

An overview of lung cancer

November is Lung Cancer Awareness Month. With public smoking bans springing up over Europe and investment in campaigns to discourage the habit in the UK, perhaps more of the future generation will see smoking as unattractive. But what about those for whom such interventions have come too late? In this article, **Michael Peake** explains why it is important to be alert to lung cancer



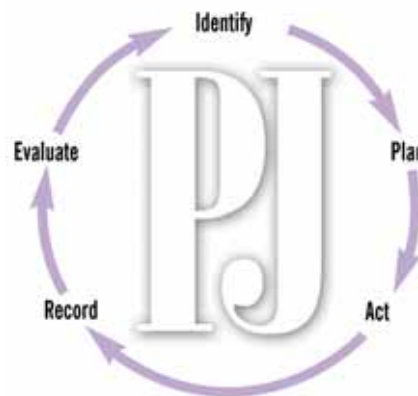
Figure 1: A chest X-ray is a cheap diagnostic tool for lung cancer

Lung cancer is a term that covers a variety of malignant tumours within the lungs and the surrounding pleural membrane, although it excludes the asbestos-related pleural tumour, malignant mesothelioma. It is one of the most common forms of cancer and the commonest cause of cancer-related death, with an estimated 1.18 million people dying worldwide from the disease in 2002.¹ In the same year, there were 33,600 deaths from lung cancer in the UK, making up 22 per cent of all cancer deaths.² This compares with 12,900 deaths from breast cancer, 16,200 from colorectal cancer and 9,900 from prostate cancer² — lung cancer now exceeds breast cancer as the most common cause of death from cancer in women in many parts of the world, including the UK. These facts are not well publicised and a long-standing lack of media interest in lung cancer has resulted in a low level of public awareness.

The incidence of lung cancer and death from it in males increased steadily between the 1950s and the end of the '80s but since then it has steadily fallen — the decline has not yet plateaued. In women, the incidence has always been below that in men, but this has steadily increased since the 1970s. The male to female ratio has shifted from almost 6:1 in the early 1970s to around 2:1 in the early 2000s. These trends parallel the trends in the prevalence of smoking in both sexes over the period, though with a 20–25 year lag time.

The mean age at diagnosis is around 70 years but this means, of course, that half of the cases occur in individuals younger than 70 years old and patients with lung cancer in

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Identify knowledge gaps

1. What symptoms or signs could indicate possible lung cancer?
2. Can you list two types of lung cancer?
3. What are the treatment options for lung cancer?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "common disease states" and "health education and promotion" (see appendix 4 of "Plan and record").

their 40s and 50s are common in clinical practice.

Across the UK there is wide variation in the incidence of lung cancer and there is a strong correlation between socio-economic status and its frequency in the population, the highest incidences being in the lowest socio-economic groups. The fact that lung cancer is most common in older, male, working class smokers probably explains why it is of less interest to the media than breast cancer.

Risk factors and prevention

Around 90 per cent of lung cancers in men and 80–85 per cent in women are believed to be caused by cigarette smoking. This means, however, that every year in the UK between 4,000 and 5,000 people who have never smoked die of lung cancer — this is more than the number of people who die of lymphoma, leukaemia, ovarian cancer, cervical cancer, etc — and it is believed that at least 20 per cent of these deaths are related to passive smoking. There is a strong correlation between the number of cigarettes smoked and duration of smoking and the risk of developing lung cancer. Between one in six and one in seven life-long smokers will die of the disease.

Other risk factors for lung cancer include exposure to asbestos or radon. People who may have been exposed to asbestos include those who have worked in ship building, insulation, boiler making or repair, carpentry or demolition industries.

Patients with chronic obstructive pulmonary disease (COPD) are also at significantly high risk of developing lung cancer and this excess risk is independent of their smoking history. In addition, patients with a previous history of cancer (especially head or neck) are considered a high-risk group.

There is a small increased likelihood of developing lung cancer if there is a family history, but the excess risk is much smaller than with breast cancer.

Symptoms and signs

In its early stages, lung cancer usually causes little in the way of symptoms. Because it is a deep internal tumour, it can grow to a considerable size in many patients before medical advice is sought. Research is ongoing into various methods of screening and early detection but routine screening is, as yet, of unproven value and is unlikely to become available in the foreseeable future, at least in the UK. It is essential, therefore, that all health care professionals and the general public are aware of the early symptoms of the disease and the fact that curative treatment is more likely to be possible the earlier a specialist is seen.

Many of the symptoms of lung cancer are non-specific and their onset is often gradual. The situation is made more complex because many smokers attribute these early symptoms to the effects of smoking itself (eg, a “smoker’s cough” and breathlessness). The most common symptoms of lung cancer are shown in Panel 1. One of the slogans used by the UK Lung Cancer Coalition is “There is no such thing as a smoker’s cough”. In other words, one should always look for the cause of a cough and breathlessness, and not just put it down to the “side effects” of smoking. Pain, weight loss, fatigue and severe breathlessness are later stage symptoms. Anybody with symptoms for longer than three weeks should be referred.

In addition, it is not only new symptoms that are important. Many smokers have some degree of COPD, one element of which is chronic bronchitis, and this can cause chronic cough. However, patients with lung cancer often say that the cough has changed recently — for example, it becomes more productive or frequent (eg, it might wake them at night or interfere with talking), it is associated with a different “noise” or, of course, their sputum becomes streaked with blood. So changes in chronic symptoms can also serve as a warning.

Pharmacists see many people wanting to buy antitussives. It is vital that those with a persistent cough see their GPs.

Diagnosis and staging

Some patients with lung cancer are detected incidentally because a chest X-ray or a computerised tomography scan is carried out for another purpose and this group often have

Panel 1: Common symptoms of lung cancer

- Haemoptysis
- Cough
- Breathlessness
- Chest or shoulder pain, or both (this is usually a continuous dull ache but at times can be sharp and worse on inspiration)
- Weight loss
- Hoarseness
- Fatigue



Clubbing of the fingers can be a sign of lung cancer

earlier stage disease. However, as already mentioned, lung cancer more often presents late to specialist care and, although this is partly explained by the pattern of symptoms, there are well documented delays caused by the lack of awareness of health care professionals.³

A chest X-ray is a cheap, simple and easily available test that shows abnormalities in most patients with lung cancer who have symptoms (see Figure 1, p521), although a normal film does not rule out the diagnosis. GPs therefore need to have a low threshold for requesting a chest X-ray in patients in high risk groups with suspicious symptoms. Pharmacists could help promote this practice by suggesting this to patients, thus empowering them.

Most patients suspected of having lung cancer in primary care are referred to a local rapid access lung cancer clinic, a network of facilities that have developed in response to the National Cancer Plan and the Government’s two-week wait policy.⁴ The main purposes of investigations from this point onwards are:

- To establish a tissue diagnosis of lung cancer and its cellular subtype
- To exclude other diagnoses
- To establish the stage of the disease
- To establish the fitness of the patient for the optimum therapy

Investigations commonly used in this process are listed in Panel 2.

Lung cancer is a deep, internal tumour which is not always easy to access in order to obtain tissue for pathological examination. It also commonly occurs in older people who have a high incidence of co-morbidities, such as COPD and ischaemic heart disease, making invasive investigation problematic. Because of these various complexities, the diagnostic pathway must be well planned and monitored to ensure patients are treated as quickly as possible, as well as to meet the Government waiting time targets.⁵

Establishing the stage of the disease is crucial to deciding the optimum treatment and is a major element in determining the prognosis (see below). Non-small cell lung cancer (see below) is staged using the international TNM (tumour, nodes, metastases) classification (see Panel 3). Only patients with stages I and II are usually suitable for surgical treatment. In most centres in the UK these patients comprise less than 20 per cent of those referred — most patients already have incurable disease by the time they reach specialist care. Spread (metastasis) of lung cancer is usually first to the mediastinal lymph nodes then, in approximate order of frequency, to the liver, adrenal glands, bones and brain.

Types of lung cancer

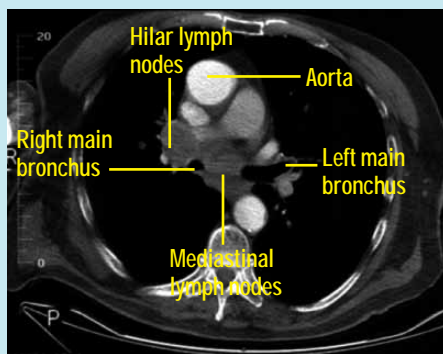
Lung cancers almost always develop in the mucosa of the bronchi and smaller airways that are exposed to inhaled carcinogens, particularly cigarette smoke. A number of different types of cell line the airways and when they undergo malignant transformation they

Panel 2: Common tests in diagnosis and staging

- Chest X-ray
- Computerised tomography (CT) scanning of thorax and upper abdomen
- Bronchoscopy
- CT guided lung biopsy
- PET-CT (positron emission tomography) scanning
- Mediastinal node sampling
- Pleural aspiration and biopsy
- Assessment of lung function (eg, spirometry)

Lung anatomy

The lungs consist of six lobes, three on each side. Lymphatic drainage from these is into lymph nodes in the hilar regions (ie, where the main airways and blood vessels come together near the middle of the thorax). These then drain into nodes in the mediastinum, the core of the thorax around the trachea and major vessels.



result in different types of cancer. The most common types of lung cancer are:

- Squamous cell carcinoma (~50 per cent)
- Adenocarcinoma (~30 per cent)
- Large cell carcinoma (<5 per cent)
- Small cell carcinoma (~15 per cent)
- Rare tumours (<5 per cent)

Small cell lung carcinoma is becoming less common and is characterised by relatively rapid growth and early spread to other organs. It is strongly associated with smoking. The other types of lung cancer (squamous cell carcinoma, adenocarcinoma and large cell carcinoma) are often grouped together for practical purposes and labelled as “non-small cell lung cancer” (NSCLC), the most common subtypes being squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma is common in smokers whereas the association between smoking and adenocarcinoma is less strong.

Prognosis

The overall prognosis of lung cancer is poor. Nearly 50 per cent of patients die within six months of diagnosis and this is largely the result of late presentation, with over two-thirds of patients having metastatic disease at diagnosis. In those with early stage disease NSCLC (stages I or II), most of whom are treated by surgery, between 50 and 70 per cent survive beyond five years. It is, therefore, essential that patients are identified and referred for specialist care as quickly as possible. However, even in patients who are not suitable for potentially curative treatment there is much that can be done to increase medium-term survival (one to three years)

Cancer therapy

An article on pp518–25 describes targeted therapy for cancer.

Panel 3: Summary of staging of NSCLC

Stages I and II (early stages) Primary tumour confined to one lung lobe with lymph node involvement limited to hilar nodes

Stage IIIA Locally more advanced with involvement of mediastinal lymph nodes

Stage IIIB Locally more advanced, sometimes with pleural effusion (accumulation of fluid between the pleura) and involvement of contralateral mediastinal lymph nodes

Stage IV Metastases to other organs (including other parts of the lungs)

and to palliate symptoms, which can worsen as the disease progresses.

Treatment

There are several major types of treatment⁶ for lung cancer: surgery, radiotherapy, chemotherapy, biological agents and palliative care. Combination treatment with two or more of these can be used. All these therapies (including chemotherapy) have been demonstrated either to improve quality of life or not to make it worse in the context of modest improvements in survival. In patients for whom there is no prospect of cure there is, therefore, a trade-off between these benefits and side effects and the inconvenience of treatment.

Surgery Suitability for surgery depends both on the patient having “technically resectable”, non-metastatic NSCLC (usually stages I or II) and being fit for major surgery. Technically resectable means that the surgeon is able to remove all the visible tumour without major damage to vital organs. However, many patients are old and have smoking-related comorbidities so are not fit for surgery (either they are unfit for a general anaesthetic or they would not be able to survive on the smaller volume of lung that would remain). Only 8 per cent of patients with lung cancer are treated with surgical resection in UK, a lower figure than in many other western countries. There is also wide variation in resection rates within the UK itself, with up to 20 per cent of patients having surgery in some centres compared with below 5 per cent in others. It is not clear to what extent this variation can be explained by the case-mix of patients, but it is likely that differences in access to specialist thoracic surgery also has a part to play.

In terms of small cell lung cancer, surgery is controversial. Most surgeons do not perform resections because a high proportion of patients have metastatic disease undetected at the time of surgery. However, small small cell lung cancers where a PET scan shows no metastases are resected in some centres and the results are good.

Radiotherapy Some patients who are unfit for surgery may be fit for radical (high-dose) radiotherapy. Radiotherapy can also be used as a palliative treatment for patients without any realistic prospect of long-term survival (ie, beyond five years). Such palliative radiotherapy is particularly useful in patients with bone pain, large airway narrowing, symptoms from cerebral metastases and persistent haemoptysis.

Chemotherapy Chemotherapy is the first line treatment for most patients with small cell lung cancer, most of whom will have a prompt and clinically useful response, both in terms of shrinkage in the size of the tumour and improvement in symptoms. This response is often relatively short-lived, but there are significant improvements in survival, with treatment adding months of life for many patients and leading to survival well beyond two years in a minority.

Chemotherapy is also used in NSCLC. It is of modest but proven benefit in terms of increasing long-term survival in patients who undergo surgery — this is called “adjuvant chemotherapy.” In advanced disease stages (IIIB and IV), it provides useful palliation of symptoms in most patients and a modest improvement in survival. The median survival (ie, the time in months when only 50 per cent of patients remain alive) is increased by 10–12 weeks, but the proportion who survive to one year is doubled.

In NSCLC the most common first-line chemotherapy is a doublet (sometimes a triplet) containing a platin (cisplatin or carboplatin) and vinorelbine, gemcitabine or paclitaxel. In locally more advanced NSCLC (stage IIIA and some IIIB) there is good evidence that a combination of chemotherapy and radiotherapy can significantly improve survival with a few patients surviving beyond five years.

Biological agents Biological agents are a new and exciting heterogeneous group of drugs. In the past few years there have been huge advances in the understanding of how tumours develop, grow and spread and many biochemical pathways that drive the various components of these processes have been identified. Clearly, if key elements of a tumour growth pathway can be identified, there is the potential to block or inhibit growth using drug therapy.

The two most promising receptors that have been identified to date are epidermal growth factor receptors (EGFR) and vascular endothelial growth factor (VEGF) receptors. A large number of agents that block these receptors when they bind to them, either by biochemical means or as monoclonal antibodies, are being studied. The first to receive a licence in the UK was erlotinib (Tarceva), an EGFR antagonist. This is an oral preparation that has been demonstrated to lead to a significant improvement in survival and symptom palliation in patients with advanced NSCLC who have relapsed after first and second line chemotherapy. A small proportion of patients indeed experience a dramatic response. The side effects are largely limited to skin rash and diarrhoea — much less troublesome than those associated with conventional chemotherapy.

Palliative care Since most patients with lung cancer are unlikely to be cured of their disease and distressing symptoms are common, high quality specialist palliative care is a vital part of any lung cancer service. Apart from the more well-known elements of palliative care such as relief of pain and breathlessness, there are a variety of specialist interventions that can have a major impact on quality of life. These include stenting of larger airways and the superior vena cava and laser treatment of large airway obstruction. Many such techniques are only available in specialist centres.

Follow-up

After treatment, patients are followed up on a regular basis by their oncologist or surgeon

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Think about your line of questioning when selling products for cough and, where appropriate, make sure people know they can ask their GP for a chest X-ray.
2. November is lung cancer awareness month. Increase awareness in your pharmacy. Leaflets and posters are available at www.roycastle.org/patient/lcam.htm
3. Set up a smoking cessation service.

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

Resource

- National Institute for Health and Clinical Excellence. Referral for suspected cancer. Available at www.nice.org.uk (accessed 18 October 2006).

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1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *Cancer Journal for Clinicians* 2005;55:74–108.
2. Toms JR (editor). *CancerStats Monograph*, London: Cancer Research UK; 2004.
3. Birring SS, Peake MD. Symptoms and the early diagnosis of lung cancer. *Thorax* 2005 60:268–9.
4. Department of Health. The NHS national cancer plan. London: Department of Health; 2000.
5. Department of Health. Waiting times for cancer – progress, lessons learnt and next steps. London: Department of Health; 2006.
6. National Institute for Health and Clinical Excellence. Diagnosis and treatment of lung cancer. Available at www.nice.org.uk (accessed 18 October 2006).

and consideration is given to second-line treatments, including chemotherapy, palliative radiotherapy or erlotinib, if there is evidence of recurrence.

The chances of response to second (and subsequent) lines of treatment are less than are associated with first-line treatment and toxicity can be worse, so careful assessment of each patient is essential to decide the potential benefits of a treatment. Patients usually remain under follow up, though at increasing intervals, until either they die or have survived five years.

Conclusion

Early detection of lung cancer is one of the major ways in which overall outcomes can be improved. Methods of screening high-risk patient groups are being studied, including the use of low-dose CT screening and sputum cytometry (an advanced form of sputum cytology using automated molecular biological techniques). Increased awareness of early symptoms of the disease will be an important element of any such strategy.

The biology of lung cancer is being unravelled and we are now in sight of being able to target treatment more precisely. This is already beginning to happen with the EGFR antagonist erlotinib mentioned above. Moreover, better standards and organisation of care resulting from the National Cancer Plan are beginning to make a major difference to the quality of care and outcomes for lung cancer patients. However, there is still much more that can be done.

Reducing the numbers of people who start smoking would clearly have a major impact on the incidence of lung cancer, but stopping smoking also significantly reduces the risk of developing lung cancer so the obvious way in which pharmacists can contribute in the area of lung cancer is to support smokers to give up. If we could stop a significant proportion of 50-year-olds smoking, it would result in a major reduction in the mortality from the disease.

However, pharmacists working in the community also advise patients with respiratory symptoms. They should advise those with persistent cough or dyspnoea to seek urgent medical advice and to consider asking their GP for a chest X-ray. I suspect that if pharmacists were more alert to the symptoms of lung cancer and the characteristics of the at-risk groups and took a proactive approach, many more patients could be detected earlier in the course of their disease and would, therefore, have a greater chance of curative treatment. Next time you advise a customer with a cough, think about the following:

- Is he or she over 50 years old?
- Is he or she a smoker or ex-smoker?
- Does he or she have COPD or symptoms?
- Could he or she have been exposed to asbestos?
- Could he or she have a previous history of cancer?

Correction

The left lung has two lobes and not three as stated in this Continuing Professional Development article. The right lung has three lobes. This can be important when viewing chest X-rays.