

Diagnosis and treatment of lung cancer: a focus on the GP's role

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Key points

- Patients with nonresolving respiratory symptoms warrant investigations to exclude malignancy.
- Staging is the cornerstone of lung cancer prognosis, and also guides treatment.
- Patients with lung cancer are best managed by multi-disciplinary teams, often with multimodality treatment.
- Early palliative care input for patients with advanced lung cancer improves quality of life.
- Smoking cessation is the most effective intervention to prevent lung cancer.

The lung cancer epidemic has mirrored changes in smoking patterns in Western countries and has caused innumerable deaths. Approaches to identification, diagnosis and treatment of the disease are changing and are discussed in this article.

Lung cancer is the second most common cancer and leading cause of cancer death worldwide, with an incidence of 1.6 million new cases annually and 1.38 million deaths in 2008.¹ In Australia, it is the fifth most common cancer and the leading cause of cancer death. There are approximately 9700 new cases of lung cancer diagnosed each year. In 2007, there were 7626 deaths from lung cancer in Australia, accounting for 19% of all cancer deaths.^{2,3}

There have been major changes in the epidemiology of lung cancer, and the treatment of patients with lung cancer has become more complex. Therefore, this article aims to provide an update on diagnosis and treatment of lung cancer with a specific focus on the role of GPs in the management process.

EPIDEMIOLOGY

The overall incidence of lung cancer in men is decreasing whereas the incidence in women, after increasing in the past decade, is now plateauing. There is an increase in the incidence of lung cancer among never smokers, particularly among females. Furthermore, this trend seems to be more prominent in East Asian countries, with adenocarcinoma being the predominant histopathology. However, smoking remains the major cause of lung cancer.

Squamous cell carcinoma was previously the predominant histology in patients with smoking-related lung cancer. However, adenocarcinoma has now become the predominant histology, both in smokers and nonsmokers.

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PRESENTATIONS AND INITIAL INVESTIGATIONS

The presentations of patients with lung cancer are variable. Patients can be completely asymptomatic and have an incidental finding of a lung nodule on a chest x-ray carried out during a preoperative anaesthetic assessment or CT scan for another purpose. Some patients may present with nonresolving or recurrent pneumonia with persisting consolidation on chest x-ray whereas others may present with cough, chest pain, shortness of breath or haemoptysis, which may or may not be associated with constitutional symptoms, such as lethargy or loss of appetite or weight. As up to 50% of lung cancer has metastasised at the time of presentation, the symptoms may be those of metastatic disease, distant from the thorax. Patients with lung cancer may be current smokers, ex-smokers or lifelong non-smokers. Regardless of smoking history, non-resolving or unexplained symptoms warrant further investigation.

A chest x-ray is the most appropriate initial investigation. Not all x-ray detected solitary lung nodules are malignant; other possibilities include hamartoma or postinfection granuloma. Comparison with previous chest x-rays, if available, may assist in understanding the nature of lung nodules. Further investigation with a CT scan of the thorax is usually required to characterise the lung nodule, and assess whether it is solitary, its location and its relationship with other structures. CT scans of other regions (e.g. abdomen or brain) may be needed depending on the symptoms.

All patients with evidence or suspicion of lung cancer should be referred to a specialist with a specific interest in, and knowledge of, lung cancer. Most commonly this will be a respiratory physician or thoracic surgeon who will be in a position to determine the need for further evaluation, including lung function testing and biopsy. Newly confirmed cases of lung cancer should be managed by clinicians who are members of a multidisciplinary team (usually including thoracic surgeons, respiratory physicians, pathologists, radiologists, nuclear medicine physicians, medical and radiation oncologists, palliative care physicians



and nurses). Depending on the stage of the disease and the patient's cardiovascular fitness levels, patients will be referred to surgeons for resection or to medical and radiation oncologists for chemotherapy and/or radiotherapy. In an increasing number of cases, multimodality treatment is appropriate.

DIAGNOSIS

It is important to make a prompt and accurate diagnosis of suspected lung cancer, and to manage the patient adhering to best practice guidelines. In most patients a tissue diagnosis is of great importance because the histological type of cancer has an impact on further management. Nonsmall cell lung cancer (NSCLC) accounts for 80% of cases of lung cancer, whereas small cell lung cancer (SCLC) accounts for approximately 15 to 20%, with rare tumours such as carcinoid accounting for less than 5%. In some situations it is possible to treat patients without a tissue diagnosis but this should be the exception.

Lung tissue is commonly obtained by one of several methods depending on the location of the tumours. For peripherally located lesions, tissue is obtained by radiologically guided fine-needle aspiration or core biopsy of a lung nodule. For centrally located lesions,

ESSENTIAL COMPONENTS IN LUNG CANCER MANAGEMENT**Establish a tissue diagnosis**

- Sputum cytology
- CT-guided fine-needle aspiration/ biopsy
- Bronchoscopy with biopsy
- Endobronchial ultrasound and transbronchial needle aspirations

Assess the extent of the disease

- Clinical assessment
- CT scan of thorax with or without abdomen, brain and bone scan
- PET scan

Assess the patient's cardiorespiratory fitness for surgery and subsequent treatment modalities

- Exercise tolerance
- Lung function
- Performance status

bronchoscopy with brushings, washings and biopsy is performed. Sometimes, surgical biopsy of mediastinal lymph nodes using mediastinoscopy is required, either as the primary method of obtaining a tissue diagnosis or as a means of confirming or excluding malignancy in enlarged nodes. A less invasive procedure for this has recently been developed, involving endobronchial ultrasound and transbronchial needle aspiration. Finally, a biopsy of metastatic sites (e.g. liver or distant lymph nodes) may be used to make a diagnosis.

STAGING

The prognosis of patients with lung cancer depends on the stage of the disease. Staging investigations for NSCLC include a CT scan of the thorax and whole body positron emission tomography (PET) scanning. Staging investigations of SCLC

KEY POINTS IN LUNG CANCER TREATMENT**Nonsmall cell lung cancer**

- Stage I: surgery
- Stage II: surgery + adjuvant platinum-based chemotherapy +/- radiotherapy
- Stage IIIA: induction chemotherapy followed by surgery and radiation or concurrent chemoradiotherapy
- Stage IIIB: concurrent chemoradiotherapy
- Advanced or metastatic: palliative chemotherapy, targeted therapy and radiotherapy

Small cell lung cancer

- Limited stage: sequential or concurrent chemoradiotherapy +/- prophylactic cranial irradiation
- Extensive stage: palliative chemotherapy +/- prophylactic cranial irradiation

include CT scans of the brain, thorax and abdomen, and bone scans. A PET scan is not currently reimbursed for staging of SCLC, although it is able to provide valuable information and would preclude the need for other investigations.

A detailed description of the staging system for lung cancer is beyond the scope of this article, and details are available elsewhere.⁴ NSCLC is staged according to the TNM (tumour, node, metastasis) staging system. Broadly, stage I is localised to the lungs and stage II is localised to the lungs with ipsilateral local lymph node involvement or a large primary, whereas stage III disease is locally advanced with mediastinal lymph node involvement. Stage IV disease indicates the presence of distant metastases or a malignant pleural effusion. Although the same staging system can be used for SCLC, more commonly a two-stage system is used. Limited

SCLC describes disease confined to one hemithorax and the ipsilateral supraclavicular nodal, whereas extensive SCLC refers to any greater extent of disease.

TREATMENT

Patients with stage I to IIIA NSCLC and those with limited stage SCLC have a potentially curable disease and should be assessed and treated by clinicians who are part of a multidisciplinary team. Treatment approaches depend on the stage of the disease, the cell type and fitness of the patient (see the boxes on this page).

Nonsmall cell lung cancer*Early (stage I and II)*

Surgery remains the mainstay of treatment for patients with early NSCLC. The extent of surgery is dependent on both the fitness of the patient as well as the characteristics of the tumour, including its size and location and the extent of local spread. Surgical procedures include pneumonectomy, lobectomy or lesser resections, such as wedge resection or segmentectomy. Overall 70% of patients with stage I disease and 50% of those with stage II disease will be cured.

Following surgical resection, adjuvant chemotherapy may result in further improvement in outcomes, particularly in patients with stage II disease. However, the size of the additional benefit is modest (approximately 5% improvement at five years)⁵ and patients need to be fit enough to tolerate treatment. Typically, four cycles of chemotherapy are administered over 12 to 16 weeks.

For those patients who have undergone complete surgical resection for a localised peripheral tumour, there is no evidence that postoperative radiotherapy improves outcomes. Surgery is not always possible because of impaired lung function or the comorbidities that patients may have. Radiotherapy is an alternative for these patients. Stereotactic radiotherapy, a relatively recent development, may result in better outcomes for these patients.

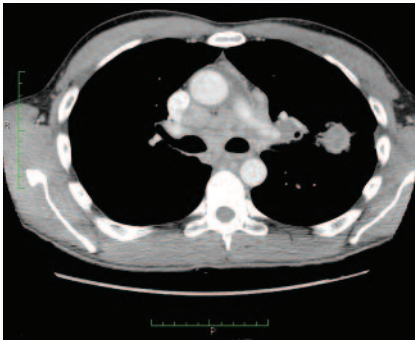


Figure 1. CT scan of a patient with locally advanced (stage IIIB) adenocarcinoma of the lung, with bilateral mediastinal lymph nodal involvement.

Locally advanced (stage IIIA and IIIB)

Patients with stage IIIA NSCLC have tumours in the lungs, with involvement of ipsilateral mediastinal lymph nodes. Possible management approaches for these patients include trimodality treatment with induction chemotherapy, followed by surgery and then radiotherapy or concurrent chemoradiation. There is controversy concerning the optimal approach and decisions as to how these

patients are treated often depend on the expertise and experience of the treating team. Approximately 25% of patients with stage IIIA disease are cured.⁶

In stage IIIB disease there is bilateral mediastinal nodal involvement that is not amenable to surgical resection (Figure 1). Similarly, tumours that involve structures, such as the mediastinum or vertebral bodies, are also not amenable to surgical resection even if there is no nodal spread. These patients, if fit enough, are treated with concurrent chemotherapy and radiation, delivered over a period of about six weeks. The intent of treatment is cure or long-term disease control, with approximately less than 10% of patients being cured.⁶

Advanced or metastatic (stage IV)

Chemotherapy, new targeted therapies and radiotherapy are the primary treatments available for 50% of patients who present with metastatic disease or develop it after failure of treatment during the early stages of NSCLC. Although these patients will ultimately succumb to their disease, there is good evidence that both

prolongation of survival and improved quality of life occur with modern chemotherapy regimens, whereas radiotherapy is effective in controlling symptoms, including pain, cough, haemoptysis and the symptoms of cerebral metastatic disease. Irrespective of the treatment approach used, good palliative care support involving the patient's GP, along with specialist medical and nursing palliative care services is important.

A major change in the approach to advanced NSCLC has been the recognition that tumour characteristics, such as histology, and the presence of genetic changes can be used to guide and 'personalise' therapy. Examples include the preferential use of pemetrexed-based chemotherapy in patients with non-squamous tumours (and its avoidance in those with squamous histology), and the first-line use of targeted therapies in patients whose tumours have mutations in genes, such as the epidermal growth factor receptor gene (*EGFR*) and echinoderm microtubule-associated protein-like 4 and anaplastic lymphoma kinase genes (*EML4-ALK*). Somatic mutation at the tyrosine kinase domain of the *EGFR* gene has been shown to be important in the pathogenesis of some forms of lung cancer. Therapy with oral tyrosine kinase inhibitors, such as gefitinib and erlotinib, has been associated with a rapid response (see Figures 2a and b) and significant progression-free survival in patients who possess the *EGFR* mutation (approximately 15 to 20% of adenocarcinomas in western countries). However, resistance eventually develops after nine to 13 months of treatment. Furthermore, approximately 5% of NSCLC contain a fusion of oncogenes (*EML4-ALK*), which are mutually exclusive from the *EGFR* mutation and occur more commonly in nonsmokers. New oral inhibitors, such as crizotinib, are being developed to specifically target this abnormality but are currently only available in the context of clinical trials.



Figures 2a and b. Chest x-ray of a patient with metastatic adenocarcinoma of the lung with an activating *EGFR* mutation before (a, left) and seven days after (b, right) commencing treatment with gefitinib. There is rapid clearing of the nodular malignant infiltrate.

Small cell lung cancer

Limited stage

SCLC is highly sensitive to chemotherapy and radiotherapy. Therefore, the primary treatment is chemotherapy (platinum-based with etoposide) combined with concurrent thoracic radiotherapy. A meta-analysis has shown that this approach improves survival and reduces local recurrence.⁷ This is given with curative intent with a five-year survival rate of 10 to 20% and median survival of up to 22 months. Brain micrometastases may be present at the time of diagnosis despite a negative brain scan, and the brain is a common site of relapse after therapy. Therefore, prophylactic cranial irradiation (PCI) is appropriate in those patients who demonstrate a good response to chemoradiotherapy and who remain in good performance status after the completion of their concurrent treatment.

Extensive stage

Platinum with etoposide chemotherapy is the first-line treatment for patients with extensive SCLC. The response rate is up to 70% initially. However, SCLC inevitably progresses. Overall, the response rate to subsequent chemotherapy in recurrent or refractory SCLC is poor. A recent study has demonstrated benefit from PCI in those patients with extensive disease who respond well to initial chemotherapy.⁸ Radiotherapy to the primary site is generally not indicated in the initial treatment of extensive SCLC.

ROLE OF THE GP (METROPOLITAN OR RURAL)

GPs play a critical role in lung cancer management, from the initial phase of diagnosis, through to liaising with all members of the multidisciplinary team and acting as patient advocates (see the

ROLE OF THE GP IN THE MANAGEMENT OF LUNG CANCER

- Smoking cessation education
- Vigilance in assessing high-risk patients with symptoms
- Liaison with specialists to ensure prompt diagnosis and treatment
- Management of chemotherapy and radiotherapy toxicities
- Palliation of symptoms such as pain and shortness of breath
- End of life care

box on this page). They act as a bridge between specialists and patients. Their role is multifaceted, including liaison with hospital specialists, management of

chemotherapy and radiotherapy toxicities, palliation of symptoms and ultimately end of life care. At the time of presentation, GPs have an important role in providing advice and support relating to smoking cessation, which is critical for any patient who is to be considered for surgical resection.

There are some patients who are not suitable for aggressive anticancer therapy, either due to advanced disease or severe comorbidities. This may be from the time of diagnosis or after progression of their disease despite therapy. Referral of these patients to a palliative care service is an appropriate option for these patients, but GPs continue to play an invaluable role in the palliation of symptoms in patients with lung cancer. Palliative care services may not be available in all geographical areas. Research has shown that early palliative care input improves quality of life, mood and even prolongs median survival.⁹ Therefore, GPs are encouraged to be involved in the palliative and end of life care of patients from the early stages of the diagnosis.

LUNG CANCER SCREENING

Over the years, there have been numerous studies examining screening for lung cancer with chest radiograph with or without sputum cytology. However, these studies did not show any population mortality benefit. Therefore, population screening with chest radiography has not been recommended.

The recent US multicentre randomised clinical trial published in the *New England Journal of Medicine* has reignited the debate about lung cancer screening.¹⁰ It demonstrated that screening with a low-dose CT scan resulted in a relative reduction in lung cancer mortality of 20% among current and ex-smokers with a heavy smoking history (30 pack years or more) aged between 55 and 74 years when compared with chest radiograph alone. This is the first study that has shown a reduction in lung cancer mortality using a

low-dose CT scan as the screening tool. This is a promising and exciting result. However, there are a number of unanswered questions that need to be addressed before a low-dose CT scan is accepted as a population-wide screening tool.

The most appropriate duration of screening was not determined by this study. There are no well-defined consensus guidelines on the management and follow up of suspicious lung nodules. Those who screen positive tend to have early localised disease; therefore, minimally invasive surgical resection may be required. However, the availability of such a service is highly variable. Furthermore, the availability of low-dose CT screening and the expertise in interpreting these images are also variable. Therefore, until these issues are addressed, it is premature to offer low-dose CT screening to all current or past heavy smokers.

CONCLUSION

Lung cancer is a major health problem. Prevention of this disease is better than cure, and consequently smoking cessation education is vitally important to curb the incidence of lung cancer. Lung cancer management is complex and highly specialised; therefore, referral of these patients to a specialist who is part of a multidisciplinary team should be the standard of care.

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