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Review Article

Lung Cancer Screening - Computed Tomography or Chest Radiographs?

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Abstract

Worldwide, lung cancer is the leading cause of mortality due to malignancy. The vast majority of cases of lung cancer are smoking related and the most effective way of reducing lung cancer incidence and mortality is by smoking cessation. In the western world, smoking cessation policies have met with limited success. The other major means of reducing lung cancer deaths is to diagnose cases at an earlier more treatable stage employing screening programmes using chest radiographs or low dose computed tomography. In the rest of the world, smoking is still on the increase, and the sheer scale of the problem limits the affordability of such screening programmes.

This short review article will evaluate the current evidence and potential areas of research which may benefit policy making throughout the world.

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INTRODUCTION

Lung cancer is the most common cause of cancer death in the UK accounting for 6% of overall national mortality and around 35,000 deaths a year. In 2008 lung cancer was estimated to account for 18% of deaths worldwide. Both one year and 5 years survival are inversely proportional to disease stage [1]. Current statistics in Scotland, which has a population of approximately 5.2 million, show an incidence of approximately 1 in 1000 with 8 in 10,000 people dying due to lung cancer [2]. Similar incidence rates exist in larger countries, and in the USA approximately 160,000 die due to lung cancer each year [3].

Smoking is the primary reason for developing lung cancer. Therefore, smoking cessation is the best prevention for this fatal illness. However, as the lung cancer epidemic has been developing, ways of detecting the disease earlier have been explored. This is based on the fact that early, Stage 1, screening

detected lung cancer has a 5-year survival rate in excess of 85%, whereas more advanced lung cancer invariably leads to death in less than 2 years [4].

Chest radiograph

In the early 1980s, a lung screening programme using 4-monthly chest radiographs in high risk patients was developed at the Mayo Clinic [5]. Subjects selected were over 45 year old male heavy smokers defined as one pack/day. They were randomly assigned to a control group (4,593 patients) or repeated chest radiograph follow up at 4 month interval (4,618 patients) after they had undergone an initial chest radiograph and sputum cytology examination that were both normal. The follow up success was 75% at 4 months, and 92 lung cancers were detected by chest radiograph (of which 7 also had sputum cytology positive findings), while 15 patients had normal chest radiograph with abnormal sputum cytology for an overall incidence of 109 (2.4%). A significant number of these lung cancers were visible in retrospect. Furthermore, 52 of the lung cancer were early stage, while the 35 were already advanced stage disease at the time of detection.

Another study in New York randomised a similar population of 10,040 subjects to annual chest radiograph only vs additional 4-monthly sputum cytology [6]. This study showed similar outcome between the two groups, with 288 detected lung cancers equally distributed between the two groups.

It was concluded from this study that the 4-monthly screening for lung cancer using chest radiography and sputum cytology, although capable of detecting up to 20% of lung cancers, was unable to improve mortality advantage over patients who were offered annual testing [7].

A more recent attempt at using chest radiograph screening was carried out in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial [8]. This study randomised 154,901 men and women aged 55-74 years to either standard care (77,456) or annual screening (77,445) for four years during the period 1993-2001. The number of lung cancer deaths was equal in both groups (1213 vs 1230) with similar stage and histology of lung cancers. Therefore, it was concluded that annual chest radiograph screening does not benefit outcome of lung cancer mortality.

From these large scale studies, as well as from the National Lung Screening Trial (see below), it is concluded that the application of routine annual chest radiography for screening of high-risk patients for lung cancer, although detecting a significant number of lung cancer cases, is not beneficial in terms of improvement of mortality.

Computed tomography

The National Lung Screening Trial (NLST) compared chest radiographs with computed tomography for the screening of patients at high risk for developing lung cancer [9]. Men and women were selected in the age group 55-74 years with a history of cigarette smoking of at least 30 pack years or had these exposure rates but had quit smoking within 15 years. The subjects were randomised to either three annual screening posterior-anterior chest radiographs (26,732) or low-dose CT (26,722). Almost 4-fold higher positive screening tests were obtained with CT (24.2% vs 6.9%), with the false positive rate slightly lower in the chest radiographs group (94.5% vs 96.4%). The incidence of proven lung cancer was higher in the CT group compared to the chest radiograph group (relative risk 1.13; 95% CI: 1.03-1.23). More importantly, mortality due to lung cancer decreased from 309 deaths per 100,000 person-years in the radiography group to 247 deaths from lung cancer per 100,000 person-years in the low-dose CT group, a decrease of 20%. In addition, the CT group benefitted from other diagnoses that positively affected mortality rates, with 6.7% fewer patients dying in the low-dose CT group.

In Europe, several studies were started to evaluate the potential role of low-dose chest CT for lung cancer screening. Three studies did not demonstrate a benefit of lung cancer screening with CT in terms of mortality, but these were insufficiently powered to reliably draw such conclusion [10-12]. There are a further five ongoing studies that are yet to report on the final results, but some will be able to give answers to the question whether CT screening improves outcome of lung cancer patients [13-17].

The (Nederlands-Leuvens Longkanker Screening Onderzoek) NELSON study is a Dutch/Belgian project, which recruited 20,000 high-risk subjects and randomised half of them for low-dose CT and the other half for chest radiograph screening [13]. It is the largest European study and has sufficient power to enable a statement whether low-dose CT screening has benefit over chest radiography screening.

Another study from Canada has just reported the first screening round results and is focused on inclusion of cytology using autofluorescence bronchoscopy as well as modelling approaches towards optimisation of predictive value for lung nodules [18].

A potential risk associated with screening is the false positive results that can lead to further investigations and additional costs. A randomized, controlled trial of low-dose CT versus chest radiography (n= 3318 in both arms) as part of the National Lung Screening Trial (NLST) demonstrated a false-positive rate of 21% and 9% for single low-dose CT and chest radiography screening, respectively [19]. A total of 7% of participants with a false-positive low-dose CT examination and 4% with a false-positive chest radiography subsequently underwent an invasive procedure.

Another potential risk associate with lung cancer screening is the potential increased risk of lifetime cancers as a result of ionising radiation. The estimated risk of cancer from exposure to CT ionising radiation is reported to be more when the screening is started earlier in life, or on annual basis, and in females. A study reported an estimated 5.5% increase in lung cancer risk attributable to annual CT-related radiation exposure and concluded that a mortality benefit of considerably more than 5% may be necessary to outweigh the potential radiation risks [20].

Screening programs are associated with additional costs, both from the screening procedure and the follow up interventions. Previous studies reported that screening for lung cancer appeared to be cost-effective in high risk, more elderly populations [21,22]. Other studies questioned the potential cost

effectiveness of lung cancer screening. However, their results were based on lower estimated effectiveness of screening than what was demonstrated by the NLST [23,24].

A more recent cost-utility analysis of lung cancer screening by low dose CT reported that repeat annual lung cancer screening in high risk adults aged 50-64 was highly cost-effective [25]. The study also indicated that offering smoking cessation interventions with the screening program improved the cost-effectiveness of lung cancer screening between 20-45%.

A contrary report was published as part of a health technology assessment, which suggested that lung cancer screening would not be cost-effective [26]. However, it should be considered that this report was issued prior to the results of most of the recent large lung cancer screening trials.

DISCUSSION

Clearly, based on the above studies, CT is superior to chest radiographs for screening in lung cancer. Although the NLST appears to have answered the question conclusively, there are still ongoing studies that may influence the manner in which screening will be approached in the future. Significant debate is still ongoing as to how often we should be screening, the optimal population that could benefit, interpretation of nodules, avoidance of false positive results and approaches including PET-CT, MRI and autofluorescence bronchoscopy for instance [27-33]. Many of these points are still undergoing evaluation, and future study results are eagerly awaited.

There are some additional points to be taken into consideration, which may still give chest radiographs a potential role for screening of lung cancer.

First, chest radiographs have matured from a technical perspective, and the wide introduction of digital chest radiographs offers a new approach to application of Computer Assisted Diagnosis (CAD). Thus, several studies have shown greater sensitivity for lung nodule detection using CAD methodologies, and this may be of benefit when using the test as a screening test [34,35]. However, a conclusive study showing the benefit of screening with chest radiography and added CAD has not been performed and could be important in this respect.

Second, chest radiographs are by far the cheaper of the two imaging modalities and more commonly available. This is an important issue, particularly in countries that are less well developed and where smoking continues to be on the increase and the lung cancer epidemic is on the rise. It may not be feasible to arrange for large-scale screening using CT and in these circumstances, one could consider reaching for chest radiographs.

Overall, it is highly likely that low-dose CT screening for patients at high risk for developing lung cancer is a cost-effective approach which will lead to improved outcome due to earlier detection and treatment of this highly lethal malignancy. In countries that have the resources available, it makes sense therefore to use low-dose CT as a screening methodology. For countries where finances or logistics render low-dose CT screening impossible to deliver, chest radiographs on an annual basis should be considered and additional use of CAD may improve sensitivity for earlier lesions.

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