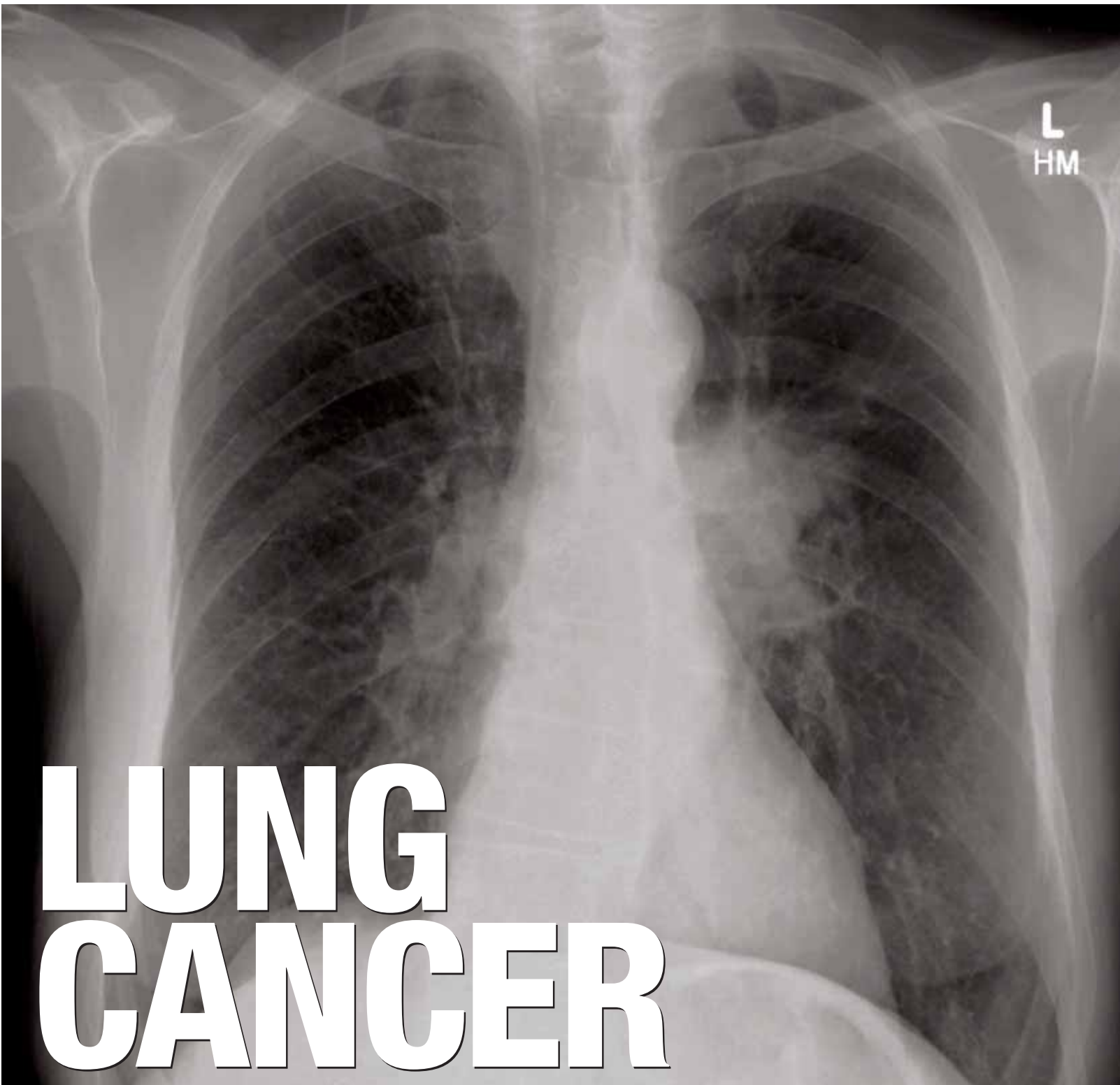


# How to Treat

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## inside

**Histology and clinical manifestations**

**Non-small cell lung cancer**

**Small cell lung cancer**

### The authors



**DR CSILLA HASOVITS**, medical oncology advanced trainee, Royal North Shore Hospital, St Leonards, Sydney, NSW.



**DR NICK PAVLAKIS**, head, department of medical oncology, Royal North Shore Hospital, St Leonards, Sydney, NSW.

## Background

LUNG cancer ranks as one of the most commonly occurring malignancies worldwide and is the most common cause of cancer-related deaths in Australia. Despite these sobering statistics, there have been recent advances in the diagnosis and staging of the disease and an emphasis on a multidisciplinary approach to the care of patients, particularly with potentially curable disease. The therapeutic options have broadened in the setting of advanced disease, with increasing recognition of the need to tailor treatment to both the patient and their histological subtype.

This article is intended to provide an overview of the current approach to lung cancer, emphasising the role of the GP in prevention, diagnosis, follow-up and supportive care (see box below), and covers some of the more recent advances.

### Incidence

According to NSW Cancer Institute statistics, lung cancer accounts for 9% of new cancer diagnoses and 19% of

### The pivotal role of the GP in lung cancer care

- Smoking cessation
- Initiation of diagnostic workup and specialist referral
- Palliative and supportive care
- Counselling and support
- Survivor follow-up and general health management

cancer deaths.<sup>1</sup> This equates to lung cancer being the fourth most common cancer diagnosed in both men and women, and the leading cause of cancer-related mortality.

Age-specific incidence and mortality rates increase with age, with a median age at diagnosis of 72 in men and 71 in women. The incidence and corresponding mortality rates have declined in men but have risen in women, reflecting changing smoking patterns between the genders.

Compared with the rest of the world, Australia has a lower incidence, related to our relatively lower smoking rates.

### Aetiology

The vast majority of cases of lung cancer are caused by cigarette smoking. The risk of cancer is associated with both the duration and intensity of smoking. This risk diminishes in a time-dependent manner after smoking cessation, approaching, though not reaching the same risk as, that of a lifelong non-smoker. An association between passive smoking and lung cancer has also been shown, with a relative risk of 1.24 for a non-smoker living with a smoker.

Certain occupational exposures have been implicated as potential carcinogens, including asbestos, silica and radon. Their effect on the risk of developing lung cancer appears to be potentiated by cigarette smoking.

Studies have evaluated the potential role of diet in modulating lung cancer risk. A diet rich in fruit and, to a lesser extent, vegetables, appears to play a protective role. However, it is difficult to assess due

to the overwhelming negative impact of smoking.

### Prevention

Smoking cessation is the most effective strategy in reducing the risk of lung cancer and, in those with the disease, can improve treatment-related outcomes and prevent the development of second primary tumours. GPs are in a key position to assist cessation by assessing a patient's smoking status and desire to quit, and being able to implement a range of proven smoking-cessation strategies.

It has been shown that advice combined with counselling increases quit rates. Additionally, clinicians can advise and institute behavioural support and proven pharmacological therapy such as nicotine-replacement therapy, bupropion and varenicline.

At present there is no demonstrated benefit of the use of any agents as chemoprevention to suppress or reverse carcinogenesis.

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## Histology and clinical manifestations

### Histology

LUNG cancer is divided into small cell and non-small cell types, with the latter accounting for 85% of cases.

The histological diagnosis of small cell lung cancer (SCLC) is made primarily on light microscopy (figure 1). In addition to the characteristic cell features, SCLC is usually associated with high mitotic rates and necrosis.

Non-small cell lung cancer (NSCLC) is further subdivided into the main histological subtypes of:

- Squamous cell.
- Adenocarcinoma.
- Large cell.
- Mixed types.
- Others (eg, sarcomatoid, carcinoid).

The squamous cell subtype accounts for about 30% of NSCLC (figure 2). It occurs more commonly in men and has a strong correlation with smoking. Due to their central location, malignant squamous cells can be detected in sputum. This subtype can be associated with paraneoplastic syndromes, in particular, hypercalcaemia due to the production of parathyroid-hormone-related peptide by malignant cells.

There has been an increase in the worldwide incidence of adenocarcinoma, now accounting for 30-50% of cases of NSCLC. It is more commonly seen in women and non-smokers, and lesions tend to be peripheral in location. Certain patterns of immunohistochemical staining, in particular, CK 7 and TTF-1 positivity, suggest adenocarcinoma arising from a primary lung lesion, rather than metastatic adenocarcinoma from a non-lung primary (figure 3).

Bronchoalveolar carcinoma is a subtype of adenocarci-

Figure 1: Small cell carcinoma demonstrating small- to medium-sized cells with minimal cytoplasm.

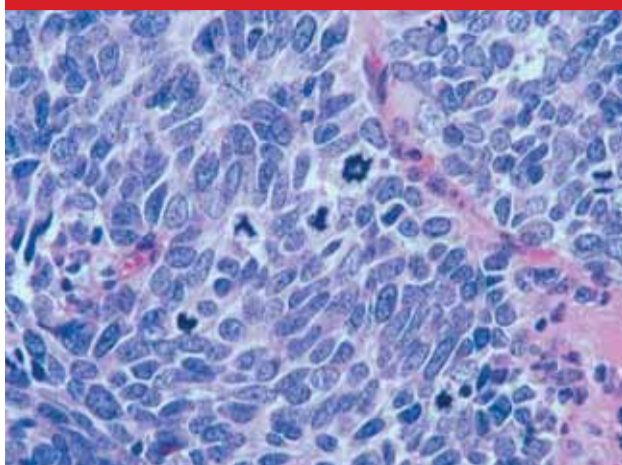


Figure 2: Squamous cell carcinoma showing keratinisation.

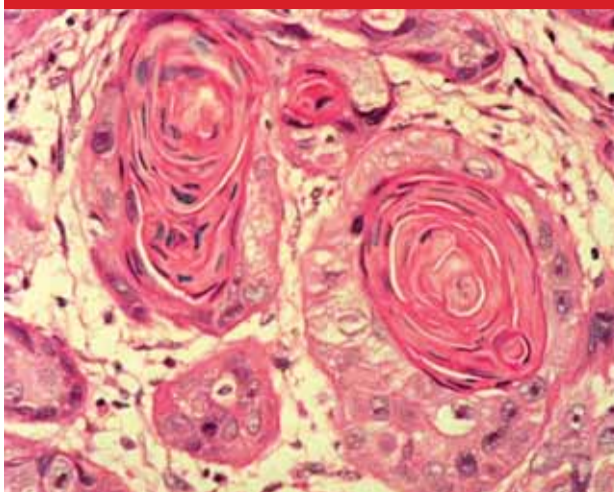
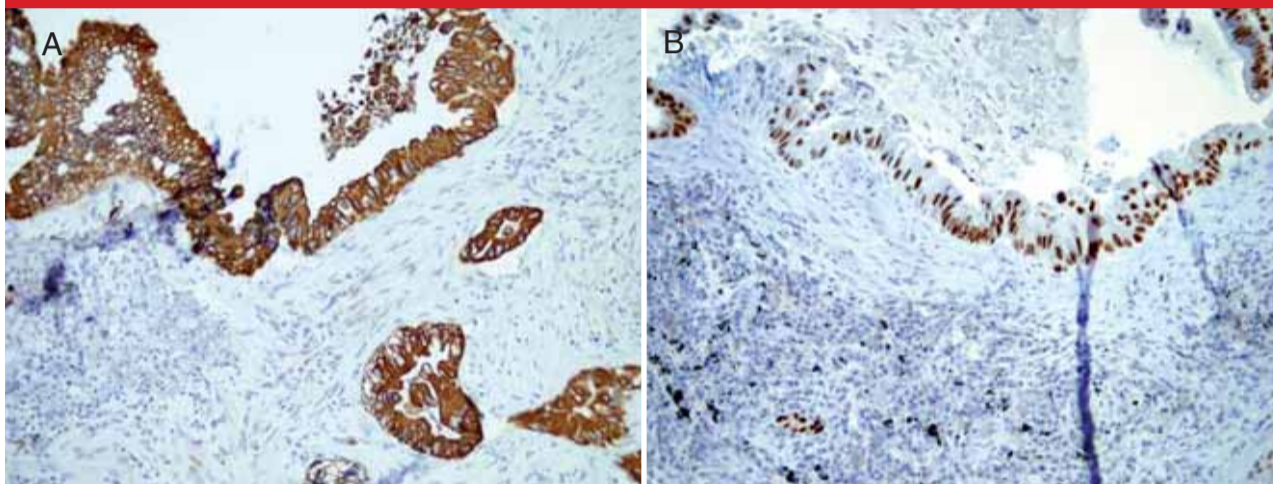


Figure 3: Adenocarcinoma showing positive staining for CK 7 (A) and TTF-1 (B).



noma with distinct biological and therapeutic characteristics. It spreads along alveolar septa without evidence of invasion through the basement membrane. Radiographically it often appears as a multicentric, infiltrative lesion that can initially be mistaken for pneumonia.

Large cell carcinoma refers to lesions that lack glandular or squamous differentiation (figure 4). It accounts for 10-25% of NSCLC. It usually presents as a large peripheral mass with central necrosis, and often demonstrates a tendency to metastasise early.

### Clinical manifestations

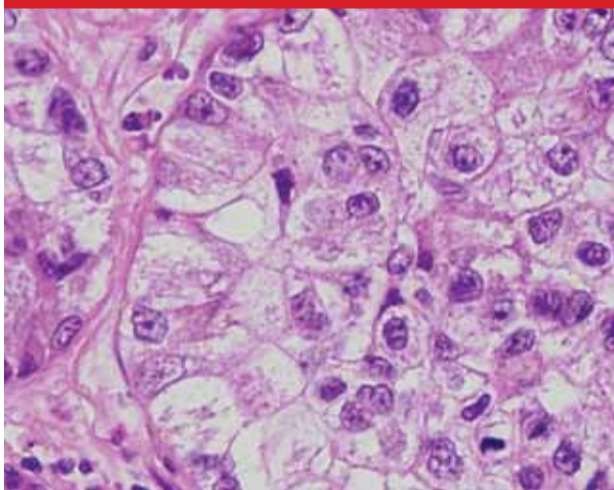
The clinical features of lung cancer reflect the:

- Extent of loco-regional involvement.
- Sites of distant metastases.
- Constitutional symptoms.
- (Occasionally) paraneoplastic syndromes.

Not uncommonly, an asymptomatic lesion may be detected as an incidental finding on chest imaging performed for another indication.

Symptoms from the primary tumour often include dyspnoea, cough and small-volume haemoptysis. Endobronchial obstruction by

Figure 4: Large cell carcinoma cells with prominent nucleoli, abundant pale cytoplasm and lacking glandular or squamous differentiation.



tumour may result in lobar collapse and the subsequent development of pneumonia or a lung abscess. Disease involving the pleura may result in pleuritic chest pain and pleural effusions.

Loco-regional extension can result in a variety of clinical manifestations, depending on the structures involved. Infiltration of the lower brachial plexus can lead to symptoms of shoulder pain, a Horner's syndrome (ptosis, miosis, dilation lag and anhidrosis), and atrophy of the intrinsic muscles of the hands — a triad of symptoms known as Pancoast's syndrome.

Involvement of the recurrent laryngeal nerve manifests as hoarseness of the voice, and oesophageal invasion may present as dysphagia. Additionally, the superior vena cava and mediastinal structures can be affected.

Constitutional symptoms, often present at the time of diagnosis, including general fatigue, poor appetite and weight loss. Symptoms related to metastatic disease are site-specific. Common sites of metastases include the liver, adrenal glands, bone and brain.

### Lung cancer screening

Despite the ongoing interest in evaluating the role of screening for lung cancer, studies evaluating CT screening have been associated with high rates of false-positive findings generating additional, potentially invasive investigations and patient anxiety. Low-dose helical CT scans remain under evaluation in randomised trials but, at present, routine screening for the early detection of lung cancer is not recommended.

## Non-small cell lung cancer

### Diagnosis

THE principles of diagnosis of NSCLC include initial evaluation of the presenting symptom, including assessment for the possibility of neoplasia, and excluding other causes (table 1). Subsequent steps involve obtaining a tissue diagnosis and accurately staging the disease for prognostic purposes and to guide treatment. Throughout this process, consideration needs to be given to the patient's performance status and comorbidities, as they may influence final treatment decisions.

A chest radiograph is often the first investigation performed in a patient presenting with respiratory symptoms (figure 5). CT of the chest, by comparison, has a much higher overall detection rate and is the standard of care for

Table 1: Lung cancer diagnostic and staging pathways

Diagnostic investigations	
<ul style="list-style-type: none"> <li>• Chest X-ray, CT (including liver and adrenals)</li> <li>• Basic blood tests — FBC, full biochemical profile</li> <li>• Tissue diagnosis*</li> </ul>	
Staging investigations	
Small cell lung cancer (SCLC)	Non-small cell lung cancer (NSCLC)
Bone scan	PET scan
CT or MRI brain	Additional tests depending on clinical stage and planned treatment: <ul style="list-style-type: none"> <li>• CT or MRI brain</li> <li>• Mediastinal lymph node biopsy (using mediastinoscopy or endobronchial ultrasound [EBUS])</li> <li>• Physiological workup for surgery</li> </ul>

\*Additional tissue for more detailed pathological evaluation may be required for predictive molecular biomarkers in NSCLC, eg, an epidermal growth factor receptor gene mutation

any patient suspected of harbouring a primary lung cancer.

Figure 5: Chest X-ray demonstrating a suspicious lesion at the left hilum.



### Histological diagnosis

Several options are available for obtaining histological confirmation of NSCLC, which should be individualised according to a patient's symptoms and the location of detected abnormalities. Ultimately the method chosen should be the one most likely to:

- Yield a diagnosis.
- Possibly contribute to staging, for example, sampling the mediastinal lymph nodes.
- Minimise the risks to the patient.

However, it is becoming imperative today, particularly in clearly inoperable cases, to obtain as much tissue as is reasonably possible to enable subsequent more detailed histological and molecular phenotyping of the cancer, as this may guide tailored treat-

ment choices (described further below).

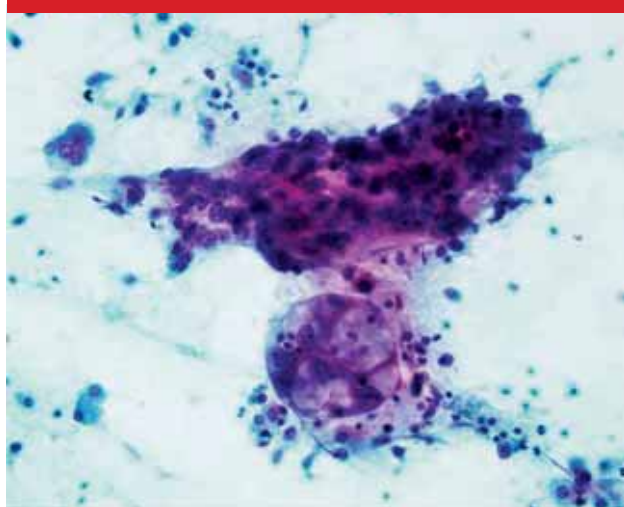
**Sputum cytology**

Sputum cytology has a sensitivity of 50-90%, and a high specificity. The diagnostic yield is best in patients with a productive cough and a centrally located lesion providing multiple samples.

**Percutaneous fine-needle aspiration**

A percutaneous fine-needle aspiration performed under radiological guidance is a useful option for obtaining a tissue sample from a peripherally located lung lesion (figure 6).

Figure 6: Fine-needle aspiration showing malignant cells.



**Fibreoptic bronchoscopy and endobronchial ultrasound**

Fibreoptic bronchoscopy is useful for evaluating suspicious endobronchial lesions up to the second or third segmental division (figure 7). The diagnostic yield approaches 100% when washings, brushings and biopsies are combined.

Endobronchial ultrasound (EBUS)-guided biopsy is a recent method for evaluating mediastinal lymph nodes in the paratracheal, aortopulmonary window, subcarinal and paraesophageal regions. This method has the potential advantage of not only providing a tissue diagnosis, but confirming pathological involvement of particular groups of lymph nodes, which has staging implications.

Figure 7: Endobronchial lesion identified on bronchoscopy.



**Investigations for staging**

Once a histological diagnosis has confirmed NSCLC, subsequent investigations should be directed at determining the stage of the disease to guide therapeutic options (table 2A and 2B).

The initial investigative pathway should include CT of the chest and upper abdomen, and PET (figure 8, page 32). When metastatic disease is clearly evident on initial CT, PET is not necessary. Additional tests such as bone scan or CT or MRI of the brain can be used to evaluate other sites of suspected metastases and to guide specific palliative management.

**Staging CT/MRI and bone scan**

A CT of the chest and upper abdomen should be obtained in all patients, particularly looking for liver and adrenal metastases. CT using bone windows may detect abnormalities of the vertebra, suggestive of bony metastatic disease. This can be confirmed on a bone scan.

Imaging of the brain, using either a CT with intravenous contrast, or MRI with gadolinium enhancement, should be performed when cerebral metastases are suspected, or to exclude these in selected patients about to undergo intensive treatment with curative intent.

**PET**

Based on the increased metabolic activity of malignant compared with normal tissues, 2-deoxy-2-fluoro-D-glucose- positron emission tomography (FDG-PET), has become an important clinical tool in staging NSCLC (figure 9, page 32). It is particularly useful in identifying distant occult metastases at presentation and should be strongly considered in any patient as part of preoperative staging. It is accurate in distinguishing benign from malignant pulmonary nodules >1cm in diameter, although false positives can occur in the context of granulomatous disease and silicosis.

**Lymph node staging**

Mediastinal lymph node sampling (by mediastinoscopy or EBUS) should be considered for any patient in whom surgical resection of the primary lesion is being considered. This is important for evaluating N3 disease, which would deem the disease inoperable, or N2 disease, when preoperative (neo-adjuvant) therapy should be considered before surgery.

On completion of staging, patients deemed to have localised disease suitable for resection should undergo preoperative physiological assessment to determine their fitness for surgery (operability). It is routine for patients to undergo pulmonary function testing, as an impaired FEV<sub>1</sub> and diffusing capacity raises the

concern of significantly impaired postoperative respiratory function. Formal cardiopulmonary testing should be performed for those with borderline operability, using a threshold of VO<sub>2max</sub> >15mL/kg/minute.

**The tumour-node-metastases staging system**

NSCLC is staged according to the tumour-node-metastases (TNM) staging system, developed by the American Joint Committee on Cancer (table 2A).<sup>2</sup> The TNM system categorises tumours on the basis of the:

- Characteristics of the primary lesion.
- Involvement of regional lymph node groups.
- Presence or absence of distant metastases.

The seventh edition was introduced on 1 January 2010 and includes modifications to the primary tumour and metastases descriptors to more accurately reflect their prognostic implications. The T and N descriptors can be based on either clinical or pathological parameters.

Using the TNM system, NSCLC is subdivided into four stages, which have been shown to correlate directly with patient survival (table 2B). Accurate staging is vital to determine the resectability of the disease, guide treatment decisions, and anticipate patient outcomes. While the TNM stage at diagnosis has the greatest impact on prognosis, it has also been shown that performance status and weight loss are independent, clinical prognostic factors.

Table 2A: TNM staging system for lung cancer\*

Primary tumour	
T1	Tumour ≤3cm, surrounded by lung or visceral pleura, invasion not proximal to lobar bronchus
T1a	Tumour ≤2cm
T1b	Tumour >2cm but ≤3cm
T2	Tumour > 3cm but ≤7cm, or with features of: <ul style="list-style-type: none"> <li>• Involvement of main bronchus, ≥2cm from carina</li> <li>• Visceral pleura invasion</li> <li>• Atelectasis or obstructive pneumonitis, extending to the hilar region although not involving the entire lung</li> </ul>
T2a	Tumour >3cm but ≤5cm
T2b	Tumour >5cm but ≤7cm
T3	Tumour >7cm, or with: <ul style="list-style-type: none"> <li>• Features of invasion of chest wall, diaphragm, phrenic nerve, mediastinal pleura or parietal pericardium</li> <li>• Spread to &lt;2cm from carina</li> <li>• Atelectasis or obstructive pneumonitis involving the entire lung</li> <li>• Separate tumour nodule in the same lobe as the primary</li> </ul>
T4	Tumour of any size that invades the mediastinum, heart, great vessels, carina, trachea, recurrent laryngeal nerve, oesophagus or vertebral body or with a separate tumour nodule in a different ipsilateral lobe to the primary
Regional lymph nodes	
N0	No regional lymph node metastases
N1	Metastases to ipsilateral peribronchial and/or hilar lymph nodes and intrapulmonary nodes
N2	Metastases to ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastases to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene and supraclavicular lymph nodes
Metastases	
M0	No metastases
M1	Metastases present
M1a	Separate tumour nodule in a contralateral lobe, pleural nodules, malignant pleural or pericardial effusions
M1b	Distant metastases

**Treatment**

Different treatment modalities are employed in the management of NSCLC, including surgery, chemotherapy, radiotherapy and palliative care (table 3, page 32). Due to the critical importance of accurate staging and the multiple modalities of investigations and treatment available across a range of specialities, the management of each case of NSCLC is ideally determined in a multidisciplinary forum.

At present, the stage of disease and the patient's performance status and comorbidities dictate the goals of treatment and the specific treatment modality, combination, sequence and duration used. However, there are emerging data regarding the role of molecular predictive markers, maintenance therapy and the emergence of novel agents that may result in the treatment of NSCLC becoming increasingly individualised.

**Stage I**

Stage I NSCLC refers to disease limited to the hemithorax, >2cm from the carina and without chest wall or parietal pleural invasion. It accounts for only 15% of cases of NSCLC. Surgery offers the best possible chance for cure.

For stage I disease there is no proven role for adjuvant chemo- or radiotherapy.

Table 2B: Correlation of stage groupings with median survival\*

Stage grouping	T	N	M	Median survival (months)
Stage IA	T1a, b	N0	M0	58
Stage IB	T2a	N0	M0	42
Stage IIA	T2b, T1a, b, T2a	N0, N1, N1	M0, M0, M0	46
Stage IIB	T2b, T3	N1, N0	M0, M0	19
Stage IIIA	T1-3, T3, T4	N2, N1, N0-1	M0, M0, M0	14
Stage IIIB	T4, Any T	N2, N3	M0, M0	10
Stage IV	Any T	Any N	M1	6

\*Adapted from Goldstraw P. International Association for the Study of Lung Cancer. *Staging Handbook in Thoracic Oncology*, Editorial Rx Press, Orange Park, FL, 2009.

For patients with clinical stage I NSCLC that is technically resectable but who are deemed medically inoperable, definitive radiotherapy is recommended as an alternative to provide loco-regional control and, potentially, cure.

**Stage II**

Stage II NSCLC is subdivided into T1-3 primary tumours with and without ipsilateral hilar lymphadenopathy. T3 tumours also encompass primary lesions occurring within 2cm of the carina.

Surgery remains the treatment of choice for stage II NSCLC. Prognosis has been shown to correlate with the depth of invasion, completeness of the resection and lymph node status.

As for stage I disease, in completely resected stage II NSCLC the routine addition of postoperative radiotherapy may have a detrimental effect on survival. In contrast, on the basis of multiple large randomised trials, adjuvant cisplatin-based chemotherapy is

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recommended for patients with completely resected stage II NSCLC. In a meta-analysis, adjuvant cisplatin-based chemotherapy improved survival rate by 13% (hazard ratio 0.87 [95% CI 0.81 to 0.94]).<sup>3</sup>

In medically inoperable stage II NSCLC, radiotherapy is recommended. In fit patients the addition of platinum-based chemotherapy concurrent with radical radiotherapy marginally improves survival compared with radiotherapy alone, with an absolute benefit of 2% at five years.

**Stage IIIa**

Stage IIIa disease consists of locally advanced primary tumours (T4) with or without ipsilateral hilar nodal involvement, or T1-3 primary tumours with mediastinal lymph node involvement. The presence and extent of N2 involvement remains a controversial area with respect to both accurate identification of nodal involvement, and treatment modality options.

Negative prognostic factors are termed together as 'bulky' N2 disease, which refers to significant pathological enlargement of mediastinal lymph nodes, and/or involvement of more than two lymph node stations. (A lymph node station is an anatomical descriptor for the location of the nodes.)

In general, patients with bulky stage IIIa disease are considered inoperable, whereas those with non-bulky disease are considered potentially resectable for cure. However, there is increasing recognition that surgery alone rarely cures these patients, leading to a shift in treatment favouring a combined modality approach.

Due to the inherent heterogeneity of this group of patients, treatment plans should be individualised and determined in a multidisciplinary setting. Combined modality therapy is the standard approach in patients with unresectable, clinically staged III NSCLC. Concurrent chemo-radiotherapy using platinum-based therapy provides a survival benefit compared with sequential therapy or radiotherapy alone.

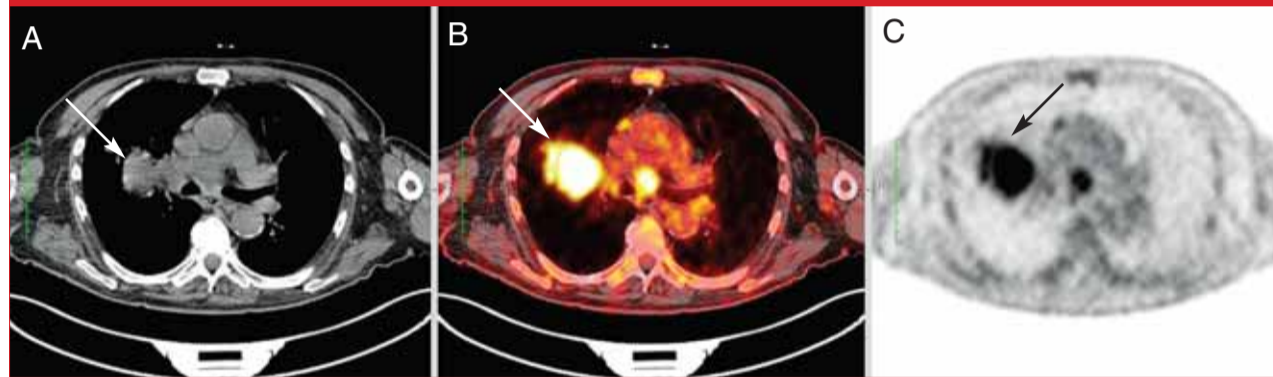
In cases considered operable, treatment approaches include neo-adjuvant chemotherapy, with or without radiotherapy, followed by surgery, or upfront surgery followed by adjuvant chemotherapy. The addition of adjuvant radiotherapy is usually considered in the context of positive resection margins or in cases considered at high risk of local recurrence.

**Stage IIIb**

Stage IIIb disease encompasses patients with either contralateral mediastinal or hilar lymphadenopathy (N3 disease) or T4 tumours, and is considered

NON-SMALL CELL LUNG CANCER		SMALL CELL LUNG CANCER	
<b>Stage I</b>	Surgery If medically inoperable: radiotherapy ± concurrent chemotherapy	<b>Limited stage</b>	Chemotherapy Concurrent chest radiotherapy Prophylactic cranial irradiation*
<b>Stage II</b>	Surgery ± adjuvant chemotherapy If medically inoperable: radiotherapy ± concurrent chemotherapy		
<b>Stage IIIA</b>	Multidisciplinary team management planning: • Neo-adjuvant chemotherapy then surgery OR • Surgery then adjuvant chemotherapy OR • Combined radical chemo-radiotherapy	<b>Extensive stage</b>	Chemotherapy Possible palliative radiotherapy to symptomatic sites Prophylactic cranial irradiation*
<b>Stage IIIB</b>	Multidisciplinary team management planning: • Radical chemo-radiotherapy OR • Palliative management (chemo- ± radiotherapy as per stage IV)		
<b>Stage IV or metastatic relapse</b>	First line: chemotherapy (see text for details) Second line: pemetrexed or docetaxel or epidermal growth factor receptor tyrosine kinase inhibitors Third line: • Erlotinib • Palliative radiotherapy if required • Palliative/supportive care		
*Prophylactic cranial irradiation is only used in responding patients and assuming baseline CNS imaging is clear			

**Figure 8: Combined PET-CT images showing a cancer and adjacent lymph node involvement. The arrows indicate a right-sided lung primary on CT (A) that is shown to be markedly glucose avid and associated mediastinal/subcarinal adenopathy on fused CT-PET images (B and C).**



unresectable disease. Concurrent chemo-radiotherapy is used for both loco-regional control and to treat micrometastatic disease, with a small proportion of patients surviving long term. This approach has demonstrated superiority over sequential therapy or radiotherapy alone.

It has also been shown that full-dose chemotherapy can be administered with manageable toxicity, and has better outcomes compared with reduced-dose regimens. However, the optimal chemotherapy regimen for use with concurrent radiotherapy has yet to be clearly defined, and there is no evidence that the use of consolidation chemotherapy after definitive chemo-radiotherapy provides a survival advantage.

**Stage IV<sup>4-7</sup>**

More than half of patients diagnosed with NSCLC present with advanced disease that is not amenable to curative-intent therapy. Furthermore, a significant proportion of patients treated with curative intent eventually relapse. The median survival of patients with stage IV disease ranges from 8 to 16 months.

In the past there was often a nihilistic approach towards patients with stage IV disease, as it was felt the toxicity of chemotherapy outweighed the relatively modest benefits in terms of response rates and survival times. However, advances in therapy have demonstrated gains in survival and overall quality of life with the use of chemotherapy and

new targeted therapies, compared with best supportive care alone. This is likely to be to the net result of a reduced incidence of disease-related complications, coupled with better management of treatment side effects, and good community-based supportive care. These advances have enabled the tailoring of therapy to individual patients and are discussed in detail under Recent advances (below). Current treatment approaches have reduced the incidence of disease-related complications and are coupled with better management of treatment side effects, and good community-based supportive care.

The current guidelines recommend starting chemotherapy early, while a patient has a good performance status, and continuing for a maximum of six cycles in patients responding to therapy. It should be stopped after four cycles in non-responders. Platinum-based doublets are recommended, that is, using a platinum drug combined with a third-generation cytotoxic agent such as paclitaxel, docetaxel, gemcitabine or vinorelbine.

For elderly patients or patients with a performance status of two, available data supports the use of single-agent chemotherapy. In patients with adenocarcinoma of the lung, pemetrexed-based chemotherapy appears to be better.

In patients with known specific gene mutations in their tumours, targeted therapy such as oral small-molecule

**Figure 9: Whole-body PET demonstrating a malignant pulmonary lesion and adjacent lymph node involvement.**



epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) can be considered upfront.

In patients who remain fit but whose disease progresses, there is evidence to support second-line therapy in improving quality of life and survival. Available proven treatments in this setting include chemotherapy (pemetrexed or docetaxel) and oral small molecule EGFR TKIs (gefitinib or erlotinib).

Radiotherapy can be used in any circumstance for palli-

ation of symptoms. Above all, a holistic approach that takes into account a patient's wishes, quality of life and fitness is paramount.

**Recent advances**

Until recently, chemotherapy had failed to substantially improve median overall survival beyond 8-10 months when used empirically in NSCLC. However, recent advances are challenging this barrier, in particular:

- The emergence of biological agents targeting the

epidermal and vascular endothelial growth factor pathways.

- Tailoring therapy according to molecular markers, histology and clinical phenotypes.
- Increasing evidence regarding the role of maintenance therapy.

**Clinical and molecular markers<sup>8,9</sup>**

EGFR plays an important role in cell signalling pathways controlling cell replication. Mutations in this receptor have been identified in NSCLC, which result in malignant cells escaping from the usual intracellular inhibitory controls, thus promoting tumour growth, angiogenesis, tissue invasion and inhibition of apoptosis.

Two orally administered TKIs that target EGFR (gefitinib and erlotinib), have shown benefit in advanced NSCLC. A number of clinical and molecular markers have been identified that help predict which patients are more likely to benefit from treatment with EGFR inhibitors.

Clinical parameters identified in phase II and III trials to be associated with an increased response rate to EGFR inhibitors include:

- Adenocarcinoma histology.
- Female gender.
- Being a non-smoker.
- Asian ethnicity.

It is likely that differences in mutations in various molecular pathways underlie these clinical markers.

Subsequent clinical correlation studies have shown that EGFR-activating mutations are associated with an increased responsiveness to TKIs. Furthermore, mutations in the *k-ras* gene are associated with primary resistance to this class of agents.

While mutations of the *EGFR* gene are more likely to occur in the selected phenotype (adenocarcinoma, female, non-smoker, Asian), this is not exclusively so, and male smokers with NSCLC may also occasionally harbour *EGFR* mutations. However, the anti-EGFR TKI erlotinib has shown survival benefit regardless of the *EGFR* gene mutation status of the tumour.

The practice implications of these clinical and molecular markers are to help define patients who are most likely to benefit from TKIs, and so tailor therapy. Phase III studies have demonstrated clinical efficacy with erlotinib in patients with advanced NSCLC who have failed previous cytotoxic chemotherapy, with improved response rates, quality of life and overall survival.

While the same benefit was not demonstrated in trials with gefitinib versus placebo, gefitinib is as effective and less toxic than docetaxel second line. Further, a recent randomised trial comparing gefitinib with combination carbo-

platin and paclitaxel in previously untreated patients with advanced NSCLC and the characteristic clinical phenotype (see above), found that progression-free survival was significantly improved in patients whose tumours contained the *EGFR* gene mutation.

The area of tailored therapy is rapidly evolving, with gene mutations other than *EGFR* already having been discovered, and with drugs blocking the associated molecular pathways under development. In addition, new generation anti-*EGFR* drugs and multi-targeted receptor TKIs are in clinical trials.

#### Histology

Historically, histology has not been considered a prognostic or predictive factor in patients with

advanced NSCLC. However, there are now emerging data that histology is a predictive marker for chemotherapy benefit and may have a role in selecting chemotherapy regimens.<sup>10</sup>

There is evidence that pemetrexed, an anti-folate chemotherapy agent that inhibits three enzymes involved in purine and pyrimidine synthesis (thymidylate synthase, dihydrofolate reductase, and glycylamide ribonucleotide formyltransferase) is more active in patients with non-squamous histology. The reverse is true of patients with squamous histology.

One possible explanation for this is the differential expression of thymidylate synthase across different histological subtypes of NSCLC. There is a higher baseline expression of thymidylate synthase in SCC

compared with adenocarcinoma. As pemetrexed is a potent inhibitor of thymidylate synthase, this may explain the variations in efficacy according to histological subtype.

#### VEGF inhibitors

Vascular endothelial growth factor (VEGF) plays an important role in the induction of angiogenesis (new blood vessel formation), which permits tumour cell proliferation and metastasis. Bevacizumab, a recombinant humanised monoclonal antibody, binds to VEGF and prevents its interaction with the VEGF receptor, blocking the endothelial-specific angiogenesis pathway.

Several trials have demonstrated improved response rates and overall survival for the combination of bevacizumab with conventional chemotherapy, compared with

chemotherapy alone, in patients with advanced NSCLC.<sup>11,12</sup> However, these trials were restricted to patients with a good performance status, non-squamous histology and no history of haemoptysis, due to the increased risk of bleeding with bevacizumab.

#### Maintenance therapy

Maintenance therapy after initial chemotherapy with either a non-cross-resistant chemotherapeutic agent or *EGFR* inhibitor is an area of active investigation.<sup>13,14</sup> While maintenance trials using conventional chemotherapy failed to demonstrate a benefit, recent data support the use of pemetrexed or erlotinib as maintenance therapy after first-line chemotherapy, with demonstrated improvements in progression-free survival.

## Small cell lung cancer



SMALL cell lung cancer (SCLC) is clinically distinct from NSCLC, demonstrating a propensity for rapid growth and early metastases. It accounts for about 15% of cases of lung cancer, a proportion that is steadily decreasing.

It occurs almost exclusively in smokers. The disease is more common in men. Changes in smoking patterns are likely to alter the epidemiology of this form of lung cancer.

#### Diagnosis and staging

SCLC tends to arise from the central airways, manifesting with respiratory symptoms due to endobronchial obstruction. Given its tendency to metastasise early, symptoms may also occur from sites of metastatic spread, such as the liver, brain and bones.

Paraneoplastic syndromes can be associated with the disease, including:

- Neurological manifestations such as Eaton-Lambert myasthenic syndrome.
- Sensory or subacute motor neuropathy.
- Subacute cerebellar degeneration and dementia
- Ectopic hormone production.

Due to its aggressive nature, the duration of pre-diagnosis symptoms is often short.

Staging investigations include CT of the chest, abdomen and brain, and bone scan (table 1). An abbreviated approach to staging can be adopted once extensive disease is documented, directed by symptoms.

The most commonly used staging system divides SCLC into limited and extensive disease. Limited disease refers to disease that confined to the ipsilateral hemithorax and that can be encompassed within a single radiotherapy field. Disease beyond this is defined as extensive, and accounts for about two-thirds of cases. While the TNM staging system (table 2A, page 31) is more descriptive, it is of limited value in SCLC due to overlapping treatment and prognosis across TNM stages.

#### Treatment

The treatment algorithm for SCLC depends on the extent of disease at diagnosis (table 3). Surgical resec-

tion is generally not considered part of that algorithm in biopsy-proven cases, due to the tendency for early metastases in the disease. Patients in whom the diagnosis is made after surgical resection of a suspicious lesion should be started on standard treatment for SCLC after postoperative recovery.

For limited disease, combination chemotherapy using a platinum-based regimen with concurrent thoracic radiotherapy is the recommended approach. A widely used regimen combines platinum chemotherapy with etoposide, for 4-6 cycles.

Concurrent chemotherapy and radiotherapy (chemo-radiotherapy) provides superior survival compared with sequential therapy, and there is a benefit to introducing it earlier. After combination therapy, prophylactic cranial irradiation has been shown to improve disease-free and overall survival by reducing the incidence of brain metastases, and is now recommended for patients who achieve a complete remission after chemo-radiotherapy.

For extensive disease, combination chemotherapy using a platinum-based agent combined with etoposide is the standard of care. For patients with significant tumour response to chemotherapy, prophylactic cranial irradiation should be considered.

Given its frequent tendency to recur, salvage treatment is often a management issue in patients with SCLC. Overall response rates to second-line therapy are low, although they are influenced by response to initial therapy and time to disease relapse.

#### Prognosis

Although SCLC is initially responsive to chemotherapy and radiotherapy, early relapse is common, often within months, resulting in an overall five-year survival of 3-8%. The median survival of patients with limited disease is 15-20 months, and is less for patients with extensive disease (about 8-10 months). Without treatment, survival is rarely beyond months.

In addition to extensive disease, other factors associated with a poorer prognosis include weight loss, poor performance status, female gender and the presence of paraneoplastic syndromes.

## Conclusion

LUNG cancer remains an important public health issue by virtue of its association with smoking and poor survival rate. It requires multidisciplinary input, and with the evolving advances in diagnosis and treatment, an increasingly individualised approach to the care of each patient. The GP plays a key role in multiple steps in the patient's cancer journey.

#### Acknowledgements

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#### Online resources

- The Australian Lung Foundation: [www.lungfoundation.com.au](http://www.lungfoundation.com.au)
- National Comprehensive Cancer Network: comprehensive guidelines for practitioners: [www.nccn.org](http://www.nccn.org)
- Cancer Council NSW: Cancer answers for patients: [www.cancercouncil.com.au/canceranswers](http://www.cancercouncil.com.au/canceranswers)
- Kylie Johnston Lung Cancer Network for patients: [www.kjlc.org.au](http://www.kjlc.org.au)

#### Conflict of interest

Dr Nick Pavlakis has served on advisory boards and received speaking honoraria and travel grants from Roche, Astra Zeneca and Eli Lilly.

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cont'd next page

## GP's contribution



**DR JON FOGARTY**  
Point Clare, NSW

### Case study

MR RG, a 58-year-old real estate agent, presents with an unusual story. While walking up the hill of the seventh hole at his local golf course, his car keys 'bleep' — a sound normally triggered by a searching whistle. When this happens again on the 11th fairway, he realises that the whistle triggering the key finder is his own, newly acquired wheeze.

RG started smoking as a teenager. He smoked 30 cigarettes a day, and as a birthday gift to himself and his family, smoked his last cigarette on his 50th birthday.

Two months before pres-

entation, he had been treated by his GP with a left lower-lobe pneumonia. He had responded well to antibiotics. He now admits to being a little short of breath and reports one episode of "coughing up a teaspoon of blood" two weeks previously.

Chest X-ray suggested persistent collapse/consolidation in the left lower lobe, and CT suggested a hilar mass.

### Questions for the author

Given that much of the treatment for lung cancer occurs at specialist level, what further investigations, if any, should be undertaken by the GP before referral?

A CT of the chest and upper abdomen encompassing the liver and adrenals should be performed to provide information regarding the primary site and screen for common sites of metastases. From there, early referral to either a respiratory physician or lung multi-



disciplinary team facilitates determination of the optimal method of obtaining a tissue diagnosis, as well as additional staging investigations and assessment of cardiorespiratory status, as appropriate.

### What is the role of multidisciplinary meetings in managing such patients?

Multidisciplinary meetings play an essential role by facilitating review of the clinical context and investigation results to formulate and reach consensus on the

appropriate treatment pathway for individual patients.

### Patients who have smoked often feel guilty for having contracted lung cancer. How do you feel this issue should be approached?

While promoting smoking cessation is an important public health measure to reduce the incidence of lung cancer, combating 'smoker's guilt' and the associated stigma is an important part of individual patient care. It is important to recognise that no lifestyle guarantees absolute protection from cancer, and all patients are entitled to best available care.

### General questions for the author

Are there any features that would suggest a diagnosis of carcinoid rather than carcinoma of lung? How does management and prognosis differ for carcinoid?

Patients diagnosed with

bronchial carcinoid tend to be younger, and an association with smoking has not been shown. Most lesions are proximal, with symptoms related to bronchial obstruction. Hormonally related symptoms are uncommon with bronchial carcinoids.

Bronchoscopic appearances can be characteristic, with a vascular polypoid mass covered by intact mucosa. However, the diagnosis is confirmed histologically with demonstration of polygonal cells with oval nuclei and of low nuclear grade and mitotic activity. Typical bronchial carcinoids have a good prognosis and surgical resection is the treatment of choice and potentially curative.

What is the significance of 'pleural plaques' on chest X-ray in an asymptomatic patient with previous asbestos exposure?

Pleural plaques indicate

previous asbestos exposure and can occur in the absence of manifestations of asbestos-related disease. Patients with pleural plaques should be regularly monitored for the development of asbestos-related disease.

### With what features does broncho-alveolar carcinoma present?

The presentation of broncho-alveolar carcinoma can vary from solitary to multiple pulmonary nodules, or a 'pneumonic' form. Clinical manifestations reflect the extent of disease. A solitary peripheral nodule is often asymptomatic, while a patient with multiple lesions may present with cough, dyspnoea and constitutional symptoms. Infiltrative forms may symptomatically and radiographically mimic lobar consolidation, with the diagnosis only considered after symptoms and signs have failed to respond to antimicrobial therapy.



# How to Treat Quiz

Lung cancer — 3 September 2010

### INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

### ONLINE ONLY

[www.australiandoctor.com.au/cpd/](http://www.australiandoctor.com.au/cpd/) for immediate feedback

#### 1. Which TWO statements are correct?

- a) Potential carcinogens for lung cancer include asbestos, silica and radon
- b) Small cell lung cancer accounts for most lung cancers
- c) The squamous cell subtype of non-small cell lung cancer (NSCLC) does not have a strong correlation with smoking
- d) Hypercalcaemia can occur with squamous NSCLC due to the production of parathyroid hormone-related peptide by malignant cells

#### 2. Which TWO statements are correct?

- a) The adenocarcinoma subtype of NSCLC is more commonly seen in women and non-smokers
- b) Large-cell carcinoma usually presents as a large central peri-bronchial mass and is slow to metastasise
- c) A peripherally located tumour is likely to present as lobar collapse, pneumonia or a lung abscess
- d) Clinical presentation of loco-regional tumour extension can include a hoarse voice, shoulder pain or Horner's syndrome

#### 3. Which TWO statements are correct?

- a) Common sites of metastases in lung cancer include the liver, adrenal glands, bone and brain
- b) CT chest does not have a higher detection rate for lung cancer than a chest X-ray
- c) Histology samples are used to confirm the diagnosis and to provide detailed histological and molecular phenotyping of the cancer

- d) The diagnostic yield from sputum cytology is greatest in patients with a peripherally located lesion

#### 4. Which TWO statements are correct?

- a) A percutaneous fine-needle aspiration can be used to obtain a tissue sample from a centrally located lung lesion
- b) The combination of washings, brushings and biopsy from a fiberoptic bronchoscopy has a low diagnostic yield
- c) Endobronchial ultrasound (EBUS)-guided biopsy can be used to evaluate mediastinal lymph nodes
- d) EBUS-guided biopsy can provide a tissue diagnosis and contribute to preoperative nodal staging

#### 5. Which THREE statements are correct?

- a) A CT of the chest and upper abdomen can identify liver and adrenal metastases
- b) Brain CT or MRI should be performed to include or exclude cerebral metastases in patients otherwise eligible for curative treatment
- c) 2-Deoxy-2-fluoro-D-glucose – positron emission tomography (FDG-PET) imaging is based on the decreased metabolic activity of malignant compared with normal tissues
- d) FDG-PET can be used to identify distant occult metastases at presentation

#### 6. Which TWO statements are correct?

- a) FDG-PET cannot usually distinguish between benign and malignant pulmonary nodules

- b) Mediastinal lymph node biopsy can distinguish N3 disease (inoperable disease) from N2 disease (disease requiring preoperative therapy)
- c) Impaired pulmonary function preoperatively does not influence the outcome of surgery for lung cancer
- d) The anatomical stage at diagnosis, patient performance status and weight loss are all independent clinical prognostic factors

#### 7. Which TWO statements are correct?

- a) For stage I NSCLC, recommended treatment is surgery with adjuvant chemo- or radiotherapy
- b) For patients with completely resected stage II disease, there is a survival advantage in having adjuvant cisplatin-based chemotherapy
- c) In patients with stage II NSCLC who are unfit for surgery, radiotherapy is not recommended as an alternative treatment
- d) Options for treatment of operable stage IIIa disease include neo-adjuvant chemotherapy, with or without radiotherapy, followed by surgery

#### 8. Which THREE statements are correct?

- a) For stage IIIb disease, concurrent chemoradiotherapy (CRT) is used for both loco-regional control and to treat micrometastatic disease
- b) More than half of patients diagnosed with NSCLC present with advanced disease that is not amenable to curative-intent therapy

- c) For stage IV NSCLC there is no improvement in survival and overall quality of life with use of chemotherapy, compared with best supportive care alone
- d) Radiotherapy can be used in any circumstance for palliation of symptoms.

#### 9. Which TWO statements are correct?

- a) Epidermal growth factor receptor (EGFR) inhibitors have shown benefit in advanced NSCLC
- b) The clinical parameters associated with an increased response rate to EGFR inhibitors include adenocarcinoma histology, female gender, non-smoking status and Asian ethnicity
- c) The survival benefit conferred by the EGFR inhibitor erlotinib is dependent on the EGFR gene mutation status of the tumour
- d) Pemetrexed, an antifolate chemotherapy agent, is more active in patients with squamous histology

#### 10. Which TWO statements are correct?

- a) Small cell lung cancer (SCLC) is characterised by slow growth and late metastatic spread, and occurs almost exclusively in non-smokers
- b) Paraneoplastic syndromes can occur in SCLC, including neurological manifestations and ectopic hormone production
- c) For limited-stage SCLC, surgical resection is generally part of the treatment regimen
- d) For limited-stage SCLC, combination chemotherapy with concurrent thoracic radiotherapy is the recommended treatment

### CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2008-10 triennium. You can complete this online along with the quiz at [www.australiandoctor.com.au](http://www.australiandoctor.com.au). Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

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Education

HOW TO TREAT Editor: **Dr Giovanna Zingarelli**  
Co-ordinator: **Julian McAllan**  
Quiz: **Dr Giovanna Zingarelli**

**NEXT WEEK** The next How to Treat looks at management of hindfoot and ankle pain. The author is **Dr Peter Lam**, specialist foot and ankle surgeon, in private practice at Chatswood, and a consultant at Sydney Olympic Park, Narrabeen, Kensington and Kogarah, Sydney, NSW.