



PRACTICE

CLINICAL UPDATES

Lung cancer

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What you need to know

- Most lung cancers present with non-specific symptoms; haemoptysis is a feature in only 20%
- Consider a chest x ray for patients who have persistent symptoms or thrombocytosis, and repeat chest x ray or computed tomography (CT) if symptoms persist
- Positron emission tomography-computed tomography (PET-CT) is used to identify distant metastases in those eligible for radical treatment after contrast-enhanced CT. If there is potential mediastinal node involvement, endobronchial ultrasound guided transbronchial needle aspiration is the optimal initial strategy for nodal sampling
- Surgery remains the standard of care in early stage non-small cell lung cancer (NSCLC). Radical radiotherapy or stereotactic ablative radiotherapy (SABR) are alternatives. Options for locally advanced NSCLC include surgery with postoperative chemotherapy or chemoradiotherapy
- Systemic therapy for metastatic NSCLC is now targeted primarily on tumour genetic mutations and biomarkers. Tyrosine-kinase inhibitor (TKIs) and immunotherapy are first line treatments for some patients with metastatic NSCLC. Combination chemotherapy is available for patients not eligible for TKIs or immunotherapy

Lung cancer is one of the commonest cancers worldwide.¹ Outcomes are among the poorest of all tumour types, with five year survival of 10-20%.² Survival is hugely influenced by stage at diagnosis, with five year survival varying from 92% to 0% for the earliest and latest stages respectively.³ In this update we discuss contemporary therapeutic options, and approaches to increasing symptom awareness and early diagnosis. Low-dose computed tomography (CT) screening is beyond the scope of this review.

Sources and selection criteria

In addition to searching Clinical Evidence and the Cochrane Collaboration, we based this article on databases of references. We also examined the citation lists of included articles.

Who gets it?

Worldwide, about three quarters of lung cancers are attributable to smoking; others are caused by occupational workplace exposure, radon exposure, and air pollution.⁴ It is more common in men, and incidence increases with age (fig 1). Recent evidence suggests a changing pattern of lung cancer with higher incidence in younger and non-smoking women, especially in Asia and countries with Asian migrant populations.⁵ As smoking rates decline in some countries, there will be a fall in incidence, but this will be in decades to come. The most effective intervention for reducing lung cancer mortality remains smoking cessation; hence better interventions to reduce smoking are imperative. Radon remediation in certain areas may also be of benefit.

How can we improve symptom awareness in people at risk?

Several studies have explored symptom appraisal and help-seeking in people with recently diagnosed lung cancer. Factors associated with later presentation include limited awareness of cancer symptoms and fear of cancer,⁶ concerns about wasting their own and general practitioners' time,⁷ and stoicism and stigma around smoking.⁸

Mass-media campaigns for symptom awareness are one approach to reducing the time that patients take to seek help about symptoms. Evidence from the "Be Clear on Cancer" campaigns in England reported potentially useful short term effects, including increased presentations to general practice and a higher proportion of earlier stage cancers⁹; similarly, a significant shift to earlier cancer stage at presentation was seen after a local symptom awareness campaign.¹⁰ A trial of a cancer symptom awareness campaign, including lung cancer, in rural Western Australia did not reduce time to diagnosis, although

this may have been due to the absence of television advertising.¹¹ There is recent evidence suggesting that early awareness campaigns have the potential to be cost-effective.¹² Social media may also have a role in raising awareness.

An alternative to mass-media campaigns is to focus symptom awareness interventions on individuals at increased risk. A behavioural intervention aimed at reducing barriers to help-seeking in current or former heavy smokers over 55 years old reported a significant positive impact on consultation rates in Scotland,¹³ and an increase in respiratory consultations in Australia.¹⁴

How should primary care clinicians respond to patients with symptoms?

For England and Wales, the National Institute for Health and Care Excellence (NICE) provides guidance on the criteria that warrant urgent action.¹⁵ For example, referral is recommended for unexplained haemoptysis in people aged over 40 years, and urgent chest x ray is recommended in smokers with appetite loss or with thrombocytosis. However, the presentation of symptoms is often complex, as many people will have comorbidities,¹⁶ and there is often no clear symptom signature.¹⁷

Only half of patients will have an isolated first symptom, and, although haemoptysis is the most predictive symptom, it occurs in only 20% patients.¹⁸ Many patients present with non-respiratory symptoms. Hence prompt recognition of patients who do not fulfil NICE criteria depends on clinicians having a low threshold for requesting a chest x ray, and a low threshold for repeating or requesting further lung imaging if patients have a normal chest x ray and ongoing symptoms. Some national guidelines suggest computed tomography in the case of persistent symptoms despite a normal chest x ray.¹⁹ Several risk prediction tools have been developed for use in primary care, but there is insufficient evidence to recommend their use.²⁰

The prospect of biomarkers to identify people with early disease is of considerable interest. This includes novel technologies to detect volatile organic compounds in the breath and blood biomarkers.

How can we redesign health systems to improve diagnosis and treatment?

The NHS in England has recently implemented a timed lung cancer diagnostic pathway aiming to streamline investigations for suspected lung cancer, allowing earlier treatment alongside a more rapid “all clear” for patients found not to have cancer.²¹

The variations seen between treating centres are thought to contribute to poorer UK outcomes. An estimated 500 deaths could be prevented annually if the proportions of patients treated with surgery and radical radiotherapy matched those in centres in the highest quintile of treatment rates.²² Similarly, there is known variation between general practitioners in their propensity to investigate patients equally.²³

What imaging, diagnostic work-up, and treatment planning should be undertaken?

The starting point is contrast-enhanced computed tomography (CT) of the thorax including neck and upper abdomen (fig 2). If initial CT demonstrates distant metastases or involvement of the supraclavicular or cervical lymph nodes, sampling allows staging and pathological subtyping (immunohistochemical and molecular analysis) in one procedure. If the disease seems

suitable for radical treatment (either surgical or oncological), positron emission tomography-computed tomography (PET-CT) is indicated due to its high sensitivity for distant metastases. PET-CT has lower specificity for mediastinal disease, so systematic nodal sampling is preferred when imaging has indicated possible nodal spread. This is usually performed by sampling under endoscopic ultrasound guidance (usually endobronchial ultrasound guided transbronchial needle aspiration) which is more sensitive and cost effective than surgical staging alone.²⁴

The requirements for pathological and genetic analysis of tumour biopsies have become more complex alongside the substantial increase in treatment options for advanced disease. The historical distinction between small cell and non-small cell lung carcinoma has evolved into more precise immunohistochemical subtyping between squamous and non-squamous non-small cell lung carcinoma, alongside assays that predict response to immunotherapy and genotyping to assess suitability for targeted therapies.

What are the latest management options? Early stage disease

Surgical lobectomy remains the preferred treatment for medically fit patients with operable early stage lung cancer, with radical radiotherapy a lower morbidity alternative for patients with limited physiological reserve. Recent developments include the roles of minimally invasive surgery and newer radiotherapy techniques.

Over recent years, practice has shifted from open lobectomy towards video-assisted thoracoscopic surgery. These two approaches showed similar outcomes in a large propensity matched analysis from the US.²⁵ To date there has been no randomised comparison, but a UK trial has recently completed recruitment and will report shortly.²⁶

Radical oncological treatment of early stage lung cancer has been revolutionised by the development of stereotactic ablative radiotherapy (SABR) for peripheral tumours. This delivers a higher dose than conventional radical radiotherapy and has better overall survival.²⁷ Several studies attempting to randomise between surgery and SABR have failed to recruit, although one study is ongoing in North America (<https://clinicaltrials.gov/ct2/show/NCT02984761>).

Locally advanced disease

Treatment options for patients with locally advanced lung cancer (involving hilar or mediastinal lymph nodes) now recommended by NICE²⁸ include surgery with adjuvant (postoperative) chemotherapy or chemotherapy and radiotherapy given in combination. The updated NICE guidance also recommends consideration of chemoradiotherapy followed by surgery for some patients, although this is rare in practice.²⁸ The recommendation is based on a new meta-analysis showing improved progression-free survival with this approach.²⁹ There is evidence that immunotherapy after chemoradiotherapy is beneficial.³⁰ Management of localised small cell lung carcinoma is with chemoradiotherapy³¹; prophylactic cranial irradiation reduces brain metastases and improves survival.

Metastatic disease

There have been considerable recent changes in the management of metastatic non-small cell lung carcinoma. For patients whose tumours harbour epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations, tyrosine kinase

inhibitors are the treatment of choice, with second line agents (third generation tyrosine kinase inhibitors or cytotoxic chemotherapy) reserved for those who progress or develop resistance. Increasingly, other molecular targets are being exploited.

The management of patients without such mutations has been transformed by the advent of immune checkpoint inhibitors (immunotherapy). Precise indications for immunotherapy (monotherapy versus combination treatment with chemotherapy, and first line versus second line treatment) depend on the extent to which the tumour expresses programmed death-ligand 1 (PD-L1), and the patient's performance status (only licensed for use in relatively fit patients), with practice evolving at a rapid rate. For those patients ineligible for or not responding to immunotherapy, palliative chemotherapy remains the standard of care.

Metastatic small cell lung carcinoma is primarily managed with chemotherapy, and consolidation chest radiotherapy is beneficial for patients who respond to chemotherapy.³²

A small proportion of people with symptoms relating to airway occlusion by tumour may benefit from local treatment with stenting, argon plasma coagulation, or photodynamic therapy.

What interventions should be offered for people living with and beyond lung cancer?

Many patients with lung cancer and their families will need psychological support to help cope with the consequences of their diagnosis and treatment. Many patients continue to smoke after diagnosis, placing them at higher risk of treatment toxicity, cancer recurrence, second primaries, and poorer survival.³³ Quitting smoking after a diagnosis can improve prognosis regardless of cancer stage.³⁴ All patients who continue to smoke must be offered interventions to help them quit. Discussions should be conducted in a manner that minimises stigma and blaming.

The only randomised study of follow-up imaging found no survival benefit from regular computed tomography after surgical resection.³⁵ In patients with metastatic disease, palliative radiotherapy is effective in the management of symptoms such as pain and haemoptysis. Early input from palliative care should be considered for patients with advanced disease, including those receiving active treatment, although access may vary internationally. Early palliative care improves outcomes, including survival.³⁶

Additional educational resources

- National Institute for Health and Care Excellence. Clinical Knowledge Summary: Symptoms suggestive of lung and pleural cancers. <https://cks.nice.org.uk/lung-and-pleural-cancers-recognition-and-referral/#!diagnosisSub>
- National Institute for Health and Care Excellence. Suspected cancer: recognition and referral (NICE guideline NG12). Section 1.1 Lung and pleural cancers. 2017. <https://www.nice.org.uk/guidance/ng12/chapter/1-Recommendations-organised-by-site-of-cancer#lung-and-pleural-cancers>
- Patient.info. Professional articles: Lung cancer. 2017. <https://patient.info/doctor/lung-cancer-pro>

Information resources for patients

- Patient.info. Lung cancer. 2017. <https://patient.info/health/lung-cancer-leaflet>
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- British Lung Foundation. Lung cancer. https://cdn.shopify.com/s/files/1/0221/4446/files/FL16_Lung_cancer_v3_2017_PDFdownload.pdf?3883777416736138941&_ga=2.86724443.296111450.1537438735-81433678.1534270194
- Roy Castle Lung Cancer Foundation. Lung cancer information. <https://www.roycastle.org/how-we-help/lung-cancer-information>
- Macmillan Cancer Support. Information and support: Lung cancer. <https://www.macmillan.org.uk/information-and-support/lung-cancer>

Education into practice

- Do you consider a chest x ray when a current or former smoker attends with non-specific symptoms?
- Consider your last patient with lung cancer. Were there opportunities for earlier investigation and diagnosis?
- Do you discuss early palliative care with all eligible patients?
- Do you offer smoking cessation interventions to patients who continue to smoke after diagnosis?

How patients were involved in the creation of this article

Comments by a patient peer reviewer have been incorporated to help capture the patient perspective.

Contributors: RDN led the drafting of the introduction, "Who gets it," and "How should primary care clinicians respond to patients with possible symptoms." JDE led the drafting of "How can we improve symptom awareness in people at risk?" MCC led the drafting of "What imaging, diagnostic work-up, and treatment planning should be undertaken." FS led the drafting of "What are the latest management options?" All authors contributed to improving these sections, and all authors contributed equally to the remaining sections. All authors have seen and approved the final version of the manuscript. We also thank Kevin Franks and Stephen Bradley for suggesting additional literature for inclusion in this review. RDN will act as guarantor.

Funding: RDN is an associate director and JDE is a member of senior faculty of the multi-institutional CanTest Collaborative, which is funded by Cancer Research UK (C8640/A23385). JDE is supported by an NHMRC Practitioner Fellowship.

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Commissioned, based on an idea from the author; externally peer reviewed.

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Figures

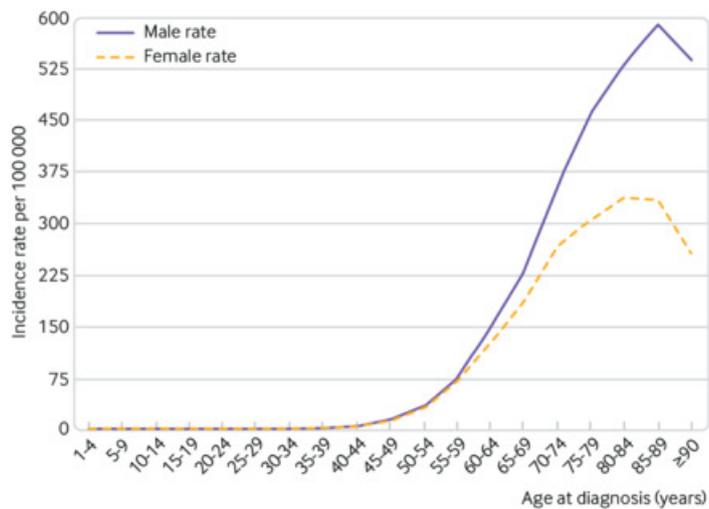


Fig 1 Incidence of lung cancer per 100 000 population by age and sex in UK 2013-15 (adapted from Cancer Research UK. Lung cancer incidence by age. 2017. <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-One>)

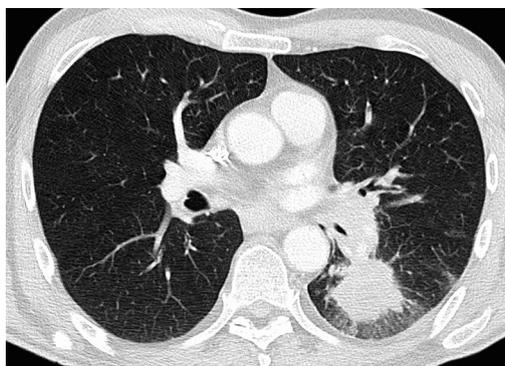


Fig 2 Computed tomography (CT) scan of the chest of a male patient with adenocarcinoma in the lower left lung (at right)

[Image: Pr Michel Brauner, ISM / Science Photo Library]