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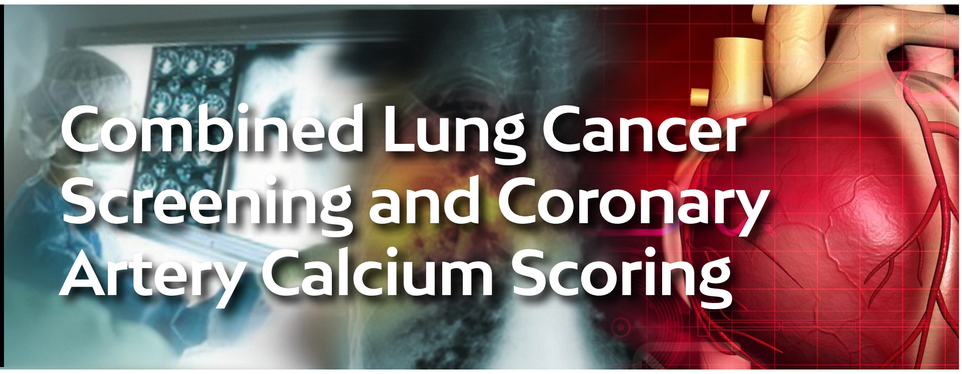

Combined Lung Cancer Screening and Coronary Artery Calcium Scoring

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About the expert

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Mr Indran Ramanathan is a cardiothoracic surgeon at Allevia Hospital Epsom and Auckland City Hospital. He practices all aspects of cardiothoracic surgery including transplantation. In his role as a cardiothoracic surgeon, he understands the importance of early detection of lung cancer and coronary artery disease, as well as the value of a combined approach to screening.

Abbreviations and acronyms:

CAC = coronary artery calcium
CAD = coronary artery disease
CT = computed tomography
CVD = cardiovascular disease
LC = lung cancer
LDCT = low-dose computed tomography
NLST = National Lung Screening Trial
NELSON = Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON)

This review discusses the indications, safety, and utility of simultaneous lung cancer screening and coronary artery calcium scoring for the detection of lung cancer and coronary artery disease using low-dose computed tomography scanning.

Cardiovascular disease (CVD) and cancer are the leading causes of death in Western countries,[1] including NZ where CVD is responsible for 10,483 deaths per year and cancer is responsible for 9,638 deaths per year.[2] Lung cancer (LC) remains the leading cause of cancer mortality in NZ (1,781 deaths per year) while coronary artery disease (CAD) is the leading cause of cardiovascular deaths (4,856 per year).[2] Both LC and CAD share common risk factors and an integrated approach to their early identification and treatment is warranted.

Relationship between LC and CAD

LC and CAD have overlapping risk factors including older age, smoking, exposure to second-hand smoke, environmental air pollution, and low socio-economic status.[1,3,4] In NZ, Māori and Indian ethnicities suffer higher rates of CAD and at an earlier age.[5] Further, Māori and Pacifica have three times the LC mortality of NZ Europeans.

Interestingly, patients who have survived LC are at increased risk of CAD.[6,7] In a retrospective assessment of cancer patients requiring coronary angiography during inpatient care, 18% had LC, and mortality rates were particularly high compared with matched non-cancer patients.[8]

In addition to overlapping risk factors a shared pathophysiological pathway may also exist. There is growing evidence of the importance of chronic systemic inflammation for both LC and CAD.[9,10] Atherosclerosis is driven by inflammation, and dysregulated inflammation underlies the pathology of LC.[11] Additional evidence of a causal role for inflammation in CAD and cancer comes from the CANTOS trial in which an inflammation-targeting therapy not only resulted in a statistically significant reduction in major adverse cardiovascular events (vs placebo) in patients with atherosclerotic disease but also a statistically significant reduction in incident LC.[12,13]

LC screening

The high mortality rate of LC in NZ is mainly attributable to diagnosis occurring in advanced stages of disease where treatment options are limited.[14] Targeted screening of individuals at highest risk of LC will identify early-stage disease, which is more responsive to curative treatment.

Low-dose computed tomography (LDCT) is a sensitive and well-validated tool for detecting early-stage LC in high-risk populations.[15,16] LDCT imaging has been shown to statistically significantly reduce mortality in high-risk individuals in two large-scale, international, multicentre, randomised controlled trials; the National Lung Screening Trial (NLST) conducted in the US[17,18] and the European NELSON trial.[19] In the NLST, three annual screenings with LDCT resulted in a 20% mortality reduction in a high-risk population (**Figure 1**), i.e., asymptomatic individuals aged 50–74 years with a tobacco smoking history of ≥30 pack-years who were currently smoking or who had quit within the past 15 years.[17] Similarly, the NELSON trial demonstrated a 24% reduction in LC mortality at 10 years with LDCT screening.[19]

Within this segment of the population that is at increased risk of LC, CVD is still the most likely cause of death in adults overall.[20] Importantly, in the NLST, death from CVD (24.1%) was almost equal to LC mortality (24.6%).[17]

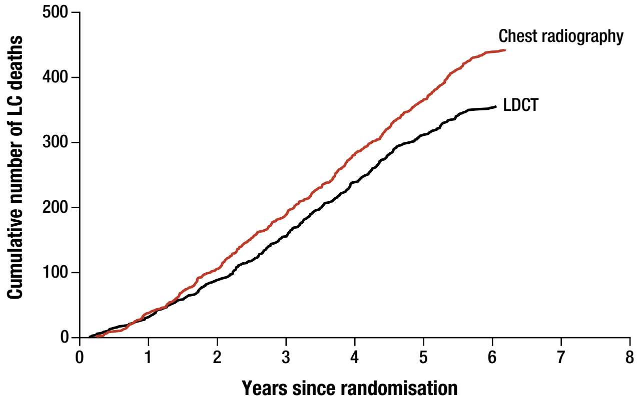

Figure 1. Deaths from LC in the LDCT versus chest radiography groups in the NLST.[17]

Given that patients undergoing LC screening typically have risk factors that predispose them to CAD, it would be advantageous to simultaneously screen for LC and assess coronary calcification burden, which is a well-known marker for subsequent adverse cardiovascular events. Approximately 75% of patients screened for LC would be expected to have coronary artery calcium (CAC).[21] The addition of lifestyle modification, statins, and aspirin to patients with significant CAC would be expected to improve cardiovascular outcomes.

LC screening guidelines

Despite LC being a significant health issue and the existence of high-quality evidence that screening high-risk individuals with LDCT results in improved outcomes, a national LC screening programme has not yet been implemented in either NZ or Australia.[14]

Further supporting the implementation of a national LC screening programme is the finding that a biennial screening programme is likely to be cost effective in the NZ setting and will improve overall population health.[22] The Royal Australian and New Zealand College of Radiologists recommends LC screening using LDCT for individuals aged 50–74 years; ≥20 pack-year history of smoking tobacco; and, if a former smoker, have quit within 20 years.[23]

LC in never-smokers

LC can be caused by risk factors other than smoking cigarettes, pipes, or cigars. Examples include exposure to second-hand smoke, air pollution, a family history of LC, and asbestos. Approximately 10–20% of LC in the US occurs in never-smokers while in Asia >30% of patients with LC are never-smokers and ≥50% of LC occur in women who are never-smokers.[24] LC screening of non-smokers particularly women is becoming increasingly advocated in Asia and may possibly be considered for well-informed Asian patients living in NZ.

CAC scoring

Smokers not only have a higher risk of LC but are also at increased risk of atherosclerosis, which can be detected by CAC scoring,[25] a non-invasive quantitation of coronary artery calcification using CT.[26]

CAC is a valid imaging biomarker of atherosclerotic plaque burden and an independent risk factor for future cardiac-related morbidity and mortality.[16,25,27] Early detection of CAD and intervention of modifiable risk factors as well as optimisation of medical treatment produces a considerable mortality reduction.[27]

Detection of CAC on standard chest CT scans is comparable with CAC detection on ECG-gated CT scans.[25,28] Hence, chest CTs performed for other health conditions, such as LC, represent an opportunity to collect CVD risk information via systematic scoring of CAC without additional radiation exposure and expense.[28]

CAC scoring has been shown to predict all-cause and CVD mortality in NLST participants, independent of current versus former smoking status.[29] In addition, CAC scoring was strongly associated with LC risk in patients with atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA), with increasing CAC scores being associated with an increased risk for LC.[30] These findings support the simultaneous use of CAC scoring in the identification of both CVD and LC risk.

CAC scoring during LC screening chest CT represents an opportunity to also identify asymptomatic individuals at increased CAD risk who may benefit from CVD prevention measures.[30,31]

CAC scoring guidelines

In terms of the most recent guidelines, the overall position of the National Heart Foundation of Australia is that CAC scoring has a role in reclassification of absolute cardiovascular risk for selected patients, in combination with traditional absolute risk assessment and as part of collaborative decision-making that includes the preferences and values of individual patients.[32]

The position builds on the previous consensus statement from the Cardiac Society of Australia and NZ (CSANZ) in which it was recommended that CAC scoring should only be undertaken if a change in therapy is being considered based on the test result.[26]

Referral criteria

According to the CSANZ, the following patient groups should be considered for CAC scoring: [26]

1. CAC scoring is of most value in intermediate-risk patients (absolute 10-year cardiovascular risk of 10–20%) who are asymptomatic, do not have known CAD, and aged 45–75 years, where it has the ability to reclassify patients into lower- or higher-risk groups.
2. CAC scoring may also be considered for lower-risk patients (absolute 10-year cardiovascular risk 6–10%) particularly in those where traditionally risk scores underestimate risk, e.g., especially in the context of family history of premature CVD and possibly in patients with diabetes aged 40–60 years.

Interpretation of CAC score and associated management recommendations in asymptomatic individuals are summarised in **Table 1**.[26]

There is no data on the cost effectiveness of CAC scoring in NZ. Because the cost of CAC scoring is currently borne entirely by the patient, the implications of CAC results should be discussed with patients before CAC testing is undertaken.[26]

CAC score	Risk of death (at 10 years)	Management
0	Very low (<1%)	Reassurance; continue healthy diet and lifestyle
1–100	Low (<10%)	Continue healthy diet and lifestyle
101–400	Intermediate (10–20%)	Aspirin recommended Statins considered reasonable
101–400 and >75th centile	Moderately high (15–20%)	Reclassify as high-risk Aspirin recommended Statins considered reasonable
>400	High (>20%)	Aspirin recommended Statins recommended (to achieve target LDL <2.0 mmol/L) Consider functional assessment

Table 1. Interpretation of CAC score and proposed management.[26]

Combined LC and CAC assessment

Although typically quantified on dedicated chest CT using an ECG-gated technique, calcium in the coronary arteries can be accurately assessed on non-ECG gated CT as well as LDCT.[16] Hence, it was hypothesised that CAC score could be concurrently acquired on LDCT LC screening, thereby allowing two disease risk assessments with a single examination.

The rationale for combining LDCT LC screening and CAC scoring is that the heart is always viewed on LDCT scans of the lungs whereas CAC CT scans are insufficient for effective LC screening due to the limited heart views, with only 40% of the lungs being visualised.[33]

Clinical studies have demonstrated that LDCT scanning is a viable and reliable option for simultaneous LC and CAD screening.[16] These include studies demonstrating the feasibility and safety of simultaneous LC screening and CAD evaluation by means of single LDCT scan with and without the assistance of artificial intelligence in quantifying CAC.[34,35]

There is considerable overlap in the patient populations for which LC screening is indicated and for which CAC scoring has been shown to be beneficial.[16] Early diagnosis in both cases results in improved outcomes and both can be screened for by a review of clinical risk factors and LDCT scan of the chest. In terms of the potential benefits of simultaneous LC and CAC assessment:

- Using a single LDCT scan avoids double the dose of radiation that would be required for two separate evaluations to evaluate the coronary arteries and the lungs.[34]
- Use of a single LDCT scan means less inconvenience for patients since they are required to attend only one rather than two evaluations.
- Using a single LDCT scan to screen for two major diseases should be more cost effective than using two separate CT scans;[33,34] however, this assumption needs to be demonstrated in formal economic analyses.[33]

Referral pathway

Currently, a national screening programme for LC does not exist and may not do so for the foreseeable future. Allevia Heart Lung Screening is the only provider of LC screening at present and also provides CAC scoring. Further, Allevia Heart Lung Screening is the only programme where LC screening and CAC scoring can be performed together.

Recommendations for LC screening vary world-wide depending on the population to be screened. Given the higher LC mortality in Māori and Pacifica, screening at an earlier age is warranted. Therefore, LC screening combined with CAC scoring should be undertaken in:

- Māori and Pacifica over 40 years and other patients over 50 years with a smoking history, significant exposure to passive smoke, air pollution, dust, or asbestos, or with a family history of LC. All of these patients should have a simultaneous CAC score performed at baseline.

LDCT for LC screening should then be performed annually. CAC scoring does not usually require repeating.

Eligibility for heart and/or lung screening can be checked at the Allevia Heart Lung Screening website. An online questionnaire, which assesses risk factors for LC and heart disease, can be completed by the patient or doctor and a recommendation for screening or otherwise is generated. Patients can then use the website to book an appointment for the scan if recommended. Once enrolled in the Allevia Heart Lung Screening programme patients will be recalled, usually annually for follow-up LC screening.

EXPERT COMMENTARY – INDRAN RAMANATHAN

The morbidity and mortality of LC and heart disease can be significantly improved with early diagnosis and treatment. Combining screening for LC and heart disease has a clear rationale as patients (often current or former smokers) may have risk factors for both LC and CAD. A single low-dose CT scan can effectively screen for LC and provide a CAC score. This is convenient for the patient, cost-effective and with lower radiation than two separate scans. Importantly, an isolated CAC score only will not image the lung apices where the majority of LCs occur. Hence, the importance of combined heart and LC screening.

TAKE-HOME MESSAGES

- LC and CAD are leading causes of mortality and morbidity.
- LC and CAD share smoking as a key risk factor and systemic inflammation as a key mechanism in their pathophysiology.
- Both disease states are amenable to early detection/quantification by LDCT scanning.
- It is well established that screening high-risk persons with LDCT reduces LC mortality.
- CAC score, as a surrogate of cardiovascular risk, can be performed on LDCT in the setting of LC screening.
- LC and CAC assessment on a single LDCT scan will allow for reduced radiation dose, greater patient convenience, and potential cost savings for the patient and/or healthcare system.

REFERENCES

1. Meijers WC, et al. Common risk factors for heart failure and cancer. Cardiovasc Res. 2019;115(5):844-53.
2. Ministry of Health. Mortality 2017 data tables (Provisional as at December 2019). Wellington: Manatū Hauora, Ministry of Health (NZ). Last update date: 18 December. Available from: https://www.health.govt.nz/publication/mortality-2017-data-tables. [Date accessed: 30/06/22].
3. Pope CA, 3rd, et al. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure-response relationships. Environ Health Perspect. 2011;119(11):1616-21.
4. Stringhini S, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1.7 million men and women. Lancet. 2017;389:1229-1237.
5. Selak, V, et al. Ethnic differences in cardiovascular risk profiles among 475,241 adults in primary care in Aotearoa, New Zealand. NZMJ 2020;133(1521):14-27.
6. Yuan M, et al. Lung Cancer and Risk of Cardiovascular Disease: A Meta-analysis of Cohort Studies. J Cardiothorac Vasc Anesth. 2018;32(1):e25-e7.
7. Yoon DW, et al. Increased risk of coronary heart disease and stroke in lung cancer survivors: A Korean nationwide study of 20,458 patients. Lung Cancer. 2019;136:115-21.
8. Mrotzek SM, et al. Assessment of coronary artery disease during hospitalization for cancer treatment. Clin Res Cardiol. 2021;110(2):200-10.
9. Amundsen T, et al. Cardiovascular disease and the risk of lung cancer, the HUNT study. European Respiratory Journal. 2013;42(Suppl 57):4636.
10. Van't Klooster CC, et al. The relation between systemic inflammation and incident cancer in patients with stable cardiovascular disease: a cohort study. Eur Heart J. 2019;40(48):3901-9.
11. Zhang J, et al. Targeting interleukin-1β and inflammation in lung cancer. Biomark Res. 2022;10(1):5.
12. Ridker PM, et al. Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet. 2017;390(10105):1833-42.
13. Ridker PM, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017;377(12):1119-31.
14. Manners D, et al. Lung cancer screening in Australia and New Zealand: the evidence and the challenge. Intern Med J. 2021;51(3):436-41.
15. Novellis P, et al. Lung cancer screening: who pays? Who receives? The European perspectives. Transl Lung Cancer Res. 2021;10(5):2395-406.
16. Waltz J, et al. The Future of Concurrent Automated Coronary Artery Calcium Scoring on Screening Low-Dose Computed Tomography. Cureus. 2020;12(6):e8574.
17. Aberle DR, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409.
18. Church TR, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med. 2013;368(21):1980-91.
19. Horeweg N, et al. Detection of lung cancer through low-dose CT screening (NELSON): a prespecified analysis of screening test performance and interval cancers. Lancet Oncol. 2014;15(12):1342-50.
20. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736-88.
21. Velangi PS, et al. Impact of 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncardiac chest CT scans on lung cancer screening CT reporting. Int J Cardiovasc Imaging. 2021;37(9):2777-2784.
22. McLeod M, et al. Impact of low-dose CT screening for lung cancer on ethnic health inequities in New Zealand: a cost-effectiveness analysis. BMJ Open. 2020;10(9):e037145.
23. Radiologists RAaNZCo. Lung Cancer Screening Position Statement, Version 1.0. 29 July 2021. Sydney NSW 2000 Australia: Royal Australian and New Zealand College of Radiologists. 2021. Available from: https://www.ranzcr.com/search/statement-from-the-royal-australian-and-new-zealand-college-of-radiologists-on-lung-cancer-screening.
24. Toh CK, et al. The impact of smoking status on the behavior and survival outcome of patients with advanced non-small cell lung cancer: a retrospective analysis. *Chest.* 2004;126:1750-1756.
25. Ravenel JG, et al. Coronary artery calcification in lung cancer screening. Transl Lung Cancer Res. 2018;7(3):361-7.
26. Liew G, et al. Cardiac Society of Australia and New Zealand Position Statement: Coronary Artery Calcium Scoring. Heart Lung Circ. 2017;26(12):1239-51.
27. Pakdaman MN, et al. Incidental coronary calcifications on routine chest CT: Clinical implications. Trends Cardiovasc Med. 2017;27(7):475-80.
28. Hughes-Austin JM, et al. Relationship of Coronary Calcium on Standard Chest CT Scans With Mortality. JACC Cardiovasc Imaging. 2016;9(2):152-9.
29. Watts JR, Jr., et al. Visual scoring of coronary artery calcification in lung cancer screening computed tomography: association with all-cause and cardiovascular mortality risk. Coron Artery Dis. 2015;26(2):157-62.
30. Garg PK, et al. Use of coronary artery calcium testing to improve coronary heart disease risk assessment in a lung cancer screening population: The Multi-Ethnic Study of Atherosclerosis (MESA). J Cardiovasc Comput Tomogr. 2018;12(6):493-9.
31. Dzaye O, et al. Coronary artery calcium is associated with long-term mortality from lung cancer: Results from the Coronary Artery Calcium Consortium. Atherosclerosis. 2021;339:48-54.
32. Jennings GL, et al. National Heart Foundation of Australia: position statement on coronary artery calcium scoring for the primary prevention of cardiovascular disease in Australia. Med J Aust. 2021;214(9):434-9.
33. Hecht HS, et al. Combined detection of coronary artery disease and lung cancer. European Heart Journal. 2014;35(40):2792-6.
34. Gaudio C, et al. Concomitant screening of coronary artery disease and lung cancer with a new ultrafast-low-dose Computed Tomography protocol: A pilot randomised trial. Sci Rep. 2019;9(1):13872.
35. Chamberlin J, et al. Automated detection of lung nodules and coronary artery calcium using artificial intelligence on low-dose CT scans for lung cancer screening: accuracy and prognostic value. BMC Med. 2021;19(1):55.

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