Screening for lung cancer in high-risk non-smokers: A step too far or time to address an unmet need?

Anand Sachithanandan, FRCSI(C-Th), FACS[1,2,3]

[1]Division of Cardiothoracic Surgery, Sunway Medical Centre, Selangor, Malaysia, [2]Division of Cardiothoracic Surgery, Subang Jaya Medical Centre, Selangor, Malaysia, [3]Lung Cancer Network Malaysia

Globally, two million new cases of lung cancer are diagnosed annually with approximately 1.8 million deaths each year. Over 60% of all cases and mortality occurs in Asia with a preponderance of non-small cell lung cancer (NSCLC), predominantly adenocarcinoma. In Malaysia, lung cancer is the second most common male cancer, marginally surpassed by colorectal malignancy with an age-standardised incidence rate (ASR) of 13.2 per 100,000 of the population and accounts for 15% of all cancers in men. It is the leading cause of cancer-related mortality. In women, it is the fourth most common cancer (ASR of 5.9 per 100,000) but only breast cancer is more fatal.[1] In Malaysia overall 5-year relative survival for lung cancer across all stages is only 11%, largely driven by late stage diagnosis in the vast majority of victims with almost 95% of cases detected in stage III or IV.[1,2] The treatment and prognosis for NSCLC is very stage dependant. Early stage NSCLC has a 5-year survival of 70-90%. In contrast, survival for advanced or late stage disease is approximately 5-10%.[3] Despite tremendous recent advances in the treatment landscape for NSCLC including bespoke oral-targeted therapies (tyrosine kinase inhibitors) for tumours with actionable driver mutations (e.g. epidermal growth factor receptor, EGFR), the emergence of antibody drug conjugates and systemic immunotherapies with potentially game-changing pathological tumour regression in patients with a high PDL-1 expression, locally advanced (stage III) and metastatic (stage IV) NSCLC presently, remains incurable.

Detection of early-stage lung cancer remains elusive and challenging as many are asymptomatic or have mild non-specific symptoms. Several landmark randomised trials[4,5] have demonstrated unequivocal benefit of low-dose computed tomography (LDCT) screening in terms of a risk reduction in lung cancer-specific mortality, largely driven by impactful stage shift with detection of more early-stage tumours, which can be treated with a curative intent and more cost-effectively. These trials however have understandably focused on high-risk groups defined by a significant tobacco history.

The demographics and tumour biology of lung cancer in Asia is different from the West with an alarming rise in the incidence of lung cancer amongst non or never smokers, mainly women. The smoking prevalence in Malaysian adults is approximately 43% and <2% for men and women respectively, but the use of e-cigarettes and vapes amongst adolescents is on the rise.[6,7] The long-term health implications of the latter remain unknown. Over 90% of male lung cancer victims here have a smoking history. Conversely, at least 60% of Malaysian women diagnosed with lung cancer are never smokers.[8] Put simply, lung cancer is no longer a male smokers disease. It has been suggested that women may be more susceptible to cigarette smoke or air pollution, perhaps due to hormonal differences including differing immune response but compelling data to support this is lacking. Exposure to second-hand smoke, air pollution including the annual transboundary haze, indoor high temperature wok-frying, chronic lung diseases like chronic obstructive pulmonary disease (COPD) and pulmonary infections including tuberculosis and possibly even COVID-19, may all increase the risk of a future lung cancer in the non-smoker. Chronic cumulative exposure to pollutants (PM 2.5) is thought to trigger an interleukin-mediated inflammatory process at a cellular level that 'activates' pre-existing dormant cancer-causing genes (e.g., EGFR) in genetically susceptible individuals.[9] EGFR is a glycoprotein involved in cell proliferation and apoptosis. The prevalence of EGFR mutations in NSCLC in Asia (40-55%) is considerably higher than in the West (15-25%).[8] This genetic predisposition is supported by data from Taiwan which demonstrated that a family history of lung cancer is a significant risk factor in never smokers. The risk is incremental, as the more first-degree relatives one has with lung cancer, the higher the risk. The TALENT study confirmed the effectiveness of LDCT screening in a pre-defined, never-smoker high-risk population with an impressive early lung cancer detection rate of 2.6%, superior to both the NLST (1.1%) and NELSON (0.9%) data.[10] A rigid adherence to existing Western derived screening criteria of high risk populations based on a tobacco history only, will be erroneous as it excludes a sizeable subgroup of at-risk non-smokers, mainly Asian females with a family history of the disease.

Despite being a dominant cancer with a high burden of late stage presentation and the leading cause of cancer-related mortality here, Malaysia does not have a national lung cancer screening programme, yet.[11] Currently, screening is opportunistic and conducted ad hoc, mostly in the private sector. Barriers to screening for lung cancer include poor awareness, fear of a cancer diagnosis, stigma, traditional cultural beliefs including fatalism, overdiagnosis, concerns of radiation exposure and financial cost due to low insurance penetration and lack of reimbursement. A previous privately funded pilot screening project (PEARL study) initiated by lung specialists here utilising LDCT was terminated prematurely

This article was accepted:
Corresponding Author: Dr Anand Sachithanandan
Email: anandsachithanandan@yahoo.com

due to poor enrolment due to a combination of poor awareness and reticence of smokers to be screened.[12] More recently, Lung Cancer Network Malaysia (LCNM) pioneered a community-level screening project with deep learning artificial intelligence (AI) algorithm enabled-chest radiography (CXR) imaging of over 10,000 individuals which demonstrated a diagnostic rate of approximately 2.5 % for detection of an indeterminate pulmonary nodule which may represent possible early stage NSCLC.[13] However, despite provision of free scans and patient navigators to guide individuals with suspicious CXRs through the screening process, uptake for the subsequent definitive LDCT was similarly poor, perhaps in part due to the fact that much of the screening was done during the COVID pandemic.

The alarming rise in lung cancer in non-smokers mandates serious consideration for screening of high risk non-smokers. This should be based primarily but not exclusively, on a family history of the disease, as second-hand smoke exposure including air pollution is difficult to quantify accurately. Women, who make up the majority of non-smokers with lung cancer, tend to have better health seeking behaviour and hopefully this will translate into better screening uptake. Screening with a CXR initially may be more palatable and affordable as a prelude to an interrogative LDCT in individuals with an abnormal or equivocal CXR, surmounting historical barriers of cost, accessibility and low specificity (false positives), from upfront LDCT imaging. It is possible future screening initiatives could be further refined with incorporation of biomarkers like plasma circulating tumour DNA or exhaled breath (volatile organic compound) analysis. The National Cancer Institute (IKN) has recently launched a similar AI-CXR lung cancer screening project as part of a broader lung health check.[14] It is a step in the right direction to 'widen the net' for early and widespread screening to facilitate effective lung cancer control in our country. The IKN project is similar to LCNM's pilot initiative (in 2020-2022) which demonstrated adoption of such AI technology to be user friendly, affordable and scalable. A similar initiative is currently underway at several NHS hospitals in the United Kingdom.[15] AI-enabled chest radiography has superior diagnostic accuracy for detection of malignant nodules, over trained radiologists.[16]

Poor uptake for lung cancer screening is a global phenomenon not unique to Malaysia. Public educational awareness campaigns coupled with appropriate sustained funding for subsidised or free screenings, ideally on a single visit at a one-stop tertiary centre can help remedy this. A hybrid sequential strategy of AI-CXR to identify and funnel the right individuals for complementary LDCT imaging may be pragmatic and transformative in large-scale timely detection of early-stage lung cancer. Screening-enabled stage shift will allow for more cost-effective therapies and save many more lives. We must acknowledge the changing face of lung cancer here with a rising number of cases in never smokers and the importance of a significant family history for the disease. Failure to embrace and utilise innovative technology with broader screening criteria is a significant missed opportunity for Malaysia that will result in more preventable deaths from lung cancer due to continued late-stage diagnosis.

REFERENCES

1. Malaysia National Cancer Registry Report 2012-2016, MOH/P/IKN/05.19(AR)
2. Malaysian Study On Cancer Survival (MySCAN), 2018. http://nci.moh.gov.my//index.php/ms/main-menu-2/laporan
3. Goldstraw P, Chanksy K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WEE, et al. The IASLC Lung cancer Staging project: Proposals for revision of the TNM stage groupings in the forthcoming (Eight) Edition of the TNM Classification for Lung cancer. J Thorac Oncol 2015; 11: 39-51.
4. The National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395-409.
5. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med 2020; 382: 503-513.
6. Institute for Public Health (IPH) 2015. National Health and Morbidity Survey 2015 -Report on Smoking Status Among Malaysian Adults.
7. Institute for Public Health (IPH) 2022. Technical Report National Health and Morbidity Survey (NHMS) 2022: Adolescent Health Survey, Malaysia.
8. Lam DC, Liam CK, Andarini S, Park S, Tan DSW, Singh N, et al. Lung cancer screening in Asia: an expert consensus report. J Thorac Oncol 2023; 18(10): 1303-22.
9. Hill W, Lim EL, Weeden, CE, Lee C, Augustine M, Chen K, et al. Lung adenocarcinoma promotion by air pollutants. Nature 2023; 616: 159-67.
10. Yang P. PS01.02 National Lung Cancer Screening Program in Taiwan: the Talent study. J Thorac Oncol 2021; 16: S58.
11. Sachithanandan A, Badmanaban B. Screening for lung cancer in Malaysia: are we there yet? Med J Malaysia Vol 2012; 67(1): 3-6.
12. Rajadurai P, How SH, Liam CK, Sachithanandan A, Soon SY, Tho LM. Lung cancer in Malaysia. J Thorac Oncol 2020; 15(3): 317-23.
13. Sachithanandan A, Lockman H, Azman RR, Tho LM, Ban I, Varughese R. The potential role of artificial intelligence-assisted chest X-ray in identifying early lung cancer patients in the community - A proposed algorithm for lung cancer screening in Malaysia. Med J Malaysia
14. Malaysia's IKN to introduce AI-based tool to diagnose lung cancer and more than 30 lung-related diseases. news Asia (September 25, 2023). Available on https://www.itnews.asia/news/malaysias-ikn-to-introduce-ai-based-tool-to-diagnose-lung-cancer-600577 (Access date 30.9.23)
15. NHS to use AI to analyse X-rays and speed up cancer diagnosis. (June 23, 2023) https://www.telegraph.co.uk/news/2023/06/23/nhs-lung-cancer-stroke-diagnosis-ai-analyse-x-rays/ (Access date 1.10.23)
16. Mahboub B, Tadepalli M, Raj T, Santhanakrishnan R, Hachim MY, Bastaki U, et al. Identifying malignant nodules on chest X-rays: a validation study of radiologist versus artificial intelligence diagnostic accuracy. Adv Biomed Health Sci 2022; 1(3): 137-143.