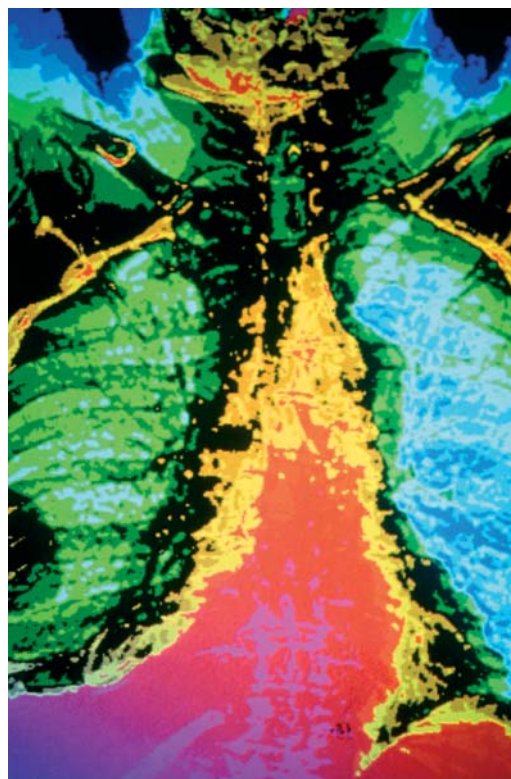


Lung cancer

— the disease and non-drug treatment

By Pamela Mason, PhD, MRPharmS

Lung cancer is the leading cause of cancer mortality and is responsible for 35,000 deaths every year in the UK. Prognosis is poor, with only 20 per cent of patients alive one year after diagnosis. This article outlines the clinical features, diagnosis and non-drug treatment of the disease



Coloured computed tomography scan showing a posterior view of the chest with the right lung affected by cancer (light blue areas)

Lung cancer (which includes cancer of the trachea and bronchi) is the third most common cause of death in the UK after heart disease and pneumonia. It is responsible for around a quarter of all cancer deaths. The mortality rate worldwide is highest in Scotland, closely followed by England and Wales. In England and Wales, lung cancer was responsible for nearly 29,000 deaths in 2002 with a male to female ratio of approximately two to one (for comparison, worldwide data for the year 2000 are presented in Table 1, p131).^{1,2} UK incidence and death figures are worse than the European and US averages.

Although the mortality rate for this disease has levelled off in men, it is still the most common cause of cancer death in this group, and men account for 60 per cent of all lung cancer cases. The incidence continues to rise in women, accounting for one in six of all

cancer deaths.¹ This is directly related to changes in smoking habits. In women, lung cancer is generally the second most common cause of cancer death after breast cancer, but women in Scotland and the north of England are more likely to die of lung cancer than breast cancer. Risk increases with age — lung cancer is less common in people under the age of 40.

The prognosis is generally poor. About 80 per cent of patients die within a year of diagnosis and only 5.5 per cent are alive after five years.¹ This is due partly to the speed with which the disease progresses and partly to the nature of the patients, most of whom are older and often suffering from smoking-related illnesses, including chronic obstructive pulmonary disease and cardiovascular disease.

Types of lung cancer

There are two main types of lung cancer, based on the characteristics of the disease and its response to treatment.

Non-small-cell carcinoma Non small-cell carcinoma accounts for 80 per cent of all lung cancers¹ and is sub divided into:

- Squamous (epidermoid) carcinoma, which is the most common type of non small-cell carcinoma, accounting for approximately 35 per cent of all lung cancers.¹ Most cases present as obstructive lesions of the bronchus. The cells are usually well differentiated and local spread is common. The development from the initial malignant change to presentation takes approximately eight years.³ Widespread metastases occur relatively late
- Large-cell carcinoma, which accounts for 10 per cent of all lung cancers.¹ It is less well differentiated than squamous carcinoma and metastasises earlier
- Adenocarcinoma which accounts for approximately 27 per cent of lung cancers.¹ It arises from mucous glands in the small bronchi and frequently from

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scar tissue. Invasion of the pleura and the mediastinal lymph nodes (those between the two pleural sacs) is common as are metastases to the brain and bones. The development from the initial malignant change to presentation takes approximately 15 years.³ It is the most common type of lung cancer associated with asbestos and is proportionally more common in non-smokers, women and older people

- Alveolar cell carcinoma (bronchiolar carcinoma) which accounts for 1 to 2 per cent of lung cancers.¹ It occurs either as a peripheral solitary nodule or as diffuse nodular lesions of multicentric origin

Small-cell carcinoma Small-cell carcinoma, often known as oat cell carcinoma, accounts for 20 per cent of all lung cancers.¹ It arises from Kulchitsky cells (endocrine cells) and these tumours secrete many polypeptide hormones. Some of these hormones feedback to the cancer cells and cause tumour growth. The time from initial malignant change to presentation takes approximately three years³ and the tumour grows rapidly.

— Risk factors

Lung cancer is most closely associated with smoking. This and other factors that can increase the risk of lung cancer are now described.

Smoking Smoking is the leading risk factor for lung cancer with over 90 per cent of lung cancer deaths estimated to be caused by it.⁴ The risk of lung cancer among current smokers is about 15 times that for people who have never smoked. It is greatest for heavy smokers and increases with more years of smoking. Among items smoked, cigarettes are associated with the greatest risk, followed by cigars and pipes. There is no evidence that smoking low tar cigarettes reduces the risk of lung cancer. The frequent

inhalation of other people's smoke by non-smokers (ie, passive smoking) increases the risk of lung cancer by a factor of 1.5.

Radon Radon is a naturally occurring odourless radioactive gas which emanates from some types of rock. The risk of developing lung cancer is increased in people who live in houses in which radon levels are high. A meta-analysis involving 4,263 cases of lung cancer and 6,612 controls found a significant dose-related increase in the risk of lung cancer with increasing exposure to radon.⁵ The effects of radon and cigarette smoking are additive. Therefore, smokers exposed to high radon levels are at particularly high risk of developing lung cancer.

Levels of radon vary widely across the UK. Reduction of indoor radon can be achieved by sealing buildings so that air cannot enter from the soil. Increasing ventilation to the lower levels of buildings can also help. Information about radon and action for risk reduction is available from the National Radiological Protection Board (www.nrpb.org).

Asbestos and other occupational factors Working with asbestos increases the risk of lung cancer. Plumbers, gas fitters, electricians, metal plate workers and carpenters form the largest high-risk groups. A synergistic relationship exists between asbestosis and cigarette smoking and the risk of lung cancer (usually adenocarcinoma). The risk is multiplied five times above the risk attributed to smoking alone.

An association with lung cancer is also claimed for arsenic, cadmium, chromium, formaldehyde, iron oxide, petroleum products and oils, polycyclic aromatic compounds (eg, in diesel exhaust), silica and welding fumes. Tumours associated with occupational factors tend to be mostly adenocarcinomas.

Poor nutrition High consumption of fruit and vegetables (particularly green vegeta-

bles) is associated with a reduced risk of lung cancer.^{6,7} The protective mechanism is not fully understood. Supplements of nutrients thought to confer benefit (eg, antioxidants) have not been shown to produce the same benefits as diets high in fruit and vegetables.^{8,9} In contrast, intervention trials have found increases in lung cancer incidence and mortality in smokers who take beta-carotene supplements.

Low physical activity A number of epidemiological studies have reported that exercise lowers the risk of lung cancer.¹⁰ The mechanism by which exercise might reduce lung cancer risk has not been investigated but may be related to the ability of exercise to reduce serum insulin, and subsequently, insulin-like growth factor (IGF)-1. Increased levels of IGF-1 is thought to be a risk factor for lung cancer.¹¹

— Clinical features

The most common presenting symptoms of lung cancer are cough and chest pain, but often there are no abnormal physical symptoms. Chest pain and discomfort are often described as fullness and pressure in the chest. Less common presenting symptoms include general malaise, weight loss and shortness of breath, although these will inevitably occur at some stage of the illness. Invasion of the pleura and ribs can cause severe pain in the shoulder and down the surface of the inner arm, while further spread may affect the vocal cord causing hoarseness.

Small-cell tumours may produce hormones at some stage, but manifestations of this are rare with the exception of finger clubbing. Other possible endocrine effects include hypercalcaemia and syndrome of inappropriate secretion of antidiuretic hormone. Enlarged supraclavicular lymph nodes can be found with small cell carcinoma. There may also be signs of pleural effusion or lobar collapse.

Lung cancer can invade the phrenic nerve. It can involve the pericardium, and also the oesophagus, producing progressive dysphagia. Obstruction of the superior vena cava can cause early morning headache, facial congestion, oedema of the upper limbs and distension of the jugular veins.

Metastases in the bone are common, leading to severe pain and fractures. The liver is frequently involved. Metastases may develop in the brain and present as a change of personality, epilepsy or as a focal neurological lesion. Secondary deposits in the adrenal glands are frequently found on post-mortem but can often be asymptomatic.

— Screening

Screening programmes, including annual chest X-ray or sputum cytology (examination

Table 1: Incidence of lung cancer in 2000

	Incidence	Incidence ASR*	Deaths	Deaths ASR*
World				
Men	965,241	35.5	848,132	31.2
Women	386,891	12.1	330,786	10.3
UK				
Men	24,300	48.1	21,959	42.9
Women	15,424	24.9	13,390	21.1

Incidence is the number of new cases arising in a given period in a specified population. *Age standardised ratio (ASR) is a measure of a rate that a population would have had the disease if it had a standard age structure. Standardisation is necessary when comparing several populations that differ with respect to age because age has a powerful influence on cancer. ASR is expressed per 100,000 people.

of cells in sputum produced by coughing) have been tried in high-risk groups, but the conclusion of a systematic review was that screening is of limited benefit.¹² Although cases may be diagnosed earlier, trials have also suggested that delay in diagnosis of lung cancer may have little impact on outcome.

A UK lung screening trial is under way using fluorescent bronchoscopy. The trial involves people at high risk of lung cancer (ie, those with a history of lung disease, heavy smoking, family history of lung cancer, asbestos exposure). It will be some years before the results of this trial are known.

— Diagnosis

Lung cancer is usually diagnosed by chest X-ray following presentation with symptoms linked to the disease. Other diagnostic procedures can be undertaken to establish the spread of the disease.

Chest X-ray By the time lung cancer is causing symptoms, it will almost always be visible on chest X-rays. Recent guidelines from the National Institute for Clinical Excellence (NICE) recommend that patients should be offered urgent referral for chest X-ray if they present with haemoptysis or any of the following unexplained or persistent (ie, lasting more than three weeks) signs or symptoms:

- Cough
- Chest or shoulder pain
- Dyspnoea
- Weight loss
- Chest signs
- Hoarseness
- Finger clubbing

- Features suggestive of a metastases from a lung cancer (eg, in brain, bone, liver or skin)
- Cervical supraclavicular lymphadenopathy

Computed tomography Computed tomography (CT) is used to further the diagnosis. The NICE guidelines state that all patients with known or suspected lung cancer should be offered a contrast-enhanced chest CT scan. A CT scan is particularly useful for identifying disease between the pleura, such as enlarged lymph nodes, or local spread of the tumour, and for identifying secondary spread of the cancer to the other lung by detecting masses too small to be seen on a chest X-ray. CT scanning should be extended to include common sites for metastases such as the liver, brain and adrenal glands.

Fibreoptic bronchoscopy Obtaining biopsy and cytological specimens is possible using fibreoptic bronchoscopy. This procedure can have adverse effects and be unpleasant for patients. The NICE guidelines state that fibreoptic bronchoscopy should be performed on patients with central lesions who are willing and able to undergo this procedure, but only after a CT scan has been performed.

Transthoracic fine-needle aspiration biopsy NICE recommends transthoracic fine-needle aspiration biopsy for diagnosis of lung cancer in patients with peripheral lesions. Peripheral lung lesions cannot be seen by fibreoptic bronchoscopy. Samples may be obtained by direct aspiration through the chest wall. Pneumothorax is common with this procedure, and mild haemoptysis may occur.

¹⁸F-deoxyglucose (FDG) positron emission tomography (PET) PET using FDG is useful for investigating solitary pulmonary nodules in cases where a biopsy is not possible or has failed. The NICE guidelines recommend its use in these circumstances, depending on nodule size, position and CT characterisation.

— Staging

There are two systems for staging lung cancer — one for non-small-cell lung cancer and one for small cell lung cancer. There are also a number of scales that report the performance status of the patient.

Non-small-cell lung cancer In non-small-cell lung cancer, accurate staging is important for making decisions about surgery. Tumour stage can be assessed by CT scanning, surgical assessment and FDG-PET scanning. Magnetic resonance imaging should not be used routinely for staging primary tumours, but is useful for assessing the extent of the disease.

Non-small-cell lung cancers are classified according to the TNM staging system. The T refers to the size of the tumour and its spread, the N to the number of lymph nodes and the M to the presence of metastases (see Panels 1 and 2).

Small-cell lung cancer The NICE guidelines recommend that small cell lung cancer should be staged by a contrast-enhanced CT scan of the patient's chest, liver and adrenals and by selecting imaging of any symptomatic area. Small cell lung cancers are classified into two groups:

- Limited stage disease — cancer that can be seen in one of the nearby lymph nodes or in fluid around the lung (pleural effusion)
- Extensive stage disease — cancer that has spread to other parts of the body apart from the lungs

Panel 1: TNM classification of lung cancer

■ Tumour (T)

- T1 Tumour is small (<3cm across)
- T2 Tumour is >3cm across, or involves main bronchus, or has caused partial collapse of lung or has penetrated visceral pleura (inner covering of the lung)
- T3 Tumour of any size that has grown into chest wall, the mediastinal pleura, the diaphragm or the pericardium or has caused the whole lung to collapse
- T4 Tumour of any size that has grown into the area between the lungs (the mediastinum), heart, oesophagus, trachea or with pleural effusion or pericardial effusion

■ Nodes (N)

- N0 No cancer in any lymph nodes (cancer is localised)
- N1 Cancer in lymph nodes nearest affected lung
- N2 Cancer in mediastinal lymph nodes on same side as affected lung or cancer in lymph nodes that lie where trachea divides
- N3 Cancer in the lymph nodes on the opposite side from the affected lung or in the supraclavicular lymph nodes

■ Metastases (M)

- M0 No metastases
- M1 Cancer spread to another lobe of the lung or another part of the body

Panel 2: Staging of non-small-cell lung cancer

Stage number	TNM classification
Ia	T1, N0, M0
Ib	T2, N0, M0
IIa	T1, N1, M0
IIb	T2, N1, M0 or T3, N0, M0
IIIa	T1, N2, M0, or T2, N2, M0, or T3, N1, M0 or T3, N2, M0
IIIb	Any T, N3, M0 or T4, any N, M0
IV	Any T, any N, M1

Further details of staging classification and performance status scales for small cell lung cancer can be found in the NICE guideline for lung cancer at www.nice.org.uk/CG024NICEguideline.

Initial treatment

Surgery is a treatment option in some patients with stage I or II non-small cell lung cancer. Radiotherapy and chemotherapy can also be offered.

Non-small-cell lung cancer Treatment of patients with non-small-cell lung cancer depends on the stage of the disease and the condition of the patient. For those with early stage disease, first-line treatment is usually surgery or radiotherapy. For those with advanced or metastatic disease, palliative interventions are likely to be appropriate. Chemotherapy may also be used in non-small-cell lung cancer (covered in the drug treatment article of this special feature on pp137–43). A summary of the NICE recommendations on treatment of non-small cell lung cancer is found in Table 2. The Scottish Intercollegiate Guidelines Network has also produced guidelines on the management of lung cancer (www.sign.ac.uk/pdf/sign80.pdf).

Surgery is only appropriate for patients who are relatively fit, who have adequate respiratory capacity, and who have early stage (usually stage I or II), histologically confirmed non-small-cell lung cancer. Selection should not be based on a patient's age. Patients need

to be carefully selected so that those who are likely to benefit are offered surgery.

The most usual types of operation involve opening up the chest (thoracotomy) and removing a whole lung (pneumonectomy) or a lobe of the lung (lobectomy). Further details about types of surgery for non-small cell lung cancer can be found in the NICE guidelines.¹

Patients who are less fit or whose tumour is too extensive for surgery, but do not have distant metastases, are likely to benefit from radiotherapy. Radiotherapy is the treatment of choice for patients with poor lung function.

There are two main types of radiotherapy schedule. Firstly, the continuous hyperfractionated accelerated radiation therapy (CHART) in which the total dose is given in small fractions three times daily for 12 consecutive days, including weekends. CHART is advocated in the NICE guidelines. Secondly, there is conventionally fractionated radiotherapy in which a similar total dose is given in 20 or 32 fractions over four or six weeks.

Adjuvant radiotherapy given before surgery has not been shown to improve outcomes. Postoperative radiotherapy is not recommended for patients who have had complete resection, but should be considered after incomplete resection of a non-small-cell lung tumour.

Small-cell lung cancer The first line treatment for small-cell lung cancer is chemotherapy. Patients with limited stage small cell lung cancer should also be offered radiotherapy.

Treating advanced disease

Advanced lung cancer causes a large number of distressing symptoms. Palliative care should be the main aim of treatment for most patients and should be an integral part of care for all patients with lung cancer.

Inoperable lung cancer may lead to obstruction of the trachea or bronchi causing disabling breathlessness, intractable cough, haemoptysis and respiratory infection. Various techniques are available for use in the palliation of these patients. Attention to the patient's overall well-being is also important. This may involve counselling and behavioural therapy, opiates for pain relief and prednisolone to improve appetite.

External beam radiotherapy External beam radiotherapy is used for palliative relief of symptoms such as breathlessness, cough, haemoptysis and chest pain.

Brachytherapy Placing radioactive material directly on, or near to, the tumour is known as brachytherapy. For lung cancer, brachytherapy is used for the treatment of intraluminal tumours and endobronchial symptoms not palliated by other means. It would not normally be used in patients who can tolerate conventional radiotherapy.

Laser treatment A further option is laser treatment. This involves passing a laser through a fiberoptic bronchoscope which can be used to vapourise inoperable intraluminal

Table 2: Summary of NICE recommendations for treatment of non-small-cell lung cancer

	Stage I	Stage II	Stage IIIa	Stage IIIb	Stage IV PS=0–1	Stage IV PS=2	Stage IV PS>2
■ Surgery	Yes	Yes	Some cases	No	No	No	No
■ Radiotherapy followed by surgery	No	No	No	No	No	No	No
■ Surgery followed by radiotherapy	Some cases	Some cases	Some cases	No	No	No	No
■ Preoperative chemotherapy and surgery	No*	No*	No*	No	No	No	No
■ Surgery followed by chemotherapy	Some cases	Some cases	Some cases	No	No	No	No
■ Surgery then chemotherapy and radiotherapy	No	No*	No*	No	No	No	No
■ Radical radiotherapy	Some cases	Some cases	Some cases	Some cases	No	No	No
■ Chemotherapy and radical radiotherapy	No	No	Yes	Some cases†	No	No	No
■ Chemotherapy	No	No	Some cases	Yes	Yes	No*	No
■ Symptomatic treatment, including palliative radiotherapy	No	No	Some cases	Some cases	Some cases	Yes	Yes

This table should be read in conjunction with the detailed NICE guidance.¹ Yes=first choice for eligible patients. Some cases=suitable for some patients (see detailed guideline). No=not recommended. *=not recommended except within a clinical trial. †=may be first choice of

treatment for patients with good performance status and localised disease that can safely be offered radical radiotherapy. PS= performance status: 0 being normal with no limitations and 4 being completely disabled and bedridden

cancer involving short segments of the trachea or main bronchi.

Stents Tracheobronchial stents are made of silicone or expandable metal springs. They are available for insertion into strictures caused by a tumour or by external malignant compression where there is weakening and collapse of the tracheo-bronchial wall.

Photodynamic therapy (PDT) PDT involves intravenous injection of a photosensitising drug. The drug accumulates in malignant tissue and is activated a few days later by photoradiation of the affected area through a bronchoscope. This is intended to reduce the bulk of the tumour, thereby reducing symptoms caused by bronchial obstruction. Porfimer sodium is licensed for photodynamic therapy of non-small-cell lung cancer. NICE is examining PDT for lung cancer and will publish guidance on its use.

Conclusion

Patients with lung cancer have a poor prognosis, but the treatments described can improve life expectancy and reduce painful symptoms. The second article in the special feature will describe the pharmacological treatments available.

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Readership survey

A readership survey was circulated with the March issue of *Hospital Pharmacist*. Surveys returned by 3 May will be entered into a draw to win a three-month trial subscription to *Medicines Complete* and a copy of *Martindale*. The survey can also be completed online at www.pjonline.com/survey.