Review Article

Implementation of lung cancer screening: promises and hurdles

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Abstract: Lung cancer screening is a subject of considerable interest in the medical community and the general population. Since the publication of the data from the national lung screening trial (NLST) in 2011, the interest in lung cancer screening has increased even more. Data from many sources provide evidence that low-dose computed tomography (LD-CT) lung cancer screening can be performed with even greater efficacy if inclusion criteria as well as nodule management are optimized. There are, however, also a number of potential hurdles for the implementation of lung cancer screening. Among these are, in particular, the high prevalence of screen-detected pulmonary nodules, the unknown extent of over-diagnosis, the potential harms of the cumulative radiation dose and the insufficient data on cost-efficiency of lung cancer screening. In this article, the most recent insights into some of the most imminent questions are reviewed to provide an understanding of the challenges we still face in lung cancer screening.

Keywords: Lung cancer screening; pulmonary nodules; lung cancer

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Introduction

Lung cancer screening has gained considerable interest in the medical community, as well as in the general population, over the last two decades. Since the publication of the data from the national lung screening trial (NLST) in 2011, the interest in lung cancer screening has increased even more. With more than 50,000 enrolled persons, the NLST could prove, for the first time, that by using lung cancer screening with low-dose computed tomography (LD-CT)—compared to screening with chest radiographs—lung cancer mortality could be improved by 20% (1). In addition to lung cancer mortality, overall mortality could also be improved in the LD-CT screening group by 6.7% (1). The promising data from the NLST encouraged several major American medical societies to recommend offering LD-CT screening for high-risk patients (2-4). In a current survey among members of the Society of Thoracic Radiology, 65.9% of the responding institutions indicated that they had an active LDCT screening program (5). Of the institutions without an active screening program, 89.3% indicated that they were considering such a program in the future (5). The results of this survey indicate that lung cancer screening has finally arrived in many centers in the US.

While LD-CT lung cancer screening is implemented in more and more US centers, there are only a few LD-CT screening projects in Europe outside screening trials. The reservation about the implementation of screening projects in Europe can, in part, be explained by the ongoing screening in many countries where results are expected to be published within the next few years. Initial data from two Italian screening trials (the MILD trial and the DANTE trial) and one Danish trial (the DLCST trial) could not confirm the positive effect of LD-CT lung cancer screening on mortality (6-8). The number of participants in all of the three trials, however, is too small to reach statistical significance.

Although the majority of the ongoing European screening trials are statistically underpowered, a pooling of the data is expected to strengthen the evidence and to provide insights into many open questions.

Promising data from the NLST and other trials provide evidence that LD-CT lung cancer screening can be performed with even greater efficacy if inclusion criteria,

as well as nodule management, are optimized. There are, however, also a number of potential hurdles for the implementation of lung cancer screening. Among these are, in particular, the high prevalence of screen-detected pulmonary nodules, the unknown extent of over-diagnosis, the potential harms of the cumulative radiation dose and the insufficient data on cost-efficiency of lung cancer screening. A broad implementation of LD-CT screening largely depends on answering most, if not all, of these questions. In this article, the most recent insights into some of the most imminent questions are reviewed to provide an understanding of the challenges we still face in lung cancer screening.

Who should be screened?

The positive effect of lung cancer screening depends, to a great degree, on the prevalence of lung cancer in the screening population. In the NLST, only persons between 55 and 74 years of age and a smoking history of more than 30 years, or former smokers who quit smoking within the previous 15 years, were included (9). These inclusion criteria defined a study population with an estimated risk of developing lung cancer, ranging from 2% to more than 20%, within 10 years (10). The positive effect of lung cancer screening could be increased even further by adding additional inclusion criteria, such as gender, passive smoking history, history of pneumonia, history of non-pulmonary tumors, or occupational exposure to asbestos.

Using the data from the NLST, a risk prediction model for lung cancer death was recently published, which used the risk factors of age, body-mass index, family history of lung cancer, pack-years of smoking, years since smoking cessation, and emphysema diagnosis to estimate the 5-year risk of lung-cancer death (11). This retrospective study confirmed that the number of prevented lung-cancer deaths increased with increasing risk quintiles (11). In the quintile with the lowest risk, only very few deaths (1%) would have been prevented. In fact, 88% of the prevented lung-cancer deaths were distributed among the three quintiles with the highest risk (11).

The impact of a more sophisticated risk model on the effectiveness of lung cancer screening is currently being investigated in the ongoing British UK lung screen (UKLS) trial. In this trial, only patients with an at least 5% risk for developing lung cancer within the next five years are included. The risk for developing lung cancer is estimated using a model developed in the Liverpool Lung Project (LLP) (12). The LLP risk prediction model includes age, sex, smoking duration, family history of lung cancer, history of non-pulmonary malignant tumor, history of pneumonia, and occupational exposure to asbestos to estimate the lung cancer risk (12). It is projected that, by using these inclusion criteria, the prevalence of lung cancer in the screening population will be twice as high as in the Dutch NELSON trial (13).

At what intervals should the screening be planned?

The screening interval has a direct impact on screening performance, as well as overall costs and the cumulative radiation dose. Long screening intervals carry the risk that, aggressively growing tumors, in which the interval between the origin of the tumor, its detectability by CT, and the point at which it manifests, is quite rapid, may not be detected in early stages. Thus, screening would detect mainly indolent, slowly growing tumors. However, short screening intervals increase the probability of detecting aggressive cancers with the shortcoming of increasing the overall costs and cumulative radiation dose.

To date, most of the prospective screening trials were designed with annual screenings for three or five years (1,6,8,14). However, although not yet investigated in a prospective trial, biennial (twice-yearly) screening could have the potential to be more cost-effective than annual screening. A current prediction model based on the UK lung cancer screening eligibility criteria and the NLST data suggests that the intervention effect of biennial screening could indeed justify the human costs (15). Prospective trials will be necessary to further investigate the effect of biennial screening on survival.

How should detected nodules be managed?

One of the major challenges of lung cancer screening is the high incidence of detection, coupled with a very low proportion of malignant nodules. In the NLST, a positive screening result was reported in 24% of all baseline LD-CT scans (1). A positive screening result was thereby defined as a non-calcified pulmonary nodule with a maximum diameter of more than 4 mm. Importantly, all but 3.6% of the detected pulmonary nodules eventually proved to be benign in nature (1). Most of the detected nodules were further evaluated with follow-up CT examinations, and only 2.6% of the nodules were surgically resected. Even though the majority of the nodules were investigated with

follow-up examinations or minimally invasively, the added cost and cumulative radiation dose, the potential risks of these examinations, and, last but not least, the anxiety of the screened persons with a positive result are of major concern. As the probability of malignancy increases with increasing nodule diameter, using a threshold for nodule diameter, which would define positivity to 7 mm, would decrease the early recall rate by up to 70% (16). By considering additional data besides the size of the nodules, such as the location of the nodule, the number of detected nodules, the sex and age of the screened person, and the extent of emphysema, the risk of malignancy of the nodules could be even better predicted and the recall rate could be reduced even further (17).

Much has been done in the last few years to provide a reliable classification scheme for screening-detected nodules. Analogously to the Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology (ACR), which is used worldwide in breast cancer screening, the ACR recently proposed a Lung Imaging Reporting and Data System (Lung-RADS) (18). A similar system, the Lung Reporting and Data System (LU-RADS), was published by another group (19). In both classification schemes, screening-detected nodules are categorized and managed according to their individual risk. Both classification schemes should be easy to apply in the clinical routine and allow standardized data collection and analysis.

How big is the risk of over-diagnosis?

One of the major uncertainties in lung cancer screening is the extent of over-diagnosis. Over-diagnosis is defined as the detection of cancer that otherwise would not become clinically apparent (20). Thus, the detection of lung cancer during screening does not necessarily result in improved lung cancer mortality, as a proportion of the detected cancers would have remained asymptomatic. Follow-up and treatment of such indolent cancers would add to the costs and potential risks of screening. Early reports concluded that the proportion of over-diagnosed cases could be as low as 5% (21). More recent data, however, indicate that the extent of over-diagnosis in the NLST could have been more than 18% (20). This estimation is almost as high as in a study based on data from an Italian cohort study, which estimated that over-diagnosis could be as high as 25% (22).

To date, there are no generally accepted criteria by which to differentiate indolent tumors from genuine ones. Strategies to reduce over-diagnosis focus on a reduction of the frequency of screening examinations, a better definition the screening population, and raising the threshold for follow-up examinations and invasive diagnosis (23).

How cost efficient is lung cancer screening?

Little is known about the cost-efficacy of lung cancer screening, which was considered to be a major hurdle for the implementation of a screening project. An actuarial analysis demonstrated, however, that, in the United States, lung cancer screening in high-risk populations would cost insurers less per life-year saved than colorectal, breast, or cervical cancer screening (24). Similar data comes from a study from Israel which showed that baseline LD-CT screening can be performed with relatively low costs per quality-adjusted life-year (QALY) (25). In this study, the estimated cost per QALY gained was as low as $20,000 (25). As health care systems differ significantly between countries, cost-efficacy analyses from one country cannot easily be translated to other countries.

What is the potential risk of the cumulative radiation dose?

The discussion about the potential risk of the cumulative radiation dose in LD-CT lung cancer screening from repeated screening CTs and potential follow-up CTs, has evened out in the last few years. In the NLST, the reported effective dose per screening CT was an average of 1.6 mSv for men and 2.1 mSv for women (25). However, due to the high number of follow-up examinations, the average cumulative radiation dose after three screening rounds added up to 8 mSv (10). This cumulative radiation dose was estimated to cause one cancer death per 2,500 persons screened (10). However, as in the NLST, lung cancer screening was able to improve the overall mortality by 7%; thus, the positive effect of screening outweighs the risk of radiation-induced cancer.

As modern CT scanners are able to scan the whole chest with less than 1 mSv, and future staging protocols will be performed with a dramatically lower recall rate, the cumulative radiation dose will decrease, and thus, the risk-benefit ratio will further improve.

Conclusions

More data from many different sources provide evidence that LD-CT lung cancer screening can be performed with

a higher efficacy if inclusion criteria, as well as nodule management, are optimized. However, to date, only NLST has been able to show the benefits of LD-CT screening with regard to lung cancer and overall mortality. The promising data of the NLST is further supported by analyses, which have demonstrated, that LD-CT lung cancer screening can be performed with even greater efficacy if inclusion criteria as well as nodule management are optimized.

In addition, more and more data provide evidence to overcome potential hurdles in lung cancer screening such as questions regarding the extent of over-diagnosis and potential harms of the cumulative radiation dose. Questions regarding cost-efficiency of lung cancer screening have to be answered for each healthcare system separately.

As most of the data derives from one single study, the NLST, the data, needs to be confirmed, at least in part, by the pooled data of the ongoing European trials.

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