Early diagnosis of lung cancer

Symptoms and the early diagnosis of lung cancer

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Significant delays remain in the diagnosis of lung cancer

Lung cancer is the leading cause of cancer death in the western world, resulting in nearly 30 000 deaths in England and Wales in 2002.[1] Advances in the management of breast, cervical, and prostate cancer have led to improved survival rates, whereas mortality from lung cancer has remained largely unchanged.[2] Even the best reported 5 year survival rates for lung cancer are only 10–15%[3 4] and, in England, in patients diagnosed between 1993 and 1995 the survival rate was only 5.5% at 5 years and 22% at 1 year.[5]

This high mortality is very largely a consequence of patients presenting late when the cancer is already locally advanced or has disseminated. Around 80% of patients with lung cancer have stage III or IV disease at presentation, therefore excluding them from potentially curative surgical resection.[6] Detection of the tumour at an earlier stage leads to an improved prognosis, patients presenting with stage IA non-small cell lung cancer and undergoing surgical resection having a 5 year survival of around 60%.[7]

Patients can (and usually do) live with lung cancer for many years before it becomes apparent. Early lung cancer is largely asymptomatic and internalisation of tumours means patients are not alerted by obvious physical changes. It takes around 8 years for a squamous cell carcinoma, for example, to reach a size of 30 mm when it is most commonly diagnosed so, by the time symptoms arise, the risk of metastasis is considerable.[8 9] Once symptoms appear they are often ignored by patients, delaying the diagnosis and treatment even further. The reasons for patient delay in diagnosis are poorly understood.

Lung cancer can present with a wide range of symptoms, the most common being cough, haemoptysis, chest and shoulder pain, dyspnoea, hoarseness, weight loss, anorexia, fever, weakness, and bone pain.[10] Guidelines based on this pattern of symptoms have been developed[11] and stress that the physician needs to be alert to the possibility of lung cancer in patients with such symptoms, particularly if they are persistent and occur in those at higher risk of lung cancer—for example, smokers and ex-smokers, especially those over the age of 50 and with chronic airflow obstruction. Unfortunately, symptoms of lung cancer are largely non-specific and recognition of new symptoms is more difficult in the presence of co-existing respiratory disease such as chronic obstructive pulmonary disease. In addition, the evidence base for these guidelines (and the forthcoming updated NICE version) is weak and contains no data on the predictive value of symptoms or symptom complexes for the presence or absence of lung cancer in a primary care based population.

In this issue of *Thorax* Corner and colleagues present the findings of an exploratory retrospective interview study commissioned by the Department of Health's policy research programme investigating patient delays in cancer diagnosis.[12] Detailed interviews were carried out in 22 patients after diagnosis but before treatment to obtain a pre-diagnosis symptom history. This history was compared with primary care and hospital records. Cough and dyspnoea were found to be the most common symptoms among a wide range reported. All patients experienced at least one new symptom before diagnosis. Although the symptoms were reported as a persistent change in health status, they were not interpreted as being serious at their onset. The median interval from the initial change in health status and the symptom prompting the first visit to the general practitioner was found to be 7 months, with a further average delay of 5 months to diagnosis. Interestingly, there were no significant differences in delays to diagnosis according to operability of the tumour.

The findings of the study by Corner *et al*, although preliminary, are of interest and confirm that there are significant patient related delays for the diagnosis of lung cancer, longer than those previously reported. Jensen *et al*[13] reviewed the time elapsed from symptoms to medical attention reported in 16 studies and found a wide variation from 7 days to 6 months. This wide range of patient delay times is likely to be a result of many factors, including socioeconomic, cultural and health care differences. The reasons why patients did not interpret their symptoms as serious or seek medical attention sooner are not reported by Corner *et al* and need further investigation. The most plausible explanation for this is that, while reported symptoms were new, they were too non-specific—especially in the context of co-existing respiratory disease—to raise alarm. A limitation of the data reported by Corner *et al* is that there is no objective validation of the presence and timing of symptoms reported before the first consultation with the GP. Patients, with hindsight of the diagnosis, may look for explanations and re-examine past events which we recognise in other clinical situations are often false. Prospective studies of the specificity and predictive value of reported symptoms for the diagnosis of lung cancer and their prevalence in high risk individuals would be required to answer these questions, although such studies are complex, expensive, and long term. Other factors that may contribute to patient delays in diagnosis include denial, fear, guilt, other psychosocial issues, poor public health education, and issues relating to access to health care. The fact that the patients in this study did not interpret the early changes as potentially serious may also mean that they were reluctant to bother their GPs with what they considered ''trivial'' complaints. Bowen *et al*[14] studied factors influencing patient delays and found that male patients had longer delays, over half of all patients needed encouragement from family or friends to see their GP, and 75% were not aware of the significance of their symptoms and had not received any advice about them. Future studies also need to explore how patients respond to changes in health status, why patients with lung cancer appear to have such relatively little contact with their GP, and whether improved public awareness of lung cancer symptoms and easier access to a wider variety of sources of healthcare advice could contribute to achieving earlier diagnosis with a consequent improvement in survival.

Attempts should be made to develop public health education programmes promoting awareness of lung cancer, a process which needs to be accompanied by the presentation of a more positive image of lung cancer, stressing the fact that early diagnosis saves lives rather than perpetuating the negative image that the current prognosis for the majority of patients is so poor.

Early symptom recognition in lung cancer will only be worthwhile if it improves outcomes for patients, especially survival. Christensen *et al*[15] found that, for patients with operable lung cancer (stage I/II), the interval between the trigger symptom initiating contact with the healthcare system and the time of operation was significantly shorter than the time between the trigger symptom and the decision not to operate for patients with stage III/IV disease. In contrast, Mydral *et al*[16] found the time from onset of symptoms to treatment was shorter in patients with stage IV lung cancer (median 3.4 months) than in those with stage I/II disease (median 5.5 months). This is likely to result from the fact that patients with advanced disease had more severe symptoms and signs and received more rapid treatment. The current study by Corner *et al*[12] did not find differences in patient delay times according to the stage of lung cancer, but the numbers studied were insufficient to answer this question. Studies investigating the effect of hospital delays in diagnosis and treatment on prognosis similarly report conflicting results. Comparison of the data in these studies is, however, made difficult by the differing definitions of patient delays and clinical differences of patient groups studied.[17–19]

Because of the non-specific nature of the symptoms in question and the fact that a paradigm shift in the behaviour of the population at most risk of developing lung cancer is highly unlikely, attempts at making major progress on early referral at a population level based on symptoms alone seem very unlikely to be successful. Other methods of early detection therefore need to be energetically explored to lower the stage at presentation in lung cancer. Screening is an attractive option because there is a relatively well defined high risk population and the potential for curative surgery in early disease. Radiological screening has been the most studied. The screening trials of the 1970/80s with chest radiography were deemed negative,[20] but the advent of faster spiral and multiple slice CT scanners have led to a renewed interest. Preliminary studies of low dose CT screening show promise and formal trials are underway.[21] The demonstration of benefits of screening programmes on the overall survival statistics of the studied population is essential before widespread use of this method is adopted. Currently, the improved survival benefits of screening are not known and interpretation of published studies is made difficult since no randomised trial has yet been reported and issues such as lead time and over-diagnosis bias add to the complexity of interpretation.[22] The natural history of malignant nodules as small as 5 mm detected on CT scans is not well described and even nodules only 10 mm in size containing 10^9 cells represent a fairly late stage in the disease process, considering that at death lung cancer tumours typically have 10^{12} cells.[9] The survival benefit of any screening programme must also outweigh the risks related to managing false positive nodules. The optimum strategy for the management of small lesions identified on screening has not been determined.

Another potential screening tool is advanced sputum cytology, enhanced by molecular genetics, immunohistochemistry, including the monoclonal antibody staining of antigens expressed by lung cancer cells.[23 24] Autofluorescence bronchoscopy may complement cytology with the potential for the detection of metaplasia and carcinoma in situ in bronchial mucosa.[25] A multimodality approach may be required to optimise early detection and management of lung cancer from screening programmes and early attempts at this approach look promising.[26]

While efforts consequent upon the National Cancer Plan[27] and the Cancer Services Collaborative have helped to reduce hospital delays, the study by Corner *et al* reminds us that significant delays remain in the diagnosis of lung cancer before the patient ever gets into secondary care. While this is clearly an important area for future research, it is probable that—in the absence of a major advance in treatment or a significant further reduction of cigarette consumption—some form of screening is the intervention most likely to have a major impact on the current poor survival statistics, and it is vital that the major funders of national research programmes grasp this difficult nettle as soon as possible.

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