Literature Review

Indonesian Society of Respirology (ISR) Consensus Statement on Lung Cancer Screening and Early Detection in Indonesia

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Abstract

Lung cancer is the leading cause of mortality for all cancer globally and in Indonesia. In Indonesia, lung cancer contributes to 12.6% of death of all cancer, making it the number one cause of cancer death, and 8.6% of all cancer incidence in 2018, behind breast, cervical, and colorectal cancer. The total cases per year are expected to almost double from 30,023 in 2018 to 54,983 cases in 2040. Smoking is among the risk factors for lung cancer, after occupational/environmental risk factors, history of lung fibrosis, and family history of cancer. There was a tendency of younger smokers in Indonesia and increased lung cancer incidence and prevalence in the younger population. The median age of lung cancer in Indonesia was younger than in any country, probably due to the younger age of smoking, early onset of carcinogens, asbestos use, and environmental. Lung cancer screening is a voluntary measure to detect lung cancer in the earliest stage, to find cancer at curable disease before symptoms appear in high-risk individuals. Lung cancer early detection is strategies to find cancer earlier after symptoms appear (cough, hemoptysis, dyspnea, chest pain). Low-dose computerized tomography of the thorax (LDCT) screening has been known to reduce lung cancer mortality compared to a chest x-ray (CXR). This Indonesian Society of Respirology consensus statement was aimed to give recommendations on lung cancer screening and early diagnosis in Indonesia.

Keywords: early detection, LDCT, screening

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INTRODUCTION

Epidemiology

With an estimated 2.2 million new cases and 1.8 million deaths in 2020, lung cancer is the leading cause of cancer death and the second most commonly diagnosed cancer worldwide.[1] In Indonesia, lung cancer contributes to 12.6% of death of all cancer, making it the number one cause of cancer death, and 8.6% of all cancer incidence in 2018, behind breast, cervical, and colorectal cancer. The total cases per year are expected to almost double from 30,023 in 2018 to 54,983 cases in 2040.[2–4] Eighty percent of smokers aged ≥15 live in low to middle-income countries.[2]

In countries like Indonesia, where smoking continues to rise and younger, the next few decades could see an increasing number of lung cancer rates.[3] Common risk factor for lung cancer includes occupational exposures (miners, heavy metal workers), smoking, second-hand smoke, family history, dietary factors, radon gas, aging, other lung diseases (COPD, TB, fibrosis), pollution, and radiation exposure.[1]

Accurate tumor staging at the time of diagnosis is of utmost importance, for it will guide the initial therapy and the prognosis.[3–5] Poorer prognosis is observed with each centimeter increase in tumor size. However, for tumors sizing beyond 6 cm, no difference in survival was observed. Five-year estimated survival of 92% in those diagnosed with T1a stages dropped significantly to just 52% and 38% for those with T3 and T4 stages, respectively.[3,6,7]

The N component assesses the involvement of regional hilar and mediastinal nodes.[8] The more nodal stations are involved, the worse the prognosis of the tumor is.[7,9] It is shown that those with several metastases have a worse prognosis than those with only single extrathoracic metastasis, with a mean survival of 6.3 months instead of 11.4 months.[5,7,10] This phenomenon further reiterates the need to be able to diagnose patients with lung cancer at the earliest possible stages as tumors in the lower stages of a curable disease.

Lung Cancer Control

Lung cancer multistep management includes lung cancer prevention, diagnosis, prompt treatments, and end-of-life care. Lung cancer preventive measures include risk identification and stratification and lung cancer screening, whereas Lung cancer diagnosis consisted of early diagnostic procedures and diagnostic procedures.

In 2021, the US Preventive Services Task Force (USPSTF) updated its 2013 recommendation on screening accuracy for lung cancer with low-dose computed tomography (LDCT).[9,11–13] USPSTF has decided not to use other known risk factors for lung cancer, such as environmental exposures, prior radiation therapy, other (noncancer) lung disease, and family history, to be weighted as additional risk factors when screening.[11] Nevertheless, this decision could miss the 'real-world' high-risk population, especially the non-smoker population.[14]

In Indonesia, there was a tendency for younger lung cancer age due to possible early exposure to smoking, indoor air pollution, asbestos, and occupational and family history of cancer to have distinct lung cancer screening approaches.[15]

Risk factors of lung cancer are aging, smoking, family history, occupational exposure, indoor air pollution, outdoor air pollution, and chronic lung diseases. The definition of a high-risk group includes age group, smoking history, and family history of lung cancer.

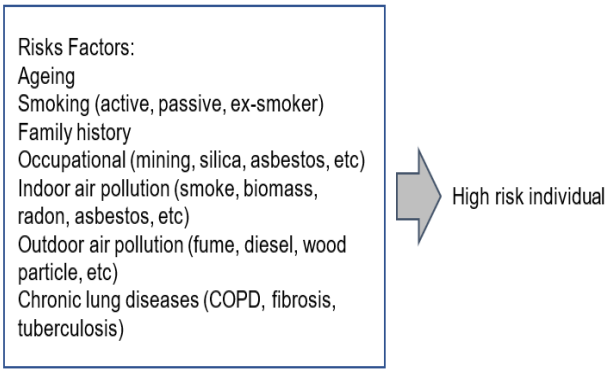

Figure 1. Risk factors and identification of high-risk individuals

A family history of lung cancer was associated with an increased risk of lung cancer, and this association was stronger in women and in never smokers.[14]

CONSENSUS STATEMENT ON RECOMMENDATIONS FOR LUNG CANCER SCREENING IN INDONESIA

Lung Cancer Screening in High-Risk Individuals

The high-risk population is strongly suggested to undergo lung cancer screening. Based on risk stratification, Group A consisted of any individuals age >45, smokers/passive smokers/ex-smokers <10 years; and Group B consisted of any individuals with age >40years old, family history/genetics of lung cancer, as follows (Figure 1).

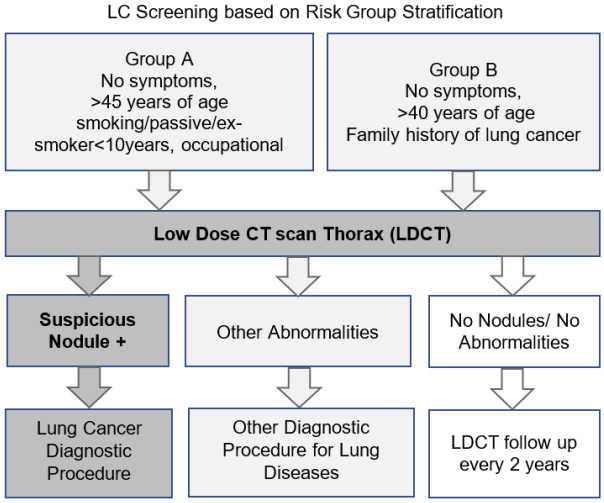

Figure 2. Screening based on risk group stratification

High-risk individuals include males aged >45 years old, a history of smoking/second-hand smoke or occupational/environmental exposure, and a history of fibrosis lung diseases. The younger age group (>40years) should be monitored with the above risks and genetic or family history of cancer. The risk assessment determines which individuals are at high risk for lung cancer. Factors such as age and tobacco smoking are weighted; lung cancer is relatively rare in individuals younger than 45 years, and smokers have a 10- to 35-fold increased risk of lung cancer compared to non-smokers, including second-hand smokers.[15]

Within five years since quitting, former smokers have a 39.1% lower risk of lung carcinoma incidents than current smokers. This risk even continues to fall with increasing years since quitting. However, compared to never-smokers, the risk of developing cancer in former smokers remains high, even after 25 years after quitting, reaching over three-fold higher than never-smokers.[16]

Other than smoking, occupational exposure to carcinogens, asbestos was historically the most common, is considered another risk factor for lung cancer as it is estimated to be found in 5 to 10% of lung cancer patients.[12] A meta-analysis of 14 case-control studies in Europe and Canada, consisting of 17,705 lung cancer cases and 21,813 controls, has found that over-exposure to asbestos was associated with a 24% and 12% increased risk of lung cancer in men and women, respectively.[17]

With its cases still prevalent in Indonesia, it is essential to know that tuberculosis could have a role in the pathogenesis of lung cancer by promoting chronic inflammation and pulmonary fibrosis, which lead to higher rates of genetic alterations and mutations.[18] Genetic is another risk factor as an inherited susceptible locus responsible for lung cancer disease has been discovered. The Genetic Epidemiology of Lung Cancer Consortium revealed a vital susceptibility locus influencing lung cancer risk, which is a region on 6q23-25 after conducting a genome-wide linkage analysis of 52 families in which several lung cancer cases occur in first-degree relatives.[19]

For people meeting the abovementioned high-risk criteria, LDCT is strongly recommended to be undergone every two years. In order to ensure compliance and screening program effectiveness, it is recommended for institutions performing lung cancer screening employ a multidisciplinary approach in which a patient is managed by specialties such as chest radiology, pulmonary medicine, and thoracic surgery.[20]

Pulmonary nodules are often defined as rounded or irregular opacities, well or poorly defined, measuring up to 3 cm in diameter.[21] They are best classified according to size, attenuation, and presence (or absence) of calcification. One of the

objectives of LDCT is to detect non-calcified nodules that might be suspicious for lung cancer, most of which are solid. Non-calcified nodules are common and present in 25–50% of LDCT scans.[22] If a single lung nodule or multiple nodes are found, further diagnosis is needed to define whether the nodule is of inflammatory or malignancy origin. After that, a follow-up LDCT is conducted after 1–2 months for further treatment. On the contrary, if no lung nodules or other non-cancerous abnormalities are detected (for example, aortic aneurysm, coronary artery calcification, or tumors/benign disease outside of the chest), a follow-up for other respiratory diseases is recommended after every 2-yearly control with LDCT.[20]

Lung Cancer Early Diagnosis in Individuals with Respiratory Symptoms

Most lung cancer is diagnosed patients present with symptoms such as persistent cough, chest pain, hemoptysis, dyspnea, or weight loss. Unfortunately, symptom occurrence usually means that their stages are already advanced. Therefore, early diagnosis achieved through screening will increase the time interval before symptoms ensue and improve survival. An ideal and effective screening will allow earlier detection of lung cancer long before patients experience symptoms, hopefully decreasing the mortality rate.[20]

However, particularly in Indonesia, the same groups of symptoms could also lead to an infectious cause that is still prevalent: tuberculosis. Therefore, once a patient has one or more of these symptoms for over two weeks, Xpert MTB/RIF Assay will be done to exclude tuberculosis as a diagnosis. After the diagnosis is confirmed for tuberculosis, these patients will undergo further investigation and evaluation for clinical tuberculosis and LDCT. The Xpert MTB/RIF assay is the opted test, which is considered sensitive and rapid (results are available in less than 2 hours). Additionally, this assay may contribute to cost savings by avoiding unnecessary treatment and misdiagnosis for people who are eventually found not to have tuberculosis.[23] Finally, if the Xpert MTB/RIF assay results are negative, patients will still be observed and assessed to decide whether the patient has clinical tuberculosis or lung cancer is suspected through LDCT.

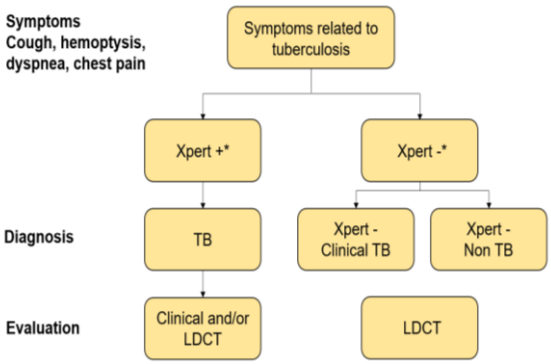

Figure 3. Algorithm of early diagnosis in individuals with respiratory symptoms[25]

Lung Cancer Screening in High-Risk Individuals with Respiratory Symptoms

In high-risk populations with both risk factors mentioned before and symptoms, LDCT will be conducted to detect nodules and early abnormalities. If nodules are found, further diagnosis with MDT will determine whether they are of inflammatory or malignancy origins before a follow-up treatment continues. If the results were negative for nodules or other abnormalities, the patient would be examined for other respiratory diseases that could explain the symptoms presenting. If so, tailored treatments will be provided.

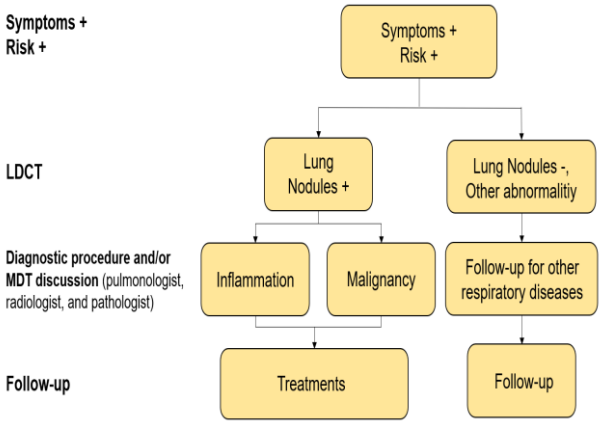

Figure 4. Algorithm of early diagnosis in high-risk individuals with respiratory symptoms[24]

Risks and Benefits of Screening

The National Lung Screening Trial (NLST) showed the benefits of LDCT screening and improved lung cancer mortality. The study, which followed 53,454 participants at high risk for lung cancer at 33 US medical centers, showed that those receiving annual LCDT have a relative reduction in mortality of 20% (p=0.004) compared to those who received single-view posteroanterior chest radiography, as also shown at NELSON trial.[25,26]

Besides the apparent reduction of mortality, a more critical, intangible parameter, quality of life (QoL), was also shown to benefit from early screening.[25] Moreover, lung cancer screening may bring another lung- or non-lung-related clinical conditions that require follow-ups to the surface, such as coronary artery calcification, COPD, or other cancers.[25,27]

The main concerning harm from screening is the unneeded invasive procedure that entails false-positive findings.[28,29] The false-positive rate in the NLST in those receiving LDCT was 23.3%. From these false-positive tests, 0.06% experienced a 'major complication after an invasive procedure.[25,26] Besides physical drawbacks, some evidence argues that lung cancer screening participation could have adverse psychological effects.[30,31] Concerns on radiation exposure have been estimated to be around eight mSv over the three screening scans in the NLST study. It could result in one death due to radiation per 2,500 people screened over a 10- to 20-year period.[32,33] In every 108 lung cancers detected by screening, one radiation-induced cancer arises.[34]

FUTURE DIRECTIONS

Unlike population-based screening programs such as breast, cervix, and colon cancer in which all individuals of a specific sex and age, regardless of any risk factors, lung cancer screening program only targets those most at risk.[35]

Another developing alternative for lung cancer screening is detecting specific biomarkers only in lung cancer. This use of blood-borne biomarkers, called 'liquid biopsies' by some, which detect circulating nucleic acids, proteins, or tumor cells, has gained popularity for monitoring advanced-stage lung cancer (Table 5).[35]

One example is the detection of specific circulating microRNAs, such as let7 miRNA, which is downregulated in lung cancer tissue, or miRNA-21, that has been shown to appear in both lung cancer cell lines and tissue.[36,37] Another non-invasive method that has been proposed is exhaled breath analysis. Ion mobility spectrometry is one of the sensitive tools in detecting volatile components (VOC) in exhaled breath of lung cancer patients; one pilot study has shown that VOCs of patients with lung cancer are easily distinguished from controls.[38]

Table 1. Potential targets of biomarkers for the early detection of lung cancer[35]

Base	Potential target biomarker
Cell-free nucleic acid	circulating tumor DNA, circulating microRNA,
Tumor-specific antibodies	antibodies to TSA, tumor-specific antigen
Circulating tumor cells	Circulating tumor cell
Exhaled-breath analysis	Exhaled-breath condensate, volatile gas

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CONFLICT OF INTEREST

None

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