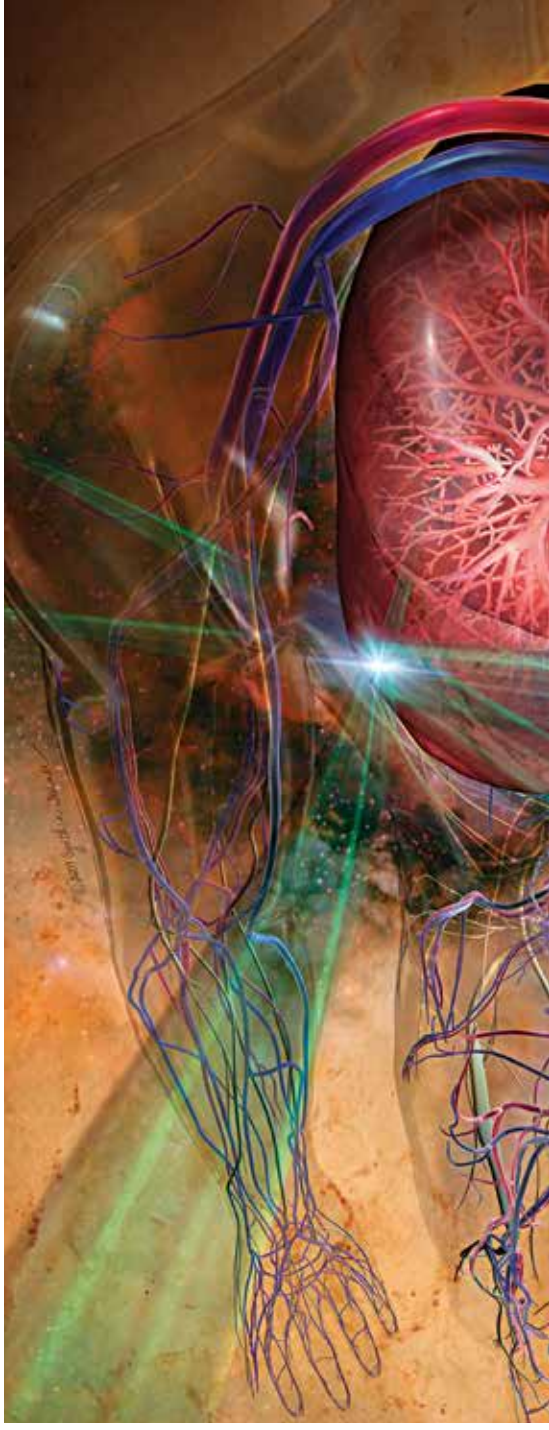
# Lung cancer

## What's new in prevention, diagnosis and treatment

**SAMANTHA ENNIS** MB BS(Hons), BAppSc(Phty)(Hons)
**VENESSA CHIN** MB BS, FRACP, PhD; **EMILY STONE** MB BS, MMed, FRACP

**Primary care practitioners have a crucial role in the prevention and early detection of lung cancer and urgent referral of patients with suspected lung cancer. Involvement of a multidisciplinary team in treatment planning is related to improved outcomes.**



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Lung cancer refers to malignancies originating from the bronchial tree or pulmonary parenchyma. It is one of the most common, lethal and preventable tumour entities. Nevertheless, significant progress in research has provided new hope through advances in lung cancer screening and diagnostic techniques, evidence of improved clinical outcomes related to smoking cessation, and new treatments such as targeted and immune therapies.

### Epidemiology

Lung cancer is the leading cause of cancer-related death worldwide and the fifth most common cancer diagnosed in Australia.[1,2] It is estimated that 9034 deaths in Australia in 2019 will be directly attributable to lung cancer.[2] Among both men and women, the incidence of lung cancer is low in those under 40 years of age and increases up to 75 to 80 years of age in most populations.[3]

Nonsmall cell lung cancer (NSCLC) accounts for about 85% of all lung cancers, and small cell lung cancer (SCLC) comprises most of the remainder.[4] This distinction is essential for staging, treatment and prognosis.

NSCLC refers to a heterogeneous group of tumours that includes adenocarcinoma (50%), squamous cell carcinoma (40%) and large cell carcinoma (10%).[5] The most common histological category of NSCLC is adenocarcinoma, both in smokers and nonsmokers. The incidence of adenocarcinoma has risen dramatically and there has been a corresponding decrease in the incidence of other types of NSCLC and SCLC. This is thought to result at least in part from changes in the design of cigarettes and their composition, particularly since the mid-20th century.[6]

### Risk factors

Several environmental, occupational and individual risk factors have been associated with the development of lung cancer, of which cigarette smoking is the most important. Current

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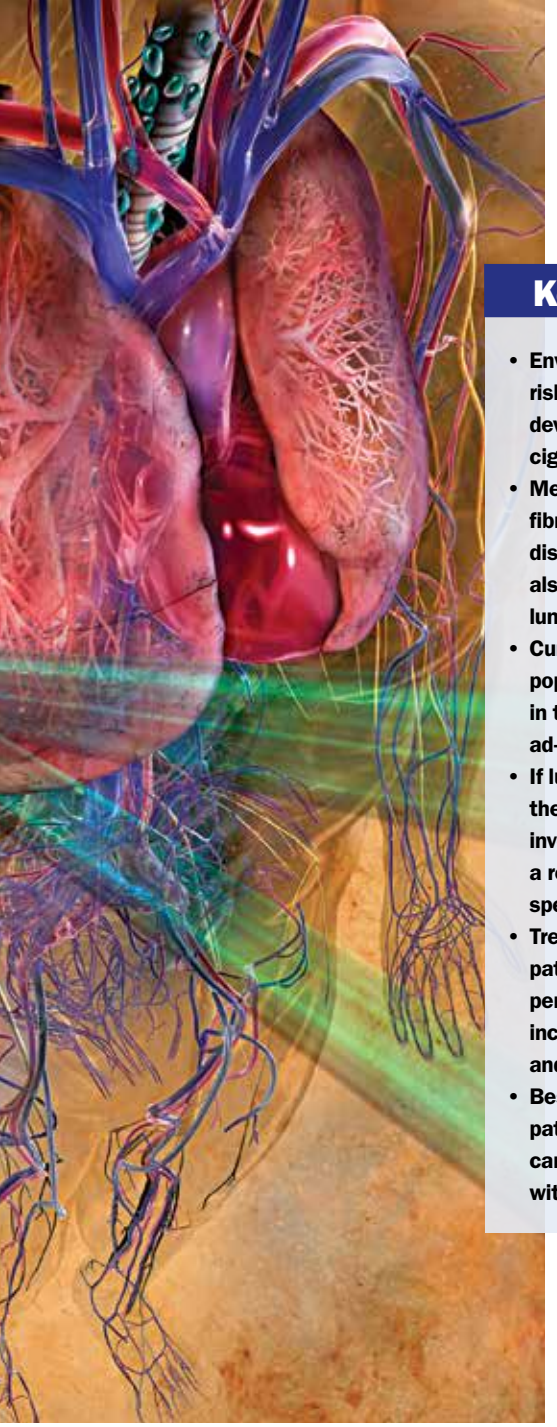
Dr Ennis is a Respiratory Registrar in the Department of Thoracic Medicine, St Vincent's Hospital Sydney. Dr Chin is a Medical Oncologist and Post Doctoral Research Officer in the Department of Medical Oncology, Kinghorn Cancer Centre, St Vincent's Hospital Sydney, Garvan Institute of Medical Research, Sydney; and Conjoint Lecturer at UNSW Sydney. Dr Stone is a Senior Staff Specialist in the Department of Thoracic Medicine, Kinghorn Cancer Centre, St Vincent's Hospital Sydney; and Conjoint Senior Lecturer at UNSW Sydney, Sydney, NSW.



## Key points

- **Environmental, occupational and individual risk factors have been associated with the development of lung cancer, of which cigarette smoking is the most important.**
- **Medical comorbidities such as pulmonary fibrosis, chronic obstructive pulmonary disease and pulmonary tuberculosis are also associated with increased risk of lung cancer.**
- **Currently, Australia does not have a population-based screening program and, in the absence of a coordinated approach, ad-hoc screening is discouraged.**
- **If lung cancer is suspected, a CT scan of the chest is the most appropriate initial investigation, although chest x-ray may be a reasonable first investigation for less specific symptoms.**
- **Treatment approaches depend on the pathological diagnosis, disease stage and performance status of the patient and include surgery, chemotherapy, radiotherapy and immunotherapy.**
- **Best-practice guidelines recommend that patients with known or suspected lung cancer be referred to a specialist who works with a multidisciplinary team.**

smokers have a nine times higher risk of developing lung cancer than nonsmokers.[7] Nevertheless, one in three women and one in 10 men diagnosed with lung cancer have no history of smoking.[8] Other risk factors include environmental toxins such as passive smoke inhalation, air pollution (in particular traffic pollution through diesel engine exhaust, coal burning in poorly ventilated houses, burning of wood and fumes from high temperature cooking using unrefined vegetable oils) and occupational exposure to radon and asbestos.[3] Medical comorbidities such as underlying lung disease, in particular pulmonary fibrosis, chronic obstructive pulmonary disease and pulmonary tuberculosis, are also associated with increased risk of lung cancer.[3,9] HIV, radiation therapy involving the chest and a family history of lung cancer also have positive associations.[3,10]

## Prevention

### Tobacco cessation

Research has shown that continued smoking among cancer patients can increase overall and cancer-specific mortality, the risk of a second primary cancer and the risk of toxic effects of cancer treatments, and is associated with significant incremental costs for subsequent cancer treatments.[11,12] Health professionals play an important role in assessing smokers' dependence on nicotine and in providing education as well as motivation and assistance to quit. Support for smoking cessation including evidence-based pharmacotherapy should be offered to all smokers who have evidence of nicotine dependence and are motivated to quit.[13] First-line options in Australia include nicotine replacement therapy, varenicline and bupropion, with the choice of pharmacotherapy based on clinical suitability and patient choice.

### Electronic nicotine delivery systems, including e-cigarettes

Electronic nicotine delivery systems (ENDS), including e-cigarettes, are battery-operated devices that heat a liquid and deliver an aerosolised product to the user.[14] Owing to the significant carcinogenic role tobacco smoking has in the development of lung cancer, electronic cigarettes have been proposed as a suitable aid for smoking cessation. Although a recent randomised controlled trial showed e-cigarettes were more effective for smoking cessation than nicotine replacement therapy, the use of e-cigarettes remains contentious.[15] E-cigarette aerosol is not harmless and contains a variety of chemical constituents that may expose users to substances known to have adverse health effects, including ultrafine particles, heavy metals, volatile organic particles and other toxic substances.[16,17]

Although the long-term health impacts of ENDS are not yet known, a recent epidemic of severe pulmonary illnesses linked to e-cigarette use is concerning. One recent report documents a case series of severe pulmonary disease in 53 generally healthy young people who had a history of e-cigarette and related product use within 90 days. Of these, 98% had respiratory symptoms at hospital presentation, the most common symptom being shortness of breath (87%). Intensive care unit admission for respiratory failure was common (58% of all patients; 62% of hospitalised patients), and one person died.[14] Until more is known, it is recommended that people refrain from using ENDS and that first-line smoking cessation therapy should continue to comprise counselling plus approved pharmacotherapies.[18] The Australian Department of Health has recently issued a statement on risks of e-cigarettes that recommends prompt identification of e-cigarette use in patients with unexplained respiratory symptoms and use of evidence- based treatments for smoking cessation.[19]

### Key resources on lung cancer for GPs and their patients

**Lung Foundation Australia**

**Lung cancer multidisciplinary team directory:**
https://lungfoundation.com.au/lung-cancer-mdt

**Support groups:**
https://lungfoundation.com.au/patients-carers/get-support/support-groups

**Cancer Council Australia**

**Optimal care pathway for people with lung cancer:**
https://www.cancer.org.au/health-professionals/optimal-cancer-care-pathways.html

**Investigating symptoms of lung cancer: a guide for GPs:**
https://canceraustralia.gov.au/sites/default/files/publications/lung-cancer-gp-guide-2012_509ae0cdd2e36.pdf

### Screening

Screening high-risk current and former smokers for lung cancer with low-dose CT (LDCT) scanning of the chest has been shown to reduce lung cancer mortality.[20,21] LDCT lung cancer screening is recommended in some countries for eligible individuals.[22] Currently, Australia has no population-based screening program and, in the absence of a co-ordinated approach, ad-hoc screening is discouraged.[23] Progress may be made towards a national screening program when important knowledge gaps in defining the optimal criteria for use of low-dose CT screening for lung cancer in high-risk individuals are addressed in the International Lung Screen Trial. This is an international multicentre prospective cohort study currently underway with multiple recruitment sites in Australia and Canada.[24]

## Presenting symptoms and initial investigations

The initial presentation of patients with lung cancer is highly variable. Incidental detection of imaging abnormalities may occur in asymptomatic patients. Imaging abnormalities can range from a solitary lung nodule to an obstructing lung mass with distal collapse. Some patients may present with nonresolving or recurrent chest infections with persisting chest x-ray changes. In symptomatic patients, the most common clinical presentations include cough, haemoptysis, dyspnoea and chest pain. There may also be constitutional symptoms such as general malaise, lethargy and unexplained weight loss. The presence of symptoms often represents advanced disease and typically portends a less favourable prognosis.[25] About 10 to 15% of patients who have lung cancer develop a malignant pleural effusion during the course of their disease;[26] however, not all pleural effusions in patients with lung cancers are malignant. At the time of diagnosis up to 50% of lung cancers have metastasised. The most common sites of metastases include the liver, bone and brain.

If lung cancer is suspected, a thorough history and physical examination should be undertaken. Depending on the symptoms and level of suspicion, a chest x-ray or CT scan of the chest should be done promptly. A pulmonary nodule is not always malignant, and on a single examination the clinical significance of a small lung nodule may be unknown. Consensus guidelines published by the Fleischner Society are widely used in clinical practice for follow-up of lung nodules detected using CT.[27] If serial CT scans are available, features that are concerning for malignancy include:

- persistent growth on two sequential scans
- increase in the density or solid component of a nonsolid or semisolid lesion
- lesions greater than or equal to 10 mm in diameter
- semisolid nodules.[28]

The goal of initial evaluation is to obtain sufficient clinical and radiological information to guide diagnostic tissue biopsy, staging and treatment. All patients with suspected lung cancer should be referred to a specialist with specific expertise in lung cancer. Best-practice guidelines recommend that patients with known or suspected lung cancer be referred to a specialist who works with a multidisciplinary team (MDT). Lung Foundation Australia has a nationwide list of lung cancer MDTs to facilitate timely referrals (Box).

Resources to assist in the initial work-up of patients with lung cancer include the Cancer Australia guideline, *Investigating symptoms of lung cancer: a guide for GPs*. The Cancer Council Victoria optimal care pathway also provides excellent guidance for primary evaluation of suspected lung cancer and recommends provision of results to the patient within one week and a prompt specialist appointment within two weeks of referral (Box).

## Diagnosis

In patients with suspected lung cancer the initial work up aims for timely and accurate diagnosis and staging so appropriate therapy can be planned and administered. A pathological diagnosis is paramount in the diagnosis of lung cancer as treatment options are determined on the basis of histological and molecular features. In some situations it may be possible to treat patients without a tissue diagnosis, but these 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 may be obtained by radiologically guided fine needle aspiration or core biopsy of the lung nodule. An important consideration before attempting this procedure is the patient's underlying lung condition and function, given the significant risk of pneumothorax, which has a reported incidence of about 20%.[29] Bronchoscopic sampling of peripheral lesions has also become possible in recent years, using advanced technologies such as ultra-miniature radial probe endobronchial ultrasound and ultra-thin bronchoscopes, which have dramatically improved diagnostic accuracy.

For centrally located lesions, endobronchial ultrasound-directed biopsy has emerged as the most common modality. This technique enables sampling of mediastinal lymph nodes, establishing diagnosis and staging concurrently. Therefore, in selected patients with accessible mediastinal and or hilar lymph nodes shown on either CT or positron

emission tomography (PET)-CT scanning, it is now feasible to achieve staging and diagnosis with endobronchial ultrasound-guided fine needle aspirate (EBUS-FNA) as the first diagnostic test.[30] Other techniques to obtain tissue in the case of centrally located lesions include bronchoscopy with brushings, washing and endobronchial biopsy. In patients with positive cervical and/or axillary nodes, pleural disease or distant metastases, percutaneous sampling of such nodes, pleural effusions or deposits to achieve diagnosis and staging may also be considered as the first diagnostic test.[30]

In patients with NSCLC, accurate subclassification is required to determine optimal treatment. Immunohistochemical stains can be used to assist in distinguishing tumours that are more likely to be adenocarcinomas from those more likely to be squamous cell carcinomas and can be completed in small biopsy and cytology samples.

The discovery of treatable oncogenic alterations has led to molecular testing being recommended as part of the standard approach to further classify NSCLC.[31] This includes testing for mutations in the gene encoding epidermal growth factor receptor (EGFR) and translocations in the genes encoding anaplastic lymphoma kinase (ALK).[31] This information is required to help determine the most appropriate first-line treatment because of the availability of tyrosine kinase inhibitors (TKIs) that specifically target these mutations. Other commonly performed tests include rat osteosarcoma gene ( *ROS1)* rearrangement (treatable with TKIs) and *PD-L1* expresssion (associated with response to immunotherapy).[31] Currently, most of these molecular tests can be performed on small biopsy samples and in cytological specimens, but the need for adequate specimens to clarify treatment pathways is nevertheless driving the need for increased tissue biopsies.

## Staging

NSCLC is staged according to the TNM (tumour, node, metastasis) staging system. Correct TNM-based staging of lung cancer is essential, given the large differences in survival according to tumour stage. International guidelines vary in their recommendations but generally include PET-CT scanning in diagnostic and staging algorithms for lung cancer.[32-34] The optimal timing of PET-CT scanning in the work up of known or suspected NSCLC is unclear. Therefore, in the absence of evidence to guide optimal timing, Australian guidelines recommend considering the use of PET-CT scanning before a diagnostic biopsy to guide the biopsy and help stage disease, or alternatively at any stage in the diagnostic work up to evaluate the extent of metastatic disease.[35]

A detailed description of the TNM staging system used in NSCLC can be found elsewhere.[36] The stages are broadly defined as follows:

- **Stage I** disease is localised to the lungs
- **Stage II** disease is localised to the lungs and ipsilateral local lymph nodes
- **Stage III** disease is locally advanced with mediastinal lymph node involvement
- **Stage IV** disease is indicated by the presence of distant metastases or a malignant pleural effusion.

In cases of SCLC, a longstanding two-stage system is commonly used in clinical discussion, although formal TNM staging is also appropriate.[37] Limited SCLC is disease confined to the ipsilateral hemithorax and regional nodes included in a single tolerable radiotherapy field. Extensive disease refers to tumour beyond the boundaries of limited disease, including distant metastases.

Confirmation of diagnosis and staging with appropriate treatment planning should ideally be subject to discussion within an MDT meeting involving the full range of specialties involved in lung cancer care, including respiratory physicians, medical oncologists, radiation oncologists, radiologists, pathologists, thoracic surgeons, palliative care physicians and allied health staff specialised in lung cancer.[38] The referring doctor, who is often the patient's GP, should be informed of the outcome of the MDT assessment in a timely fashion.

## Treatment

Recommendations for lung cancer treatment are based on cancer subtype (NSCLC, SCLC), stage and the results of molecular testing of biopsy tissue. Patients with stage I to IIIA NSCLC have potentially curable disease. Aggressive therapy may also be appropriate for patients with limited SCLC. Treatment approaches depend on the pathological diagnosis, stage and performance status of the patient. As above, the treatment plan should ideally be subject to discussion at a lung cancer MDT meeting.[39-40]

Treatment modalities include surgery, chemotherapy, radiotherapy and immunotherapy.[41] Treatment recommendations for NSCLC are summarised in the Table; these recommendations are drawn from the United States National Comprehensive Cancer Network (NCCN) guidelines and are generally applicable to Australian practice, with some modifications based on drug availability.[32] There are many treatment nuances to be considered, which are beyond the scope of this article and which involve personalised considerations such as patient-related issues (performance status, comorbidities and patient preference) and tumour-related issues (such as postoperative margins, staging details, local symptoms such as pain and molecular analysis of tumour tissue).

## Treatment considerations in all patients

### Clinical trials

Clinical trials remain important as treatment options for lung cancer, particularly in advanced disease, as newer agents may only be available through trials. Current guidelines recommend that all patients with lung cancer be considered for clinical trial eligibility.[32]

### Early palliative care referral and support groups

Palliative care referral may have a significant impact on outcomes and should be considered early in treatment planning, particularly in circumstances of advanced disease.[42] To assist patients with a recent diagnosis of lung cancer, the Lung Foundation Australia website provides information including links to telephone resources such as lung cancer support nurses, educational resources such as webinars that provide information and advice on living with lung cancer, education seminars and support groups around Australia (Box).

**Table. General treatment options for nonsmall cell lung cancer stages I to III (based on the US National Comprehensive Cancer Network guidelines[32])**

| Stage | Standard treatment | Treatment if nonresectable/ medically inoperable |
|---|---|---|
| IA | Surgical exploration and resection + mediastinal lymph node dissection | Definitive radiotherapy including SABR |
| IB | Surgical candidate: surgical exploration and resection +mediastinal lymph node dissection + consider adjuvant chemotherapy for high-risk patients | N0: Definitive radiotherapy including SABR (consider adjuvant chemotherapy for high risk stages IB-IIB)<br>N1: Definitive chemoradiation |
| II | Surgery + chemotherapy | Concurrent chemoradiation |
| IIIA | Chemoradiation<br>Can consider surgery with adjuvant (or neoadjuvant) chemotherapy and postoperative radiation | Chemoradiation |
| IIIB | Chemoradiation | –* |
| IV | Systemic therapy (chemotherapy, targeted therapy, immunotherapy) | –* |
| All stages | Smoking cessation should be offered to all lung cancer patients who are current smokers to improve clinical outcomes | – |

N0 = no hilar or mediastinal lymph node involvement. N1 = ipsilateral hilar lymph node involvement.
SABR = stereotactic ablative body radiotherapy.
* By definition, stages IIIB and IV are nonresectable.

## Treatment considerations particular to NSCLC

### Stages I and II

Surgery remains the mainstay of treatment for the minority of patients who have early stage NSCLC. The extent of surgery depends on the fitness of the patient, taking into account performance status, lung function and exercise tolerance, and the characteristics of the tumour, including its size and location and the extent of local spread. However, surgery is not always possible because of impaired lung function or comorbidities.

Recently, a new standard of care for the treatment of inoperable, peripherally located stage I NSCLC has been introduced. Stereotactic ablative body radiotherapy (SABR) delivers numerous small, highly focused and accurate radiation beams to deliver potent doses in one to five treatments to tumour targets in extracranial sites.[43] A recent Phase 3 randomised controlled trial confirmed that SABR resulted in superior local control of the primary disease and prolonged overall survival without an increase in major toxicity compared with standard radiotherapy.[44] The role of targeted therapy is not well defined in early stage lung cancer. Concurrent chemoradiotherapy is recommended for patients with inoperable stage II (node positive) disease.[32]

### Stage III

Patients with stage IIIA NSCLC have tumours in the lungs, with involvement of the ipsilateral mediastinal lymph nodes. Treatment of locally advanced disease remains controversial and the treatment approach may vary depending on local expertise and experience. While chemoradiotherapy is the mainstay of treatment in stage III disease, surgery is sometimes appropriate for patients with stage IIIA disease. About 25% of patients with stage IIIA disease may achieve clinical cure.[45] In stage IIIB disease there is bilateral mediastinal involvement that is not amenable to surgical resection. In patients with good performance status, administration of a platinum-based doublet chemotherapy regimen concurrently with radiotherapy is recommended. No targeted agent has yet been established as effective in conjunction with this chemotherapy and radiotherapy regimen. However, recent clinical trial data have shown a survival benefit with durvalumab (a PD-L1 blocking immunotherapy agent) when administered for one year after chemoradiation in unresectable stage III NSCLC,[41] and durvalumab is approved in Australia for use in patients whose disease has not progressed following platinum-based chemoradiation therapy.

### Stage IV

Most patients treated for NSCLC have stage IV disease, and common sites of metastases include lymph nodes, the pleura, liver, adrenal glands, bone and brain. Recent therapeutic advances for subgroups of metastatic NSCLC can largely be attributed to the accumulation of molecular knowledge, with up to 69% of patients having potentially actionable molecular targets.[46] First-line treatment choices include chemotherapy, targeted therapies and immunotherapy with pembrolizumab in patients with high levels of PD-L1 expression.

### Driver mutations

One of the most important groups of driver mutations that have been identified in NSCLC affects EGFR and is seen mostly in the adenocarcinoma subtype. These mutations occur more frequently in patients of Asian ethnic origin, in women and in nonsmokers. A recent meta-analysis of over 115,000 patients with NSCLC identified *EGFR* mutations in about 14% of European patients and more than 30% of Chinese patients.[47]

EGFR TKIs such as erlotinib and gefitinib are first-line therapy in treatment of *EGFR* mutation-positive (M+) NSCLC. Several large randomised controlled trials have shown their superiority in terms of progression-free survival, objective response rate and quality of life compared with chemotherapy. A landmark trial (the IPASS study) showed superiority of EGFR TKIs over chemotherapy in *EGFR* M+ NSCLC.[48] Later-generation TKIs (e.g. afatinib) show an encouraging

improvement in overall survival compared with earlier generation TKIs, but they also have more toxic effects than the first-generation drugs. Recently, the third-generation irreversible inhibitor osimertinib has been shown to be superior to first-generation TKIs in the front-line setting, both in terms of progression-free survival and toxicity; however, it is not currently funded on the PBS for this indication.[49] Most *EGFR* M+ patients eventually develop mutations that confer acquired resistance to these agents and exhibit disease progression. The most common resistance mutation is known as T790M. Osimertinib is a treatment option for this population and is available on the PBS.

Another major driver mutation that is important in NSCLC therapy is rearrangement of the anaplastic lymphoma kinase (*ALK*) gene, often referred to as *ALK*-positive tumours. *ALK*-positive lung cancer represents 2 to 7% of NSCLC and the median age at diagnosis is around 50 years, mostly in never smokers or light smokers with adenocarcinomas.[50] Targeted therapeutic agents, the ALK TKIs, include first-generation crizotinib and second-generation ceritinib and alectinib. Crizotinib is well tolerated but does not cross the blood brain barrier, meaning that the development of intracranial metastases is a common problem.[51] Ceritinib, although more potent with good brain penetration, is poorly tolerated due to gastrointestinal side effects.[52] Alectinib has excellent brain penetration and is well tolerated and is available on the PBS for any line of therapy.[53]

A third, but less common, driver mutation in NSCLC occurs with rearrangement of the c-ros oncogene 1 (*ROS1*).[54] Crizotinib can be used to treat *ROS1*-positive NSCLC, serving as a ROS1 inhibitor.[54]

### Immunotherapy

Immunotherapy is becoming increasingly used in patients with NSCLC. The development of antibodies targeting PD-1 (nivolumab and pembrolizumab) and PD-L1 (atezolizumab) have advanced the treatment of lung cancer. Pembrolizumab and atezolizumab have been shown to be effective in the first line combined with chemotherapy; however, these combinations are not available on the PBS.[55-57] Pembrolizumab has been shown to be an effective agent in the first line as a single agent, in those with PD-L1 expression greater than 50%.[58] All agents have been shown to be superior to chemotherapy in the second-line setting. However, the response to immunotherapy is not universal and has been shown to be about 20% in NSCLC.[59] Currently, patients have access to immunotherapy on the PBS in two circumstances:

- in the first-line setting, if the tumour PD-L1 expression is greater than 50%, pembrolizumab alone is funded
- in the second-line setting after failure of chemotherapy both nivolumab and atezolizumab are also available.

**Early diagnosis and appropriate therapy can improve outcomes even in cases of advanced disease**

## Treatment considerations particular to SCLC

SCLC is an aggressive lung tumour strongly associated with cigarette smoking. At presentation, SCLC is typically disseminated. Although SCLC is very chemoradiosensitive and high response rates are obtained with treatment, the relapse rate is high and the prognosis is poor. The most important prognostic factor in patients with SCLC is the stage of disease at presentation. For patients with limited stage disease, median survival ranges from 15 to 20 months and the five-year survival rate is 10 to 13%. By contrast, for patients with extensive stage disease the median survival is eight to 13 months and the five-year survival rate is 1 to 2%.

### Limited extent disease

SCLC is highly sensitive to chemotherapy and radiotherapy. Combined platinum-etoposide for four cycles remains the gold standard chemotherapy in patients with limited stage SCLC with a good performance status, particularly when concurrent radiation therapy is appropriate.[60,61] A standard three-weekly cisplatin plus etoposide regimen is superior to the daily administration of cisplatin plus etoposide in terms of local control and patient tolerance.[62] Prophylactic cranial irradiation is also an option in patients with limited disease who respond to initial treatment.[63]

### Extensive disease

Standard of care first-line treatment for extensive stage SCLC is based on platinum chemotherapy (carboplatin or cisplatin) with etoposide. Rapid responses with symptomatic improvement are often seen and the response rate is initially as high as 60 to 80%.[64] Complete remission, however, is only observed in 15 to 20% and, generally, SCLC inevitably progresses. Overall, the response rate to subsequent chemotherapy is poor. Recently, a Phase 3 study investigating the humanised monoclonal PD-L1 antibody atezolizumab has shown promise when added to traditional chemotherapy, resulting in significantly longer overall survival and progression-free survival compared with chemotherapy alone.[65]

## Conclusion

Lung cancer is the most common cause of cancer death in both men and women in Australia. All people with lung cancer require prompt evaluation and consideration of treatment. Primary care practitioners have a crucial role in prevention (through smoking cessation) as well as early detection and urgent referral in cases of suspected lung cancer. Involvement of an MDT in treatment planning for lung cancer is regarded as best practice and is related to improved outcomes. Early diagnosis and appropriate therapy, including the use of newer therapies such as immunotherapy, can improve outcomes even in cases of advanced disease. Consensus guidelines and resources are available to help primary care practitioners with diagnosis and referral. **RMT**

### References

A list of references is included in the online version of this article (www.respiratorymedicinetoday.com.au).

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**SAMANTHA ENNIS** MB BS(Hons), BAppSc(Phty)(Hons); **VENESSA CHIN** MB BS, FRACP, PhD
**EMILY STONE** MB BS, MMed, FRACP

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