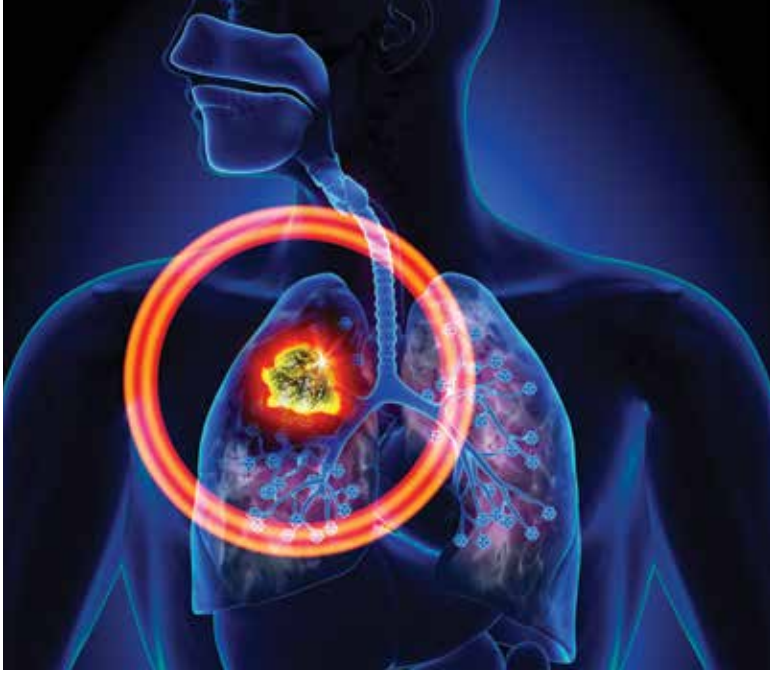
Lung cancer screening update

Where are we now?

TRACY L. LEONG MB BS(Hons), FRACP, MPH
DANIEL P. STEINFORT MB BS, FRACP, PhD
KWUN M. FONG MB BS(Lon), FRACP, PhD

Screening with low-dose CT can detect lung cancer in its early stages when treatment is potentially curative, and is able to reduce deaths from this cancer. However, there are challenges to overcome and no national screening program currently exists in Australia.



© DECADE3D/STOCK ADOBE.COM

Key points

- **Lung cancer screening with low-dose CT reduces mortality in high-risk patients.**
- **Screening programs for lung cancer have been implemented in the USA and Canada.**
- **Feasibility for a similar lung cancer screening program in Australia has been demonstrated.**
- **Implementation of a screening program in Australia should involve careful selection of eligible populations and protocols to ensure that the efficacy of screening is optimised and potential harms are minimised.**
- **Until then, when contemplating CT screening in an asymptomatic high-risk individual consider whether the intended screening process will be of comparable quality and effectiveness as the National Lung Screening Trial.**
- **Decision aids are widely available to help GPs guide patients to reach an informed evidence-based decision.**

Lung cancer is the leading cause of cancer mortality worldwide and was responsible for 1.6 million deaths in 2012.[1] It contributes substantially to the burden of disease in Australia, with a loss of 53,400 years of potential life and health care expenditure in excess of $160 million in the 2004–05 financial year.[2,3] Prognosis is poor, with a five-year survival of 15%.[4] This is largely because most patients present when the cancer is in an advanced stage – five-year survival falls from 73% in patients with localised disease to 13% in those with distant metastases.[5]

Although smoking prevention and cessation remain the most important strategies for reducing the burden of lung cancer, former smokers continue to be at risk of developing lung cancer.[6] Early detection in those at high risk has the potential to identify lung cancer at a stage when it is amenable to curative treatment.

In the landmark US National Lung Screening Trial (NLST), screening people at high risk with low-dose CT (LDCT) resulted in a 20% relative reduction in lung cancer mortality, and LDCT screening is now recommended for high-risk individuals in the USA and Canada.[7-9] Australian interest in LDCT screening for lung cancer dates back to the 2001 National Cancer Control Initiative Helical CT Screening for Lung Cancer workshop. The Cochrane review on lung cancer screening originally published in 1999 has been updated several times regarding the use of CT screening for lung cancer, most recently in 2013.[10]

The Queensland Lung Cancer Screening Study has demonstrated the feasibility of a similar LDCT screening protocol in Australia, but there is currently no national screening program for either the general population or high-risk groups.[11,12] Although screening is unequivocally able to reduce deaths from lung cancer, implementation of such a program in Australia faces the challenges of defining an eligible population, managing recruitment and adherence, optimising

RESPIRATORY MEDICINE TODAY 2016; 1(1): 34-36

Dr Leong is a Consultant Respiratory Physician at Austin Health, Melbourne. Dr Steinfort is a Consultant Respiratory Physician at Royal Melbourne Hospital and Peter MacCallum Cancer Centre and the David Bickart Clinician Research Fellow at The University of Melbourne, Melbourne, Vic. Professor Fong is a Consultant Respiratory Physician and Director of the University of Queensland Thoracic Research Centre at The Prince Charles Hospital, Brisbane, Qld.

protocols and achieving cost-effectiveness. This article discusses the evidence, challenges and ongoing research in LDCT screening.

Evidence supporting low-dose CT screening

CT screening for lung cancer was initially reported in Japan, with the International Early Lung Cancer Action Program Investigators subsequently providing evidence of potential benefit.[13-15] More recently, many consider the NLST to have provided sufficient evidence for making positive recommendations. This US-based trial randomly assigned 53,452 high-risk volunteers to three rounds of annual screening by either chest x-ray or LDCT, with a median of 6.5 years of follow up.[7] Participants were current or former smokers with a smoking history of 30 pack-years or more and, for former smokers, cessation of smoking no more than 15 years previously. Key findings from this study are summarised in the Box.

Since then, the US Preventive Services Task Force (USPSTF) has recommended annual screening with LDCT for adults aged 55 to 80 years with at least a 30 pack-year smoking history who currently smoke or have quit within the past 15 years.[8] The US Centers for Disease Control and Prevention have summarised the recommendations from the USPSTF and other US organisations.[16] CT screening for lung cancer carries a USPSTF Grade B recommendation, implying reimbursement under the US Affordable Care Act, and is funded for the US Medicare population up to the age of 77 years.

The Canadian Task Force on Preventive Health Care has also released its recommendation for annual screening with LDCT, for up to three consecutive years, for adults aged between 55 and 74 years who are current or former smokers with at least a 30 pack-year smoking history.[9] Importantly, its guideline emphasises that, to minimise screening-related harm, LDCT should occur in health care settings with personnel who have experience in diagnosing and managing lung cancer.

Challenges in low-dose CT screening

The problem of false-positive findings

A major obstacle to LDCT screening for lung cancer is the high proportion of false-positive findings. The NLST reported a 96% false-positive rate, with other studies consistently showing false-positive rates exceeding 90%.[7,17,18] However, limited evidence from population-based and research trials suggests that the prevalence of benign nodules may be comparatively lower in Australia, as a proportion of the benign nodules identified in North American studies are attributable to conditions that are not as common in Australia.[11,19-21]

Positive results from screening require further investigation, and the findings of published studies show this has occurred at a significant rate in patients with benign disease. In the Detection and Screening of Early Lung Cancer with Novel Imaging Technology (DANTE) study, 22% of patients who underwent surgical procedures after a positive LDCT screening result were ultimately proven to have benign disease, and 73% of NLST participants with benign findings underwent at least one invasive procedure.[7,22] In addition to the potentially considerable distress associated with a positive screening result, false-positive findings compromise the risk–benefit ratio and cost-effectiveness of screening.[23,24] Thus, minimisation of false-positive results is critically important to the long-term success of LDCT screening.

False-positive findings can be reduced through careful characterisation of detected nodules. The protocol in the Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON; Netherlands–Belgian Lung Cancer Screening trial) markedly reduced the rate of positive scans to 2.6%, through use of a volume-based nodule management algorithm based on likelihood of malignancy, in contrast to standard diameter measurement where any finding is considered positive.[25-27]

Key findings from the National Lung Screening Trial[7]

The National Lung Screening Trial, a large randomised controlled trial in the USA that assigned more than 53,000 high-risk volunteers to annual screening with either chest x-ray or low-dose computed tomography (LDCT), found:

- a relative reduction in lung cancer-specific mortality of 20% (95% CI, 6.8–26.7%; p=0.004) in the LDCT arm
- a relative reduction in death from any cause of 6.7% (95% CI, 1.2–13.6%; p=0.02) in the LDCT arm
- a rate of positive screening results of 24.2% with LDCT and 6.9% with chest x-ray
- of the positive screening results, 96.4% in the LDCT group and 94.5% in the chest x-ray group were false-positives

Selection of at-risk population

Risk calculators

Another way to improve the effectiveness of lung cancer screening is through targeting the highest-risk smokers. Although smoking is the most important factor in identifying patients at risk of lung cancer, it is a poorly specific method for identifying those at highest risk of death from lung cancer. Use of smoking history alone to select those suitable for lung cancer screening will include some low-risk individuals and exclude some high-risk individuals.[28]

Calculators incorporating clinical information, such as age, sex, education, body mass index, family history of lung cancer and self-reported emphysema, in addition to smoking duration and intensity, have been shown to accurately predict the likelihood of an individual developing lung cancer within five years.[29] Using these calculators to identify the highest-risk individuals to undergo screening (and exclude low-risk individuals from screening) has been suggested to increase the number of lung cancer deaths prevented over five years and to reduce the number needed to screen to prevent one lung cancer death.[29,30] As a consequence, this approach may substantially improve the cost-effectiveness of screening.[31]

Biomarkers

Biomarkers may be an alternative method for detecting individuals at highest risk of lung cancer. Airflow obstruction on lung function testing has been shown to predict a higher likelihood of lung cancer, but is not

considered in any currently available risk calculators. Use of noninvasive biomarkers in blood or exhaled breath to risk-stratify patients remains investigative, although it may form an important component of future screening strategies. For example, a microRNA 'signature' has been used to risk-stratify individuals with positive LDCT findings and achieved a fivefold reduction of the LDCT false-positive rate.[32] Alternatively, research suggests microRNA is detectable in plasma before disease is detectable by LDCT, indicating the potential for identifying the individuals at highest risk before imaging is performed.[33]

Ongoing studies into low-dose CT screening

A published review has summarised the findings of the available randomised controlled trials of LDCT screening, including some that are ongoing.[34] In particular, the final results from screening in the Netherlands and Belgium (NELSON) are eagerly anticipated. This is the only large-scale trial to compare LDCT with no screening, and it is powered to detect a 25% decrease in lung cancer mortality after 10 years. It will form part of a data pooling plan from seven European randomised controlled trials, with a total of 36,000 participants randomly assigned to receive LDCT or no screening.[35] Furthermore, these studies will be informative in the debate regarding nodule management, in comparing linear axial CT with volumetric evaluation.

The cost-effectiveness analysis from the Queensland Lung Cancer Screening Study is also awaited; this will have implications for practice and policy when considering population-based LDCT screening for lung cancer in Australia.[36] The LungScreen WA Project will also contribute useful data regarding the potential population eligible for LDCT screening for lung cancer.[37] Lastly, NHMRC funding has been obtained for an Australian multicentre LDCT risk-stratification study, with Canadian and US collaborators, that aims to overcome the high false-positive rate found with the NLST protocol, with a secondary aim of identifying an optimal nodule management protocol.

Conclusion

For the first time, screening people at high risk of lung cancer is proven to reduce lung cancer-specific mortality. Local factors will influence cost-effectiveness and nodule management efficacy. Work is needed to identify optimal risk stratification of eligible individuals, ensure organised management of screen-detected nodules by multidisciplinary teams, and engage funders and policy makers to ensure that this approach represents high-value medicine. In the absence of a co-ordinated program, ad hoc screening is not recommended. Smoking cessation initiatives remain the best strategy to prevent lung cancer, and should play an integral role in any organised screening program. RMT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Dr Leong: None. Dr Steinfort and Professor Fong are undertaking an NHMRC-funded trial of risk stratification for lung cancer computed tomography screening after a pilot study in Queensland. Professor Fong is the Chair of the Lung Foundation Australia's lung cancer consultative group.

Lung cancer screening update

Where are we now?

TRACY L. LEONG MB BS(Hons), FRACP, MPH
DANIEL P. STEINFORT MB BS, FRACP, PhD
KWUN M. FONG MB BS(Lon), FRACP, PhD

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.
2. Australian Institute of Health and Welfare (AIHW), Cancer Australia. Lung cancer in Australia: an overview. Cancer series no. 64. Cat. no. CAN 58. Canberra: AIHW; 2011.
3. Australian Institute of Health and Welfare (AIHW). Health system expenditure on cancer and other neoplasms in Australia: 2008–09. Cancer series no. 81. Cat. no. CAN 78. Canberra: AIHW; 2013.
4. Australian Institute of Health and Welfare (AIHW). Lung cancer in Australia. Canberra: AIHW; 2016. Available online at: http://www.aihw.gov.au/cancer/lung (accessed October 2016).
5. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2007; 2: 706-714.
6. Peto R, Darby S, Deo H, et al. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ 2000; 321: 323-329.
7. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395-409.
8. Moyer VA. Screening for lung cancer: US preventative services task force recommendation statement. Ann Intern Med 2014; 160: 330-338.
9. Canadian Task Force on Preventive Health Care. Recommendations on screening for lung cancer. CMAJ 2016; 188: 425-432.
10. Manser R, Lethaby A, Irving LB, et al. Screening for lung cancer. Cochrane Database Syst Rev 2013; (6): CD001991. doi: 10.1002/14651858.CD001991.pub3.
11. Marshall HM, Bowman RV, Ayres J, et al. Lung cancer screening feasibility in Australia. Eur Respir J 2015; 45: 1734-1737.
12. Standing Committee on Screening. Position statement: lung cancer screening using low-dose computed tomography. Canberra: Australian Government Department of Health; 2015.
13. Sone S, Li F, Yang Z-G, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Cancer 2001; 84: 25-32.
14. Sobue T, Moriyama N, Kaneko M, et al. Screening for lung cancer with low-dose helical computed tomography: anti-lung cancer association project. J Clin Oncol 2002; 20: 911-920.
15. International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006; 355: 1763-1771.
16. Centers for Disease Control and Prevention. Lung cancer screening guidelines and recommendations. Atlanta: CDC; 2016. Available online at: http://www.cdc.gov/cancer/lung/pdf/guidelines.pdf (accessed October 2016).
17. Lopes PA, Picozzi G, Falaschi F, et al. Four-year results of low-dose CT screening and nodule management in the ITALUNG trial. J Thorac Oncol 2013; 8: 866-875.
18. Blanchon T, Bréchot JM, Grenier PA, et al. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). Lung Cancer 2007; 58: 50-58.
19. Hammerschlag G, Cao J, Gumm K, Irving L, Steinfort D. Prevalence of incidental pulmonary nodules on computed tomography of the thorax in trauma patients. Intern Med J 2015; 45: 630-636.
20. Swensen SJ, Jett JR, Hartman TE, et al. Lung cancer screening with CT: Mayo Clinic experience. Radiology 2003; 226: 756-761.
21. Jett JR. Limitations of screening for lung cancer with low-dose spiral computed tomography. Clin Cancer Res 2005; 11: 4988s-4992s.
22. Infante M, Chiesa G, Solomon D, et al. Surgical procedures in the DANTE trial, a randomized study of lung cancer early detection with spiral computed tomography: comparative analysis in the screening and control arm. J Thorac Oncol 2011; 6: 327-335.
23. Freiman MR, Clark JA, Slatore CG, et al. Patients' knowledge, beliefs, and distress associated with detection and evaluation of incidental pulmonary nodules for cancer: results from a multicenter survey. J Thorac Oncol 2016; 11: 700-708.
24. Raymakers AJ, Mayo J, Lam S, FitzGerald JM, Whitehurst DG, Lynd LD. Cost-effectiveness analyses of lung cancer screening strategies using low-dose computed tomography: a systematic review. Appl Health Econ Health Policy 2016; 14: 409-418.
25. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009; 361: 2221-2229.
26. Xu DM, Gietema H, de Koning H, et al. Nodule management protocol of the NELSON randomised lung cancer screening trial. Lung Cancer 2006; 54: 177-184.
27. Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol 2014; 15: 1332-1341.
28. Tammemägi MC, Church TR, Hocking WG, et al. Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts. PLoS Med 2014; 11: e1001764.
29. Katki HA, Kovalchick SA, Berg CD, Cheung LC, Chaturvedi AK. Development and validation of risk models to select ever-smokers for CT lung cancer screening. JAMA 2016; 315: 2300-2311.

30. Kovalchik SA, Tammemägi M, Berg CD, et al. Targeting of low-dose CT screening according to the risk of lung-cancer death. N Engl J Med 2013; 369: 245-254.
31. Black EC, Gareen IF, Soneji SS, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. N Engl J Med 2014; 371: 1793-1802.
32. Sozzi G, Boeri M, Rossi M, et al. Clinical utility of a plasma-based miRNA signature classifier within computed tomography lung cancer screening: a correlative MILD trial study. J Clin Oncol 2014; 32: 768-773.
33. Boeri M, Verri C, Conte D, et al. MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer. Proc Natl Acad Sci U S A 2011; 108: 3713-3718.
34. Marshall HM, Bowman RV, Yang IA, Fong KM, Berg CD. Screening for lung cancer with low dose computed tomography: a review of current status. J Thorac Dis 2013; 5 Suppl 5: S524-S539.
35. Field JK, van Klaveren R, Pedersen JH, et al. European randomized lung cancer screening trials: post NLST. J Surg Oncol 2013; 108: 280-286.
36. Marshall HM, Bowman RV, Crossin J, et al. Queensland Lung Cancer Screening Study: rationale, design and methods. Intern J Med 2013; 43: 174-182.
37. McWilliams A, Brims F. Research: LungScreen WA project – addressing the hurdles for lung cancer screening. Medicus 2015; 55: 38-39.