Lifelong Learning

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Diagnosis and Treatment of Lung Cancer: A Focus on the GP's Role

The lung cancer epidemic has mirrored changes in smoking patterns in many 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] However, 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 offers 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, but 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 non-smokers.

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 non-resolving 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. Since as much as 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 post-infection granuloma. Comparison with previous chest x-rays, if available, may assist in understanding the nature of lung nodules. Further investigation of the thorax with a CT scan 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 (eg, 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

Key points

- Patients with non-resolving respiratory symptoms warrant investigations to exclude malignancy.
- Staging is the cornerstone of lung cancer prognosis and 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.

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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

Key points in lung cancer treatment

Non-small 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

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 either 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 by 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. Non-small 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, 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, recently developed, involves endobronchial ultrasound and trans-bronchial needle aspiration. Finally, a biopsy of metastatic sites (eg, 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 include CT scans of the brain, thorax and abdomen, and bone scans. A PET scan 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.[2] 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 supracla-vicular 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).

Non-small 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 and 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, particu-

larly in patients with stage II disease. However, the size of the additional benefit is modest (approximately 5% improvement at five years)[3] 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.

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.[4]

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 about six weeks. The intent of treatment is cure or long-term disease control, with less than 10% of patients being cured.[4]

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, with specialist medical and nursing palliative care services, is important.

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

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 erlotinib, has been associated with a rapid response 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, about 5% of NSCLC contain a fusion of oncogenes (EML4-ALK), which is mutually exclusive from the EGFR mutation and occurs more commonly in non-smokers.

New oral inhibitors, such as crizotinib, are being developed to specifically target this abnormality but are currently available only in the context of clinical trials.

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.[5] 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.[6] Radiotherapy to the primary site is generally not indicated in the initial treatment of extensive SCLC.

Role of the GP

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 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, 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, but GPs continue to play an invaluable role in the palliation of symptoms. Research has shown that early palliative care input improves quality of life, mood and even prolongs median survival.[7] 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.[8] 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 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 expertise in interpreting these images are also variable, so until these issues are addressed it is premature to offer low-dose CT screening to all current or past heavy smokers.

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

Conclusion

Lung cancer is a major health problem. Since prevention of this disease is better than cure, smoking cessation education is vitally important. 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.

References are available on request

SAMA Warns Doctors Against Working in the United Arab Emirates

The South African Medical Association (SAMA) has warned local health professionals against applying for positions in the United Arab Emirates (UAE) and similar countries in the wake of the incarceration of respected veteran paediatrician, Prof Cyril Karabus, in Abu Dhabi.

SAMA has also advised doctors already working in the UAE to withdraw their services to avoid the risk of a Karabus-type experience.

"We advise SA doctors and other health professionals to avoid working in the UAE and would ask that those already there, consider withdrawing their services in the interest of their own safety," Dr Mzukisi Grootboom, SAMA chairperson, notes in the statement.

Prof Karabus, a retired Red Cross Children's Hospital paediatric haematologist, was arrested while in transit through Dubai in August after having been tried and convicted in absentia in 2003 for the death of a three-year-old patient he had treated during a locum at an Abu Dhabi hospital in 2002. He and his family were returning from his son's wedding in Canada and was unaware of the decade old judgment against him.

It took five court appearances and almost eight weeks in prison before the physically unwell 78-year-old medical specialist was finally granted bail in October.

There have been several subsequent hearings, but all have been postponed. One of the main stumbling blocks has been the inability of the prosecution to produce the original medical records of the case.