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EDITORIAL

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 many countries 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 across the world.

Key words: Lung cancer; Chest radiograph; Computed tomography; Screening; Health economics

Core tip: The use of low dose computed tomography (CT) for lung cancer screening is superior to the use of standard chest radiograph (CXR), and therefore standard CXR should not be used for this purpose. However, the application of novel computer assisted diagnosis software may influence the utility of CXR and may ultimately be a cost-efficient method in those countries where delivery of low-dose CT is not feasible due to infrastructure or costs constraints.

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INTRODUCTION

Lung cancer is the most common cause of cancer death in the United Kingdom accounting for 6% of overall national mortality and around 35000 deaths a year. In 2008 lung cancer was estimated to account for 18% of deaths world wide. 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 10000 people dying due to lung cancer[2]. Similar incidence rates exist in other countries, and in the United States approximately 160000 deaths are due to lung cancer each year[3].

Most lung cancers are smoking related and smoking cessation is the most effective way of preventing this frequently fatal illness. The disease can be cured, especially if caught 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]. As the lung cancer epidemic has grown and spread, ways of detecting the disease earlier, to improve the cure rate, have been explored. These have mainly been based around imaging using the chest radiograph (CXR) and computed tomography (CT).

CXR

In the early 1980s, a lung screening programme using 4-monthly CXRs in high risk patients was developed at the Mayo Clinic[5]. Subjects selected were over 45 years old male heavy smokers defined as one pack/day. They were randomly assigned to a control group (4593 patients) or repeated CXR follow up at 4 mo interval (4618 patients) after they had undergone an initial CXR and sputum cytology examination that were both normal. The follow up success was 75% at 4 mo, and 92 lung cancers were detected by CXR (of which 7 also had sputum cytology positive findings), while 15 patients had normal CXR 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 classified as stage Ⅰ (early disease; 35 of these were peripheral lesions), 4 were stage 2 disease (3 perihilar and 1 with hilar enlargement) while the 35 had stage 3 disease (15 peripheral lesions, 4 perihilar and 13 with hilar enlargement).

Another study in New York randomised a similar population of 10040 subjects to annual CXR 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 CXR screening was carried out in the Prostate, Lung, Colorectal and Ovarian cancer screening trial[8]. This study randomised 154901 men and women aged 55-74 years to either standard care (77456) or annual screening (77445) 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 CXR screening does not benefit outcome of lung cancer mortality.

From these large scale studies, as well as from the National Lung Screening Trial (NLST) (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.

CT

The NLST compared CXRs 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 CXRs (26732) or low-dose CT (26722). 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 CXRs group (94.5% *vs* 96.4%). The incidence of proven lung cancer was higher in the CT group compared to the CXR group (relative risk 1.13; 95%CI: 1.03-1.23). More importantly, mortality due to lung cancer decreased from 309 deaths per 100000 person-years in the radiography group to 247 deaths from lung cancer per 100000 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 20000 high-risk subjects and randomised half of them for low-dose CT and the other half for CXR 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 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 *vs* chest radiography (n = 3318 in both arms) as part of the 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.

The largest and most recent study, the NLST, also had an economic analysis and cost-effectiveness analysis performed[27]. This study demonstrated that the additional healthcare costs of performing low-dose CT screening would cost $1631 per person, with the incremental costs per life-year gained and the costs per quality adjusted life year gained coming in at $52000 and $81000, respectively. Importantly, there was quite a wide range of life year gains depending on age (optimal age range 60-69 years), risk for developing lung cancer (highest risk groups benefitting most) and gender (with women benefitting least). This caused a range of costs for quality adjusted life year gained anywhere between $32000-$615000. The study did not show a cost-effective benefit for chest radiography screening.

DISCUSSION

Clearly, based on the above studies, CT is superior to CXRs 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 positron emission tomography-computed tomography, magnetic resonance imaging and autofluorescence bronchoscopy for instance[28-34]. 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 CXRs a potential role for screening of lung cancer.

First, CXRs have matured from a technical perspective, and the wide introduction of digital CXRs 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[35,36]. 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, CXRs 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. There is a high false negative rate using the CXR. CXR screening programmes should be backed up with cross-sectional imaging with a low threshold in place for investigating even small abnormalities detected on the CXR with CT scan. It may not be feasible to arrange for large-scale screening using CT and in these circumstances, one could consider using the CXR.

Whilst NLST demonstrated that benefits from early detection of lung cancer outweighs the risk of ionizing radiation, the potential risk is substantial. In NLST, participants received an average exposure of 8 mSv over 3 years of screening/diagnostic examinations which can potentially cause 1 cancer in every 2500 screened[37]. Recently, multiple studies have been investigating the feasibility of radiation dose reduction to sub-mSv level whilst the diagnostic accuracy is maintained[38,39]. Since there is a high contrast resolution between air and lung nodules, significant radiation dose reduction can be achieved while maintaining good diagnostic quality. Various strategies such as reduced tube voltage, tube current, or both is being used. The application of iterative reconstruction would maintain spatial resolution in low dose studies whilst maintain diagnostic accuracy[40].

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, CXRs on an annual basis should be considered and additional use of CAD may improve sensitivity for earlier lesions.

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