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Edited by:

Tao Li, MD, Ph.D.

University of Washington School of Medicine, USA

Editorial

Lung Cancer Screening: Still not the Definitive Answer

Addonisio G* and Morana G

Department of Radiological, General Hospital Ca' Foncello, Italy

Lung cancer is the second malignant neoplasia, by incidence, (accounting for 14% of the total number of tumors), preceded only by prostate cancer in males (28%) and breast cancer in females (29%). In both males and females, lung cancer is the first death cause for cancer [1].

Trends in lung cancer mortality rates [2] show a slow but constant decline in male sex, after the peak in the 90s, whereas in females a gradual increase in mortality occurred since the 80s, but decreased since 2002.

There is a well-recognized cause-effect relationship between lung cancer and tobacco use: tobacco is calculated to be responsible for around 80% of lung cancer deaths, although other risk factors are recognized, especially in female sex. Moreover, cigarette smoke is responsible for around 30% of cancer deaths from different cancer sites: superior airways and digestive ways especially, understandably, but also urinary bladder and pancreas [3].

Lung cancer accounts for around 30% of cancer deaths. 50% of cases are diagnosed in a late stage, with 5-year-survival rates not higher than 5% in patients with metastatic cancer. 5-year-survival in patients with low stage tumors is 53% and more than 70% in stage 1A [4]. The rationale for lung cancer screening lies in the possibility to identify a high-risk population (smokers

Corresponding author

Addonisio G, Department of Radiological, General Hospital Ca' Foncello, Treviso, Italy, Email: gaddonisio@ulss.tv.it

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of middle - advanced age), for whom early diagnosis could effectively ameliorate the prognosis.

In lung screening, the best outcome indicator is specific mortality. The aim of a screening program must therefore not only be the early disease diagnosis, but also the proof that therapy of low-stage neoplasms can reduce specific mortality in absence of adverse events related to diagnosis and therapy itself [5]. Survival, on the other side, is not a valid marker of efficacy for a screening test, because of three well-known biases.

Lead-time bias indicates the anticipation of disease diagnosis by screening, which improves survival but doesn't modify the exitus that is specific mortality, as it not postpones the date of death.

Lenght bias depends on the fact that different clinical expression of the target disease can have non homogeneous progression. While most aggressive lung cancer types, such as NSCLC, can arise in the time interval between screenings and when diagnosed are already inoperable, slow-growing tumors, less aggressive, have a long pre-clinic phase and can be easily diagnosed with a screening test: it follows that screening has a

bigger probability to find slow-growing lesions, pretending to be more useful than it really is.

Overdiagnosis bias happens when a screening test finds slow-growing lesions that could remain silent for all the patient's life [6]. Autoptic studies of the last decades have shown that only a small percentage of lung tumors actually bring patients to death [7].

Screening trials with the use of chest radiography, with or without cytologic analysis of sputum specimens, had unsatisfactory results: they didn't lead to improved survival rate, did not reduce mortality from lung cancer nor did they reduce mortality from every cause [8-12].

At the beginning of the 90s, CT with low radiating dose (LDCT) seemed to give a new drive to lung screening: CT has a higher sensibility in detecting small lung nodules, compared to standard chest X-ray, even with a low-dose-protocol. LDCT shows a 3-fold increase in lung nodules detection compared to standard chest X-ray, and a 4-fold increase in neoplastic nodules detection; but above all, it shows a 2-to-4-fold increase in low-stage neoplasms detection, according to different papers [13].

Single-arm observational screening studies, randomized or not, have shown that screening allows an increase in diagnoses of low-stage lung cancer, when theoretical probabilities of success are higher, increasing stage shift (that is the reduction of advanced stage neoplasms diagnosis and the increase of low stage lesions diagnosis) and survival, but they failed to demonstrate an impact on specific mortality [14-17]. Moreover, all most important trials, except for I-ELCAP [18], had too small a statistical sample or too short follow-up programs to reach definitive conclusions.

Different studies brought contradictory results: the ELCAP study estimated that 10-year survival to be 80%, but other studies have reduced or even denied this result; and the ability of screening tests to cause a stage shift [19] was questioned.

The randomized controlled studies with LDCT all share the problem of the sample size, too small to demonstrate a statistically significant reduction in mortality from lung cancer. The only trial with a significant sample size is the NSLT [20]: 33 medical centres in the Usa, which enrolled more than 53.000 patients, between 55 and 74 years of age, all smokers with a history of at least 30 pack-years, or former smokers who had quit in the last 15 years; the control arm was administered a standard chest X-ray. The trial was interrupted sooner than the expected time because the primary endpoint had been reached: a 20% decrease in mortality from lung cancer in the low-dose Ct group compared to the radiography group. The premature interruption of the trial doesn't allow us an univocal position on the over diagnosis bias, although the slow-growing neoplasms have been quantified, in the CT arm, in around 20% of the tumors in 1A stage. The results are still under evaluation, especially about the risk-benefit relationship of the protocol and its sustainability in these times of crisis of the national welfares.

Many european screening studies are presently ongoing [21-25], whose preliminary results have been made public, but they all have a sample unable to demonstrate a statistically significant reduction of specific mortality. A project exists, to combine all different studies' results, to obtain a more significant sample.

Many questions remain unsolved, concerning the development of a screening trial. Are the inclusion criteria correct? Is ethically acceptable to exclude high-risk subjects who are younger or to include less young patients who have important comorbidities? Are the results of NSLT applicable to categories with a smaller risk or to different ethnic groups?

One possible solution of the problem is to select more precisely the risk of developing a lung neoplasm. In the study of Tammemagi [26] a predictive model of the risk to develop lung cancer was developed, which includes not only age and smoke anamnesis, but also different criteria (such as ethnical group, body mass index, history of preceding cancer or COPD), all with their risk coefficient.

But restricting the number of enrolled subjects is not enough, because the problem of the false positives remains: one of the possible solutions is the calculators of malignancy of the lung nodule, available on the web too, based on the analysis of different parameters of the patients and of the lung nodule itself.

In conclusion, the only screening trial which has obtained convincing results in terms of specific mortality is the NSLT, but the premature interruption of the project because the minimum useful benefit had been reached leaves many questions unsolved. More information will come from the completion of the ongoing european trials and from a deep analysis of the risk-benefit ratio and of the economical sustainability of the proposed protocols.

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