EARLY CANCER DETECTION TEST FOR LUNG (EarlyCDT-Lung)

EXECUTIVE SUMMARY
(Adapted from the report by SYFUL AZLIE MD FUZI)

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Background

Most patients with lung cancer are diagnosed when they present with symptoms, at advanced stage disease, and curative treatment is no longer an option. An effective screening test has long been desired for early detection with the goal of reducing mortality from lung cancer. While low-dose computed tomography (LDCT) screening has shown promising result in the detection of early disease and has now been broadly documented to have the potential to reduce lung cancer mortality, it comes with risks of radiation-induced cancer, false-positive test results, unnecessary follow-up testing and increased financial costs, as well as over diagnosis. Currently, there has been a shift in the emphasis of biomarker using blood specimens as it is readily available through minimally invasive procedures and their measurements can be easily standardized. Following this, a commercially available assay, the EarlyCDT-Lung that measures autoantibodies to tumour associated antigens (TAAs) for the detection of lung cancer has been developed. Despite the magnitude of lung cancer cases been reported in Malaysia, there is no national lung cancer screening programme established yet. This review is timely to address the need for early detection of lung cancer in facilitating more effective non-invasive cancer control approaches in the country. Therefore, the purpose of this Health Technology Assessment (HTA) is to evaluate whether EarlyCDT-Lung would be effective, safe, and cost-effective as a screening tool for early lung cancer detection among high-risk group in the management of lung cancer in Malaysia. This assessment was requested by a Senior Consultant Pulmonologist from Serdang Hospital.

Technical Features

EarlyCDT-Lung is a sophisticated blood test that detects autoantibodies against seven TAAs found in different types of lung cancer. An indirect enzyme linked immunosorbent assay (ELISA) is utilised to detect antibodies to a panel of antigens that includes p53, NY-ESO-1, CAGE, GBU4-5, HuD, MAGE A4, and SOX2. A positive result is reported if antibodies to any one of the seven antigens are detected at a concentration above a defined cut-off. In combination with imaging techniques, EarlyCDT-Lung is now commercially available to assist clinicians in the early detection of lung cancer in a high-risk population. It can help reduce the number of patients in 'watchful waiting' and aid early lung cancer detection, leading to earlier intervention and better patient outcomes. A blood test like this could be repeated frequently and CTs only start when there is a positive blood test. EarlyCDT-Lung has been marketed in the United States since 2012 while received its CE mark as a general in vitro diagnostic in May 2017 and was updated in March 2019.

Policy Question

i. Should EarlyCDT-Lung be used as a screening tool for early lung cancer detection among high-risk group in Malaysia?
ii. Does using the EarlyCDT-Lung reduce the incidence of patients with late stage (III/ IV) lung cancer or unclassified presentation at diagnosis?

Objective:

i. To determine the diagnostic accuracy of EarlyCDT-Lung in increasing early-stage lung cancer detection.
ii. To determine the effectiveness and safety of EarlyCDT-Lung for lung cancer screening in the high-risk group, with regards to patient outcomes such as mortality, quality of life (QoL), and adverse events or complications.
iii. To determine the economic, organisational, social, ethical and legal implication of using EarlyCDT-Lung in screening setting.

Research questions:

i. What is the diagnostic accuracy of EarlyCDT-Lung for the detection of lung cancer in the high-risk group?
ii. Does screening with EarlyCDT-Lung improve lung cancer mortality?
iii. Is EarlyCDT-Lung cost-effective?
iv. What is the organisational, social, ethical and legal implication related to EarlyCDT-Lung?

Methods

Part A: Systematic Review of Literature

Literature search was developed by the main author and *Information Specialist* who searched for published articles pertaining to EarlyCDT-Lung test for early lung cancer detection. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to January 2022, EBM Reviews - Health Technology Assessment (4th Quarter 2016), EBM Reviews - Cochrane Database of Systematic Review (2005 to January 2022), EBM Reviews - Cochrane Central Register of Controlled Trials (January 2022), and EBM Reviews - NHS Economic Evaluation Database (4th Quarter 2016). Parallel searches were run in PubMed, US FDA and INAHTA database. Search was limited to articles in English and in human. The last search was performed on 10th February 2022. Additional articles were identified from reviewing the references of retrieved articles.

Part B: Economic Evaluation

An economic evaluation was conducted to assess cost-effectiveness and to calculate ICER of EarlyCDT-Lung compared to no screening among high-risk lung cancer patients in Malaysia using decision analytic modelling. Sensitivity and specificity of EarlyCDT-Lung were obtained from the literature. One-year probability of lung cancer among high-risk group and probability of late-stage diagnosis was calculated based on Malaysia Cancer Registry

Results and conclusion:

Part A: Systematic Review of Literature

A total of 390 records were identified through the Ovid interface and PubMed while 26 were identified from other sources (references of retrieved articles). Following the removal of four duplicates, 412 titles

were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 29 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the 29 full text articles, eight were included. The eight full text articles which were finally selected in this review comprised of two systematic review and meta-analysis, one randomised controlled trial (RCT), three observational studies (two prospective cohort and one nested case-control), and two economic evaluation studies. All studies included were published in English language between 2011 and 2021 and were mostly conducted in the United States, United Kingdom, Scotland, Denmark, Germany, and China.

Diagnostic accuracy and effectiveness

In the diagnosis of all stages lung cancer, the sensitivity of single or individual tumour-associated autoantibody (TAAb) ranged from 15.0% to 55.2% and the specificities ranged from 84.4% to 98.0%. However, combination or a panel of multiple TAAbs may improve sensitivity (70.3%) but at the cost of specificity (86.3%). For single TAAb in the diagnosis of early-stage lung cancer, the sensitivity and specificity were 55.6% and 89.3%, respectively. For the combination or a panel of multiple TAAbs, sensitivity of 71.1% with specificity 87.1% were reported. In addition, the diagnostic value of EarlyCDT-Lung for the same panel of 7-TAAbs appears to be higher than the panel of 6-TAAbs in the diagnosis of lung cancer, either at all stage (sensitivity 47.0% versus 38.0%; specificity 90.0% versus 89.0%) or early-stage disease (sensitivity 40.0% versus 29.7%; specificity 91.0% versus 87.0%). In the context of large community-based trials, a positive EarlyCDT-Lung test followed by LDCT 6-monthly for up to two years significantly reduced the numbers of late-stage (III/IV) lung cancers (58.9% versus 73.2%) as compared with standard clinical care. Indirectly, more early-stage (I/II) disease were diagnosed (41.0% versus 27.0%). However, there were no significant differences in lung cancer mortality (0.28% versus 0.39%) and all-cause mortality (1.43% versus 1.76%) as well. The EarlyCDT-Lung has previously been tested in high-risk cohorts or lung cancer patients matched with control subjects on age, gender, and smoking status. As a result, this assay performed best (sensitivity) in heavy smokers with at least 50 tobacco pack years (44.0%), patients older than 75 years (55.0%), and advance stage disease (40.0%); gender does not seem to influence outcome. No studies of EarlyCDT-Lung in the target population reported health-related quality of life outcomes.

Safety

Only one study reported the incidents of adverse events directly related to the EarlyCDT-Lung test (collection of blood sample), and all were considered minor. There was one injection site haematoma, one panic attack, and one pre-syncope.

Economic implication

Economic evaluation of an autoantibody test has been very limited and to date, two cost-effectiveness analyses have been undertaken. The first revealed that EarlyCDT-Lung is likely to be cost-effective compared to CT surveillance alone in patients with incidentally detected nodules who are estimated to have an intermediate-risk of

lung cancer and a rescheduled for CT surveillance alone, with USD 24,330 to USD 24,833 per quality-adjusted life-year (QALY) gained, depending on the test accuracy parameters used (two alternative sets of estimates for sensitivity and specificity were considered based on published literature: 41%/93% and 28%/98%, respectively). Second study reported at £70 per test, the EarlyCDT-Lung will have a positive impact on patient outcomes and coupled with CT surveillance is a cost-effective approach to the management of patients with indeterminate pulmonary nodules (IPNs) compared to surveillance alone with an incremental cost-effectiveness ratio (ICER) of less than £2,500.

Organisational
No guideline presently recommends the use of blood-based biomarkers in clinical practice as an initial screening test in those at high risk although there are now commercially available. Recently, the National Institute for Health and Care Excellent (NICE) stated that there is not enough evidence to recommend routine use of EarlyCDT-Lung for assessing the risk of lung cancer in solid lung nodules.

Social, ethical and legal
No evidence retrieved on social, ethical and legal issues related to EarlyCDT-Lung in screening setting.

Part B: Economic Evaluation
From the decision analytic modelling, the base-case analysis indicated that a positive EarlyCDT-Lung followed by LDCT and biopsy as compared with no screening yielded an ICER of MYR 37,169.04 per QALY gained. A sensitivity analysis suggested that the cost of EarlyCDT-Lung is the major factor that influenced the cost-effectiveness ratio.

Conclusion:

Part A: Systematic Review of Literature
The availability of evidence on the diagnostic value differs between autoantibodies for identifying patients at all stages or early-stage of lung cancer. There was fair to good level of retrievable evidence to suggest that EarlyCDT-Lung has low to moderate sensitivity but good specificity as serum diagnostic biomarkers of lung cancer in population screening among high-risk group. A positive EarlyCDT-Lung test followed by LDCT significantly reduced the numbers of late-stage lung cancers and indirectly more early-stage lung were diagnosed as compared with standard clinical care. However, there were no significant differences in lung cancer mortality and all-cause mortality. Given the existing evidence, economic evaluation conducted in countries that implemented LDCT as a screening tool with an addition of EarlyCDT-Lung was found to be cost effective. Future research focusing on novel TAAb panels that offer better diagnostic performance is encouraged.

Part B: Economic Evaluation
For the implementation of screening program using Early-CDT-Lung, the strategy needed to be in line with the LDCT and biopsy after the test screening. The population screened needed to be monitored

closely and the treatment options needed to be considered after the patients tested and confirmation of cancer diagnosis.

Recommendation

Based on the above review, EarlyCDT-Lung has the potential to be used to complement LDCT in population screening for early lung cancer detection among high-risk group in Malaysia. However, its use should take into consideration the availability and acceptability of LDCT as a screening tool. Competitive price of EarlyCDT-Lung may improve the cost-effectiveness of this screening strategy.