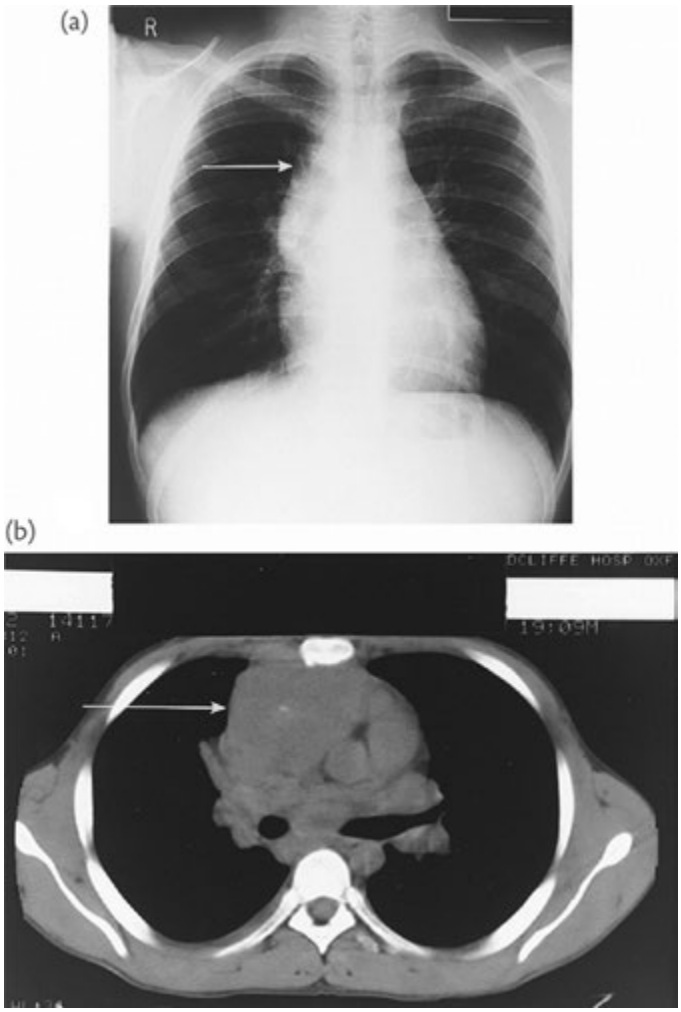

Fig. 18.19.4.4 Chest radiograph (a) and CT scan (b) showing a large middle mediastinal mass (arrows) which on histology showed features of Castleman's disease.

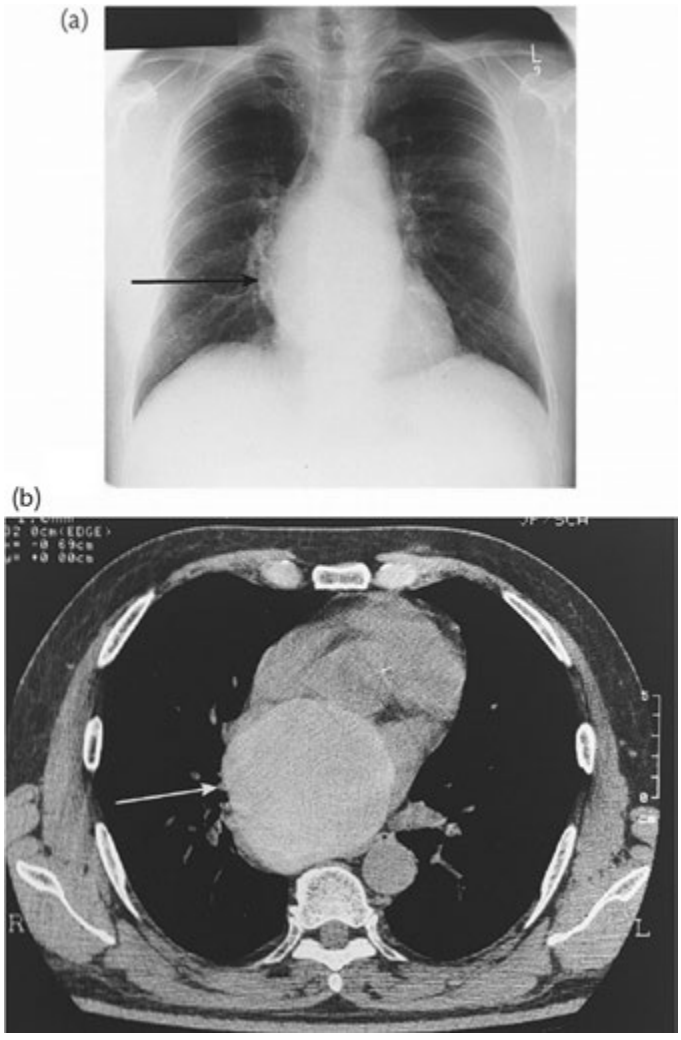

Fig. 18.19.4.5 Chest radiograph (a) and CT scan (b) showing a large mass in the mediastinum (arrows) due to a bronchogenic cyst that had been present for 20 years. It was removed when compression of the oesophagus resulted in dysphagia.

Posterior mediastinal masses

Enteric cysts

Enteric cysts (oesophageal duplication and neurenteric cysts) are rare. Oesophageal duplication cysts adhere to the oesophagus and arise from abnormal development of the dorsal foregut. They are typically lined by gastric or oesophageal mucosa, and may also be evident in the middle mediastinum. Neurenteric cysts arise from developmental areas where the dorsal foregut and notochord are in close proximity. They are classically lined by enteric and neural tissue and are commonly associated with vertebral anomalies. Both types may coexist with other gastrointestinal malformations. Surgical resection is recommended and the prognosis good.

Oesophageal tumours are commonly symptomatic prior to visible radiographic change (Fig. 18.19.4.6).

Vascular abnormalities

Vascular anomalies are not limited to the posterior mediastinum (Fig. 18.19.4.7). However, aneurysms of the descending thoracic aorta can result in abnormal shadows in the posterior mediastinum. Contrast enhanced imaging will differentiate from other posterior mediastinal lesions.

Neural tumours

Tumours, particularly those found in the paravertebral gutters, are likely to be neural in origin. Benign tumours tend to be asymptomatic, while malignant tumours cause pressure effects. Occasionally, spinal cord compression results from direct extension into the intravertebral foramen.

Tumours arising from peripheral nerve cell sheaths include neurilemmoma (schwannoma) and neurofibroma, and also their malignant counterparts. Tumours of the autonomic chain include ganglioneuroma and neuroblastoma.

A neurilemmoma is the commonest neural tumour arising in the mediastinum. These are most common in middle age, and most are asymptomatic. Neurilemmomas can extend into the intravertebral foramen, producing a dumb-bell appearance, and may erode adjacent bone, hence CT scanning or MRI should be undertaken prior to surgical excision.

Neurofibromata are also common. These may be solitary, with clinical and radiological features very similar to those of a neurilemmoma, or more generalized in neurofibromatosis. Surgical resection is recommended, partly because of the small risk of developing malignant neurosarcoma which carries a poor prognosis.

Ganglioneuroma arise from the autonomic plexus and are usually perispinal in position. Associated endocrine symptoms include hypertension, flushing, sweating, and diarrhoea. These tumours are often very large before they become clinically apparent. Prognosis is good after surgical resection.

Ganglioneuroblastoma and neuroblastoma represent the malignant end of the spectrum and predominantly arise in childhood. Neuroblastoma in particular are highly invasive, with metastatic spread and systemic symptoms common at the time of presentation. Surgical resection is preferred, with adjuvant chemotherapy and radiotherapy considered on an individual basis.

Ependymomas rarely occur in the mediastinum and are thought to derive from paravertebral ependymal rests. They have a predilection for the posterior mediastinum.

Bochdalek posterior diaphragmatic hernia

Developmental diaphragmatic defects may result in congenital herniation of gastrointestinal contents through the posterior part of

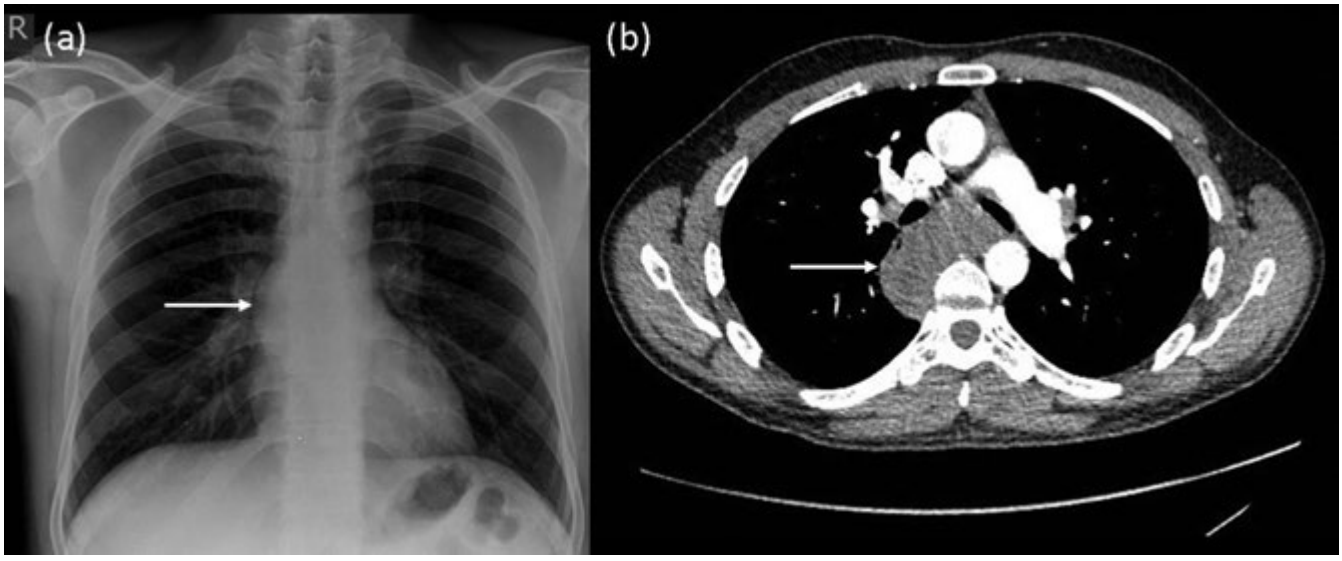

Fig. 18.19.4.6 Following presentation with worsening dysphagia; a benign oesophageal leiomyoma was confirmed histologically following endoscopic biopsy.

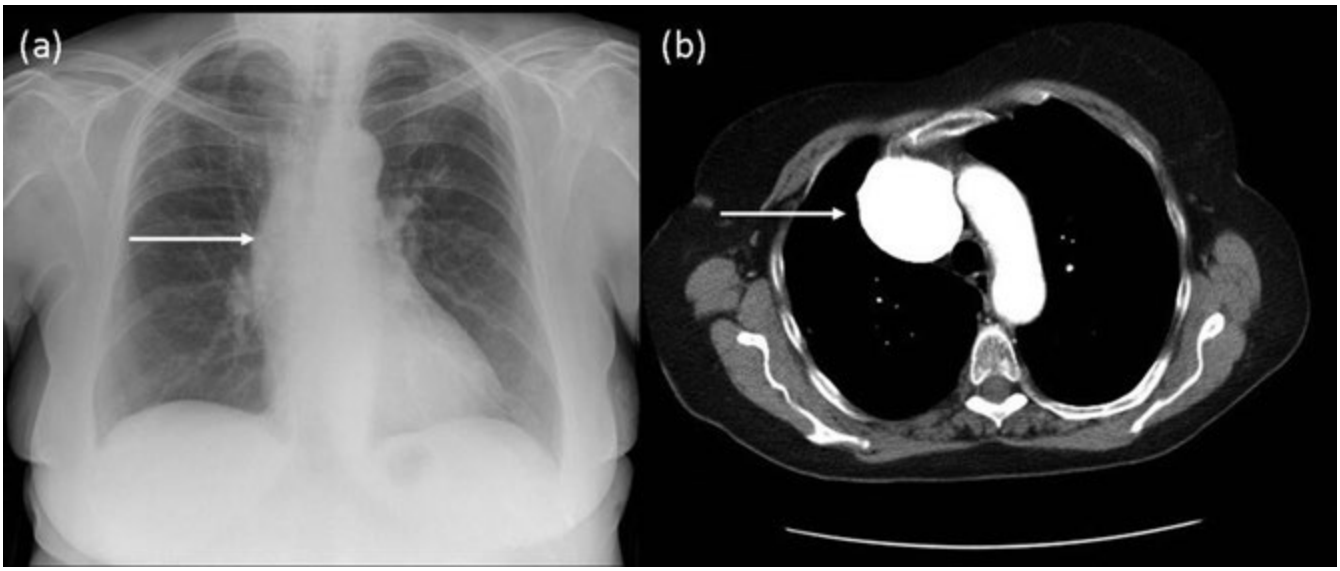

Fig. 18.19.4.7 Aneurysmal dilatation of the superior vena cava (a and b) resulting in incidentally detected radiographic abnormality (arrows).

the diaphragm. These often present clinically in infancy, although may be incidentally detected in approximately 6% of adults.

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