

# A practical and adaptive approach to lung cancer screening: a review of international evidence and position on CT lung cancer screening in the Singaporean population by the College of Radiologists Singapore

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**ABSTRACT** Lung cancer is the leading cause of cancer-related death around the world, being the top cause of cancer-related deaths among men and the second most common cause of cancer-related deaths among women in Singapore. Currently, no screening programme for lung cancer exists in Singapore. Since there is mounting evidence indicating a different epidemiology of lung cancer in Asian countries, including Singapore, compared to the rest of the world, a unique and adaptive approach must be taken for a screening programme to be successful at reducing mortality while maintaining cost-effectiveness and a favourable risk-benefit ratio. This review article promotes the use of low-dose computed tomography of the chest and explores the radiological challenges and future directions.

*Keywords:* computed tomography, lung cancer, position paper, public health, screening

## INTRODUCTION

Lung cancer is the leading cause of cancer-related death among men and women worldwide. In 2012 alone, an estimated 1.59 million deaths were caused by lung cancer globally.<sup>(1)</sup> In Singapore, it causes the most cancer-related deaths among men and the second most cancer deaths (after breast cancer) among women. In 2010–2014, lung cancer killed almost as many women as breast cancer, with 1,912 (16.4%) deaths compared to 2,051 (17.6%) from breast cancer.<sup>(2)</sup>

Although the incidence rate of lung cancer among Singaporeans has decreased since the late 1970s, where rates among men were 61.2 per 100,000 per year to 33.7 per 100,000 per year between 2010 and 2014, it remains the second most common cancer in men and the third most common cancer in women. This drop in lung cancer rates in men is likely attributable in part to the reduced prevalence of cigarette smoking. In contrast, the incidence rate of lung cancer in women has remained relatively stable since the 1970s, at 13.9 per 100,000 per year to 11.4 per year in 2010–2014.<sup>(2)</sup>

The importance of screening is highlighted by the fact that 75% of patients with lung cancer present with symptoms due to advanced disease that is not amenable to cure.<sup>(3)</sup> Despite advances in therapy, five-year survival rates remain dismal at an average of 18% for lung cancer patients.<sup>(3,4)</sup>

Since many lung cancer cases are attributed to smoking, it is crucial to implement a national smoking cessation programme in conjunction with screening. Based on United States (US) data, tobacco smoking is thought to be causal in 85%–90% of all lung cancers.<sup>(5)</sup> It is thought that worldwide progress in smoking cessation is now reflected in declining lung cancer rates and mortality in men worldwide. A robust combined screening and smoking cessation programme would enable the lung screening programme to gain in mortality reduction from all causes of death related to smoking, as well as capitalise on improved cost-effectiveness due to reductions in the indirect cost of tobacco smoking in overall healthcare spending. The impact of smoking on direct and indirect costs to healthcare spending in Singapore is not insignificant and is estimated to be around SGD 839 million, based on 2002 data.<sup>(6)</sup>

## INTERNATIONAL LUNG SCREENING GUIDELINES AND TRIALS

Results from the largest US lung screening trial to date, the US National Lung Screening Trial (NLST) demonstrated a relative reduction in mortality from lung cancer with low-dose computed tomography (LDCT) screening of 20%.<sup>(7-12)</sup> The rate of death from any cause was reduced by 6.7% in the LDCT group.

The recommendations for this position paper are based, in part, on guidelines by the US Preventive Services Task Force

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(USPSTF), which were published in 2014 and largely informed by the results of the NLST. The USPSTF recommendations support LDCT lung cancer screening for healthy adults aged 55–80 years with a smoking history of 30 pack-years or more and who have smoked within the previous 15 years.<sup>(13,14)</sup> The total duration of screening was not specified, but screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits their life expectancy or the ability to have curative lung surgery (Grade B recommendation).

In practical terms, under the US Affordable Care Act, any procedure that receives a Grade B recommendation from the USPSTF is covered by private insurers without requiring copayment. In 2015, the US federal agency Centers for Medicare and Medicaid Services (CMS) announced its decision to start covering lung cancer screening once per year under the Medicare programme for long-time smokers at high risk for the disease. During the initial screening, the beneficiary must produce a written order for LDCT lung cancer screening obtained during a lung cancer screening counselling session from a physician, physician assistant, nurse practitioner or clinical nurse specialist. The CMS also specifies radiologist and imaging centre eligibility criteria.

In Europe, there are no reimbursed screening programmes to date, but several large randomised controlled trials have emerged from European countries, such as the Dutch-Belgian NELSON trial, DLST from Denmark and Italung, DANTE and MILD from Italy.<sup>(15–19)</sup> The European Society of Radiology (ESR) and the European Respiratory Society (ERS) published an ESR/ERS white paper in 2015 on lung cancer screening that concluded that lung cancer screening using LDCT reduces mortality and recommended lung cancer screening within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres.<sup>(20)</sup>

Data is also available from two trials conducted in Japan. The Japanese studies notably included both smokers and non-smokers in their screening cohort<sup>(21,22)</sup> as part of community-based screening programmes. The screening programme at Hitachi Medical Center began in 2001 and screened 31,739 participants with chest computed tomography (CT) scans at least once. By 2009, an estimated 36% of Hitachi residents ages 50–79 had undergone CT screening. For men and women ages 50–79, lung cancer mortality fell by 24%.<sup>(23)</sup>

The Japanese approach to screening non-smokers and smokers alike was successful in demonstrating that its model may reduce lung cancer deaths among non-smokers, considering that more than half of the study participants were non-smokers and 60% of screen-detected cancers were found in non-smokers. The group surmised that an observed reduction in lung cancer mortality among Hitachi residents was due, at least in part, to the effect of CT screening on lung cancer mortality among non-smokers. The selection criteria for selected populations in recent trials of lung screening with LDCT are summarised in Table I.

## CHALLENGES

### Fundamental differences in lung cancer epidemiology between Singapore and Western populations

Recent data has emerged from Asia-Pacific countries, and from Singapore in particular, that demonstrates an alarming disparity in lung cancer patterns compared to Western countries. A strikingly high proportion of lung cancer was detected among never-smokers (47.7% from local data in 2011), compared to data from Western countries, where the proportion of lung cancer among never-smokers was much lower at 10%–15%.<sup>(24)</sup>

Another large discrepancy is the greater incidence of adenocarcinoma (77.6% from local data in 2011) in the local population compared to rates of adenocarcinoma in the US (38.5%) and other Western countries.<sup>(25,26)</sup> This reflects the Asia-Pacific trend of higher rates of adenocarcinoma, particularly in women.<sup>(27–32)</sup> Although local data trends are still currently being studied, there may be evidence of a fundamental difference in genetic predisposition among Chinese non-smokers, in addition to the effects of exposure to environmental risk factors.<sup>(5,27–52)</sup> The link between adenocarcinoma of the lung and never-smoker status is also likely to play a role, based on the observation that adenocarcinoma is more common in never-smokers.<sup>(33–35,38,39,41,44)</sup>

### False positives and complications during workup

The NLST defined any non-calcified nodule with a maximum diameter  $\geq 4$  mm as a positive screening result, which subsequently led to a large number of false-positive scans. A total of 27% of scans in the first two screening rounds were positive.<sup>(7)</sup> The NELSON and some other European trials used a much higher threshold of approximately 10 mm in diameter (50 mm<sup>3</sup> volume) for a positive screening result, but also established an indeterminate group of nodules measuring 5–10 mm in diameter (50–500 mm<sup>3</sup> volume) that required earlier follow-up than the yearly screening interval. These nodules were considered a positive screening result only if significant growth ( $> 25\%$  volume change) was found.<sup>(15,19)</sup> By using this approach, the number of scans with positive screening results was reduced from 27% in the NLST to 2.7% in the NELSON study.

The invasive diagnostic workup of small nodules includes bronchoscopy, which is limited by the location of the nodule. For some peripheral nodules ( $> 1$  cm), transthoracic CT-guided biopsy or resection by video-assisted thoracoscopic surgery is recommended. The risk of serious complications such as pneumothorax requiring drainage, infection or haemorrhage depends on the patient's underlying functional status and varies according to the centre.

### Overdiagnosis of lung cancer

Overdiagnosis may be defined as detection of small lesions that are confirmed to be malignant but do not grow, spread or cause death. It includes individuals who die from other causes apart from lung cancer. This may cause harm during screening, in the form of additional cost, anxiety and morbidity associated with cancer diagnosis and treatment.

**Table 1. Summary of selection criteria, follow-up duration and number of enrolled individuals of several major trials.**

Study	Selection criteria		No. of patients screened; follow-up duration
	Age (yr)	Tobacco smoking; delay since weaning	
DLCST	50–70	≥ 20 pack-yr; 0–9 yr	2,052; 58 mth
DANTE	60–74 (only men)	≥ 20 pack-yr; 0–9 yr	1,276; 34 mth
ITALUNG	55–69	≥ 20 pack-yr (active/former)	1,406; 36 mth
MILD	≥ 49	≥ 20 pack-yr; 0–9 yr	1,190 annual CT; 120 mth 1,186 biannual CT; 53 mth
NELSON	50–75	≥ 15 pack-yr <sup>‡</sup> ; 0–9 yr	7,907; 60 mth
NLST	55–74	≥ 30 pack-yr; 0–15 yr	26,722; 78 mth
UKLS	50–75	A 5-yr lung cancer risk of ≥ 5%, based on the Liverpool lung project v2 risk prediction model	4,055; 12 mth
HITACHI*	50–69	Smokers and never-smokers	31,739; 14 yr
TAO <sup>†</sup>	40–74	Smokers and never-smokers	5,483; 36 mth

\*Hitachi, Ibaraki, Japan. †Telecommunications Advancement Organization (TAO) of Japan, Matsumoto Research Centre. ‡NELSON inclusion criteria: number of cigarettes smoked is ≥ 15 per day for 25 years OR ≥ 10 cigarettes per day for 30 years AND still smoking or having quit < 10 years ago.

Currently, LDCT screening overdiagnosis rates are not available. The NLST data showed that the percentage of Stages IA and IB lung cancers detected by screening was high, which leads to the assumption that overdiagnosis may be a potential harm. However, mortality rates from lung cancer suggest that all histological foci of lung cancer pose a threat to health, regardless of their CT phenotype or how they are discovered.

### Radiation

Current LDCT protocols enable scans to be performed at an effective dose of 1.0–1.7 mSv, based on local data. This translates to an approximate excess lifetime cancer risk that is estimated to be 0.02% in male smokers and 0.05% in female smokers at three yearly screening rounds.<sup>(20)</sup> The risks did not increase whether the starting age for screening was 30, 40 or 50 years, suggesting that radiation risk becomes important only if the pre-test risk for lung cancer is small. Since the baseline cancer risk is 0.8%–2.2% in the various screening trials, the risk-benefit ratio is in favour of screening over no screening.<sup>(20)</sup>

### Cost-effectiveness

Data from the NLST demonstrated that lung screening in the US could be cost-effective, showing that screening for lung cancer, compared with no screening, is estimated to cost about USD 81,000 per quality-adjusted life-year (QALY) gained.<sup>(53)</sup> Although no upper limit threshold for cost-effectiveness has been firmly established within the US, leading health economists have recommended a threshold between USD 100,000 and USD 150,000 per QALY gained.

A study from Japan<sup>(22)</sup> demonstrated cost-effectiveness in a community-based lung cancer screening programme, with estimated costs of approximately USD 2,290 for women and USD 728 for men, respectively, to save one person-year in the 55–59 year-old cohort. The same study also calculated the cost of CT screening per person to be USD 50 (5,000 Japanese Yen).

## RECOMMENDED INCLUSION AND EXCLUSION CRITERIA FOR SINGAPORE LUNG CANCER SCREENING WITH CT

Based on the aforementioned data from international and regional studies, we propose the following inclusion and exclusion criteria.

For high-risk groups, the inclusion criteria are: aged between 55 and 75 years, tobacco smoking history of at least 30 pack-years, and current smoker or ex-smoker who quit smoking within the last 15 years. Once evidence is more robust, possible additional inclusion criteria are any of the following risk factors in never-smokers aged between 50 and 75 years: (a) never-smoker, female, east Asian (NESFEAS) phenotype; (b) family history of lung cancer; and (c) history of exposure to known carcinogens and air pollution.

Suggested exclusion criteria are comorbidities precluding therapy for further investigation and cure, and lack of consent for the same.

## SUGGESTIONS AND SOLUTIONS

### Multidisciplinary teams

Multidisciplinary expertise is essential; accredited screening programmes would have access to a set of professionals, including radiologists, respiratory physicians, oncologists, pathologists and cardiothoracic surgeons.

### Combined smoking cessation programme

A mandatory and concurrent smoking cessation programme would give access to trained staff who would provide effective smoking cessation advice and treatment, enabling the screening programme to reap the full benefits of further mortality reduction from all causes related to smoking as well as cost-effectiveness savings from tobacco abstinence. The overall impact of smoking on direct and indirect costs to healthcare spending in Singapore is estimated to be SGD 839 million, from the 2002 study mentioned earlier.<sup>(6)</sup>

### Risk model and broad screening

Pre-test probability can be increased by using a risk model and considering additional risk factors, particularly the NESFEAS phenotype. This guideline proposes a unique approach that adopts additional inclusion criteria over previous guidelines, acknowledging evidence from Asian data that supports a fundamental difference in risk profile within the local population. It also considers data from Japanese LDCT screening studies that demonstrates the cost-effectiveness and mortality reduction of general screening of the population above a certain age (40 years and 50 years in two different studies), regardless of smoking history.<sup>(21,22)</sup>

The incidence of lung cancer in Japan is similar to that of Singapore, with an age-standardised incidence rate per 100,000 of 35.7 and 15.5 for male and female Singaporeans, and 38.8 and 12.9 for male and female Japanese, respectively, implying that it is a healthcare concern of similar importance.<sup>(4,5,45,46,54-56)</sup> Notably, the gross domestic product per capita of Singapore exceeds that of Japan (Singapore 87,855 vs. Japan 41,275 international dollars).

### Standard workflow model

Image acquisition, nodule evaluation, management of positive screen results, monitoring of false-positive results and procedural complications should be formalised into a standard operating procedure to ensure consistency and rigour in the application of guidelines. A dedicated workflow is required to provide seamless patient care from initial screen to biopsy and smoking cessation counselling.

### Computer-aided detection and deep learning algorithms

Nodule evaluation and follow-up by computer-aided detection (CAD) and deep-learning algorithms are foreseen to become major components of any successful lung cancer screening programme in the future.<sup>(57-70)</sup> A major benefit of using deep-learning algorithms is the reduction in reliance on human labour, thereby increasing cost-effectiveness. There are already studies showing that commercial CAD systems have excellent sensitivity for the detection of lung cancer nodules of at least 11 mm in size (sensitivity > 95.4%).<sup>(68)</sup>

Although the Japanese, European and North American lung screening trials all demonstrated cost-effectiveness in their data, we propose that increased cost-effectiveness can be achieved with utilisation of deep-learning computer software. Software for automated detection of nodules is already available in the market, but further enhancement is required to automate decision-making for first-round screen-detected nodules, follow-up intervals for subsequent rounds and discharge from screening. Sensitivity and false positive rates have been shown to be improved by employing massive-training artificial neural networks, which are a form of deep-learning system.<sup>(63)</sup> A human operator (i.e. radiologist) would only need to intervene once a nodule was flagged by the computer algorithm as suspicious, either due to the baseline size and appearance of the nodule during the first-round scan or a size/volume increase during the second-round scan. This significantly reduces the number of manpower hours expended and cost per screen.

### Radiation dose reduction

Radiation burden reduction can be achieved by performing all screen studies with multidetector LDCT using at least 64 detector rows and isotropic high spatial resolution with a slice thickness of 1 mm, achieving effective doses of 1–3 mSv.

Further dose reductions are now possible with improvements in CT technology. Using iterative reconstruction techniques and automated exposure control, radiation exposure can be substantially reduced by up to 80%, to a level of 0.2 mSv per study.<sup>(71-77)</sup> This form of ultra-LDCT (ULDCT) with very low radiation doses is limited by poorer image quality in patients with high body mass index and poor assessment of ground glass nodules.<sup>(77)</sup> Nonetheless, early studies have shown that there is no significant reduction in nodule detectability with ULDCT compared to usual LDCT.<sup>(73)</sup>

### Screening registry

A national lung cancer screening registry should be established to collect submitted data from individual centres. This includes a biobank of pathological results and tumour markers, and a radiological image bank. The data would be used for longitudinal studies over a five- to ten-year period. Further studies of local data are required to examine the differences in cancer epidemiology and tumour receptor mutations among the local population of lung cancer patients compared to those from non-Asian countries.

### Future developments in biomarker screening

Future developments in biomarker screening for lung cancer should be actively pursued and adopted into guidelines as soon as they become practically available. These include lung cancer biomarkers detected via breathalyser analysis, blood tests and urinalysis.

### Cost-benefit analysis

Finally, a local cost-benefit analysis should be conducted in Singapore to evaluate the costs to implement this screening programme, both with and without deep-learning automation. This cost-benefit analysis would help institutions estimate the value and economic advantages of developing deep learning screening programmes for lung cancer.

## CONCLUSION

The difference in patterns of lung cancer epidemiology between the local Singaporean population and European and North American cohorts necessitates an adaptive approach to lung cancer screening in Singapore. One particular group that has been identified to be at high risk in the local population is NESFEAS individuals.

This position paper proposes a practical, current and unique evidence-based approach to lung cancer screening to ensure a better fit for the local disease pattern. Multidisciplinary expertise is essential, and accredited screening programmes would have access to professionals including radiologists, respiratory physicians, oncologists, pathologists, nurse specialists and cardiothoracic surgeons. A dedicated workflow to provide

seamless patient care from initial screen to biopsy and smoking cessation counselling would be required. After adoption of these guidelines, a comprehensive national lung cancer screening registry should be incorporated into the programme to monitor disease trends and provide robust evidence on efficacy.

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