Review Article

Lung cancer screening: where do we stand?

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Contributions: (I) Conception and design: F Minervini; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: F Minervini; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: A screening program for cancer in selected patients population could be a very effective measure to reduce morbidity and mortality rates. Several trials analyzed the efficacy of screening programs in lung cancer patients but nonetheless a worldwide adopted screening tool is lacking to date. Several uncertainties still exist but the scientific evidence about the efficacy of lung screening programs is already available.

Keywords: Lung cancer; screening; prevention

Received: 25 June 2019; Accepted: 13 November 2019; Published: 12 December 2019.
doi: 10.21037/pcm.2019.11.04
View this article at: http://dx.doi.org/10.21037/pcm.2019.11.04

Introduction

Lung cancer is the leading cause of cancer death among both sex combined. Around 44,500 people are diagnosed with the disease each year in the UK, more than 230.000 in the USA and the estimates for 2019 are comparable, if not even worse (1).

Lung cancer has one of the lowest survival rates, along with liver and pancreatic cancer. Despite recent advances in surgery, chemotherapy/immunotherapy and radiotherapy, morbidity and mortality high rates of lung cancer remain an unsolved problem. Even if the 5 years survival rate for all stages combined is slowly improving (12% for lung cancers diagnosed from 1975–1977 up to 18% for lung cancer diagnoses between 2003 and 2009), lung cancer remains the leading cause of cancer death in 87 countries in men and 26 countries in women (2).

Screening = prevention?

According to the Hippocratic "Prevention is better than cure", the role of prevention in reducing lung cancer mortality could be of key importance. The objective of a screening program should be to identify a disease at an early stage namely when the treatment will be most successful increasing in this way the life expectancy and quality of life (QoL). Lung cancer prevention includes avoidance of risk factors such as smoke, radon or asbestos exposure as well as effective screening policies.

Screening programs for cancers in selected patient populations has become a cornerstone of health care system in several countries. If we consider the benefits in reducing mortality and morbidity from the adoption of screening recommendations in the context of breast, colorectal or prostate cancer it seems to be obvious the urge of a lung cancer screening program worldwide.

Early trials reviewing the utility of chest radiography (CXR) and sputum cytology as screening modalities did not demonstrate any mortality benefit.

In 1983 was published a study about the Mayo Lung screening program using 4-monthly CXRs in high risk patients. Male heavy smokers over 45 years old were randomized to a control group (4,593 patients) or to a group that received repeated CXR follow up every 4 months (4,618 patients) after a normal initial CXR and sputum cytology. Ninety-two lung cancers were detected by CXR and of these, 52 were classified as stage I, 4 were stage II disease while the 35 had stage III disease (3).

However, the analysis of final results of this randomized trial showed that offering both CXR and sputum cytology to high-risk outpatients every 4 months did not give any mortality advantage over standard medical practice that included recommended annual testing (4). About 30 years later, a randomized study (PLCO trial) conducted in the USA involving 154.901 participants showed that annual screening with CXR had no effect in reducing lung cancer mortality compared with usual medical care (5).

The same conclusion has already been drawn in the National Lung Screening Trial (NLST), published in 2011 (6). The NLST selected from August 2002 through April 2004 53,454 participants at high risk for lung cancer in the age group between 55 and 74 years. The high risk status was defined as history of cigarette smoking/exposure of at least 30 pack years or ex-smokers (with similar exposure) but without smoking within 15 years. Subjects were randomly assigned to undergo three annual screenings with low-dose computed tomography (LDCT) (26,722 participants) or single-view posteroanterior CXR (26,732). The percentage of adherence to the screening program represents one of the strengths of this trial (>90%). Positive screening tests was obtained in 24.2% of the participants with low-dose CT and in 6.9% with radiography altogether. The interesting result of the NLST was the observation of a 20.0% decrease in mortality from lung cancer in the group who underwent low-dose CT as compared to the radiography group. Even the mortality rate from any cause was reduced in the low-dose CT group, as compared with the radiography group, by 6.7% (95% CI, 1.2–13.6; P=0.02).

A total of 92.5% of stage IA/IB lung cancers in the low-dose CT group and 87.5% of those in the radiography group underwent, as first line treatment that occurred within 6 months of diagnosis, surgery alone or in combination with chemotherapy +/− radiotherapy. Very few adverse events have been reported (1.4% in the low dose CT group and 1.6% in the radiography group) following a diagnostic procedure after a positive screening test. A small number of subjects (16 in the CT group and 10 in the radiography group) died within 2 months after the invasive diagnostic procedure but a direct correlation between death and procedure has not been demonstrated.

In 2015 a group of Italian researchers tried to corroborate the result of the NLST by publishing the DANTE (Detection And screening of early lung cancer with Novel imaging Technology) trial which included 60-to 74-year-old male smokers or former smokers of at least 20 pack-years who had quit less than 10 years before recruitment (7). All participants of both arms had a baseline CXR and 3-day sputum cytology, but only subjects in the LDCT arm also underwent a baseline CT scan of the thorax on the same day. In the four years after randomization LDCT screening rounds were planned in the LDCT arm in addition to a medical interview along with a physical examination focused on respiratory symptoms. Subjects of the control arm received only a yearly clinical examination.

In the DANTE trial the screening program permitted to detect more lung cancers and more early stage lung cancers than the control group. In contrast to the NLST however, no benefit was showed regarding lung cancer specific mortality or all-cause mortality. Therefore, the lack of statistical significance did not permit a precise and conclusive statement about the efficacy of the LDCT screening.

Two years after the DANTE trial, Paci and other members of the ITALUNG working group randomised 1,613 subjects (aged 55–69 years, smokers or ex-smokers at least 20 pack-years in the last 10 years) to annual LDCT screening for 4 years and 1,593 to usual care (8). An overall mortality reduction of 17% (RR 0.83; 95% CI, 0.67–1.03) and 30% lung cancer specific mortality (RR 0.70; 95% CI, 0.47–1.03) were observed but, like the DANTE trial, ITALUNG was not powered to demonstrate statistical significance.

A similar limitation has been encountered by Wille and colleagues who published in 2015 the Danish Lung Cancer Screening Trial (DLCST) (9). This trial included participants of younger age (50–70 year), with a smoking history of 20 pack-years, and 30% predicted FEV1 and showed no difference in mortality in the screening group. A high risk subgroup analysis (subjects more obstructive lung function and >35 pack-years) showed non significant 20% lower hazard ratio for lung cancer related mortality in the screening group. This finding reflects the same favorable effect of screening reported in the NLST. Presumably, several factors are responsible for the lack of benefit in DANTE and DLSCT but, in our opinion, suggesting emphysema as eligibility criteria for the screening is a plus point of the DLSCT because it can be useful in order to personalize the screening strategy.

The MILD trial, published recently by several Italian authors, provided further evidence that prolonged screening beyond five years could improve the benefit of early detection and achieve a greater overall and mortality reduction in lung cancer patients when compared to NLST trial (10). Even if not still published, a very large

randomized trial including more than 15,000 patients (the NELSON trial) showed good results that were presented at the International Association for the Study of Lung Cancer's (IASLC's) 19th World Conference on Lung Cancer (WCLC) in Toronto, Canada. In the screening group, participants underwent a CT scan at baseline, one, three and five and one-half years after randomization. About 69 percent of screen-detected lung tumors were classified as Stage 1A or 1B. CT scanning decreased mortality by 26% in high-risk men and up to 61% in high-risk women over a 10-year period. The key point in the management of lung nodules in the NELSON trial is represented by the use of volumetry and volume doubling time to identify potential cases of early lung cancer (11).

The importance of volumetric analysis of the nodules is recommended as well in the European position statement on lung cancer screening (12). In particular, Oudkerk and colleagues emphasize the imperative of using a volumetric approach, as reported in the NELSON trial, in order to try to reduce the number of false positive which, in the NLST, was 96.4% of the positive results in the low-dose CT group and 94.5% of those in the radiography group (6,12).

Oudkerk and colleagues analyzed first the available literature addressing several issues in order to implement a LDCT screening program in Europe. Key points of this statement are the use of a risk stratification approach, smoking cessation policy combined with the CT screening program, comprehensive information of the patients about potential risks derived from radiation exposure or intervention in case of false positive and introduction of national quality assurance boards as supervisory bodies of minimum technical standards.

All these trials have given rise to several questions, most of them still unanswered.

How to apply this screening program to people with different risk profiles? How long should the screening continue? How often? These issues are not insignificant and need to be deepened and clarified.

Race, gender or geographical differences in the context of a screening program can lead to disparities in cancer care due to several reasons (economic status, access to health care services, level of education) and, therefore, identification of such differences is mandatory in order to minimize disparities and maximize screening benefits.

The German Lung cancer Screening Intervention (LUSI), for example, reported gender heterogeneity with a statistically reduction in lung cancer mortality among women (HR 0.31; 95% CI, 0.10–0.96, P=0.04), but not among men (HR 0.94; 95% CI, 0.54–1.61, P=0.81) (13).

Gender differences are relevant as well as geographical or race peculiarities. The majority of European or American trials focused their attention on the smoking subpopulation but different risk profiles can be observed, i.e., in China. The incidence of lung cancer in Chinese never-smoking women is higher than their counterparts in the UK and the USA (28% *vs.* 15.4% *vs.* 2.3%) as is lung cancer related mortality (14). Given the different risk profile in China, Sheehan and colleagues, using simulation models, compared the impact of Chinese guidelines to lung cancer policy model developed for the United States by the U.S. Centers for Medicare & Medicaid Services (CMS). The authors have assumed that a screening program based on the Chinese screening guidelines would prevent about 20,000 (2.9%) more lung cancer deaths until 2050 compared to the CMS guideline (15).

In addition, about 90% of the patients included in the NLST were white with a minor percentage of African American (4.5%). On the contrary, a study conducted with a minority-based population at the University of Illinois at Chicago (African American 69.6%, Latino/Hispanic 10.6% but with a higher percentage of current smokers if compared with the NSLT, 72.8% *vs.* 48.1%) showed a high percentage of positive CT scans (16). Based on their results, the authors concluded that a more-detailed risk profile evaluation may be more effective than considering age and smoking status as the most important criteria to target a screening program.

A further problem is represented from the false positive results ranging in the literature between 10% and 43% (17). False-positive and indeterminate results require additional follow-up with CT scans, or interventions such as percutaneous needle biopsy, or even surgical biopsy. All these procedures bring with them risks and potential harms as well as psychological burdens for the patients to such an extent that if lung cancer screening can affect QoL is still a topic of discussion.

A systematic review published by Slatore and colleagues analyzed the consequences of a screening program using a LDCT reported in six studies focusing the attention on patient-centered outcomes like QoL, distress and anxiety (18).

The authors didn't find any long-term differences in anxiety, QoL or distress but an increased psychological discomfort in the short term following positive or indeterminate results during the screening. These conclusions are consistent with findings reported by other studies (19,20) but differ from outcomes reported in the participants group of the Pittsburg Lung Screening Study (PLuSS). In this trial, individuals with a suspicious CT finding in the PLuSS

trial experienced an increased perceived risk of cancer and fear of cancer after screening (21). Presumably, a different performance in patient-doctor communication can explain the above mentioned discrepancy.

Improving the quality of communication with the screening program participants and, of course, the reduction of false positive should be key points in order to improve patient outcomes.

Last but not least, providing high-quality care but, at the same time, containing cost is a nowadays crucial to ensure economic stability of the health care system.

The cost-effectiveness of the screening program must be investigated even if seems to be demonstrated in countries that have the resources available (22,23).

Several pilot studies and basic screening programs are currently ongoing in Europe, mostly in the UK (24,25). A common point of these abovementioned screening programs is the use of "Lung Health Checks" in which smokers subject are invited to receive an evaluation including symptoms history, lung function test and tobacco addiction treatment and eventually a LDCT. The "Manchester screening program", which uses even mobile CT units, showed a lung cancer detection rate of 4.4% across two screening rounds of which 80% were early stage (I–II) with an overall false positive rate of 3.5% (0.8% in the second round) (26). Because of these promising outcomes, the National Health System is nowadays trying to extend and support such screening programs in the entire country (27).

In Asia several trials are ongoing but the screening programs are addressed frequently to the entire population due to a high incidence of lung cancer (between 10% and 30%) among never smokers (28). However, based our knowledge, there are to date no large randomized trials conducted in Asia.

Conclusions

Despite the clear findings of the NLST and NELSON trial, due to the doubts regarding the cost and potential complications associated with false positive screening, a widespread adoption of a lung cancer screening program is still lacking to date.

Nowadays, precisely because of the two above mentioned trials, we know that a CT screening program applied on high risk population can be an effective tool to curb the epidemic generated by lung cancer but the identification of risk profiles needs to be established. The development of new technologies and approaches for early diagnostic such as circulating cells or tumor DNA, nano sensors or cancer specific protein fragments, can potentially be used to reduce screening examinations and to personalize screening intervals based on an individual's risk.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors Alfredo Addeo and Giuseppe Banna for the series "Non-Small Cell Lung Cancer (NSCLC)" published in *Precision Cancer Medicine*. The article has undergone external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/pcm.2019.11.04). The series "Non-Small Cell Lung Cancer (NSCLC)" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pcm.2019.11.04
Cite this article as: Minervini F, Scarci M. Lung cancer screening: where do we stand? Precis Cancer Med 2019;2:34.

