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Diagnosis of Lung Cancer: Improving Survival Rates

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Abstract

Lung cancer is a major global health burden with high incidence rates but poor long-term survival. Currently the majority of cases are diagnosed at an advanced stage when surgical resection is not feasible.

Screening for lung cancer has been a major focus of research for the last 40 years. Despite this there is still a lack of evidence to promote its use outside of a clinical trial.

More recently interest has focussed on promoting earlier recognition of symptomatic disease among both the general public and primary care physicians, in order to encourage more timely investigation and referral to secondary care. The hope is that this approach may increase the proportion of disease identified in the early stages, allowing more surgical resections and improved 5-year survival rates.

This paper provides an overview of the current evidence base regarding early diagnosis of lung cancer and provides some examples of innovations to promote this.

Background

Lung cancer is a major worldwide health burden, responsible for 1.3 million deaths in 2004, equating to 2.3% of all deaths. Death rates from lung cancer are predicted to continue to rise, with the disease being responsible for 2.8% of all deaths (1.67 million) by 2015[1].

Despite advances in treatment, survival rates from lung cancer in the UK have improved by only a few percent in the last 40 years. 5-year survival for patients diagnosed between 1991 and 1993 was 5%[2]. Eurocare-4[3] has highlighted the difference in survival between England and other European countries. 5-year survival rates in England, for patients diagnosed between 1995 and 1999, were 8.4% compared with the average European rate of 12%. These figures are in even greater contrast to reported 5-year survival rates in the USA of 15.7%, for patients diagnosed between 1995 and 2001[4]. Analysis of Eurocare-4 also showed that 1-year survival rates in England were lower than the European average, probably reflecting poorer access to care. This would suggest a particular need to promote earlier diagnosis in the UK, in trying to improve survival.

Survival is dependant on disease stage at diagnosis, with marked variation between earlier and later stage disease. 5-year survival for localised disease is around 49% compared with 2% for disease with distant metastases at presentation[4]. Unfortunately the majority of lung cancers are already disseminated at the time of presentation[4,5].

Screening

Much interest has focussed on diagnosing lung cancer earlier in order to try to improve radical treatment rates and reduce mortality. Initially this interest focussed on screening. The first randomised controlled trial took place in London in the 1960's[6]. This looked at a 6-monthly chest-x-ray for 3 years versus a chest x-ray at the beginning and end of the 3 year period. Diagnosis and resection rates were higher in the group receiving more frequent chest x-rays but lung cancer mortality was similar in both groups. Three American studies[7] in the 1970's and 80's looked at the use of either chest x-ray alone or in combination with sputum cytology. The Mayo Lung Project[8] compared 4-monthly chest x-ray and sputum cytology to standard care. Participants randomised to the standard care arm were advised to have a chest x-ray and sputum cytology yearly. This showed that resection rates increased by 14% (32% to 46%) in the group undergoing screening when compared to the group receiving standard care alone, but no stage shift was evident. 5-year **survival** in the screened group reached 33% in comparison to 15% in the non-screened group.

To avoid confusion by the biases inherent in screening, the ultimate proof of benefit is disease-specific mortality. Unfortunately, lung

cancer **mortality** was no different in the 2 groups (3.2/1000 person-years versus 3.0/1000 person-years). This lack of improvement in mortality was also evident in the other two studies: the Johns Hopkins[8,]and Memorial Sloan-Kettering studies[9]. Both looked at the addition of 4-monthly sputum cytology to annual chest x-ray. There was also a contemporaneous study[10], in Czechoslovakia, comparing chest x-ray plus sputum cytology every 6 months, for 3 years, with chest x-ray and sputum cytology at the beginning and end of the 3 years. This study essentially replicated the findings of the Mayo Lung Project, with an increased number of cancers detected in the more frequently screened group but with no difference in lung cancer associated mortality[11]. None of these studies had a 'no screening' control group.

Therefore, based on these studies, it would not be possible to recommend either chest x-ray or sputum cytology as a screening test for lung cancer. Indeed, a Cochrane systematic review[12] has suggested that more frequent screening with chest x-rays is associated with an 11% relative increase in lung cancer mortality, when compared with less frequent screening.

Table 1: Summary of key randomised-controlled trials of the use of chest x-ray with or without sputum cytology for screening for lung cancer

Study	Intervention	Control	Sample	Key Findings	Limitations
North London study[6]	3 year study of 6-monthly chest x-ray	Chest x-ray at the start and end of the 3-year period	Men aged ≥40 Current, Ex and never smokers Volunteers from industrial establishments ~25,000 control arm and ~29,000 intervention arm	Increased diagnosis and resection rates in the group receiving more frequent chest x-rays. No difference in lung cancer mortality between the two groups.	Lack of a 'no-screening' group. Possibility that randomisation was inadequate – greater number of ex-smokers in the control group, greater number of men aged 60-64 and >70 in the intervention group[12] No follow-up beyond the 3 years of the study.
Mayo Lung Project[8]	4-monthly chest x-ray plus sputum cytology	Standard care (patients advised to have annual chest x-ray and sputum cytology)	Male smokers ≥45 years old, who smoked at least 20 cigarettes/day Fit for lobectomy Attendees at the Mayo clinic ~4,600 in each arm	Increased resection rates and greater 5-year survival in the 'screened' group. No stage shift evident No difference in lung cancer mortality between the two groups.	Lack of a 'no-screening' group. Significant number of cancers identified in the 'screened' group were on 'non-study' chest x-rays. Contamination of the control group by non-study x-rays (led to detection of 26% of the identified

					cancers in this group).
Johns Hopkins Lung Project[8,13]	Annual chest x-ray plus 4-monthly sputum cytology	Annual chest x-ray	Male smokers(≥20 cigarettes/day) aged ≥45 years ~5,200 in each arm	No difference in the number of lung cancers diagnosed, resection rates or lung cancer mortality between the two groups. Greater number of squamous cell carcinoma identified in the intervention group.	Underpowered to evaluate the efficacy of sputum cytology as a screening test[12]
Memorial Sloan-Kettering Cancer Center Lung Cancer Screening Programme[8,9]	Annual chest x-ray plus 4-monthly sputum cytology	Annual chest x-ray	Male smokers ≥45 years old. Current (or within the last year) smokers of ≥20 cigarettes/day ~5,000 in each arm	No difference in the number of lung cancers diagnosed, resection rates or lung cancer mortality between the two groups	Underpowered to evaluate the efficacy of sputum cytology as a screening test[12]
Kubík et al 1986[10]	3 year study of 6-monthly chest x-ray and sputum cytology followed by annual chest x-ray for 3 years	Chest x-ray and sputum cytology at the beginning and end of the 3 year period, followed by annual chest x-ray for 3 years	Men aged 40-64 Attending the chest clinic Lifetime cigarette consumption of >150,000 cigarettes ~3,170 men in each arm	Increased rate of diagnosis in the more frequently screened group during years 1-3. No stage shift No difference in lung cancer mortality between the 2 groups	Lack of a 'no-screening' group

Chest x-rays are less sensitive for the detection of lung cancer than CT. Evaluation of the chest x-rays taken as part of the Mayo Lung Project identified that 90% of peripheral lung cancers and 65-70% of central tumours, that were detected by 4-monthly chest x-ray had, in retrospect, been visible on previous x-rays[14]. Interest has therefore moved to the use of computed tomography (CT) for screening. This was made possible by the advent of low-dose spiral CT, which reduced both the radiation dose and scan time[15]. Early reports showed increased rates of detection over chest x-ray, with the vast majority of detected tumours being stage I [16,17,18]. The largest observational report of CT screening is the International Early Lung Cancer Action Project (I-ELCAP)[19]. A total of 31,567 participants, aged over 40 and deemed to be at lung cancer risk due to either cigarette smoking or occupational exposure, had a baseline CT. All patients had to be fit to undergo thoracic surgery, if required. 27,456 repeat scans were performed between 7 and 18 months after the previous screening. 479 cancers were identified, 405 on the initial scan and 74 on annual screening. There were 5 interim diagnoses. Overall 85% of tumours were clinical stage I with 72% confirmed pathological stage I. 10-year lung cancer survival, for all participants, was 80%, increasing to 88% in those with clinical stage I disease.

However, a key criticism of CT is that it identifies nodules that will ultimately turn out to be non-malignant. During the prevalence screen in the I-ELCAP study[19], 13% of CTs identified non-calcified nodules requiring further investigation, including serial CTs, PET-CT and percutaneous biopsy. Only 9.6% of these participants were subsequently proven to have lung cancer. Even higher rates of benign nodule identification have been quoted in other studies[20,21,22,23] and up to 20% of invasive procedures following CT screening are for benign disease [20,21,23].

An additional concern is overdiagnosis, such that patients receive treatment for slowly growing tumours that may never have caused them any problems in their lifetime, a phenomenon that is already recognised in other screening programmes[24,25]. Several studies have calculated tumour volume doubling times for screen-detected cancers. These have shown that many of the screen-identified tumours are slow growing, with doubling times well in excess of the 40-70 days calculated from epidemiological data of non-screen identified cancers[26].

At present there is insufficient evidence to recommend low dose CT as a screening test for lung cancer, although there are several randomised controlled trials currently underway seeking definitively to answer this question [27,28,29].

There are several other areas currently under investigation for use as screening tests for lung cancer, including narrow band and

autofluorescence bronchoscopy. One observational study looked at the use of bronchoscopy, along with CT, as a primary tool in screening[20,30]. Volunteer current and former smokers underwent sputum induction for quantitative cytometry and CT before being offered autofluorescence bronchoscopy. 561 subjects were enrolled in the study, with 378 undergoing bronchoscopy. 14 primary lung cancers were identified of which 4 (29%) were CT occult and only detected by autofluorescence bronchoscopy. All of these CT occult cancers were squamous cell carcinomas. Because of the observational nature of the study, the significance of the use of this approach on mortality is unknown.

Biological tools, such as testing serum for tumour-associated antibodies, detection of gene-promoter hypermethylation in sputum samples, exhaled breath volatile organic compounds and detection of novel proteins in serum or sputum are also in development[31]. Unfortunately, none of these is currently ready for use in clinical practice.

At the current time, no form of screening for lung cancer can be recommended.

Symptom recognition and reporting

Interest has now switched to looking at whether lung cancer can be diagnosed earlier in its natural history by focussing on promoting symptom recognition and reporting. 90% of patients are symptomatic at the time of diagnosis[32], often experiencing multiple symptoms[33,34,35]. Many of those presenting will have been symptomatic for many months, with reported delays to healthcare of up to 2 years[33]. Much work has focussed on investigating this, with reported median delays from onset of symptoms to presenting to health care ranging from 7 to 31 days[35,36,37,38,39]. Public knowledge of lung cancer symptoms generally appears to be poor[35,37,40,41]. Patients often develop symptoms but are unaware that they could be related to a sinister cause: it appears that between 50 and 75% of lung cancer patients may not be aware of the significance of their symptoms[35,37]. Only when further symptoms develop, or their general health deteriorates, will they seek advice[33,35]. In particular, systemic symptoms such as lethargy and weight loss seem to be associated with longer delays, whereas haemoptysis tends to prompt a more rapid response[33,39].

It has also been noted that even those deemed to be at risk of lung cancer, predominantly current and ex-smokers, do not always perceive themselves to be at risk[35,41]. Even when patients recognise a change in their health, there are many barriers to presentation. Themes that have been identified include fear of wasting the doctors time, feeling unworthy of treatment - particularly in relation to being a

smoker, being unsure as to whether the symptom/change experienced is 'normal', putting the symptom down to being part of the ageing process, minimising symptoms, stoicism and the difficulty of separating out current changes in health care from co-morbid conditions[40,41].

Delays have also been identified once patients present to their primary care team, with many patients having to present on more than one occasion before onward referral/further investigation. This is despite clear advice in the British National Institute for Clinical Excellence (NICE) guidelines regarding chest x-ray referral[42]. The delay from first presentation to referral to a respiratory specialist has been reported to range from a mean of 34 days[38] to 73 days (range 0->175)[37,36,39,43,44]. Bowen & Raynor's study[37] also showed that, of the 76% of patients who first consulted their own family doctor, only one third of patients were referred following their initial consultation, with a further third referred by another doctor in the practice, suggesting a 2nd consultation. A Danish study looked at potential reasons for the delay in onward referral of symptomatic patients and identified several contributing factors. In patients with co-morbid diseases, symptoms were often ascribed to this rather than potential lung cancer[45]. Chest x-rays reported as normal were associated with a longer delay, with primary care teams being falsely reassured. 25% of lung cancer diagnoses in the UK are made during an acute admission, despite the patient having presented previously to their primary healthcare team with a symptom that could be indicative of lung cancer[46].

Improving the early diagnosis of lung cancer in Britain has become a government priority, with the formation of the National Awareness and Early Detection Initiative (NAEDI), a key component of the 2007 cancer reform strategy[47]. This hypothesizes that delays lead to more advanced disease at diagnosis with associated poor 1- and 5-year survival rates and potentially avoidable deaths. Abdel-Rehman et al calculated that if UK survival rates were similar to those in Europe, then nearly 1000 deaths/year, within 5 years of the diagnosis of lung cancer, could be avoided[48].

The NAEDI pathway highlights many areas, which could be targeted in order to try to promote earlier diagnosis[49].

Figure 1 The NAEDI pathway[49] (From Richards 2009)

(JPEG file)

One such strategy is to use social marketing techniques to raise awareness of lung cancer symptoms and to encourage a more timely presentation to health care services. Social marketing uses

commercial marketing techniques to change individual and organisational behaviours and policies[50].

Similar approaches have already been used in other cancers, an example of which is the West of Scotland Cancer Awareness Project (WoSCAP)[51]. This project used a mass media campaign combined with general practice education to raise awareness of the symptoms of oral and colorectal cancer. Awareness of symptoms was improved and, in those presenting who were aware of the campaign, presentation was timelier in 60%.

An initial social marketing pilot has been carried out in lung cancer, in Doncaster, the largest metropolitan borough in the UK, which has a high rate of lung cancer[52,53]. And a high rate of social deprivation. The social marketing campaign and primary care education programme was initially designed as a way of addressing a recognised health inequality. Six areas, covered by eleven general practice surgeries, with the highest lung cancer risk, were identified. In these areas, brief intervention training was undertaken with the general practitioners, practice nurses and local pharmacists. Following this there was a public awareness campaign launched comprising leaflets, advertising on bus banners and billboards (Figure 2), local media events and coughing bus stops.

Figure 2 Poster used on billboards

(JPEG file)

This project increased awareness of the importance of seeking medical advice for a prolonged cough and resulted in a statistically significant increase in chest x-ray referrals. Lung cancer diagnosis rates were also increased although this was not at a statistically significant level. No stage shift was evident but the numbers at different lung cancer stages were too small for subgroup analysis[53,54].

If the responses to this campaign could be replicated on a larger scale, and people could be encouraged to present earlier with their symptoms, then their disease should be identifiable in a more timely fashion. In turn this will hopefully increase the number of patients suitable for curative treatment as well as impacting on the numbers receiving active treatment (chemotherapy and/or radiotherapy). Both actions should lead to improved survival of patients with lung cancer.

Conflict of Interest

The authors declare no conflict of interest

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