Cancer Australia Lung Cancer Screening Enquiry
Response from Thoracic Society of Australia and New Zealand

Context of lung cancer in Australia

Lung cancer remains the leading cause of cancer mortality in Australia, accounting for 18% of cancer deaths in 2019.(1) Prognosis remains poor with a five-year survival of 17%. This is largely due to diagnosis often occurring in advanced stage of disease. Targeted screening of at-risk populations seeks to identify patients with early stage disease which is more likely to be amenable to curative treatment.

International evidence and national evidence for benefits and harms of lung cancer screening

Benefits

Over the last decade, several randomised controlled trials have been performed to examine population-based lung cancer screening. In 2011, the landmark National Lung Screening Trial (NLST) was published.(2) In this multicentre study, over 53,000 individuals between the ages of 55 and 75 years, with a current 30 pack year smoking history or smoking cessation period less than 15 years, were recruited. Participants received three annual rounds of screening either with low-dose CT or standard chest radiography. The study found a 20% reduction in lung cancer specific mortality in the low-dose CT group. Subsequent to these findings, the United States Preventative Services Task Force (USPSTF) released a recommendation of targeted annual screening for lung cancer using low-dose CT.(3)

More recently, the findings of the largest European randomised controlled trial, the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) were released.(4) This study included over 15,000 participants, aged between 55 and 74 years, with 15 pack year current or less than 10 years cessation smoking history. Participants were randomised to receive low-dose CT or no screening at year 1, 2, 4, and 6.5. After ten years of follow up, 26% and 39% reductions in lung cancer associated deaths in males and females respectively, compared with the non-screening group, were demonstrated.

Furthermore, a systematic review and meta-analysis of randomised controlled trials published until June 2019, confirmed that low-dose CT screening is superior to usual care in lung cancer survival.(5) The magnitude of benefit of screening is, however, heavily dependent upon the risk profile of the target group.

The applicability of such findings to the Australian setting is awaiting the results of the International Lung Screen Trial (ILST). This multicentre prospective cohort study with

recruitment sites in Australia, Canada and Hong Kong, looks to build upon preceding trials by utilising the PLCOm2012 risk prediction model or USPSTF criteria for eligibility.(6)

Harms

Three chief concerns of low dose CT screening for lung cancer are false-positive findings, overdiagnosis, and risk of radiation exposure. False-positive tests are one of the primary potential harms of any screening modality, along with the resultant diagnostic work-up and any complications thereof. In the NLST, the false-positive rate for low dose CT was approximately 27% in each of the first two rounds, decreasing to 16.8% in the third round.(2) While the majority of false-positive findings were followed with imaging modalities, 0.6% of all low-dose CT screens had an invasive diagnostic procedure and 0.06% had a complication arising from an invasive procedure.

Overdiagnosis describes the detection of a cancer through screening which would never have become symptomatic or been discovered otherwise, and may have consequences of provoking anxiety and potential for complications of unnecessary treatment. Utilising NLST data and a natural lifetime history model, Patz et al. estimated this rate to be 11%. (7)

Radiation exposure from annual screening CT examinations is sometimes raised as a reason to minimise screening. Radiation risk from low-dose CT screening is generally extrapolated from models of lower radiation doses. Based on the assumptions of an average estimated effective radiation dose of 1.5 mSv and annual screening, Frank et al. estimated an excess risk of 0.07% for males and 0.14% for females. (8) In context, Rampinelli *et al,* estimated that radiation from 10 years of screening would induce one major cancer yet detect 108 screen-detected lung cancers. (9)

Cost-effectiveness of targeted lung cancer screening in Australia

Cost-effectiveness analyses often quote cost per quality-adjusted life-year (QALY), in which the QALY attempts to incorporate quality of life effects as well as longevity. Villanti *et al*. estimated cost per QALY in a cohort of high-risk subjects (≥30 pack-years) aged 50 to 64 years undergoing annual screening for 15 years.(10) Their base-case analysis yielded a cost-utility ratio of US$28,000 per QALY. This is in contrast to US$8,552 per QALY for colonoscopy and US$53,000 per QALY for biennial mammography. The study concluded that the cost-effectiveness of lung cancer screening was in line with other accepted cancer screening interventions and supported inclusion of annual low-dose CT screening for lung cancer in a high-risk population in clinical recommendations.

Australian cost-effectiveness studies have been contradictory. Prior to NLST results, Manser *et al.* estimated that lung cancer screening in Australia could be cost-effective

under ideal conditions.(11) Wade *et al.* used NLST data with Australian cost and survival data to estimate the cost per QALY-gained to be AU$233 000.(12) The large difference between this estimate and the formal NLST cost-effectiveness analysis (US$81 000) may be due to inclusion of all-cause mortality benefit and using a lifetime horizon. (13)

However, it must be acknowledged that cost-effectiveness estimates often vary widely, due to not only the underlying studies that quantify the various benefits and harms, but also due to variability in cost estimates, differences in what types of costs are included (e.g., lost productivity) and the choice of perspective (provider/patient vs societal). In addition, intangible effects, such as anxiety, are difficult to apply to numerical cost estimates.

Target population

The target population is individuals at the highest risk of developing lung cancer. Current U.S. and Canadian eligibility criteria is based on age (55 to 75/80 years) and smoking history (>30 pack years and, for former smokers, <15 years since quitting). Multivariate logistic risk prediction models, particularly the $PLCO_{m2012}$ model at a threshold of >1.5% six-year lung cancer risk, are more sensitive at detecting those with lung cancer than current screening eligibility criteria.(14) The PLCOm2012 model and >1.5% suggested eligibility threshold has been externally validated in a large Australian population again with improved sensitivity (69.4% vs 57.3%) but reduced specificity (72.0% vs 75.2%) compared to current U.S. criteria. (15) Therefore, we suggest that the target population should be individuals with $PLCO_{m2012}$ > 1.5%.

Recruitment

Identification and recruitment of eligible Australians is challenging and has been discussed elsewhere.(16) Existing population-based mass screening interventions (for example breast cancer screening with mammography or bowel cancer screening with Faecal Occult Blood Testing [FOBT]) systematically and repeatedly invite all eligible individuals via direct contact from the respective programs using principles based on the Population Based Screening Framework.(17) Eligible individuals are identified from administrative datasets based on their age and sex only. Currently, there are no administrative datasets that routinely collect variables required for lung cancer screening eligibility assessment such as smoking history. Therefore, if population-based recruitment for lung cancer screening were to be implemented, a two-step process would be required. Individuals in the age-defined cohort would be approached to consider screening and complete a self-reported $PLCO_{m2012}$ risk assessment. Those who meet eligibility criteria could then progress to screening. This approach is inefficient as only 10-14.5% of 55-74 years olds meet eligibility criteria.(15, 18)

An alternative approach would be for General Practitioners to identify appropriate high-risk individuals and refer those for screening, similar to existing targeted screening initiatives such as breast MRI for breast cancer screening in high-risk woman and colonoscopy for those with strong family history of bowel cancer. Potential benefits include leveraging strong patient-GP relationships to encourage screening and being able to incorporate lung cancer screening into other existing targeted screening initiatives. Such an approach will require appropriate remuneration for primary care to provide this service and may be limited by over-screening performed by general practitioners.(19)

Ensuring consistency with eligibility criteria

Lung cancer screening with LDCT only reduces lung cancer specific mortality in those with the highest lung cancer risk, which is limited to approximately 10% of the age-defined population.(20) There is no available evidence that screening lower risk individuals, including passive and never smokers, reduces lung cancer mortality. Individuals however may seek screening for other purposes, including to gain reassurance or peace-of-mind that they are cancer free. Between 72%-95% of Australian ever-smokers have a preference for undergoing screening yet preference is associated with worry about and perceived seriousness of lung cancer but not associated with eligibility status.(21, 22) Screening of lower-risk individuals has increased in the U.S. after lung cancer screening implementation.(23) Limiting ad-hoc screening through primary care for those who do not meet eligibility criteria will be critical to maximising overall benefits while minimizing harms and costs.

Role of general practice

General practice will have a critical role in the success of any screening initiative. Specific roles may include recruiting high-risk individuals to undergo screening, counselling concerned yet ineligible lower-risk individuals against seeking screening, managing screening detected abnormalities including incidental findings, providing smoking cessation interventions and support long term cancer survivorship in those with screen-detected malignancy.(24) Educational and financial support to primary care to provide these services will be required. Currently, Australian GPs generally over-recommend lung cancer screening and are performing lung cancer screening with both LDCT and CXR against recommendations, associated in part with education from radiology providers and cognitive factors such as seeking reassurance that their patient does not have cancer.(25-27)

Access to specialist services for management of screen-detected abnormalities

Implementation of lung cancer screening will necessitate adequate provision of specialist services to diagnose, stage and treat more early-stage screen-detected lung cancers. In a large Victorian cohort of lung cancer patients, only 50% underwent

surgery within the current recommended timeliness target of 42 days (as set by the Optimal Care Pathways).(28, 29) Increased caseload on specialist interventional radiology and thoracic surgical services is likely and capacity for this demand requires pre-implementation evaluation. Equitable access to screening and downstream management for vulnerable populations including regional/remote areas, Aboriginal and Torres Straight Islanders and people from non-English speaking backgrounds is required.

Consumer communication throughout the screening process

Patient communication and counselling will be critical across all phases of the screening process. As mentioned earlier, reassuring screening-ineligible individuals against screening will be critical to restricting screening to high risk individuals. For screening-eligible individuals, the decision to undergo screening should ideally be an informed and shared decision made with a full understanding of potential benefits and harms. Funding for screening in the U.S. has mandated the use of a patient decision aid (PtDA) as part of a shared-decision making process for screening.(30) The real-world effectiveness of patient-decision aids is unclear as risks of screening are often understated and screening preference has not been shown to correlate with screening uptake.(31, 32) An Australian-developed lung cancer screening patient information tool, including PtDA, may reduce screening preference for lower-risk individuals and reduce decisional conflict among screening-eligible individuals.(33)

False-positive findings, usually benign pulmonary nodules, are common and can cause adverse psychological effects including anxiety, stress and worry.(34) While these psychological effects are usually limited to less than 12 months duration, the associated disutility has a major impact on the incremental quality-adjusted cost-effectiveness of screening. (12, 35) This is balanced by an improvement in psychosocial factors in screened individuals compared to controls who were not screening suggesting a psychological benefit from reassurance provided by screening.(36) Adequate pre- and post-test counselling on the significance of pulmonary nodules detected by screening may minimise the associated negative psychological effects and improve overall cost-effectiveness, yet informed decision making did not impact on health-related quality of life measures in the NELSON trial. (37) Patient information tools provided to screening participants, ideally tailored to nodule malignancy risk, need to be developed and tested prior to widespread screening implementation.

Conclusions and Recommendations

- The Lung Cancer Special Interest Group of TSANZ strongly supports the establishment of a large, government-funded, lung cancer screening pilot, similar to previous pilot studies that preceded mammography and FOBT screening implementation.(38, 39)

- International evidence of the efficacy of LDCT lung cancer screening of high-risk individuals at reducing lung cancer mortality is sufficient to for the practice to be recommended.
- Recruitment needs to target individuals with a $PLCO_{m2012}$ risk of >1.5%, but various recruitment methods needs critical evaluation.
- We support a coordinated program that adapts population-based screening principles with strong governance, rather than an uncoordinated approach.
- Critical implementation issues relate to recruitment, limiting screening to high-risk individuals, engagement with primary care, consumer information throughout the screening process and resourcing specialist services for timely management of screen-detected cancers. These issues need to be specifically evaluated in the proposed pilot.
- Cost-effectiveness and affordability of screening needs to be formally assessed as part of the pilot.

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