The potential role of artificial intelligence-assisted chest X-ray imaging in detecting early-stage lung cancer in the community—a proposed algorithm for lung cancer screening in Malaysia

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ABSTRACT

Introduction: The poor prognosis of lung cancer has been largely attributed to the fact that most patients present with advanced stage disease. Although low dose computed tomography (LDCT) is presently considered the optimal imaging modality for lung cancer screening, its use has been hampered by cost and accessibility. One possible approach to facilitate lung cancer screening is to implement a risk-stratification step with chest radiography, given its ease of access and affordability. Furthermore, implementation of artificial-intelligence (AI) in chest radiography is expected to improve the detection of indeterminate pulmonary nodules, which may represent early lung cancer.

Materials and Methods: This consensus statement was formulated by a panel of five experts of primary care and specialist doctors. A lung cancer screening algorithm was proposed for implementation locally.

Results: In an earlier pilot project collaboration, AI-assisted chest radiography had been incorporated into lung cancer screening in the community. Preliminary experience in the pilot project suggests that the system is easy to use, affordable and scalable. Drawing from experience with the pilot project, a standardised lung cancer screening algorithm using AI in Malaysia was proposed. Requirements for such a screening programme, expected outcomes and limitations of AI-assisted chest radiography were also discussed.

Conclusion: The combined strategy of AI-assisted chest radiography and complementary LDCT imaging has great potential in detecting early-stage lung cancer in a timely manner, and irrespective of risk status. The proposed screening algorithm provides a guide for clinicians in Malaysia to participate in screening efforts.

KEYWORDS:
Lung cancer; cancer screening; artificial intelligence; chest radiography; low-dose computed tomography

INTRODUCTION

Lung cancer is one of the most common forms of cancer worldwide, accounting for 11.4% of newly diagnosed cancer cases in 2020, with Asia accounting for approximately 60% of all new cases.[1,2] It is the leading cause of cancer-related mortality globally, resulting in approximately 1.8 million deaths, or 18% of cancer-related deaths in 2020.[1] In Malaysia, lung cancer accounts for approximately 10% of cancer cases and is a leading cause of cancer-related mortality.[3,4] Lung cancer records the lowest observed survival of all reported malignancies in the country (5-year survival rate of 9.0%; 95% confidence interval 8.4 to 9.7).[5]

The poor prognosis has been largely attributed to the fact that most patients present late with advanced stage disease.[6] Data from the National Cancer Institute of the United States of America indicate that comparatively high 5-year relative survival rates (61.2%) were observed for individuals presenting with localised disease.[7] MySCan similarly reported gradually reduced 1-year, 3-year and 5-year relative survival with increasing stages of lung cancer.[5] Hence there is an urgent unmet need for improved, accessible, cost-effective and less invasive approaches for identification, risk assessment and prioritisation of screening in high-risk individuals.[8] This has led to extensive research into molecular biomarkers[8,9] and diagnostic algorithms[10,11] to complement existing screening methods.

Low dose computed tomography (LDCT) has been widely touted as the optimal modality for lung cancer screening by several bodies, but its implementation in Malaysia has been sporadic and opportunistic at best.[6] LDCT screening in at-risk populations, namely those with a significant tobacco

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smoking history, has been truly life-saving with an impressive (20 to 61%) reduction in lung cancer-specific mortality, driven by impactful stage shift with the detection of more early-stage tumours.[12,13] Early-stage disease is more amenable to treatments with a curative intent. Surgical resection as part of multi-modal therapy in medically fit patients offers the best long-term prognosis in terms of disease-free survival and overall survival.[14,15] Early-stage lung cancer treatment is considerably cheaper.

Screening for lung cancer, however, is an imperfect science. A systematic review by the US Preventive Services Task Force suggests that screening high-risk individuals with LDCT may produce false-positive results, leading to unnecessary and invasive procedures, overdiagnosis, increased distress, and to a lesser extent, radiation-induced cancers.[16] In addition, lung cancer screening is also hampered by the cost of and accessibility to LDCT imaging. Alarmingly, in Asia including Malaysia, the incidence of lung cancer in non-smokers continues to rise, especially in women and those of Oriental ethnicity. Air pollution and family history have emerged as significant risk factors in never-smokers. The TALENT study, which 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 the NELSON study), provides compelling evidence to screen for the disease in at-risk families due to the genetic predisposition evinced by the rising risk with the more first-degree relatives one has with lung cancer.[12,17] However, based on current LDCT screening guidelines, detection of lung cancer in the non-smoker or never smoker remains elusive. Therefore, there is a pressing need for an innovative yet practicable approach to facilitate early detection of lung cancer in non-smokers.

Chest radiography is proposed as an initial step to precede LDCT in lung cancer screening, given its ease of access and affordability. It allows screening in a wider population, which circumvents the issue of low-risk individuals not being screened. Chest radiography may also help reduce the rates of overdiagnosis with LDCT. Historically, chest radiography was used as a screening tool for lung cancer, but hampered by lower accuracy and diagnostic yield. The use of artificial-intelligence (AI)-assisted chest radiography, however, is superior to conventional historical imaging and is expected to improve the detection of an indeterminate pulmonary nodule (IPN), which may represent an early lung cancer. Patients with IPNs can then be appropriately counselled and further investigated with an LDCT. Published data suggests the incorporation of AI can enhance the diagnostic sensitivity of chest radiographs (from 66.4 to 74.7%) and reduce the number of false positive findings per radiograph from 0.25 to 0.18.[18] The technology is especially helpful for junior or trainee radiologists and general physicians. For the detection of lung cancers visible on the chest radiograph in screening of ‘healthy’ populations, the performance of stand-alone AI algorithms was comparable to that of an experienced radiologist, with sensitivity, specificity, positive predicted value, negative predicted value and false-positive rates of 83%, 97%, 1.3%, 100% and 3.0%, respectively.[18]

A consensus statement was developed to determine a standardised lung cancer screening algorithm using AI in Malaysia, based on currently available evidence. Practical considerations and potential limitations with implementing such an algorithm are also discussed.

MATERIALS AND METHODS

This consensus statement was formulated by a multidisciplinary panel of five experts of primary care and specialist doctors via virtual meetings held in March-April 2023. The multidisciplinary panel consists of one cardiothoracic surgeon, one respiratory physician, one radiologist, one oncologist and one general practitioner, all with significant experience in diagnosing, staging and treating lung cancer, both in the public and private healthcare sectors in Malaysia. Four panel experts are members of the Lung Cancer Network Malaysia (LCNM), a not-for-profit non-governmental, disease-centric organisation dedicated to addressing all aspects of lung cancer care here, including preventative (tobacco control) strategies, screening of high-risk individuals, diagnosis, staging and treatment. The consensus findings agreed upon by the panel experts are supported by published evidence. Relevant articles in English published up to February 2023 were considered and reviewed. Finally, a lung cancer screening algorithm is proposed for implementation locally.

RESULTS AND DISCUSSION

Current Landscape in Lung Cancer Screening

LDCT is a non-contrast procedure recommended as part of lung cancer screening in individuals considered at risk of lung cancer.[10] While large randomised trials have demonstrated the utility of LDCT screening in reducing lung cancer-related mortality in high-risk individuals,[12,13], a Malaysian, government-driven effort to evaluate the feasibility and outcomes of using LDCT for lung cancer screening was terminated prematurely due to limited recruitment.[6] Proposed reasons for the failure of the program included a lack of awareness, stigma, fatalism and fear of a cancer diagnosis.[6] This phenomenon is not limited to Malaysia, as reluctance towards screening has also been reported in the United States, resulting in low uptake rates (3.3 to 12.5%).[19] More contemporary data from the UK (Lung Screen Uptake Trial) targeting screening of smokers in socioeconomically deprived areas of England reported better uptake rates (53%) highlighting the value of thoughtful added strategies: primary care invitations, pre-notification letters, scheduled appointments and reminders with a second scheduled appointment.[20] Interestingly, uptake was better when the screening offer was framed within a broader ‘lung health check’ rather than offered solely as a cancer check, and when there was no upfront mention of smoking cessation.[20-22]

Screening is a process and not an isolated test. Financial affordability, not just for the initial diagnostic investigations but any subsequent therapy required, is a real-world concern and an impediment to screening. A report by the Health Technology Assessment Section, Ministry of Health Malaysia substantiated this observation, citing insurance coverage as a major barrier to LDCT screening in Malaysia.[23] Slightly above half of Malaysians (56.6%) have no private health insurance;[24] without insurance, LDCT proves to be a financial burden for individuals on limited and fixed income.[23] These combined observations may jeopardise the feasibility of using LDCT exclusively for lung cancer screening in the country.

Innovative Screening Procedure Using AI

One possible approach to facilitate the identification of high-risk individuals is to implement a risk-stratification step, upon which clinical recommendations may be made for LDCT screening or monitoring. This risk-stratification step would reduce dependence on unreliable self-reported measures of cigarette consumption as a means to identifying high-risk individuals. It would also address the unmet need of disease detection in non-smokers.

Chest radiography (chest X-ray) has been proposed as an ideal technique for risk stratification, in identifying thoracic nodules—a potential indicator of early lung cancer. It is one of the most commonly-conducted imaging tests in medicine and a staple component of routine diagnostic clinical work. While LDCT is superior to radiography in sensitivity,[13] chest radiography holds clear advantages in terms of ease of access and affordability. In addition, LDCT has been associated with a higher proportion of false positive findings involving invasive diagnostic procedures compared to chest radiography.[25] However, studies have demonstrated that approximately 20% of visible lung cancers are missed at initial chest radiography,[26,27] underscoring the importance of improving diagnostic accuracy by complementing the two screening modalities.

In order to improve chest radiography sensitivity in the first step of screening, incorporation of AI technology is proposed. AI is an umbrella term for technology that includes machine learning and deep learning, which enables machines to mimic human intelligence and consequently have a transforming effect on medicine. It has led to the development of multiple computer-assisted detection techniques, designed to assist radiologists and general physicians in recognising anomalies on chest radiographs.[11] The chest X-ray interpretation tool utilises deep learning algorithms, which can automatically detect and localise abnormalities, including a possible early lung cancer. The deep convolutional neural network has been shown to enhance radiologists' performance in detection of malignant nodules using chest radiographs, across varying levels of clinician experience.[28-30] Several screening initiatives involving AI-assisted chest radiography and LDCT have commenced, including the recent deployment of the Qure.ai software (Mumbai, India) into National Health Service hospitals in the United Kingdom. A multi-centre retrospective study performed in the United States had demonstrated high performance of Qure.ai's algorithm (qXR) in the detection of missed or mislabelled chest radiography findings, with high sensitivity (96%), specificity (100%) and accuracy (96%).[31] Separately, an analysis of over 13,000 chest X-rays demonstrated the superior ability of qXR to study nodules and detect malignant nodules on chest radiography, compared to radiologists. qXR detected nodules with a specificity of 0.90 (ranging from 0.87 to 0.92), sensitivity of 0.99, and AUC ranging from 0.98 to 0.99. Malignant nodules were detected using qXR with a sensitivity ranging from 0.95 to 1.00, specificity from 0.96 to 0.99, and AUC from 0.99 to 1. On the other hand, the sensitivity of radiologists' performance in detecting nodules ranged from 0.74 to 0.76, with a specificity ranging from 0.98 to 0.99. In detecting the malignant nodules, specificity ranged from 0.98 to 0.99, and sensitivity fell between 0.88 and 0.94.[32]

Proposed Alternative Screening Approach Introduced in a Pilot Project

The National Comprehensive Cancer Network guidelines define high-risk individuals as those with a family history of lung cancer, advancing age and significant smoking history (> 20 pack years). Unfortunately, this may mean the non-smoking cohort of lung cancer victims, in which women are greatly over-represented, remain inadvertently neglected. Considering the higher prevalence of females amongst non-smoking patients with lung adenocarcinoma, an update in screening criteria is pressingly needed. The combination of AI-assisted chest radiography and LDCT funnels the right patients for LDCT imaging and captures the typically 'neglected' such as non-smoking females.

A local pilot project was initiated in the Klang Valley from May 2021 until February 2023 by AstraZeneca, LCNM and Qualitas Medical Health Group, which incorporates AI-assisted chest radiography into lung cancer screening in the community. The goal was to evaluate the feasibility of using AI-assisted chest radiography as an objective risk-stratification step to help funnel at-risk individuals for LDCT screening. Chest radiography was introduced as a diagnostic tool to incidentally pick up IPNs in individuals who came forward to their primary care general practitioner (GP) for reasons other than a suspected lung cancer diagnosis. IPNs are defined as non-calcified lung nodules, with solid, part-solid or ground-glass opacities, which, assuming a spherical nodule, have diameters ranging from 7 to 20 mm.[33] Detection of an IPN is a useful indicator of lung malignancy, as the risk for lung cancer ranges between 6 to 65% depending on the size, morphology and attenuation of the IPN, and clinical context.[34]

In the pilot project, AI-assisted chest radiography was performed for individuals visiting primary clinics with presenting symptoms (such as a bothersome cough or chest discomfort), or asymptomatic individuals coming for routine health assessment. Depending on the radiography results, the GPs customised their consultations based on each individual's risk profile. High-risk individuals (i.e. current smokers or ex-smokers aged between 45 to 75 years with at least a 20-pack year tobacco history) with a normal radiograph were recommended annual LDCT screening. This is supported by a study showing improved outcomes in patients who attended LDCT follow-ups, whose cancers were missed at the first screening.[35] On the other hand, GPs referred IPN-detected individuals, regardless of their risk profile, to one of three tertiary specialist hospitals for an LDCT scan to ascertain the presence of an underlying lung malignancy. To date, 16,551 AI-assisted chest radiographs have been conducted in the clinics, with 389 IPNs detected (2.35%). Follow-up of IPN-detected individuals are currently underway to determine the percentage of lung malignancy

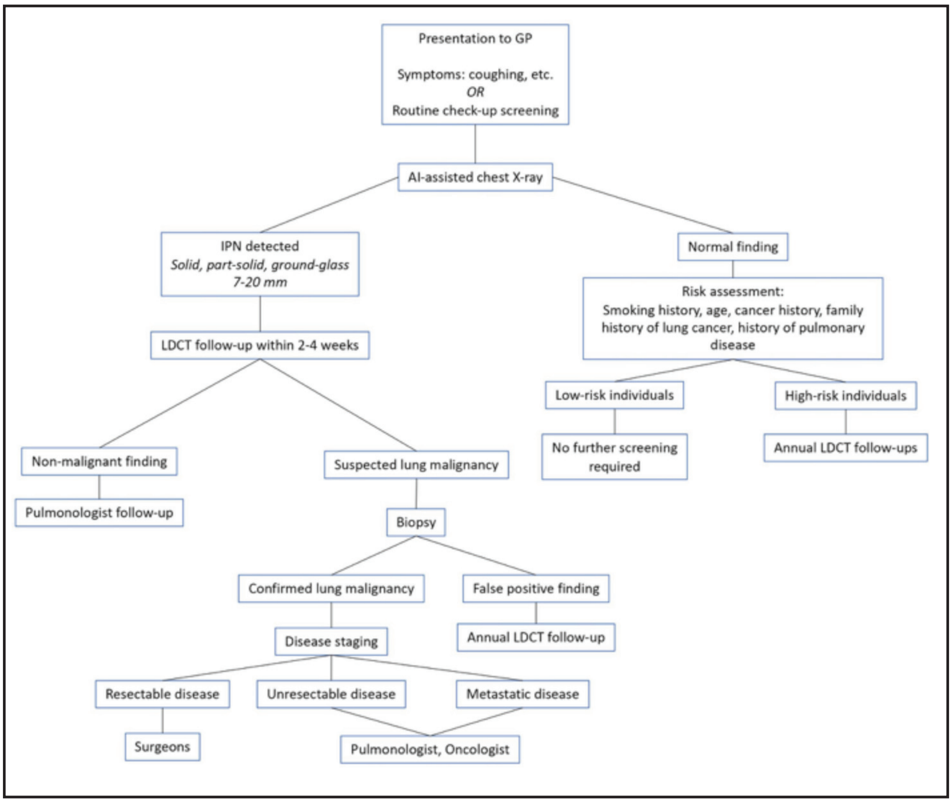

Fig. 1: Proposed algorithm for lung cancer screening in Malaysia, with an objective risk-stratification step using AI-assisted chest X-ray where individuals who show IPN detection are counselled to undergo LDCT, suspected lung malignancies are biopsied, and confirmed lung malignancies are staged and treated appropriately (AI: Artificial intelligence, GP: General practitioner, IPN: Indeterminate pulmonary nodule, LDCT: Low-dose computed tomography).

detected from the incidental discovery of an IPN. This is an important pending data gap but preliminary feedback via telephonic survey suggests uptake for the subsequent LDCT imaging was unfortunately, generally poor. Going forward, barriers to screening need to be elucidated and addressed thoughtfully. Nevertheless, this pilot project with AI-assisted screening serves as fertile groundwork for transforming lung cancer screening in Malaysia.

The proposed alternative screening approach takes both cost and practicality into consideration. Presently, a high-risk population-based LDCT lung cancer screening program is less pragmatic. The incorporation of AI-assisted chest radiography as an affordable risk-stratification step is highly relevant as an intermediary diagnostic tool in Malaysia (Fig. 1).

The inclusion of AI-assisted chest radiography in the screening for lung cancer is essential in order to improve the long-term survival of lung cancer patients, by setting stage shift as an endpoint for cancer screening. Detection of early lung cancer which is more amenable to curative treatment will not only translate into enhanced patient survival, but is also more cost-effective in the long run. Our preliminary experience with AI-enabled chest X-rays (qXR [Qure.ai]) suggests the software is easy to use, affordable and scalable. Feedback from our colleagues in general practice was most favourable. Our colleagues had found the whole process to be user-friendly and felt empowered to swiftly decide on the next course of action. Patients, too, were similarly highly satisfied to receive a detailed report in minutes, and medical advice at a single consultation. Failure to adopt and appropriately utilise such technology may be a significant missed opportunity for Malaysia.

Requirements for Screening Centre and Equipment
The implementation and effective conduct of AI-assisted chest radiography requires the expertise of a multidisciplinary team (MDT) comprising a radiologist, oncologist, pulmonologist, pathologist, thoracic surgeon, nurse and a co-ordinator experienced in the diagnosis and treatment of lung cancer and in programmes pertaining to it. It is imperative for screening centres to be certified according to a standardised methodology. Continued education of the staff and site accreditation also contribute to the effectiveness of a screening programme. A registry is also desired to keep track of screening statistics and outcomes. Information on equipment specifications and radiographic settings/protocol should also be elucidated and made easily accessible for clinicians' reference. Informed consent of patients undergoing screening must include salient information on accuracy of the screening program, such as biopsy rates. Patients should also have access to tertiary specialist centres with a dedicated multidisciplinary team to support the investigation of a detected pulmonary nodule.

Expected Outcomes with AI-assisted Chest Radiography
Among the goals of lung cancer screening with a risk-

stratification step using AI-assisted chest radiography are to increase the uptake of screening amongst the public, and to improve outreach to otherwise-unscreened low-risk populations (particularly non-smokers and females). Screening is anticipated to bring forward the stage distribution at diagnosis, early detection improves survival and reduces the risk of mortality due to late treatment.[36-38] We anticipate that a stage shift in cancer detection will enhance the possibility of successful curative treatment, as well as reduce attending side effects associated with long-term or multiple lines of treatment. By extension, overall treatment cost is expected to reduce.

Chest radiography is a widely known and well-accepted investigation by the public. Implementation of an affordable and easily accessible screening modality for lung cancer is anticipated to increase public awareness of and participation in lung cancer screening efforts locally. Additionally, screening provides a timely opportunity to educate individuals regarding the risks of smoking, thus, education should be carefully integrated into the screening process to encourage and support smoking cessation.

Potential Limitations in Implementing an AI-assisted Lung Cancer Screening Programme

AI-assisted medical imaging for screening has gained an important role in supporting efficient and quick clinical decision-making. However, there are a number of potential limitations pertaining to the implementation of AI-assisted lung cancer screening. Firstly, the attitude of both clinicians and patients to the adoption of AI can be mixed and unpredictable. In general, radiologists have been optimistic on the whole about the potential of AI, but many understandably still harbour concerns that the technology may disrupt or undermine their professional reputation or livelihood. Hence, there is a need to educate all stakeholders to address concerns and allay anxieties. Another challenge impeding clinical implementation of AI-assisted screening is reproducibility, due to various differences in the image acquisition protocols between different studies and research institutions. These differences can affect the signal-to-noise ratio and the characteristics of extracted images. Consequently, variations in imaging features between patients may be due to acquisition parameters, rather than biological. This limitation could be addressed through the exclusion of features strongly influenced by acquisition parameters, or through standardising image acquisition by using open imaging protocols.

Technical integration is also a significant setback for implementation of AI software into routine radiology practice. Computational power required for advanced AI algorithms may exceed local capabilities, and this may drastically slow down scanner performance. This could be overcome with cloud-based solutions like our software, although this may be accompanied with its associated concerns, such as data security and privacy, and internet performance. In addition, regular updates over the lifecycle of an AI system is to be expected.

One of the concerns with lung cancer screening is that a subset of smokers might use a seemingly normal result as an excuse to continue smoking, although current evidence on this is limited. Vigorous and sustained smoking cessation efforts must accompany lung cancer screening for current smokers. Our preliminary experience with AI-chest radiography imaging as a triage or prelude to definitive LDCT screening of an IPN is promising, with a diagnostic rate of approximately 2.5% in a local urban population. Primary care is fast shifting from symptom-based therapy to preventative and predictive or pre-emptive care. Feedback from our primary care colleagues suggests that this technology is a potential game-changer as it is simple and swift to utilise, generates a high-quality image and detailed radiology report within minutes, thereby empowering the general practitioner immediately on the next course of action. The benefits of enhanced diagnostic accuracy, a shorter turnaround time and ease of use are obvious and immense. The follow-up of patients with IPNs, however, has been challenging, in part due to the fact that the project was conducted throughout the coronavirus disease 2019 (COVID-19) pandemic and thus was hampered by travel restrictions, periods of quarantine and the stigma of both diseases. Furthermore, well-established barriers to screening, including an understandable fear of a possible cancer diagnosis, fatalism, poor health literacy and high financial cost, remain. Going forward, we have sought to mitigate this with free screenings and use of patient navigators.

CONCLUSION

Lung cancer remains a leading cancer and cancer-killer in Malaysia, with the worst reported 5-year survival of all the major solid tumours.[2-5] A preponderance of late-stage presentation is to blame and is likely to worsen in the coming years due to recent COVID-19 disruptions. Despite tremendous advances in the diagnostic and treatment landscape for lung cancer (namely genomic molecular profiling and next generation sequencing, as well as emergence of novel bespoke therapies such as systemic immunotherapy and oral targeted therapies), detection of more early-stage disease via impactful screening coupled with effective tobacco control is imperative to save more lives. This consensus statement addresses the need to 'widen the net' for early and widespread screening of lung cancer to facilitate effective cancer control in our country. The combined staged strategy of AI-assisted chest radiography and complementary LDCT imaging has great potential in detecting early-stage lung cancer in a timely manner, and irrespective of risk status. The proposed screening algorithm provides a guide for clinicians in Malaysia to participate in screening efforts. Active lung cancer screening enables stage shift towards detection of more early-stage disease, which is more effective and economical to treat, in addition to better prognosis in terms of both patient survival and quality of life.

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