Diagnosis of lung cancer in primary care: a structured review

William Hamilton and Deborah Sharp


Background. Lung cancer has the highest cancer incidence and mortality in the UK. Despite this, an individual GP encounters only one new presentation approximately every 8 months, so gains relatively little experience of its diagnosis. This is partly addressed by referral guidelines which aim to help GPs in selection of patients for chest X-ray or referral for specialist investigation.

Objective. The purpose of this study was to review the primary care presenting features of lung cancer, in the light of the UK Referral Guidelines for Suspected Cancer.

Methods. A structured literature review was carried out.

Results. Little research has been undertaken in primary care, and the predictive values for most symptoms are unknown. Approximate likelihood ratios could be calculated for six symptoms or signs: haemoptysis 13; fatigue 5.7; cough 5.3; finger clubbing 3.9; weight loss 2.9; and dyspnoea 1.5–5.7, but none of these figures derived from single primary care studies. Three recommendations for urgent investigation of possible lung cancer in the UK Referral Guidelines are questioned: for unexplained dyspnoea, hoarseness or cervical lymphadenopathy. For all these presentations, other serious diagnoses are more likely.

Conclusion. The UK Guidelines for referral of suspected lung cancer have a weak evidence base.

Keywords. Diagnosis, lung cancer, primary care.

Introduction

Over 38 000 new lung cancers occur each year in the UK. It is the most common new cancer in men, and the third most common in women, after breast and colorectal cancers.1 The incidence in men has been falling steadily since the 1970s, but is rising in women. These changes reflect smoking behaviour. Survival rates with lung cancer are very poor, so mortality has a similar pattern to incidence. Lung cancer causes 26% of male and 17% of female cancer deaths. Mortality is related to the stage at diagnosis, with—as is usual in cancer—the best prognosis in early stage cancers.

As earlier diagnosis is believed to improve prognosis, various screening trials have been undertaken, but with disappointing results.2–4 Further trials of spiral computerized tomography (CT) are in progress.5–7 At present, no screening instrument has been found to be useful; the main prospect for earlier diagnosis is prompt recognition of the symptoms and signs of the cancer. This will usually be in primary care.

The role of primary care in early diagnosis

In the UK, almost all of the population are registered with a GP, who diagnoses and treats the large majority of conditions. If lung cancer is a possible diagnosis, the GP can organize simple investigations, such as blood tests, sputum cytology or a chest X-ray. If there is still diagnostic difficulty or these investigations are abnormal, the GP can refer to a chest physician for specialized investigations. It can be difficult for the GP to decide whether a patient warrants urgent specialist referral for investigation of a possible cancer.9–11 This difficulty arises because many symptoms which could indicate cancer, such as haemoptysis or cough, also have benign causes, and the benign causes are more common. Despite lung cancer being such an important cause of death, at the level of the individual GP it is rare. A GP would expect to encounter a new lung cancer every 8 months, which means that they will build up relatively little personal experience of its diagnosis.

The UK Referral Guidelines for Suspected Cancer (called the UK Guidelines from now on) have been developed to facilitate selection of patients for urgent referral.12 The guidelines were published when the ‘2-week’ clinics were established offering rapid access to specialist opinion and investigation for patients fitting...
mesothelioma. In very few studies were likelihood ratios or predictive values for particular features described. Where reasonable, these were calculated from figures reported in the studies.

### Results

#### Presentation of lung cancer

A small number of lung cancers present without symptoms. They are discovered by chance, usually when a chest X-ray has been taken for another purpose. Asymptomatic cancers make up 7–13% of hospital case series, with the higher percentages reported in studies of screening radiology. A study from Swedish primary care also found that 10% of lung cancers had been diagnosed at an asymptomatic stage.

Therefore, the large majority of lung cancers present with symptoms, usually to primary care. Furthermore, most lung cancer patients report their symptoms quickly to their doctor. In one UK study, the median interval between the patient’s first symptoms and reporting them to their doctor was 3 weeks (interquartile range 2–8). This partly accounts for lung cancer having the shortest symptom to diagnosis interval of all the major cancers, with rapid investigation by GPs also contributing.

#### Symptomatic diagnosis

Many symptoms have been described with lung cancer, ranging from the common, such as haemoptysis, to the rare, such as the para-neoplastic syndromes. There are also many case reports of ‘atypical’ presentations, often of metastases. The primary care literature only deals with the common presenting features.

The prior probability of lung cancer depends on age and sex. The crude rate for all males in 1999 in Scotland was a mean 99.6 lung cancers per 100 000 patient years. The highest male rate of 738 per 100 000 was in the age band 75–79 years. For females, the overall rate was 66.8 per 100 000 patient years and the highest rate of 342 was in the same age band. No study has reported different presenting features for the two sexes.

#### Individual symptoms or signs

It is remarkable that there are so few reports of the incidence of symptoms in primary care. Because of this,
<table>
<thead>
<tr>
<th>Presenting feature</th>
<th>Percentage of patients with the feature</th>
<th>Estimated likelihood ratio (LR)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In primary care</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Without cancer</td>
<td>With cancer in secondary care</td>
<td></td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>0.4–1.6% 29</td>
<td>3% have it as a first symptom 21,29</td>
<td>21–35% 20,22,30,40</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.5% 41</td>
<td>10–14% 21,23</td>
<td>14–24% 20,21,27,31</td>
</tr>
<tr>
<td>Cough</td>
<td>4.7% have cough as main reason for consulting 41</td>
<td>25, 33% 21,23</td>
<td>40–80% 20,22,31,32,36,37,42–44</td>
</tr>
<tr>
<td>Finger clubbing</td>
<td>Unknown</td>
<td>Unknown</td>
<td>29–33% 45,46</td>
</tr>
<tr>
<td>Weight loss</td>
<td>2.1% 29</td>
<td>6.0–10% 23,29</td>
<td>17% lost one-tenth of weight; 20 higher figures if weight loss undefined 42,27,36,42,43,47</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>2.8% aged 50, 10% aged 67 48</td>
<td>15–17% 21,23</td>
<td>30–84% 20,29,31,32,36,37,43,44</td>
</tr>
<tr>
<td>Chest and shoulder pain</td>
<td>Unknown, but common</td>
<td>5–12% 21,23,29</td>
<td>26–53% 20,31,32,36,37,43,44</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Unknown, but common</td>
<td>2% 21</td>
<td>2–9% of all cancers; 55% of inoperable cancers 31,36</td>
</tr>
<tr>
<td>Cervical lymphadenopathy</td>
<td>Unknown</td>
<td>Two studies found no cancers in 80 and 249 patients 49,50</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
the evidence base for the UK Guidelines is weak for almost all the recommendations, which are to be used at the primary–secondary care interface. In contrast, there are several hospital case series detailing patients’ symptoms. In general, it is unwise to extrapolate from secondary care to primary care, as GPs will have exercised judgment in selecting which patients to refer.9,52 Furthermore, in the interval between referral and final diagnosis, the symptom profile may have changed.25

**Haemoptysis.** The figures used for calculation of the likelihood ratio in Table 3 derive from a screening study of American men in the 1950s, and are at best a crude estimate for UK primary care. Therefore, the UK Guidelines have very little evidence for their recommendation of a chest X-ray for all patients with haemoptysis. It is possible to identify the site of bleeding (and therefore the probable diagnosis) in at least half of secondary care patients using only traditional history taking and examination.53 The proportion may well be larger in primary care. As it is unlikely that the prognosis of lung cancer will be significantly worsened by a delay of 1 or 2 weeks, it is reasonable management to defer an X-ray when there is a clear alternative explanation for the symptom, such as an acute bronchitis.54

**Haemoptysis and a negative chest X-ray.** A difficult decision arises if a chest X-ray in a patient with haemoptysis is negative. This negative X-ray may mean that the patient has a benign cause for their bleeding, or that they have a small, or centrally located, tumour hidden by the mediastinum. No primary care studies have addressed this problem. However, hospital reports give clear guidance. In every series, when patients with haemoptysis and a normal X-ray were investigated either by bronchoscopy or by CT, there was an important yield. By bronchoscopy or by CT, there was an important yield. Furthermore, a high proportion of these cancers were at a stage that was surgically resectable. The proportion of primary care patients who have a malignancy in this scenario may be smaller than this. However, it is unlikely to be so small as to make referral for investigation inappropriate, especially as the prognosis of unresectable cancer is so poor. The guidelines recommend urgent referral for persistent haemoptysis with a negative chest X-ray. Persistence is undefined, but a practical interpretation would be further haemoptysis after the negative X-ray. This is pragmatic guidance, presumably based on a wish to avoid invasive investigation of every person with haemoptysis and normal radiology. However, delays should be avoided in this group, who may be those with most to gain from early diagnosis. This applies particularly to smokers.40 Counter-intuitively, it may be more important to refer urgently those with haemoptysis and a negative X-ray—as they may be curable—rather than those with an X-ray abnormality.

**Weight loss and fatigue.** Loss of weight is particularly a feature of the para-neoplastic syndromes, but this may simply reflect the association of such syndromes with small cell cancer, itself associated with weight loss.22,27 The problem for the GP is that loss of weight is a relatively common complaint in primary care, yet no primary care study has reported the different underlying causes. Most primary care patients with weight loss have other features which provide clues to the diagnosis.59 In the absence of diagnostic clues, a GP would usually perform simple investigations, and a chest X-ray may be one of these. This is recommended in the UK Guidelines. The further recommendation in the Scottish version of urgent chest physician referral when a patient describes fatigue or loss of weight for 6 weeks, but has a negative chest X-ray, is much more debatable. About 8% of patients with this clinical picture have an underlying malignancy,59 but gastrointestinal, urological and haematological cancers are much more likely than lung cancers.50

There is more research on fatigue in primary care. One study recorded all malignant diagnoses after a presentation of fatigue to primary care: 3.7% of patients had a malignancy diagnosed in the next 4 years. However, 3.4% of patients who had not complained of fatigue also developed a malignancy.61 Given the very high incidence of fatigue complaints in general practice, it is hard to justify a blanket recommendation of a chest X-ray, even if restricted to smokers over 50 years.

**Cough.** As respiratory infection generally causes a short-lived cough, most research has focused on persistent cough.52–64 One prospective study in German primary care followed 329 consecutive patients with chronic persistent cough, but uncovered no lung cancers.65 In a trial of regular screening chest X-rays, a higher proportion of those who ultimately developed lung cancer than those who did not develop a cancer had a cough. The difference in cough prevalence between cases and non-cases was apparent from ~2 years before diagnosis at screening. This suggests that some cancer patients have a new and persistent cough up to 2 years before diagnosis.66 Cough is not a homogeneous entity; there are subtleties such as its character. Patients may describe a change in the nature of their cough, which is important enough for them to report and for their doctors to arrange investigation. The guidelines suggest a chest X-ray in an unexplained or persistent cough acknowledge this possibility, and reflect a sensible compromise between the (absent) evidence and common sense. The Scottish version of the guidelines recommends that those with unexplained cough for 6 weeks and a normal X-ray should be referred urgently for exclusion of lung cancer. This is more controversial, as almost no patients with this clinical picture transpire to have a malignancy.67,68
Chest and shoulder pain. Chest and shoulder pain are common primary care complaints, with the GP initially concerned about cardiac and musculoskeletal disease, respectively. When they are a presenting feature of lung cancer, they are associated with a later staging and a poorer prognosis.69 Shoulder pain may signify a Pancoast tumour with involvement of the brachial plexus. However, a GP will encounter less than one Pancoast tumour in their clinical lifetime, while they will treat musculoskeletal disorders almost daily. Clearly not every unexplained shoulder pain warrants a chest X-ray. It seems reasonable to defer radiological investigation until orthopaedic conditions have been excluded.

Dyspnoea. The recommendation to take a chest X-ray for unexplained or persistent dyspnoea is uncontroversial, as it is likely to help with the diagnosis even if no cancer is shown. However, the Scottish recommendation for urgent referral for exclusion of cancer after 6 weeks of symptoms and a negative chest X-ray is contrary to the published evidence. Reports from two specialist clinics examining patients with dyspnoea and a negative chest X-ray found no lung cancers in the 157 referred patients.70,71 In a Danish clinic established specifically for primary care referrals with dyspnoea, only one of the 284 patients transpired to have lung cancer.72 Thus, dyspnoea as an isolated symptom is a very rare presentation of lung cancer. Indeed, referral of a dyspnoeic patient for urgent exclusion of cancer could be counter-productive, as the most common diagnosis in such patients is heart failure, which could be missed if the specialist is focusing on cancer.72 Urgent referral of stridor is uncontroversial as the underlying cause generally requires urgent treatment.

Hoarseness. Hoarseness is extremely common in primary care.73 Of the malignant causes, laryngeal cancer is more likely than lung cancer. Therefore, examination of the vocal cords should be the priority. Some primary care enthusiasts are confident in vocal cord examination, and have detected lung cancer as well as laryngeal cancer,74 but most GPs would refer to an ear, nose and throat specialist for further investigation.

Smoking. The large majority of lung cancers arise in those who smoke. Smoking also causes many other chest diseases such as chronic bronchitis.75 As both benign and malignant chest disorders share some symptoms, e.g. cough, knowing a patient’s smoking habit is only of moderate help in differentiating benign from malignant disease. Nonetheless, the much higher incidence of lung cancer in smokers makes investigation of sinister symptoms particularly appropriate. Indeed, smokers have been targeted in most of the recent screening trials.8 However, there is a risk in such an approach: of assuming non-smokers to be at negligible risk of cancer, as potentially curable tumours may be missed.

Finger clubbing and lymphadenopathy. There are no primary care studies of clubbing, but secondary care studies confirm the association with lung cancer.35,46 No study has reported whether it occurs as an isolated phenomenon, or is usually accompanied by other features of lung cancer. However, the recommendation of a chest X-ray is practical, despite the lack of evidence. Three primary care studies of cervical lymphadenopathy emphasized the ability of GPs to identify which patients with lymphadenopathy had a malignancy.49–51 Again the recommendation of a chest X-ray in unexplained lymphadenopathy is uncontroversial, though the number of lung cancers uncovered will be low.

Sputum cytology. Sputum cytology is available in primary care, though its sensitivity and predictive values in this setting are unreported. It is not mentioned in the UK Guidelines. In screening programmes, 15–20% of lung cancers were detected by cytology.76 When patients at high risk for cancer are studied, the sensitivity can be as high as 36–46%.24,77–79 False-positives are extremely rare, so the positive predictive value of the test is very high. However, the low sensitivity makes a negative cytology result of limited value in the exclusion of cancer. The main place for sputum cytology is now considered to be in the investigation of patients with a worrisome symptom and a negative chest X-ray, or in patients too ill to undergo bronchoscopy.80,81

Conclusion

A recurrent theme in this review is the dearth of primary care studies. The incidence of many important symptoms is largely unknown. Published research gives little help about who should be referred and, possibly more importantly, who should not.

However, there is one other relevant factor: the experience of the doctor and patient. For colorectal cancer, which has a much stronger evidence base, the predictive value of individual symptoms rises between presentation in the community and presentation to primary care, and is highest in patients referred for investigation of possible cancer.82 This implies that doctors are able to identify (at least partly) those who are likely to harbour cancer.11 Equally, patients can also identify which symptoms are important.83 Most people can recognize when their symptom, such as cough in lung cancer, is in some way different from before. They can express their concern in a way that makes their GP act on the concern. This process, which happens daily in general practice, is probably too subtle to be identified in quantitative research, where all coughs are studied together.

However, lung cancer research does give some answers, and should form the basis of guidelines where at all possible. In this respect, the UK Guidelines may be
misleading at times, because they focus on the possibility of lung cancer and do not consider other diagnoses. For patients with unexplained dyspnoea, hoarseness or cervical lymphadenopathy, other important diagnoses are more likely than lung cancer. It is reasonable to recommend a chest X-ray for these problems: referral for exclusion of lung cancer after a negative chest X-ray is much less reasonable, even if the patient has persistent symptoms. The only situation where there is strong research support for referral despite a negative chest X-ray is with persistent haemoptysis.

It is interesting that where there is an evidence base, some of the recommendations in the UK Guidelines can be questioned. This does not reduce the need for more basic research into the incidence of lung cancer symptoms in primary care: on the contrary, it increases it.

Declaration

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9 Campbell NC, MacLeod U, Weller D. Primary care oncology: essential if high quality cancer care is to be achieved for all. Fam Pract 2002; 19: 577–578.
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