AN UPDATE ON LOW-DOSE COMPUTED TOMOGRAPHY FOR LUNG CANCER SCREENING

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Abstract

Since the publication of the National Lung Screening Trial (NLST) showing a mortality reduction with use of low-dose computed tomography (LDCT), there has been considerable interest about the use of this modality to screen for lung cancer. This article reviews the NLST and the current evidence behind screening for lung cancer in smokers. It also attempts to look at different lung cancer risk models to help better define the ideal target population and last touches on the cost-effectiveness of LDCT screening in patients at high risk of lung cancer.

Key words: Lung cancer, Computed tomography, Screening

Introduction

Lung cancer is an important tobacco-related malignancy globally accounting for an estimated 1.3 million deaths per year, which represents 28% of all cancer-related deaths.[1] In 2015, lung cancer incidence rates in Pakistan were the third highest after breast cancer and lip and oral cavity cancer. However, it accounted for the second highest number of cancer deaths after breast cancer.[2] In light of the significant health-care costs and mortality associated with this malignancy, efforts have been made to develop adequate screening tools for the early detection of lung cancer. This article will attempt to briefly look at the current evidence and recommendations regarding lung cancer screening in the current or former smokers.

Background

Initial efforts at developing a screening tool for the detection of lung cancer centred on using chest radiography (CXR). The early studies did not show any morality benefit of using CXRs as a screening tool for lung cancer,[3] a fact that was confirmed in 2011 with the publication of the Prostate, Lung, Colorectal and Ovarian (PLCO) trial.[4] The investigators randomised 154,901 patients to receive four screening CXRs at baseline, year 1 and year 2 and year 3 versus regular care. Patients were followed for 13 years or till 31st December, 2009, whichever were earlier. The investigators found no mortality benefit of using chest X-rays to screen for lung cancer.

At the same time, interest had begun to develop on the use of low-dose computed tomography (LDCT). In the 1990s and 2000s, uncontrolled studies using LDCTs demonstrated that more lung cancers, specifically more Stage I cancers, could be identified using annual LDCT screening.[5-8] However, none of these studies was able to demonstrate a morality benefit of using annual LDCT scans to screen for lung cancer. It was felt that perhaps these studies were underpowered to demonstrate such an effect. In light of this encouraging data, a larger trial called 'The National Lung Screening Trial' (NLST) was conducted in the United States.[9]

NLST

The NLST involved 53,454 individuals from 33 centres who were randomised from 2002 till 2004 to receive annual LDCT or CXR. This number was deemed necessary to indicate a 21% reduction in mortality with a power of 90%. To be eligible for the trial, an individual had to be between 55 and 74 years of age at the time of randomisation, has a history of cigarette smoking of at least 30 pack-years and, if a former smoker, has to quit within the previous 15 years. Participants underwent three screenings at baseline, year 1 and year 2.

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Any non-calcified lung nodule > 4 mm in diameter was considered 'screen positive' as was any evidence of a pleural effusion or lymphadenopathy. These patients were then investigated further. As a result of these criteria, the proportion of screen positives was high at 24.9% in the LDCT group versus 6.9% in the control group (CXR group).

The lung cancer detection rates in the study and control groups were 645 and 572/100,000 person-years, respectively. The lung cancer mortality rates in the study and control groups were 247 and 309/100,000 person-years, respectively. Both of these changes were significant and there was an effective 20% reduction in lung cancer-related mortality rate in the LDCT group ($P = 0.004$).[9]

The investigators determined that 320 participants would need to be screened to see a decrease of one death from lung cancer. In other words, the absolute risk of lung cancer deaths was reduced from 1.66% to 1.33%, or three fewer deaths per 1000 participants screened in the LDCT arm. Of note, the study was terminated early after an independent data and safety board determined that the primary end point had been met.

The results of another randomised trial entitled the 'Netherlands-Leuven Longkanker Screening Network' trial involving 15,822 participants are still awaited and have not yet been published.[10] Based on the results of the NLST in 2013, the U.S Preventive Services Task Force recommended annual screening for lung cancer with LDCT in adults aged 55–80 years of age who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. They stated that screening should be discontinued once a person has not smoked for 15 years or develops a health problem that limits life expectancy or the ability or willingness to curative lung surgery.[11]

Rationale for using lung cancer risk stratification tools

Although the NLST did show a survival advantage, it was also associated with a high number of false positives. In an attempt to better refine these criteria, Kovalchik et al.[12] developed a prediction model for lung cancer deaths. The selected risk factors for their prediction model included age, body mass index, family history of lung cancer, pack-years of smoking, years since smoking cessation and emphysema diagnosis. They created five quintiles of patients who were divided according to their risk of lung cancer. The 5-year risk of lung cancer was as follows: 0.15–0.55% in quintile 1, 0.56–0.84% in quintile 2, 0.85–1.23% in quintile 3, 1.24–2.00% in quintile 4 and >2.00% in quintile 5. They observed that 60% of participants at highest risk for lung cancer deaths (quintile 3 through 5) accounted for 88% of the screening-prevented lung cancer deaths, while the 20% of participants at lowest risk (quintile 1) accounted for only 1% of prevented lung cancer deaths. Their findings led support to the idea of risk-based targeting of smokers.

Similarly, Tammemägi et al.[13] developed a validated model ($PLCO_{M2012}$) with data from the PLCO control and intervention groups who ever smoked. They compared the accuracy of $PLCO_{M2012}$ criteria with NLST criteria. Their criteria included age, level of education, body mass index, family history of lung cancer, chronic obstructive pulmonary disease, CXR in the previous 3 years, smoking status, history of smoking and quit time. They noted that as compared to NLST, $PLCO_{M2012}$ had more sensitivity (83% vs. 71% $P < 0.001$) and positive predictive value (4.0% vs. 3.4% $P = 0.01$), without loss of specificity (62.9% vs. 62.7% $P = 0.54$). Furthermore, 41.3% fewer lung cancers were missed.

Another simpler approach was taken by Sanchez-Salcedo et al.[14] when they applied NLST criteria in two different lung cancer screening studies from the United States and Europe. They noted that 36% and 59% of participants in the two studies, respectively, met NLST criteria. Although applying the NLST criteria alone would have missed 39% of all lung cancers, the addition of 'presence of emphysema' or 'meeting NLST criteria' resulted in detection of most lung cancers (95% in the United States study and 88% in the European study).

Lung cancer amongst light or never smokers

Another issue that has been raised by researchers is the emphasis on heavy current and former smokers in the NLST. Pinsky and Berg[15] noted that when NLST criteria were applied to data from the Surveillance, Epidemiology and End Results, the 2010 census and the National Health

Interview Survey, only 27% of patients with lung cancer would have been eligible for screening. This suggests that a large portion of people who develop lung cancer are being missed by application of NLST criteria. When the authors applied a broader age range and lower smoking threshold, they were able to capture 68% of all lung cancers.

The issue of lung cancer in light or never smokers becomes even more important when looking at a non-Caucasian population since 90% of participants in NLST were Caucasian. Studies from Japan have suggested a higher proportion of lung cancer amongst women and also amongst light or never smokers in their population when compared to western populations.[16] At present, a randomised control trial on non-/light smokers is being conducted in Japan.[17] Once the results of this trial are available, more can be deduced on the efficacy of LDCT screening in non-/light non-Caucasian smokers.

Until more is known from trial data, there is no recommendation to screen patients who are light smokers; however, on an individual basis, physicians may want to consider patients with emphysema and/or a strong family history of lung cancer.

Assessing the costs

The NLST estimated its cost-effectiveness (CT vs. chest X-ray) at $52,000 per life year gained and $81,000 per quality-adjusted life year gained.[18] Other systemic reviews indicated the cost-effectiveness estimates for LDCT screening for lung cancer range of $18,452–$66,480 per life year gained.[19-20] These numbers are acceptable in the United States where a threshold of $100,000 is considered acceptable; however, the cost may be prohibitive in the third world or some European countries. According to the World Health Organisation, an intervention that costs <3 times the national annual per capita gross domestic product is considered cost-effective.[21] In light of the costs entailed, including the potential harms such as; the high false positive rate found in the NLST individual countries would be advised to first assess the prevalence of lung cancer in their population amongst different age groups before developing a country-specific lung cancer risk model. Such an approach may be a more fiscally responsible one.

Conclusion

The NLST has clearly demonstrated a 20% reduction in lung cancer mortality when LDCT screening is used for heavy current or former smokers. In the absence of other data, the physician may use NLST criteria for lung cancer screening. Alternatively, application of a lung cancer risk assessment model may allow for more rational use of resources. For individual countries, the development of national cancer databases is imperative to better apply LDCT screening for smokers depending on how lung cancer presents in their particular populations.

Finally, the results of the above-mentioned studies are still awaited and will continue to shed more light on the issue of lung cancer screening with LDCT.

Conflict of Interest

The authors declare that they have no conflict of interest.

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