Lung Cancer Screening – Low-Dose Chest Computerized Tomography

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Abstract

Lung cancer is the leading cause of cancer death worldwide, accounting for millions of deaths each year. It is a disease with high morbidity and mortality that has a poor prognosis due to its late presentation. Prevention and early screening are the most effective strategies to reduce the epidemiological burden.
The most important risk factor for lung cancer is smoking, which is used as a basis in the formulation of risk prediction models. These models, apart from assisting in the careful selection of individuals at risk, enable to foresee some of the disadvantages inherent to screening. Low-dose radiation CT has proven to be a viable tool as part of an organized screening, ensuring high-resolution, non-contrast-enhanced images with less artifacts to be available for accurate detection and evaluation of nodules at ultra-low doses. Current available evidence is still sparse and doubts remain as to the appropriate population targets, optimal frequency and duration of screening, and criteria for defining a "positive screen".
Success in screening is dependent on a holistic and multidisciplinary approach, which is a critical step towards reducing the burden of disease and improving the health and well-being of individuals and communities around the world.

Keywords: pulmonary cancer, screening, low dose CT scan

Justification and Objectives

Introduction

Lung cancer is the leading cause of cancer death in the world responsible for 1.6 million deaths per year, [1] this approximates to 20% of all cancer deaths globally.[2] The most important risk factor for lung cancer is smoking.[3] Smoking is estimated to account for about 90% of all lung cancer cases.[4]

Across Europe there are around 400,000 new cases of lung cancer and over 300,000 deaths annually.[5] The burden of lung cancer is expected to rise across the globe in the coming years despite advances in diagnostics and treatment.[6] Long term survival remains poor, the average European 5-year survival is 12%.[7] In contrast, 5-year survival in patients diagnosed early (stage I-II) can be as high as 75%.[8]

The role of Computerized Tomography (CT) in the detection of lung cancer was first described in the 1990s and was shown to be superior to chest X-ray (CXR) in a number of subsequent observational studies.[9] In 2011, the National Lung Screening Trial (NLST) confirmed for the first time a significant mortality reduction in ever-smokers aged 55-74 years.[10] Since the publication of. NLST, several American bodies have recommended screening with LDCT be offered to individuals that match the NLST eligibility.[9] In Europe, the NELSON study confirmed a 26% mortality rate reduction in males and 39% in females at 10 years.[11]

Therefore, the approach to lung cancer should focus on prevention and an early diagnosis in order to increase survival.

Who to screen?

Smoking and older age are the 2 most important risk factors for lung cancer.[3,12,13] Other risk factors for lung cancer include environmental exposures, prior radiation therapy, other (noncancer) lung diseases, and family history.[14]

More recently, regarding a better individual eligibility for screening, **Risk Prediction Models** were created. Among the existing risk prediction models there are discrepancies regarding predictive performance.[15] The $PLCO_{M2012}$, Bach and TSCE models have been shown to be more sensitive than the NLST criteria in predicting 6-year lung cancer incidence.[16] There is also evidence in favor of the $PLCO_{M2012}$ in terms of greater sensitivity, positive predictive value for lung cancer detection and cost-effectiveness.[17] Despite its still scarce evidence, simulation studies suggest that risk prediction models to determine eligibility for lung cancer screening could be associated with reduced lung cancer deaths and the number of participants needed to screen to prevent 1 lung cancer death.[18]

Some model proposals are briefly described in Table 1.

Risk Factors		Risk Prediction Models						
		NLST	TSCE	LLP	Knoke	Bach	$PLCO_{M2012}$	TALENT
Age		✓	✓	✓	✓	✓	✓	✓
Sex			✓	✓		✓		
Smoking	Status	✓	✓	✓	✓			✓
	Duration	✓	✓	✓	✓	✓	✓	
	Intensity	✓	✓		✓	✓	✓	
	Type of cigarette			✓				
	Age at start and end			✓				
	Years since cessation		✓		✓	✓	✓	
Race							✓	
Education							✓	
Occupation								✓
Body Mass Index							✓	
Chronic Obstructive Pulmonary Disease				✓			✓	
Personal history of cancer				✓			✓	
Family history of lung cancer				✓			✓	✓
Personal history of pneumonia / tuberculosis				✓				✓
Asbestos exposure				✓		✓		

Legend: TSCE: Two-Stage Clonal Expansion; LLP: Liverpool Lung Project Risk; PLCOM2012: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial Model 2012, TALENT: Taiwan Lung Cancer Screening for Never Smoker Trial

Table 1: Summary of Risk Prediction Models (adaptation of table 2)[15]

Content

Lung Cancer Screening

By definition, screening is a systematic activity to identify an asymptomatic disease or risk factors, as a way to an early diagnosis and treatment that improves the prognosis.[19] The key prerequisite to ensure screening viability is to create a program supported on an imaging method (i.e. CT scanners) with adequate diagnostic accuracy that allows careful evaluation, while keeping the radiation dose as low as reasonably achievable.[15] Modern CT scanners provide high-resolution, low-noise images for accurate detection and measurability of nodules at ultra-low dose.[20,21] The reading protocol should target two objectives: first, to avoid misdetection and second, to leave out insignificant findings.[15] In this sense, the radiologist, which is responsible for interpreting images, plays a crucial role in formulating differential diagnoses and managing patients. However, to date, few radiologists are trained[15] in this area. Education, training, certification and quality assurance of reading radiologists is warranted, notably to avoid overcalling, which might result in over-investigation of minor findings or overtreatment of findings that can be controlled by active surveillance.[22,23] Recently, a computer-aided diagnosis model based on artificial intelligence was developed – **Lung Cancer Prediction Convolutional Neural Network (LCP-CNN)** – derived and validated using data from NLST.[24] Its use allowed better TC readings from radiologists and pneumologists, increasing average sensitivity and specificity in reading both at very low thresholds (5%) and high thresholds (65%) of risk for malignancy.[24] However, the available evidence regarding the use of artificial intelligence as an auxiliary tool in imaging assessment is still scarce, requiring additional investigation.[25]
There have been different definitions of a positive screen result, resulting in different management guidelines.[15] In an effort to standardize the interpretation, reporting and

recommendations for the management of pulmonary nodules in LDCT screening, the American College of Radiology established the Lung-RADS classification (Lung CT Screening Reporting And Data System) with management guidelines based on diameter.[26] While threshold size for solid nodules was ⩾4 mm in the NLST (longest diameter), Lung-RADS used ⩾6 mm for solid nodules at baseline.[27] This change in threshold led to a decrease in false-positive rate (12,8% versus 26,6%), but also resulted in reduced sensitivity (84,9% versus 93,5%) on a retrospective assessment of NLST data.[28] Under International Early Lung Cancer Action Program criteria, nodule management also depends on nodule diameter with a positive screen result for solid nodules ⩾15 mm or smaller nodules (6–14.9 mm) demonstrating malignant growth at 3 months.[29] In the **TALENT** study, lung cancer detection rate was 2.6%, which was even higher than NLST study (1.1%) and NELSON study (0.9%).[30]

European screening programs have used another approach, based on volumetry, in order to overcome the limitations of two-dimensional measurements, which include large intra- and inter-reader variability.[31] The NELSON study defined non-calcified solid nodules as positive screens if they had a volume >500 mm^3 or nodules with a volume of 50–⩽500 mm^3 and a 25% increase in volume at a 3-month follow-up.[32,33]

The British Thoracic Society guidelines recommend risk assessment of nodules >8 mm or >300 mm^3 using the Brock model.[15] Nodules with ⩾10% risk of malignancy are then referred for PET-CT.[22]

Of particular concern is the incidence of solid nodules that were missed on a previous scan or developed in the interval between screening rounds. With an annual incidence of 3%–13%, these nodules are not uncommon and turn out to be lung cancer in 6% of participants, thus exhibiting a greater risk of malignancy with smaller size compared to baseline nodules.[33,34] Guidelines regarding screening rounds were derived from the NLST, NELSON and CISNET (Cancer Intervention and Surveillance Modeling Network) studies. The NLST screened annually for 3 years.[27] The NELSON trial screened at intervals of 1 year, then 2 years, then 2.5 years.[35] The CISNET modeling studies suggest that annual screening with LDCT provides greater benefit in decreasing lung cancer mortality and in life-years gained compared with biennial screening.[36] The recommendations of other societies are resumed in table 2.

<u>Table 2:</u> Follow-up recommendations of American Societies

	Age	**Population**	**Smoking Load**	**Follow-up**
American Association for Thoracic Surgery (2012)	55 – 79 years	American smokers	30 packs / year	annually
	⩾ 50 years	Smokers with cumulative risk of developing lung cancer of ⩾5% over the following 5 years	20 packs / year	annually
American Cancer Society (2013)	55-74 years	Smokers or ex-smokers (< 15 years) in fairly good health	30 packs / year	annually
American College of Chest Physicians (2018)	55 – 77 years	Asymptomatic smokers or ex-smokers (< 15 years) without comorbidities	⩾ 30 packs / year	annually
National Comprehensive Cancer Network (2022)	55-77 years	Asymptomatic smokers or ex-smokers (< 15 years)	⩾ 30 packs / year	annually
	⩾ 50 years	Smokers with at least 1 additional risk factor for lung cancer	⩾ 20 packs / year	annually
American Academy of Family Physicans (2021)	Insufficient evidence			

Discussion

Lung cancer is the leading cause of cancer death in the world responsible for 1.6 million deaths per year.[1] Lung cancer has a generally poor prognosis, with an overall 5-year survival rate of 20.5%,[37] largely associated with smoking. Prevention and early screening are the most effective strategies in reducing its epidemiological burden. Rapid medical-technological evolution, particularly in the field of imaging, has allowed the development of low-dose radiation CT, a complementary diagnostic exam already known for its high diagnostic accuracy, but now performed at low doses of radiation.

Smoking and older age are the 2 most important risk factors for lung cancer [3,12,13] being used in several programs as unique criteria in selecting individuals for screening. In order to implement a cost-effective screening program, it is recommended to identify the population based on risk prediction models.[15] These models, besides helping in the careful selection of at-risk individuals, allow us to anticipate and prevent some of the screening disadvantages´.[15]

Questions remain regarding the optimal screening frequency and duration, appropriate population targets, defining criteria for a "positive" finding, and identifying diagnostic follow-up protocols that minimize evaluations of false-positive findings.[38,39,40] Studies seem to agree in screening asymptomatic adults from 50 to 80 years of age who have smoked at least 20 pack years, either active or former smokers (if abstinent for less than 15 years).[41] The ideal approach regarding identification, definition and management of "positive findings" remains under investigation. While most studies as NLST and Lung-RADS identify nodule abnormalities based on size,[25] studies as NELSON base their interpretation on volumes calculated by a specialized software. A retrospective interpretation of data from the International Early Lung Cancer Action Program (I-ELCAP) study cohort and NLST suggested that setting a more conservative threshold (eg, >6 mm) would decrease the false-positive rate (resulting in fewer unnecessary procedures or follow-up studies) with minimal impact on the detection of cancers.[42,43] Another retrospective study applied the Lung Imaging Reporting and Data System (Lung-RADS) criteria from the American College of Radiology to the NLST data and found a decrease in the false-positive rate but also a concomitant decrease in the sensitivity of screening.[28] There appears to exist an agreement within studies concerning screening rounds, supporting an annual during the first 2-3 years.[27,35,36]

The success of the screening is dependent on a holistic and multidisciplinary approach. Strict algorithms defining the exact workflow and procedures triggered by positive screen results and incidental findings have to be implemented.[15] Pneumologists, radiologists and family doctors work together to ensure a correct orientation of individuals inside the screening program. Pneumologists have a crucial role in identifying people eligible for Lung Cancer Screening (LCS).[15] Family doctors, sharing the decision-making process and promoting tobacco cessation need to ensure that the eligible risk population understands the importance of LCS and is informed of its potential benefits, risks and harms.[15] The role of radiologists in LCS is to ensure that LDCT is optimized with regard to high image quality, minimum dose and the most appropriate management of screen-detected "positive" nodules and incidental findings.[15]

Conclusion

Lung cancer is a pathology with high morbidity and mortality, presenting a poor prognosis at the expense of its late presentation. Therefore, prevention and early detection through screening are extremely important in modifying the natural history of the disease and can contribute to a significant increase in survival.

An overhaul of European healthcare systems could lead to the introduction of low-dose radiation CT as part of organized screening, a tool that has been shown to be viable in the screening process. This process can be achieved by creating carefully designed pilot programs in several countries that promote a healthy lifestyle, awareness of risk factors, education measures aimed at smoking cessation and, finally, encourage LDCT screening for people of high risk

Lung cancer screening is a critical step toward reducing the burden of disease and improving the health and well-being of individuals and communities around the world.

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