DR GABRIEL GALEA

Lung Cancer Screening: An Overview

DA VINCI HEALTH

INTRODUCTION

Lung cancer is a heterogeneous and often aggressive disease. Despite advances in lung cancer treatment and an overall reduction in the rate of heavy smoking over the last half century, lung cancer remains the most common cancer and the leading cause of cancer death worldwide and in Malta.[1,2]

The theoretical benefits of lung cancer screening are clear; it is a common disease with a significant prognostic benefit when detected early.[3] A cheap, non-invasive and widely available screening tool was the major obstacle to large-scale, successful lung cancer screening. Historical attempts at lung cancer screening using chest radiographs with or without cytological analysis of sputum specimens were largely unsuccessful, mainly due to the limitations of chest radiographs in the detection of early-stage lung cancer. The advent of low-dose chest CT (LDCT) around the turn of the millennium led to the establishment of several large-scale trials determining whether screening with LDCT would reduce mortality from lung cancer among high-risk persons.[4-6]

WHAT IS LOW-DOSE CHEST CT?

Due to an inherently high contrast resolution between air and lung nodules, chest CT can be performed using a low radiation dose while maintaining good diagnostic quality. There is no consensus on what level of radiation is considered 'low dose' and the techniques that affect dose in CT will vary from centre to centre. In general, diagnostic quality CT screening can be accomplished at an overall average effective dose of 2 mSv or less.[7] For comparison, an average lumbar spine x-ray series (lateral and anteroposterior) is approximately 1.5-2 mSv.[8]

RESULTS OF LARGE TRIALS IN LUNG CANCER SCREENING

The National Lung Screening Trial (NLST) conducted in the United States on 53,454 current or former heavy smokers is the largest randomized controlled trial to date. It was launched in 2002 with initial findings reported in 2010 and the most recent follow-up data published in 2019. Participants were randomly assigned to either receive a LDCT scan each year for three years or one chest X-ray each year for three years. LDCT screening showed a higher sensitivity in detecting early-stage lung cancer, a 20% reduction in lung cancer mortality and no increase in radiation-induced lung cancer after 13 years of follow-up.

In Europe, the Dutch-Belgian Randomised Lung Cancer Screening Trial (NELSON) on 15,792 patients is the largest trial performed to date, beginning in 2003 with the final round of follow-up in 2015. Participants aged 50-74 who were current or heavy smokers were randomly assigned to either a screening group that underwent CT screening at baseline, year 1, year 3, and year 5.5 or a control group that received no screening. The results showed that LDCT screening led to a 24% reduction in lung cancer deaths in men and a 33% reduction in lung cancer deaths in women after ten years of follow-up.[5]

Smaller trials including those performed in Italy and the United Kingdom showed similar results with regard to reduction in lung cancer mortality in patients undergoing lung cancer screening.[9,10]

SCREENING GUIDELINES

Screening guidelines vary slightly between countries and will continue to be refined over the coming years as data pools grow and follow-up periods are lengthened. The main parameters to be defined are patient age and smoking history as both are intrinsically linked to lung cancer risk. Any slight variations in inclusion criteria become significant when applied across the numbers of large-scale population screening. Participants at greatest risk for lung cancer mortality are older and usually have more comorbid conditions; this needs to be balanced against the higher screening costs (mainly due to increased detection of incidental findings of questionable significance that nevertheless require further workup) for these patients and their often-reduced life-expectancy due to age and other comorbidities.

The US current screening program recommends annual screening for lung cancer with LDCT in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years. A pack year is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

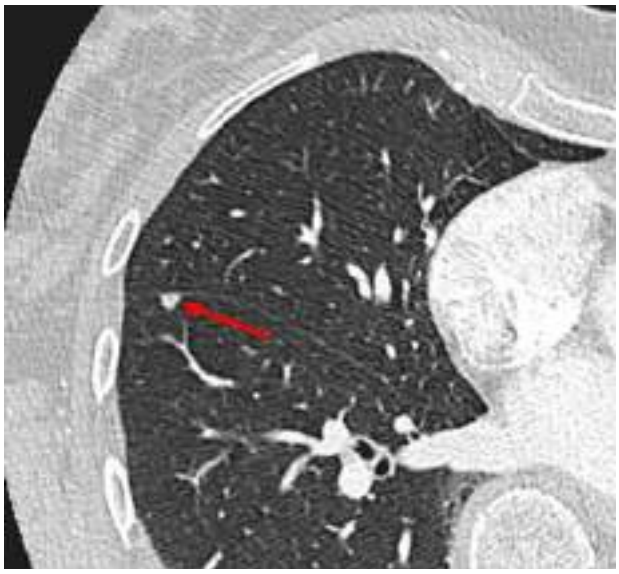
For example, 20 pack years implies one pack of cigarettes per day for 20 years, two packs per day for 10 years, and so on. Screening should be discontinued once a person has not smoked for 15 years, or develops a health problem that substantially limits life expectancy. This is the official recommendation of the U.S. Preventive Services Task Force which is an independent panel of national experts in disease prevention and evidence-based medicine.

Other guidelines are more conservative and less costly. Canadian guidelines now recommend screening using LDCT every year for up to three consecutive years in individuals aged 55 to 74 who have at least a 30 pack-year history of smoking.[11,12] The Netherlands have also begun rolling out a national lung cancer screening program targeting individuals who are between 50 and 75 years old and who have smoked at least 15 cigarettes per day for at least 25 years or at least 10 cigarettes per day for at least 30 years. Participants in this program will receive a LDCT scan every year for three years and then every two years for the subsequent four years if the initial scans are negative.[13]

In 2023, the UK began rolling out a lung 'health check' program which involves identifying and inviting 'ever' smokers aged 55-74 from GP records, then assessing eligibility and frequency interval for LDCT screening using a risk assessment algorithm.[14]

Definitive European Union-wide lung cancer screening recommendations have not been implemented yet, however in 2022 the European Commission recommended that as part of the *Europe's Beating Cancer Plan*, screening of patients aged 50-75 years who are current or ex-smokers who have quit smoking within the previous 15 years should be introduced. More detailed and concrete recommendations are awaited.

Figure 1: Triangular perifissural/subpleural nodule (red arrow) in right lower lobe typical of an intrapulmonary lymph node. Lung-RADS 2.



LUNG RADS CLASSIFICATION

The Lung-RADS (Lung Imaging Reporting and Data System) is a classification proposed to aid with reporting of lung nodules detected on LDCT and standardise follow-up and management decisions. The details of the Lung-RADS classification are beyond the scope of this article however it is broadly as follows. An inexhaustive explanation as well as recommendations in italics are given below. The figures below illustrate a few examples of common lung nodules and their Lung-RADS categories.

Lung-RADS 0 (incomplete)

- Prior CTs not available for comparison, lungs incompletely imaged or incidental infection in the lungs

Lung-RADS 1 (negative, <1% chance of malignancy); *continue annual screening*

- No lung nodules or benign lung nodules including calcified nodules (benign granulomas) or fat-containing nodules (hamartomas)

Lung-RADS 2 (benign appearances or behaviour, <1% chance of malignancy); *continue annual screening*

- Nodules in a subpleural location with oval, lentiform or triangular appearances in keeping with physiological intrapulmonary lymph nodes
- Solid nodules <6 mm at baseline or new nodule <4 mm or ground glass nodules <30 mm at baseline

Lung-RADS 3 (probably benign, 1-2% chance of malignancy); *6-month follow-up*

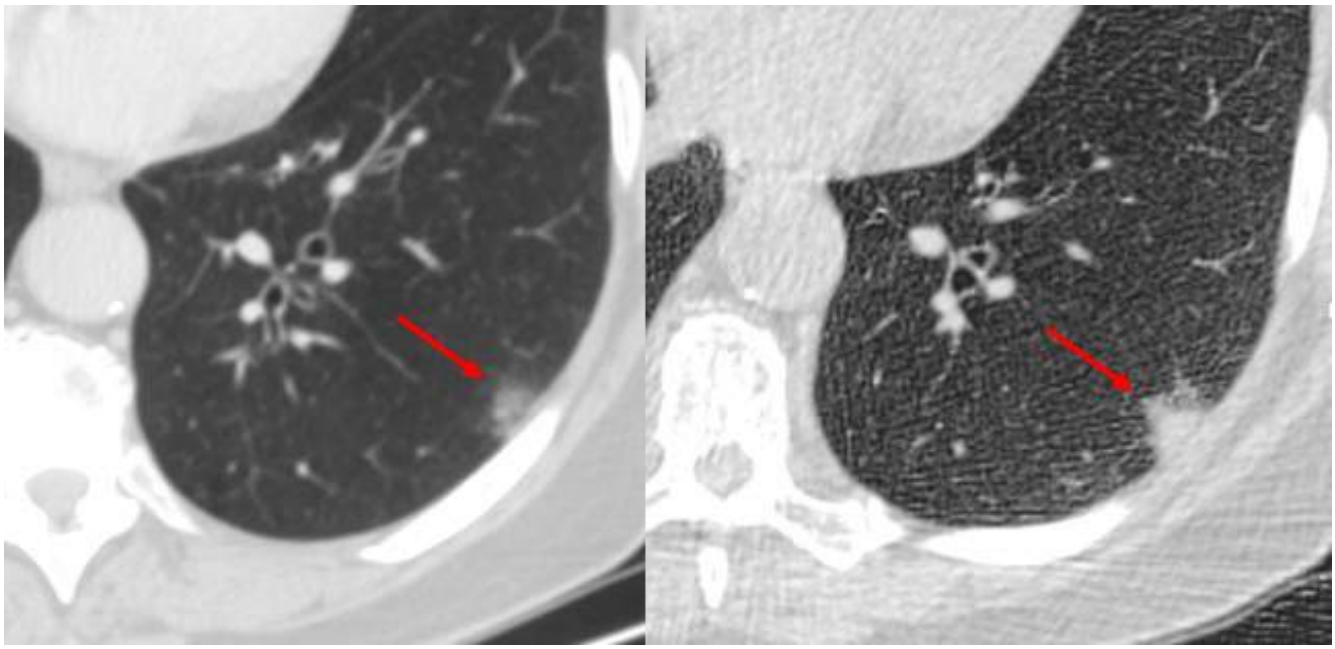
- Solid nodules 6-8 mm at baseline or new nodules measuring 4-6 mm
- Part solid nodule ≥6 mm total diameter at baseline or ground glass nodule ≥30 mm at baseline
- Thick-walled lung cyst with enlarging cystic component

Lung-RADS 4A (suspicious, 5-15% chance of lung cancer); *3-month follow-up or PET-CT in certain circumstances*

- Nodules measuring ≥8 mm to <15 mm at baseline or nodules <8 mm but showing growth
- New nodules 6 mm to <8 mm

... DIAGNOSTIC QUALITY CT SCREENING CAN BE ACCOMPLISHED AT AN OVERALL AVERAGE EFFECTIVE DOSE OF 2 MSV OR LESS. FOR COMPARISON, AN AVERAGE LUMBAR SPINE X-RAY SERIES (LATERAL AND ANTEROPOSTERIOR) IS APPROXIMATELY 1.5-2 MSV

Figure 2: Left image shows a part-solid nodule (red arrow) measuring 12 mm in total diameter with a small solid component (solid nodule with ground glass 'halo'). Lung-RADS 3. Follow-up CT 1 year later shows a part-solid nodule with a growing solid component, reclassified as Lung-RADS 4.



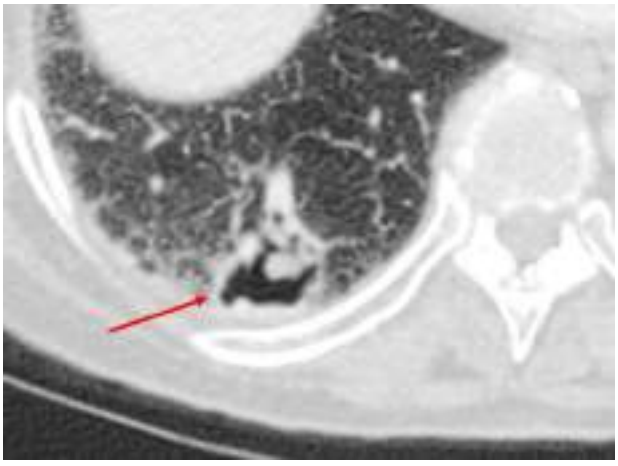
Lung-RADS 4B (very suspicious, >15% chance of malignancy); *Multidisciplinary team management with options including follow-up, chest CT with contrast, FDG/PET-CT and/or tissue diagnosis*

- Solid nodule ≥15 mm at baseline or new/growing nodules ≥8 mm
- Thick-walled cyst with increasing wall thickness/nodularity
- Nodule growing slowly over multiple screening exams

Lung-RADS 4X (very suspicious, >15% chance of malignancy); *Multidisciplinary team management with options including follow-up, chest CT with contrast, FDG/PET-CT and/or tissue diagnosis*

- Category 3 or 4 nodules with additional imaging features that increase the suspicion of malignancy

Figure 3: Thick-walled cyst (red arrow) classified as Lung-RADS 4A which showed increased nodularity on a follow-up CT, upgraded to Lung-RADS 4B.



CHALLENGES OF LUNG CANCER SCREENING

The benefits of lung cancer screening are clear. Detection of lung cancer at an earlier stage leads to a better outcome with historical data reporting a 52% 5-year survival at stage I compared with a 5% 5-year survival at stage IV. Lung cancer screening aims to detect lung cancer at an earlier stage.

The risks and disadvantages of lung cancer screening are not insignificant, however. There is a radiation risk from the yearly exposure needed for lung cancer screening although studies performed so far did not show an increased risk of lung cancer at long-term follow-up. There is also a small but material risk, as well as a cost, from invasive investigations (FDG/PET-CT, bronchoscopy and CT-guided biopsy) performed for false-positive nodules i.e. the flagging of benign nodules as suspicious. [10,15]

One of the major challenges in lung cancer screening and screening programs in general, is effective recruitment and retention of patients. Patient recruitment can be done by public information campaigns or by targeted recruitment through a patient's general practitioner; the latter is a more challenging method in countries where there is no named GP assigned to individual patients. It is important to explain to the participant the importance of screening, the different examination steps and the time each step will take as well as the difference between a screening CT and a standard CT with regard to radiation exposure and diagnostic quality. Lung cancer is unique as a cancer in that smokers may feel stigmatised or even guilty about smoking. There is a perception among smokers that lung cancer is a punishment[16] and it is important to present screening in a positive way to increase acceptance. The Manchester arm of the UK Lung Cancer screening trial chose to name their programme as 'lung health check' which feels more positive in an attempt to increase participation.

Perhaps the biggest challenge facing lung cancer screening around the world is a shortage of health care professionals. In particular, if lung cancer screening were to become widespread, there would be a dramatic shortage of expert thoracic radiologists to read the LDCT scans, and a double reading by experts, as carried out in European studies, does not seem realistic for large-scale screening. The two most viable options to tackle this are to train general radiologists in lung cancer screening or to fully embrace computer-aided diagnosis (CAD) in reading LDCT. CAD has been shown to be at least as good as radiologists at detecting nodules and is already an important part of most screening programs. CAD's sensitivity for nodule detection comes at a cost of increased false-positives. It is hoped that the development of deep-learning-based algorithms with particular emphasis on correct Lung-RADS category categorisation of nodules will lead to higher automation with results on par with radiologists.

CONCLUSION

LDCT lung cancer screening will almost certainly see widespread implementation in Europe in the medium- to long-term, with current evidence suggesting a clear benefit to patients. The medical community must overcome some important challenges before this widespread implementation. It is essential that the screening parameters and patient inclusion criteria are refined. Patient recruitment will be a particular challenge, unique to each country's healthcare system. A solid plan for training and enlargement of the current workforce is one of the most important and challenging hurdles to surmount, particularly for radiologists. Artificial intelligence will undoubtedly play an important role although the exact role remains unclear and will need to be prospectively validated. Finally, quality assurance needs to be implemented and a European or worldwide registry for collection of lung cancer CT screening data should ideally be developed, with regular assessment of the continued utility of lung cancer screening.

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