Lung cancer - clinical update

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Introduction

Lung cancer is one of the commonest cancer worldwide [1]. Outcomes are amongst the poorest of all tumour types, with 5-year survival of 10-20% [2]. Survival is hugely influenced by stage at diagnosis, with 5-year survival varying from 92% to 0% for the earliest and latest stages respectively [3]. In this update we will discuss contemporary evidence based therapeutic options, and approaches to increasing symptom awareness and early diagnosis. Low-dose CT screening is beyond the scope of this review.

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. 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.

Note: suggest adding an image of lung cancer incidence about here

How can we improve symptom awareness?

Several studies have explored symptom appraisal and help-seeking in recently diagnosed people. 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 symptom awareness campaigns 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 cancers [9]; similarly, a significant stage shift was seen in 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 be 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, reported a significant positive impact on consultation rates in Scotland [13], and an increase in respiratory consultations in Australia [14].

Note: suggest adding an image of Be Clear on Cancer intervention about here

How should primary care clinicians respond to patients with symptoms?

In England and Wales referral and investigative activity prompted by symptoms is covered by a NICE guideline that covers specific symptoms and outlines criteria warranting urgent actions [15]. For example, referral is recommended for unexplained haemoptysis in those aged over 40, and urgent chest X-ray in smokers with appetite loss, or with thrombocytosis. However, the presentation of symptoms is often complex, as some people will have co-morbidity [16], and there is often no clear symptom signature [17].

Only half of patients will have an isolated first symptom, and whilst 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 CT in the case of persistent symptoms despite a normal chest x-ray [19]. A number of risk prediction tools have been developed for use in primary care, although there is currently insufficient evidence to recommend their use [20].

The prospect of biomarkers to identify people with early disease is an area 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 stream-line investigations for suspected lung cancer allowing earlier treatment, alongside more rapid communication of an 'all clear' for patients found not to have cancer [21].

There are variations between treating centres that are thought to contribute to poorer UK outcomes. An estimated 500 deaths could be prevented annually if the proportions treated with surgery and radical radiotherapy matched those in centres in the highest quintile of treatment rates [22]. Similarly, there is known variation between GPs 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. Where initial CT demonstrates distant metastases or involvement of supraclavicular/cervical lymph nodes, sampling allows staging and pathological subtyping (immunohistochemical and molecular analysis) in one procedure. Where the disease appears 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 whenever 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 significant increase in treatment options for advanced disease. The historical distinction between small cell (SCLC) and non-small cell lung carcinoma (NSCLC) has evolved into more precise immunohistochemical subtyping between squamous and non-squamous NSCLC,

alongside assays that predict response to immunotherapy, and genotyping to assess suitability for targeted therapies.

Note: suggest adding a picture of some form of chest imaging here

What are the latest management options?

Early stage disease

Surgical lobectomy remains the standard of care for medically-fit patients with operable early stage lung cancer, with radical radiotherapy a lower morbidity alternative for patients with limited physiological reserve. Recent controversies in this area 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 disease free and cancer specific survival in a large propensity matched analysis from the US [25]. To date there has been no randomised comparisons, 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 on-going in North America [https://clinicaltrials.gov/ct2/show/NCT02984761].

Locally advanced disease

Treatment options for patients with locally advanced lung cancer (involving hilar/mediastinal lymph nodes) include surgery with adjuvant (post-operative) chemotherapy, or chemotherapy and radiotherapy given in combination (concurrent chemo-radiation, now recommended by NICE [28]). There is some evidence that immunotherapy post-chemoradiotherapy is beneficial [29]. Management of localised SCLC is with chemo-radiotherapy [30]; prophylactic cranial irradiation reduces brain metastases and improves survival.

Metastatic disease

There have been considerable recent changes in the management of metastatic NSCLC. For patients whose tumours harbour EGFR or ALK mutations, Tyrosine Kinase Inhibitors [growth factor receptor blockers?] are treatments of choice, reserving second line agents [3rd generation TKI or cytotoxic chemotherapy] 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). Practice is evolving rapidly. Precise treatment regimens (immunotherapy alone vs combination treatment with chemotherapy, and first vs second line treatment options) depend on the extent to which the tumour expresses Programmed Death-Ligand 1, and the performance status of the patient. Immunotherapy is licensed only for those who are relatively fit. For patients who are ineligible or not responding to immunotherapy, palliative chemotherapy remains the standard of care.

Metastatic SCLC is primarily managed with chemotherapy, and consolidation chest radiotherapy is beneficial for patients who respond to chemotherapy [31].

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

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

Many patients and their families need psychological support to help cope with their lung cancer diagnosis and treatment. Continuing to smoke following diagnosis increases the risk of treatment toxicity, recurrence, second primaries, and poorer survival [32]. Quitting smoking after a diagnosis can improve prognosis regardless of stage [33]. All patients who continue to smoke must be offered interventions to help them quit. Discussions should be conducted in a manner that minimizes stigma and blaming.

The only randomised study of follow-up imaging found no survival benefit from regular CT following surgical resection [34]. In patients with metastatic disease, palliative radiotherapy is effective in the management of symptoms such as pain and haemoptysis. Early palliative care input should be considered for patients with advanced disease, including those in active treatment, although access may vary internationally. Early palliative care improves outcomes, including survival [35].

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BOXES:

"What you need to know"

- Most lung cancers present with non-specific symptoms; haemoptysis a feature in only 20%
- Consider a CXR for patients who have persistent symptoms or thrombocytosis, and repeat CXR / CT if symptoms persist
- PET-CT is used to identify distant metastases in those eligible for radical treatment after contrast-enhanced CT. Where there is potential mediastinal node involvement, EBUS-TBNA is the optimal initial strategy for nodal sampling for nodal sampling
- Surgery remains standard of care in early stage NSCLC. Radical radiotherapy or SABR are alternatives. Options for locally advanced NSCLC include surgery with post-operative chemotherapy or chemoradiotherapy.
- Systemic therapy for metastatic NSCLC is now targeted primarily on tumour genetic mutations and biomarkers. TKIs and immunotherapy are now first line treatments for some patients with metastatic NSCLC. Combination chemotherapy is available for patients not eligible for TKIs and immunotherapy.

"How patients were involved in the creation of this article"

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

"Education into practice"

- Do you consider a chest x-ray when a current or ex-smoker attends with non-specific symptoms?
- In your recent cases, were there opportunities to have considered the diagnosis and investigated sooner?
- Are you offering your patients all the diagnostic work up and treatment that they should be being offered?
- Are early palliative care referrals being discussed with patients?
- Are smoking cessation interventions offered to your patients who continue to smoke after diagnosis?

"How this article was created":

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

ADDITIONAL EDUCATIONAL RESOURCES:

'Sharing information with patients: Guidance for Healthcare Professionals Discussing Options for Patients who have Lung Cancer' British Thoracic Society. Free, open access
https://www.brit-thoracic.org.uk/document-library/clinical-information/lung-cancer/sharing-information-with-lung-cancer-patients/

NICE Clinical Knowledge Summary regarding symptoms suggestive of lung and pleural cancers. Free, open access
https://cks.nice.org.uk/lung-and-pleural-cancers-recognition-and-referral#!diagnosis

NICE Guideline NG12 section 1.1 Lung and pleural cancers. Free, open access
https://www.nice.org.uk/guidance/ng12/chapter/1-Recommendations-organised-by-site-of-cancer#lung-and-pleural-cancers

Lung cancer overview for Medical Professionals. Free, open access
https://patient.info/doctor/lung-cancer-pro

INFORMATION RESOURCES FOR PATIENTS:

Patient.co.uk has a concise overview. Free, open access
https://patient.info/health/lung-cancer-leaflet

Cancer Research UK. Free, open access
https://www.cancerresearchuk.org/about-cancer/lung-cancer

British Lung Foundation leaflet. Free, open access
https://cdn.shopify.com/s/files/1/0221/4446/files/FL16_Lung_cancer_v3_2017_PDFdownload.pdf?3883774167361389 41&_ga=2.86724443.296111450.1537438735-81433678.1534270194

Roy Castle Lung Cancer Foundation provide resources for patients. Free, open access
https://www.roycastle.org/how-we-help/lung-cancer-information

Macmillan Cancer Support provide information and support. Free, open access
https://www.macmillan.org.uk/information-and-support/lung-cancer

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