

REVIEW

Recognising Lung Cancer in Primary Care

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ABSTRACT

Significant advances in the management of both early and advanced stage lung cancer have not yet led to the scale of improved outcomes which have been achieved in other cancers over the last 40 years. Diagnosis of lung cancer at the earliest stage of disease is strongly associated with improved survival. Therefore, although recent advances in oncology may herald breakthroughs in effective treatment, achieving early diagnosis will remain crucial to obtaining optimal outcomes. This is challenging, as most lung cancer symptoms are non-specific or are common respiratory symptoms which usually represent benign disease. Identification of patients at risk of lung cancer who require further investigation is an important responsibility for general practitioners (GPs). Diagnosis has historically relied upon plain chest X-ray (CXR), organised in response to symptoms. The sensitivity of this modality, however, compares

unfavourably with that of computed tomography (CT). In some jurisdictions screening high-risk individuals with low dose CT (LDCT) is now recommended. However uptake remains low and the eligibility for screening programmes is restricted. Therefore, even if screening is widely adopted, most patients will continue to be diagnosed after presenting with symptoms. Achieving early diagnosis requires GPs to maintain an appropriate level of suspicion and readiness to investigate in high-risk patients or those with non-resolving symptoms. This article discusses the early detection of lung cancer from a primary care perspective. We outline risk factors and epidemiology, the role of screening and offer guidance on the recognition of symptomatic presentation and the investigation and referral of suspected lung cancer.

Keywords: Cancer diagnosis; Chest X-ray; CT chest; General practitioner; GP; Lung cancer; Lung cancer screening; Oncology; Primary care

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INTRODUCTION

Lung cancer is a primary cancer of the lung and is classified histologically as small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). The most common histological subtypes of NSCLC are adenocarcinoma, squamous cell and large cell cancers.

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Excluding non-melanoma skin cancers, lung cancer is the both the commonest type of cancer worldwide and the single largest cause of cancer mortality [1]. In England, lung cancer accounts for 13% of all cancers, following only breast and prostate cancer in terms of incidence [2], but is the leading cause of cancer deaths [3].

Improvements in early diagnosis and treatment have led to improved outcomes for many cancers. Since 1971, age-standardised 5-year survivals from breast cancer, prostate cancer and colorectal cancer in England and Wales have increased from 53% to 87% [4], 37% to 85% [5] and 24% to 59% respectively [6]. In contrast, the age-standardised 5-year survival for lung cancer has only increased from 5% to 10% [7]. Advances in the systemic treatment of advanced lung cancer with the use of tyrosine kinase inhibitors (TKIs) and immunotherapy have led to significant survival benefits for some patients [8–10]. The relatively infrequent expression of targets for these treatments and poor prognosis associated with advanced lung cancer have prevented these advances significantly impacting on overall survival. The introduction of stereotactic radiotherapy (SABR) has increased the radical treatment rate for early stage lung cancer without reducing surgical resection rates [11]. Lung cancer outcomes differ according to stage at diagnosis, with a 1-year survival of 81.7% for stage I and 15.5% for stage IV lung cancer in England and Wales [12]. Therefore, despite the substantial promise offered by novel therapies, achieving early diagnosis is likely to remain a crucial part of improving outcomes.

Most patients with lung cancer first present to their general practitioner (GP) [13–16]. Lung cancer often presents with symptoms that are very commonly encountered in primary care, making early diagnosis challenging. A large UK-based population study demonstrated that although cough is one of the most frequent symptoms of lung cancer, only 0.2% of patients who had a cough for 3 weeks were ultimately diagnosed with lung cancer [17]. The UK's National Cancer Diagnosis Audit reported that the median primary care interval (time from first presentation to referral) for lung cancer was 14 days, the second highest of 15 cancers

reported. Prolonged primary care intervals of 60 and 90 days were experienced by 17.9% and 10.8% of patients respectively [18]. A third of patients diagnosed with lung cancer have attended their GP with symptoms attributable to their cancer three or more times before diagnosis [19]. Unfortunately, most lung cancers are still diagnosed at an advanced stage [20] and a third of lung cancers are diagnosed during emergency presentations [21]. The priority for most of these patients will be for prompt referral and investigation. Some patients with a high probability of malignant disease presenting with significant symptom burdens, rapid clinical deterioration or a high risk of acute hospital admission may benefit from synchronous referral to community palliative care services.

In common with other cancers, system factors are likely to affect the promptness of diagnosis. Some evidence suggests that settings that permit greater access to investigations are associated with improved survival [22]. Systems in which primary care practitioners have a strong role in rationing access to secondary care have been associated with poorer survival for the ten most common cancers, including lung cancer [23]. This suggests that the gate-keeping role of primary care practitioners may be a barrier to early diagnosis. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RISK FACTORS AND EPIDEMIOLOGY

Risk factors for the development of lung cancer include tobacco exposure, asbestos exposure, other occupational exposures, older age, male sex, chronic obstructive pulmonary disease (COPD), family history and air pollution.

Tobacco exposure remains the single greatest risk factor for developing lung cancer. In the UK, an estimated 71% of lung cancer deaths have been attributed to smoking and an additional 1% to environmental tobacco smoke ('second-hand smoke' or 'passive smoking') [24]. A Canadian study determined lifetime

risks of lung cancer as 17.2% and 11.6% for male and female smokers respectively, compared to 1.3% and 1.4% for never-smokers [25]. The risk is increased by both the total quantity of tobacco to which an individual is exposed and the duration of time of which an individual remains a smoker [26]. The relative risk of lung cancer death is approximately 15 times higher in smokers compared to never-smokers, as demonstrated in a seminal cohort study [27]. Upon stopping smoking the relative risk of developing lung cancer declines rapidly; however, ex-smokers remain at an elevated level of risk compared to never-smokers [28].

Despite the well-understood link between smoking and lung cancer, clinicians should remain mindful that a significant proportion of lung cancers occur in patients who have never smoked, estimated at between 10% and 15% in one North American study [29].

Evidence of airway obstruction, typically associated with chronic obstructive pulmonary disease (COPD) and emphysema, is an independent risk factor for developing lung cancer, with a relative risk at least double that of matched populations without airway obstruction [30–32]. This remains significant even when factors such as over diagnosis of COPD are taken into account [33]. COPD and lung cancer have therefore been characterised as linked diseases, possibly sharing common pathological mechanisms [34].

After smoking, the working environment is the next most significant risk factor with 13% of lung cancers in the UK attributed to occupational exposures [24]. Asbestos accounts for a large proportion of these cases [35], though other occupational carcinogens include silica (e.g. through glass manufacture and sand-blasting processes in textile manufacturing), diesel engine exhaust and aerosols inhaled whilst painting and welding [36]. Meanwhile, a further 8% of UK lung cancer cases have been attributed to air pollution [24].

While there are clear associations between these environmental and demographic factors and the incidence of lung cancer, it is important to recognise that lung cancer does still

occur in younger patients and never-smokers. There is an increased prevalence of driver mutations, including epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations in patients with lung cancer who are younger and those who have never smoked. These driver mutations predict response to TKI therapy, which can lead to improved survival in patients with advanced disease [9, 10].

Lung cancer remains more common amongst men than women in the UK, with crude incidences of 77 and 66 per 100,000 population [37]. This is likely to be mediated strongly by differences in smoking behaviours, with 21.1% of males and 16.5% of females in the UK smoking in 2013 [38]. The incidence of lung cancer amongst men is declining globally, but is increasing amongst women in high income countries, reflecting patterns of increasing tobacco use in women and declining use in men [39].

Genetic factors play a role in the development of lung cancer [40] with a meta-analysis indicating that risk is 82% higher in those in whom a sibling has been diagnosed with lung cancer, after adjustment for smoking and other potential confounders [41].

Lung cancer incidence increases with age [42] and the median age of diagnosis in England and Wales was 72 years for women and 73 years for men in 2016 [12]. Although lung cancer is rare under the age of 40, clinicians should not dismiss the possibility of lung cancer in younger patients.

SYMPTOMS AND SIGNS

The referral recommendations from the National Institute for Health and Care Excellence (NICE) are outlined in Box 1 [43]. This guidance was updated in 2015 with new recommendations that GPs refer all patients over age 40 years with unexplained haemoptysis and that consideration be given to plain chest X-ray (CXR) for patients with thrombocytosis and/or appetite loss.

Box 1: Recommendations from NICE guideline [NG12] suspected cancer: recognition and referral [43] Refer people using a suspected cancer pathway referral (for appointment within 2 weeks) for lung cancer if they:

- Have chest X-ray findings that suggest lung cancer or
- Are aged 40 and over with unexplained haemoptysis

Offer an urgent chest X-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over if they have 2 or more of the following unexplained symptoms, or if they have ever smoked and have 1 or more of the following unexplained symptoms:

- Cough
- Fatigue
- Shortness of breath
- Chest pain
- Weight loss
- Appetite loss

Consider an urgent chest X-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following:

- Persistent or recurrent chest infection
- Finger clubbing
- Supraclavicular lymphadenopathy or persistent cervical lymphadenopathy
- Chest signs consistent with lung cancer
- Thrombocytosis

The earliest stage of lung cancer is often not associated with any symptoms. The most common symptoms associated with lung cancer tend to be both common in benign presentations in the community and particularly amongst smokers. Therefore the discriminative utility of most of these symptoms in isolation is low. Positive predictive values (PPVs) for different symptoms of lung cancer, both alone and in combination, have been determined from a case-control study and are presented in Fig. 1. Importantly PPVs for each symptom are higher in smokers and those over the age of 70 years [44]. With the highest PPV of 2.4–7.5% [45], unexplained haemoptysis always warrants further investigation. Haemoptysis, however, is a

feature of only about a fifth of lung cancers [46, 47], so the absence of this symptom should not provide reassurance.

While guidelines have streamlined access to diagnosis for some, concern has been raised that this approach might prioritise patients with classical presentations, such as haemoptysis, at the expense of those with symptoms which reflect less advanced disease and would therefore have the most to gain from early diagnosis [13]. In fact, in 2013 only 28% of lung cancer cases in England were diagnosed through the country's '2-week-wait' urgent referral pathway. In many cases appropriately urgent action may have occurred outside the 2-week-wait pathway, for example through automatic referral following a suspicious CXR or through routine surveillance for pulmonary nodules. Although declining as a proportion, diagnoses following emergency presentations remained the commonest route of diagnosis at 35% [48]. Such diagnoses are associated with the poorest outcomes, although the reasons for this are likely to be complex and probably include the poorer performance status, more advanced disease and greater levels of socio-economic deprivation of patients who present in this way [49].

In order to reduce the time intervals between patients experiencing symptoms and presenting to their GP, significant efforts have been made to improve public awareness. Evaluations of England's 'Be Clear on Cancer' campaign have suggested the programme contributed to encouraging increases in presentations to primary care with prolonged cough and an increase in the proportions diagnosed with early stage lung cancer [50, 51]. A longer-term assessment, however, has suggested that such campaigns require sustained commitment in order to maximise their impact [52]. In Australia, a cluster randomised trial of a complex intervention which included a public awareness campaign showed no reduction in the interval between symptoms and diagnosis [53], although the authors speculate that the intervention may not have achieved the breadth of media coverage required to show an effect.

A simple risk assessment tool has been developed which can generate positive predictive values for one symptom or two symptoms

Cough	Fatigue	Dyspnoea	Chest pain	Loss of weight	Loss of appetite	Thrombocytosis	Abnormal spirometry	Haemoptysis	
0.40 0.3, 0.5	0.43 0.3, 0.6	0.66 0.5, 0.8	0.82 0.6, 1.1	1.1 0.8, 1.6	0.87 0.6, 1.3	1.6 0.8, 3.1	1.6 0.9, 2.9	2.4 1.4, 4.1	PPV as a single symptom
0.58 0.4, 0.8	0.63 0.5, 0.9	0.79 0.6, 1.0	0.76 0.6, 1.0	1.8 1.1, 2.9	1.6 0.9, 2.7	2.0 1.1, 3.5	1.2 0.6, 2.6	2.0 1.1, 3.5	Cough
	0.57 0.4, 0.9	0.89 0.6, 0.3	0.84 0.5, 1.3	1.0 0.6, 1.7	1.2 0.7, 2.1	1.8	4.0	3.3	Fatigue
		0.88	1.2 0.9, 1.8	2.0 1.2, 3.8	2.0 1.2, 3.8	2.0	2.3	4.9	Dyspnoea
			0.95 0.7, 1.4	1.8 1.0, 3.4	1.8 0.9, 3.9	2.0	1.4	5.0	Chest pain
				1.2 0.7, 2.3	2.3 1.2, 4.4	6.1	1.5	9.2	Loss of weight
					1.7	0.9	2.7	>10	Loss of appetite
							3.6	>10	Thrombocytosis
								>10	Abnormal spirometry
								17	Haemoptysis

Fig. 1 Positive predictive values (%) for lung cancer for individual risk markers, and for pairs of risk markers in combination (against a background risk of 0.18%). (1) The top row (bold) gives the PPV for an individual feature. The cells along the diagonal relate to the PPV when the same feature has been reported twice. Other cells show the PPV when a patient has two different features. (2) The top figure in each cell is the PPV. It has only been calculated when a minimum of ten cases had the feature or

in combination stratified for smokers and non-smokers [54]. Assessment of this tool (Fig. 1) has shown that, when used, it is associated with

combination of features. The two other figures are the 95% CIs for the PPV. These have not been calculated when any cell in the 2 × 2 table was below 10. (3) The yellow shading is when the PPV is above 1%. The amber shading is when the PPV is above 2%. The red shading is for PPVs above 5.0%. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature. Ref. [54]

increased investigations such as CXR, urgent referrals and lung cancer diagnoses [55]. Two algorithms have also been created which

incorporate symptoms as well as other risk factors to generate risk scores [17, 56].

Positive examination findings are usually only associated with advanced disease, so examination will typically be unremarkable. Since an individual GP will, on average, encounter only one new case of lung cancer each year [57], the prospects of identifying lung cancer through rare signs such as hypertrophic pulmonary osteoarthropathy and Horner's syndrome are exceedingly unlikely. In clinical practice, patient and physician intuition of the possibility of serious underlying disease is probably much more important [58]. Given that the 'risk threshold' NICE has adopted for further investigation or referral for suspected cancer is 3% [43], GPs should feel empowered to refer patients at relatively low levels of risk [59].

In situations in which a decision for further follow-up or investigation has not been made, GPs should advise their patients to represent if symptoms fail to resolve or new symptoms develop. Although little evidence exists for the effectiveness of 'safety netting' [60], the experience of significant event audit suggests it is an important strategy to reduce the risk of delayed diagnosis [61]. Safety netting is recommended as part of the NICE guidelines for suspected cancer referral [43] and GPs should be aware that there is a medico-legal expectation that safety netting is adequately undertaken and documented [62].

INVESTIGATION OF SUSPECTED LUNG CANCER

The first-line investigation of suspected lung cancer remains the CXR. CXR has the advantages of being cheap and accessible [58], with a low radiation dose of 0.02 mSv equivalent to 3 days of natural background radiation [63]. Unfortunately, CXR has a significant false negative rate, with a sensitivity of approximately 75–80% [64–67]. One study has reported that 10% of the CXRs of lung cancer patients were initially reported as normal, with a further 13% which were reported as abnormal but with no suspicion of lung cancer [64]. Despite its limitations, evidence suggests that strategies to

increase CXR uptake can yield improvements in referral rates and possibly improve early detection of lung cancer [51, 68].

Previous guidance that all patients with radiologically demonstrated community-acquired pneumonia should have a repeat CXR after 6 weeks to confirm resolution has been refined to include only those at highest risk of malignancy, such as smokers and those aged over 50 years [69]. Evidence from a population-based cohort study provides some reassurance that such an approach is reasonable, given that only one in 57 patients who did have lung cancer 1 year following their pneumonia were under the age of 50 and that overall only 40% of patients attended for a repeat CXR within 90 days [70].

Computed tomography (CT) scans of the chest are much more sensitive than CXR, although the majority of available evidence relates to screening contexts, rather than the investigation of symptomatic patients. In the US National Lung Screening Trial (NLST), low dose CT (LDCT) yielded sensitivity and specificity of 93.8% and 73.4% compared to 73.5% and 91.3% for CXR, respectively [71]. In most contexts conventional CT continues to be used for symptomatic investigation. NICE recommends contrast-enhanced CT of the thorax including also the liver and adrenal glands [72]. This is usually arranged from secondary care following an urgent referral from a primary care physician for suspected lung cancer, although in some regions GPs may have direct access to CT. In the UK the National Optimal Lung Pathway [73] has set out standards for lung cancer service providers to improve the quality and efficiency of pathways for patients with suspected lung cancer including the timing of investigations. This pathway aims to reduce the time between referral, CT scan and review by respiratory physician with an interest in lung cancer.

Access to and use of CT varies greatly across different health systems. Fewer CT scans are performed in the UK than other Western European countries [74]. Higher rates of CT use in the US have been identified as a concern given the resulting radiation exposure [75]. LDCT uses an estimated radiation dose of 2 mSv, compared

to 7 mSv from conventional CT [76]. Increased availability of LDCT in the future could help reduce the total radiation exposure.

Widening access to urgent CT scans for GPs (sometimes termed ‘direct access’) has been suggested as a means to improve early stage diagnosis [77]. In Denmark, a country where GPs serve a similar gate-keeping role to their counterparts in the UK, a cluster-randomised controlled trial found that giving GPs access to LDCT to investigate possible lung cancer led to no statistically significant decrease to the time to diagnosis. Following adjustment for non-engagement in the intervention group it was found that patients in the control group were at a higher risk of experiencing a long diagnostic interval [78]. The relatively low levels of engagement, which reached only around half of eligible GPs, might suggest that achieving uptake of direct access investigations requires a broader shift in practice rather than simply permitting their use.

Patients with haemoptysis have also routinely been investigated with bronchoscopy to exclude lung cancer. Diagnostic evaluations of CT have suggested that bronchoscopy can be omitted in most cases if malignancy is not identified on CT [79, 80].

SCREENING

The US Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial has provided the largest and most conclusive body of evidence that screening asymptomatic populations with CXR does not reduce lung cancer mortality [81]. The US National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality with annual LDCT in an asymptomatic high-risk population [82]. The US Preventative Task Force (USPSTF) has since recommended annual screening with LDCT for those aged 55–80 who have a 30-pack-year smoking history and are current smokers or have smoked within the last 15 year [83]. Uptake of screening in the USA, however, remains low [84, 85]. This may be due to the lack of a fully co-ordinated national approach [86]. The European Union position statement

on lung cancer screening set out specific actions that were required before the widespread implementation of lung cancer screening [87]. The UK National Screening Committee (NSC) does not currently recommend lung cancer screening. The NSC is expected to review this decision following the publication of final results from the Dutch-Belgian NELSON trial [88]. These results were presented at the International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC) 2018 in Toronto. The presented data demonstrated a significant reduction in lung cancer mortality in the screened male population. There was a greater reduction in mortality in the screened female population, but this cohort was smaller and this difference did not reach significance. Combined population data and overall mortality data has not yet been presented.

Potential harms of LDCT screening must be weighed against any potential benefits. These include increased exposure to ionising radiation [89], invasive investigation and follow-up for benign changes and over diagnosis of cancers which if left undiscovered would not have affected patients [90–93]. The experience of the Danish Lung Cancer screening trial suggests that the problem of overdiagnosis in particular could be greater than that previously estimated in the National Lung Cancer Screening Trial [94]. Unfortunately, evidence from the USA suggests that in discussing lung cancer screening, clinicians’ communication of the possible harms is very limited [95]. These harms are reduced by targeting screening programmes on the population at highest risk of lung cancer.

Analysis of the Surveillance, Epidemiology and End Results (SEER) database has shown that only 26.7% of patients with lung cancer in the USA would have been eligible for LDCT screening by NLST criteria [96]. The use of composite risk prediction tools, such as The Liverpool Lung Project [97] or PLCO_{M2012} models [98], may better identify the high-risk population and increase the proportion of lung cancers that may be detected by screening. A significant proportion of patients who go on to develop lung cancer will not have been eligible for LDCT screening. Of those who are eligible,

some will choose not to undergo screening and the possibility remains of developing lung cancer between annual LDCT screening (interval cancers). It is therefore likely that the majority of lung cancers will continue to be diagnosed by appropriate investigation of symptomatic patients by vigilant clinicians.

CONCLUSIONS

Improving early diagnosis of lung cancer is crucial to improving outcomes. The majority of patients with lung cancer present to their GP with symptoms and the early identification of lung cancer remains a key challenge. The low cost, safety and availability of CXR justify a low threshold for use of this investigation by GPs. In the context of patients with ongoing symptoms and/or significant risk factors, however, clinicians should be aware of the imperfect sensitivity of CXR and exercise appropriate vigilance. Depending on the level of risk, strategies including safety netting, planning a repeat CXR after an appropriate interval or an urgent referral for further investigation such as CT or secondary care assessment may be reasonable.

While screening with LDCT may offer improved outcomes to the highest-risk populations, most patients who develop lung cancer will not be eligible for screening meaning that the role of GPs in recognising symptomatic disease will remain crucial.

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