

Low-dose computerized tomography in lung cancer screening

Abstract

Lung cancer screening has been a passionately debated topic since the late 1990s. Five-year survival is 53.5 %, 26.1 %, and 3.9 % when cancer is confined to the lung at the time of diagnosis, when there is regional nodal involvement, and when there is distant metastasis, respectively. The goal of lung cancer screening (LCS) is to shift the timing of the diagnosis to an earlier point, thus, the disease is localized to the lung, and then appropriate treatment can reduce the mortality of lung cancer. Study results from several lung cancer screening trials worldwide, including the United States, Japan, the Netherlands, Denmark, and Italy demonstrated that low-dose computerized tomography (LDCT) scanner used in LCS can increase the detection rate of lung cancer at an earlier stage. At the time of screening, the information about smoking cessation should be provided to all current smokers, while the multidisciplinary clinic affords a second opportunity to counsel patients about the benefits of quitting smoking. After two rounds of screening, there are fewer false positives as a result of comparison with the baseline screening CT that may reveal two years of pulmonary nodule stability. Decreasing the number of false -positive lung cancer screens is an area for future research. Genetic profiles and the results of the baseline screening examination can potentiate further refining the risk modeling. Risk modeling could define the frequency of follow-up in addition to who should be screened. In conclusion, LCS with LDCT has shown that there are indolent lung cancers that may not be fatal. Further studies are urgently needed if the maximization of the risk-benefit ratio in LCS has to be achieved.

Keywords: lung cancer, screening, low-dose computerized tomography

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Abbreviations: ACCP, American College of Chest Physicians; ASCO, American Society of Clinical Oncology; CT, computed tomography; LDCT, low-dose computerized tomography; LCS, lung cancer screening; LLP, Liverpool Lung Project; NCCN, National Comprehensive Cancer Network; NLST, National Lung Screening Trial

Introduction

In the late 1990s, lung cancer screening has been a passionately debated topic, including the Early Lung Cancer Action Program and screening programs in Japan.¹⁻⁴ Promoting cigarette smoking cessation is necessary due to a much higher risk in smokers although lung cancer does occur in non-smokers. For the decade from 2000 to 2010, the relative risk of death from lung cancer in men and women who are current smokers, compared to men and women who are non-smokers, were 24.97 and 25.66, respectively.⁵ Five-year survival is 53.5 %, 26.1 %, and 3.9 % when cancer is confined to the lung at the time of diagnosis, when there is regional nodal involvement, and when there is distant metastasis, respectively.⁶ The goal of lung cancer screening (LCS) is to shift the timing of the diagnosis to an earlier point, thus, the disease is localized to the lung, and then appropriate treatment can reduce the mortality of lung cancer.⁶ Study results from several lung cancer screening trials worldwide, including the United States, Japan, the Netherlands, Denmark, and Italy demonstrated that low-dose computerized tomography (LDCT) scanner used in LCS can increase the detection rate of lung cancer at an earlier stage.^{1-4,7-9}

Lung cancer screening guidelines

Growing list of organizations have issued guidelines for lung cancer screening with LDCT, including American Lung Association

(<http://www.lung.org>), the National Comprehensive Cancer Network (NCCN) (<http://www.nccn.org>), the American Association for Thoracic Surgery, and the American Cancer Society (<http://www.cancer.org>), widely following the eligibility criteria and structure of the National Lung Screening Trial (NLST).¹⁰⁻¹² The joint statement of the American College of Chest Physicians (ACCP) and the American Society of Clinical Oncology (ASCO) warned that screening should occur only in settings that can deliver the comprehensive care provided to NLST subjects.¹³ The American Cancer Society recommended that clinicians with access to high-volume, high-quality lung cancer screening and treatment centers should initiate a discussion about screening with apparently healthy patients aged 55 years to 74 years who have at least a 30-pack-year smoking history and who currently smoke or have quit within the past 15 years before any decision is made to initiate LCS.¹¹

Management of the patients

The patients with positive findings, either pulmonary nodules or incidental findings is best cared for within a multidisciplinary clinic although CT screening for lung cancer may be effectively performed within the framework of a diagnostic radiology department. The clinic should include representatives from several medical specialties, including pulmonology, thoracic surgery, cardiology, interventional radiology, and smoking cessation that will allow suitable pulmonary nodule follow-up. Pulmonary nodule follow-up should be performed following established guidelines, such as those developed by the NCCN, for solid, semi-solid, and ground glass nodules. At the time of screening, the information about smoking cessation should be provided to all current smokers, while the multidisciplinary clinic

affords a second opportunity to counsel patients about the benefits of quitting smoking. If a pulmonary nodule is identified to be malignant at biopsy, then further assessment by a multidisciplinary clinic can allow the patient to make an informed decision about medical care.¹⁴

Obstacles to lung cancer screening with low-dose computed tomography

The mortality benefit of LCS can only be realized if persons at risk actually participate in the LCS program. Concerns about radiation effects and discomfort of LCS process are related to reluctance to undergo screening whereas financial costs are a large obstacles to screening, particularly when downstream costs are considered.¹⁴ The primary concern with the radiation dose from computed tomography (CT) screening is the possibility of radiation-induced carcinogenesis.^{15,16} Subsequent follow-up examinations to work up positive findings lead to the patient's lifetime exposure although performing at low dose CT in the initial screening. The cumulative dose of even this low-dose CT scans can contribute risk although the NLST results were based on scanning annually for three years.¹⁴

Over diagnosis, an inherent part of any screening program is the detection of indolent or occult disease that would not otherwise have become clinically significant or impacted patient outcome. Downside of over diagnosis may cause unnecessary morbidity, mortality, anxiety, cost, and labels a patient with a disease.^{17,18} In the NLST, there were an excess number of lung cancers in the CT arm, compared to the chest radiograph arm. Nevertheless, over diagnosis is difficult to measure, even in a controlled trial.¹⁴ Smoking behaviors are complex, and screening is one variable in the problem. However, any LCS program should be closely affiliated with a smoking cessation program to apply this "teachable moment" and hopefully change smoking behavior in its subjects. In the NLST, 96 % of the positive results in the LDCT arm were false positive. Positive screens in the majority of cases were managed with at least one follow-up CT to determine stability of the pulmonary nodules. After two rounds of screening, there are fewer false positives as a result of comparison with the baseline screening CT, that may reveal two years of pulmonary nodule stability. Decreasing the number of false -positive lung cancer screens is an area for future research.¹⁴

Discussion

The eligibility criteria for the NLST to define high-risk persons are used in the current recommendations for LCS as the following: former or current cigarette smokers between the ages of 55 and 74, with at least 30 pack-years smoking history. The former smokers should have quit smoking within the last 15 years.¹⁴ LDCT screening is also included in the NCCN guidelines, based on lower level evidence, in persons 50 or older, with at least a 20 pack-year smoking history, and one additional risk factor.¹² LDCT screening for lung cancer is not intended for persons with clinical symptoms, such as weight loss, chest pain, or cough. Standard-dose CT with intravenous contrast-medium administration is the present standard of care in these symptomatic patients.¹⁴ The additional risk factors are a family history of lung cancer, a personal history of cancer or lung disease, occupational exposure to asbestos, silica, chromium, arsenic, cadmium, nickel, beryllium, and diesel fumes, and radon exposure that were based on the results of the International Early Lung Cancer Action program, including persons 40 years of age and older, with either a history of cigarette smoking, exposure to secondhand smoke, or occupational exposure to asbestos, radon, beryllium, or uranium.¹⁹

The number of diagnosed lung cancers per population screened would be higher, and fewer persons would be unnecessarily exposed to the related risks when eligibility criteria for lung cancer screening are further refined.¹⁴ In this regard, additional models have been developed to calculate a person's lung cancer risk.^{20,21} These models have the potential of enrolment into lung cancer chemoprevention strategies in addition to having the potential of selecting patients for screening.^{20,21} The Spitz model and the Liverpool Lung Project (LLP) model were published in 2007 and 2008, respectively.^{20,21} All models include risk factors, such as age, occupational exposure, and smoking duration. The Spitz model included physician-diagnosed emphysema, and family history of cancer in first-degree relatives whereas the LLP multivariate risk model included smoking duration (never, 1-20 years, 21-40 years, 41-60 years, > 60 years), family history of lung cancer (never, early onset [< 60 years], late onset [> 60 years]), prior diagnosis of occupational exposure to asbestos, prior diagnosis of malignant tumor, and prior diagnosis of pneumonia.^{20,21} Risk prediction models can be assessed by several qualities, such as accuracy, clinical utility, calibration, and discrimination. Discrimination is the ability of the model to differentiate between those persons who will develop disease versus those who will not develop disease.²² Risk estimates can potentially reduce the cost of LCS by focusing those at highest risk and have been used to design large-scale randomized control lung cancer screening trials. Genetic profiles and the results of the baseline screening examination can potentiate further refining the risk modeling. Risk modeling could define the frequency of follow-up in addition to who should be screened.¹⁴

Conclusion

In the results of the NLST, around 20% reduction in lung-cancer specific mortality with LDCT screening in a high-risk population was demonstrated and contributed to a turning point in LCS. LCS with LDCT has shown that there are indolent lung cancers that may not be fatal. Further studies are urgently needed if the maximization of the risk-benefit ratio in LCS has to be achieved.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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