

INVITED REVIEW

Early detection of lung cancer: Low-dose computed tomography screening in China

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Abstract

Lung cancer is currently the leading cause of cancer-related death in China and western countries for both men and women. Overall, the five-year survival rate of lung cancer is approximately 15%, whereas the five-year survival for patients with surgically resected early-stage disease is 60–80%. Screening is conceptually a good strategy for reducing the mortality rate of lung cancer. Randomized controlled trials in the 1960s and 1970s found that chest radiographic screening did not result in a reduction in mortality for high-risk individuals. Recently published data from the National Lung Screening Trial (NLST) showed a 20% reduction in lung cancer mortality in subjects who underwent low-dose computed tomography (LDCT) screening compared to those randomized to conventional chest X-ray. The encouraging results of the NLST, however, could not be confirmed by the preliminary results of ongoing European trials. More results from European randomized controlled trials are expected in the next few years. Recently, a number of lung cancer screening studies using LDCT have been initiated in China. This article briefly summarizes the results of the current and previous lung cancer screening trials worldwide, and focuses on the current status of LDCT lung cancer screening in China.

Introduction

Lung cancer is currently the leading cause of cancer-related death in China and western countries for both men and women.^{1,2} Lung cancer accounted for approximately 13% (1.6 million) of the total new cancer cases and 18% (1.4 million) of the total cancer deaths in 2008 globally.³ The morbidity and mortality rates of lung cancer in China are much higher than the worldwide average.⁴ During the last three decades, mortality from lung cancer has increased by 465% in China, and moreover, the number of lung cancer-related deaths will soar from 450 000 in 2008 to an estimated 850 000 or higher in 2030.^{5,6} Similar to developed countries, the majority of patients with lung cancer in China are diagnosed at an advanced tumor stage, and only a small proportion of patients have curable disease at the time of presentation. Overall, the five-year survival rate for lung cancer is approximately 15%, whereas the five-year survival for patients with surgically resected early-stage disease is 60–80%.⁷ The prognosis for patients with lung cancer is strongly correlated to the stage of the disease at the time of diagnosis; therefore early detection through screening could potentially decrease lung cancer mortality by diagnosing the disease at a potentially

more curable stage. Although previous randomized screening trials evaluating the role of chest radiography with or without sputum cytology have not resulted in a reduction in mortality, recent studies suggest that low-dose computed tomography (LDCT) may have promise as a screening tool for the early detection of lung cancer in high-risk asymptomatic individuals.^{8–19}

Current status of low-dose computed tomography (LDCT) screening trials

Early attempts to decrease lung cancer mortality by screening were performed in the 1960s and 1970s, focusing on chest X-ray (CXR) with or without sputum cytology analyses.^{8–12} However, no reasonable evidence that screening for lung cancer using these methods could reduce lung cancer mortality was found. In fact, recently released results from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial have shown once and for all that CXR screening does not result in the saving of lives from lung cancer.¹³ Until the 1990s, CT was not considered to be a viable option for lung cancer screening. This changed with the publication of a study by Naidich *et al.*, which demonstrated that a LDCT technique

could be used, which allowed for sufficient resolution to detect lung nodules while minimizing patient radiation dose.²⁰ Naidich *et al.* further speculated that LDCT may have applications for lung cancer screening in high-risk populations.

To evaluate the potential of CT as a screening tool, several observational screening trials using LDCT were conducted in Japan and the United States (US) in the early 1990s. These studies provided several valuable results.^{14–17} Firstly, it was confirmed that LDCT detects more lung cancers than chest radiographs (4 times more frequently with LDCT than with CXR). Secondly, LDCT is highly effective at detecting early-stage lung cancers (84–93% of screening-detected cancers are stage I). Thirdly, resection of stage I cancers prolongs survival time. Recently, a large scale study on lung cancer screening by LDCT (International Early Lung Cancer Action Program, I-ELCAP) resulted in a diagnosis of lung cancer in 484 participants out of 31 567 asymptomatic persons at risk for lung cancer, a high ratio of clinical stage I of 85% in the diagnosed patients, and a high estimated 10-year survival rate of 88% in the subgroup with clinical stage I lung cancer, confirming previous reports on LDCT screening.¹⁸

Although encouraging and promising, none of the aforementioned trials were able to prove mortality reduction by their single-arm design. To prove that LDCT screening results in a definite improvement of lung cancer mortality, randomized controlled trials (RCTs) had to be conducted. For this reason, a number of RCTs were established in the US and Europe in recent years.^{21–29} The National Lung Cancer Screening Trial (NLST) is by far the largest of the RCTs evaluating CT screening for lung cancer.²¹ It enrolled 53 454 participants in 33 centers all over the US. Active or former smokers with a smoking history of 30 pack-years or more, and an aged between 55 and 74 years, were included. Former smokers were only included if they quit smoking within the previous 15 years. Upon enrollment, participants were randomly assigned to one of two screening arms in which they were screened with LDCT or chest radiographs. In each of the two screening arms, the participants were screened three times at yearly intervals. Overall, 1060 lung cancers were diagnosed in the LDCT arm and 941 in the radiography arm. During the 6.5 years of follow-up, 247 deaths from lung cancer were observed in the LDCT group and 309 in the radiography group. This corresponds to a relative reduction in lung cancer mortality of 20% with LDCT screening. All-cause mortality was 6.7% lower in the LDCT screening arm than in the control arm.¹⁹ In Europe, currently eight smaller RCTs on LDCT screening for lung cancer are being or have been performed in several countries: NELSON in the Netherlands and Belgium; DLCST in Denmark; DANTE, MILD, and ITALUNG in Italy; LUSI in Germany; Depicscan in France; and UKLS in the United Kingdom.^{22–29} Results of MILD, DLSCT, and DANTE trials have been published thus far;

however, not all were able to detect a significant reduction in cancer-related mortality.^{23–25} Underlying reasons for these discrepancies between the US and European trials are not yet fully understood. Different inclusion criteria with respect to age and the severity of smoking history likely played a role, and different types and severities of comorbidities or geographic risk factors need to be considered, as well as the method of the diagnostic and therapeutic workup of screening-detected nodules. A pooling of the European randomized trial data is under discussion right now, and it is hoped that the findings will strengthen the evidence and address open questions. More results from European trials are expected in the next few years.

LDCT lung cancer screening in China

With the widespread availability of spiral and multidetector CT scanners in China, especially with LDCT screening for lung cancer gaining widespread acceptance in clinical practice, there was considerable interest in the possibility of a lung cancer screening service in China. As a result, a number of lung cancer screening studies using LDCT have been conducted in China since the early 2000s. These studies were mainly carried out in several economically developed urban areas or high-risk rural areas in China, such as Beijing, Tianjin, and Xuanwei of Yunnan provinces. The number of participants in these studies ranged from a few hundred to more than 5000.^{30–35}

In a pilot study published in 2002, Nie *et al.* screened 300 asymptomatic high-risk individuals aged 45 years or older using LDCT and CXR, of whom 240 smokers had smoked 10 pack-years or more and 60 individuals had chronic obstructive pulmonary disease.³⁰ Non-calcified nodules were detected in 56 (19%) participants by LDCT, while only nine (3%) by CXR. Lung cancer was detected in four (1.3%) by LDCT and three (1.0%) by CXR. All four of the lung cancers were stage I. Lobar or segmental bronchial abnormalities were detected in nine (3%) participants by LDCT, and three of them proved to be early central lung cancer. No bronchial abnormality was detected by CXR. The preliminary results suggested that LDCT could greatly improve the likelihood of detection for small non-calcified nodules and mild bronchial abnormalities, and, thus, of peripheral and central lung cancer at an early stage.

The Cancer Hospital at the Chinese Academy of Medical Sciences in Beijing, one of the only two I-ELCAP sites in China, has been conducting a lung cancer screening study since 2005, using the I-ELCAP protocol to screen asymptomatic participants. From July 2007 to June 2012, 4690 participants aged 40 years or older underwent LDCT screening for lung cancer. According to the National Comprehensive Cancer Network guidelines for lung cancer screening risk assessment (version 1.1, 2012), all subjects were assigned to

three groups: high-risk, moderate-risk, and low-risk. In terms of gender, smoking history, and second-hand tobacco smoke exposure, two other groups named male and female never-smokers who were exposed to second-hand tobacco smoke were identified. A total of 26 cases (27 lesions) were diagnosed as lung cancer (11 in men, 15 in women). The screening detection rate of lung cancer was 0.6% (26/4690). Except for small cell lung cancer (limited-disease), 25 (26 lesions) on baseline LDCT were non-small cell lung cancer (76.0% were stage I) and the rate of surgical resection was 88.5% (23/26). The diameter of resected lung cancers ranged from 5.0 mm to 29.5 mm (median, 16.3 mm). For female never-smokers aged 40 years or older who were exposed to second-hand tobacco smoke, the incidence of lung cancer was higher than that of the high-risk group and male never smokers who were exposed to second-hand tobacco smoke (1.4% vs. 0.9% vs. 0.4%). These results indicate that LDCT screening can identify smaller lung cancers and most cases are detected at an early stage. In light of the relatively higher incidence, researchers also stressed that further study is needed to focus on female never-smokers with second-hand tobacco smoke exposure in China.³¹

The 5th Affiliated Hospital of Sun Yat-Sen University, the other I-ELCAP site in Zhuhai, China, recently evaluated the change in outcomes from CT screening for lung cancer before and after collaboration with the I-ELCAP, as well as changing from a single-row detector to a multi-row detector CT scanner (MDCT). All participants in the screening program were 40 years of age or older. From 1994 to 2002, a single slice spiral CT was used; the screening protocol was established empirically at this institution. From 2003 to 2009, a 16-slice MDCT was used and this institute became the first I-ELCAP site in China. Collaboration included the use of the I-ELCAP protocol, image reading training, teaching file training, and attendance at international conferences. During 1994 to 2002, 3348 participants were enrolled, with 3582 participants during 2003 to 2009. Their age, gender, smoking, and family cancer histories were comparable. The screening detection rate of lung cancer was 1.1% (36/3348) versus 1.0% (34/3582) ($P=0.6$); mean size was 18.6 mm versus 15.6 mm ($P=0.04$); stage I lung cancer was 67% versus 91% ($P=0.38$); median intervals between last routine screening and surgery was 213 days versus 96 days ($P<0.001$); and the five-year survival rate as a result of lung cancer was 75% versus 95% ($P=0.032$) in the pre and post collaboration groups, respectively. The nodule positive rate was 6.2% (208/3348) versus 9.8% (351/3582) ($P<0.001$), and the rate of surgery for benign disease was 18% (8/44) versus 8% (3/37) ($P=0.4$) in pre and post collaboration groups, respectively. These results demonstrated that smaller lung cancer were detected, the interval between last routine screening and surgery was shorter, surgery for benign disease decreased, and survival rate increased using CT screening for lung cancer in Zhuhai after the collabora-

tion with I-ELCAP and with multiple detector CT. Consequently, the technology improvements, along with a well-defined protocol, improved outcomes of CT screening for lung cancer in Zhuhai, China.³²

Recently, several large-scale lung cancer screening programs have been initiated with special funds from central or local governments in China. In 2010, a national demonstration program was initiated with a special fund from the Chinese Central Government Public Health Special Subsidy, focusing on screening projects on lung, upper digestive tract, colorectal, liver, and nasopharyngeal cancers in rural areas of China.^{33,34} A lung cancer screening project was undertaken using LDCT in three regions that have a high incidence and mortality from lung cancer: Xuanwei city in Yunnan province, Dagang Oilfield in Tianjin, and Haidian District in Beijing. From July 2010 to June 2013, 8145 individuals underwent LDCT screening for lung cancer; 137 (1.68%) lung cancers were detected at baseline analysis, but only 47 (34.3%) cases were stage I. In 2012, the Chinese Government launched a national key public health program, the Cancer Screening Project in Urban Areas of China, which was initiated by the Ministry of Health (renamed the National Health & Family Planning Commission in 2013) and funded by the Ministry of Finance, aimed at promoting the early detection and treatment of the five top cancers (lung, breast, colorectal, liver and upper digestive tract cancers) in urban areas of China.³⁵ The lung cancer screening project was designed to provide a free lung cancer screening service using the low-dose spiral CT technique (≥ 16 -slice, 120 kVp, ≤ 30 mAs, 1–1.25 mm slice thickness) among the community-based, high-risk population in 14 provincial-level regions in China for five years. An estimated 210 000 (3000 cases/year/province \times 14 provinces \times 5 years) individuals will receive free baseline lung screenings between 2012 and 2017. In late 2013, a lung cancer screening program was sponsored and funded by the Beijing Municipal government, aimed at establishing, as well as optimizing, a LDCT lung cancer screening protocol, which would act as an early lung cancer screening regimen for future studies at local medical institutes and examination centers in Beijing. More than 8000 enrolled participants will be screened for the next three years in this study.³⁶

Conclusions

Lung cancer morbidity and mortality have increased rapidly in China over the past 30 years, with tobacco consumption and environmental pollution being the major risk factors. Besides smoking cessation and reducing air pollution, early detection and treatment is an important aspect of lung cancer prevention and control in China. For the time being, LDCT is the most promising tool for large-scale population-based lung cancer screening. However, the transition of screening from the realm of research to clinical care is still riddled with

uncertainties. A number of open questions regarding the definition of persons at risk, the timing and intervals of screening, the management of screening-detected nodules, over diagnosis, and cost-effectiveness need to be addressed further. Additional randomized trials using LDCT are ongoing and will hopefully address these unanswered questions. Such trials may eventually demonstrate the real impact of early detection on mortality at a population level.

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Disclosure

No authors report any conflict of interest.

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