

Pneumologia

Lung cancer screening – a necessity? – Brief literature review

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Abstract

English:

Lung cancer ranks among the first in terms of mortality rates in the world, which is why a screening program for people at risk is imperative. However, nowadays, thanks to new diagnostic technologies and oncological therapies, lung cancer has maybe come to be classified as a chronic disease. Low-dose computer tomography is currently the best method for lung cancer screening, and the screening criteria are already established internationally. Very important is the psychological or therapeutic support given to patients in the attempt to quit smoking, as well as other methods of prevention and combating pollution.

Keywords

lung cancer • screening • low-dose CT

Screening-ul pentru cancerul pulmonar - o necesitate? - O scurtă evaluare a literaturii

Rezumat

Romanian:

Cancerul pulmonar se situează printre primele afecțiuni în ceea ce privește rata mortalității din lume, motiv pentru care un program de screening pentru persoanele cu risc este imperativ. Cu toate acestea, în zilele noastre, datorită noilor tehnologii de diagnosticare și terapiilor oncologice, cancerul pulmonar a ajuns să fie clasificat drept o boală cronică. Tomografia computerizată cu doze mici este în prezent cea mai bună metodă de screening pentru cancerul pulmonar, iar criteriile de screening sunt deja stabilite la nivel internațional. Foarte important este suportul psihologic sau terapeutic acordat pacienților în încercarea de a renunța la fumat, precum și alte metode de prevenire și combatere a poluării.

Cuvinte-cheie

cancer pulmonar • screening • CT cu doză mică de radiații

Background

One of the most important healthcare problems is lung cancer, which is the first cause of death among men and the second cause of death for women, after breast cancer, around the globe, for people under 70 years old. According to Globocan 2020, even though breast cancer is at 11,7% rate of incidence, lung cancer follows quickly with only 11,4%

of all types of cancer. There's a major difference between Eastern Europe, with an incidence of 57,1% and a death rate of 15,3%, and Western Europe which doubles the incidence, but with a similar death rate 15,3%. Comparing the gender distribution, according to GLOBOCAN, there is another major difference between Eastern and Western Europe, in terms

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of the percentage of women who are diagnosed with lung cancer in Western Europe, so if men represent 49% of people diagnosed with lung cancer in both sides of the continent, women represent 11,6% in Eastern Europe and in Western Europe 25%. It should be noted that these data are the 2019 reports, which do not predict the impact of the pandemic that has influenced the evolution of cancer in Europe since 2020 (1, 2). So, in this case, screening for lung cancer is a priority for Romania and Europe as well.

Bronchopulmonary neoplasm is expected to be responsible for more than a quarter of a million cancer deaths (3). This is explained by the main risk factor, smoking, which nowadays is equally important for women and men, especially because we have more women who are smokers compared to the historical trend when only men used to smoke. Other risk factors include occupational exposures to radon, asbestos, and silica, exposure to air pollutants, lung diseases such as pulmonary fibrosis, HIV infection, genetic factors, and finally, obesity (4).

The prognosis of these patients is poor because the life expectancy for 5 years is only 20% since most patients are diagnosed when metastatic disease is already installed and therefore, we are dealing with an advanced stage of the disease, that requires palliative care.

But why is this happening? The explanation is that other types of cancer – colorectal, breast, cervical, and prostate have established cost-effective screening methods and benefit from media campaigns to raise awareness of the risks involved, making it possible to detect cancer at an early stage, when it's still curable.

Methods

We analysed published data about lung cancer and screening methods, from specialized literature (books, international articles, and recommendations from international guidelines) between the years 2004-2022. The search words were “lung cancer screening”, “lung cancer” and “bronchoscopy”.

Results

Benefits of Lung cancer screening

Lung screening is important to detect early cancers and increase the overall cure rate and allow more limited surgical resection to achieve a cure. The screening program is a multidisciplinary program, if that screening is properly performed and results properly interpreted, is important to have a good follow up of patients, to make sure the program is effective.

The success of lung cancer screening can be assessed using various outcome measures, including cancer detection rates,

stage at detection, survival, disease-specific mortality, and overall mortality.

Enrollment in lung cancer screening may also positively effect smoking cessation rates (5).

How to screen for lung cancer?

The approach to lung cancer screening has been done through a variety of methods over time, but regardless of the method adopted, cancer screening involves associating imaging examination of the lung with a patient with risk factors for smoking.

Who is suitable for lung cancer screening?

New eligibility criteria for bronchopulmonary cancer screening, according to the 2021 United States Preventive Services Task Force (USPSTF) Recommendation Statement for Screening for Lung Cancer, have reduced the minimum age for screening from 55 to 50 years and smoking / year packages to be from 30 to 20 packages. Patients over the age of 80 who have been smoking cessation for more than 15 years should stop screening for bronchopulmonary cancer (6).

Screening should be discontinued once the individual has not smoked for 15 years or has a limited life expectancy. One of the goals and hopeful consequences of the USPSTF recommendation is to expand lung cancer screening to underserved populations who are at high risk of lung cancer, as well as women.

The Canadian Task Force on Preventive Health Care recommends screening asymptomatic adults age 55 to 74 years with at least a 30 pack-year smoking history who smoke or quit smoking <15 years ago with LDCT every year for three consecutive years (7).

A multidisciplinary expert group from France, advised screening a target population, age 55 to 74 years who have a 30 pack-year smoking history with LDCT scan, after informing individuals about the risks and benefits of screening (8). The Cancer Care Ontario Programme (CCOP) issued guidelines in 2013 targeting the same group of patients but suggesting biennial screening after two consecutive years of negative scanning (9).

Even though we are talking about different programs, lung cancer screening currently involves examining LDCT and anti-smoking counseling programs.

a) CT examination with low dose radiation dose

Refinements of CT scanning techniques have led to the evaluation of low-dose helical computer tomography (LDCT) for lung cancer screening. New multidetector CT scanners generate high-resolution imaging with significantly less radiation exposure than diagnostic chest CT scanning. LDCT refers to a non-contrast study obtained with a multidetector CT scanner during a single maximal inspiratory breath-hold

with a scanning time under 25 seconds. High-resolution (1.0 to 2.5 mm interval) images are reconstructed using a soft tissue or thin-section algorithm. The estimated effective radiation dose due to LDCT is described elsewhere.

There are a lot of tests that can show us the health of our lungs, but among the most effective is low-dose computed tomography. This investigation allows to obtain detailed images of the pulmonary anatomy and therefore have a higher accuracy for this anatomical segment.

Pulmonary nodules, often found in CT scans, are a type of pathological image that alerts the patient and causes him to come to a pulmonary consultation. Such images do not necessarily signify neoplastic pathology, as the existence of calcified nodules due to older lung infections or other benign pathologies is common. However, in such situations they still require close monitoring, but do not require an immediate therapeutic attitude. Fleischner Society Guidelines for managing incidental pulmonary nodules recommend that multiple solid pulmonary nodules that are 6 mm or larger, initial follow-up at 3-6 months is required, regardless of the risk factors and for low-risk patients, the guidelines suggest an optional additional follow-up at 18-24 months (10).

If the nodule is considered to be large and its size changes between two investigations, then the likelihood of malignancy is high, especially if the patient has risk factors such as smoking, exposure to air pollution, noxious substances or preexisting pulmonary pathology. Excision and biopsy of the respective nodule, bronchoscopy, mediastinoscopy, as well as other CT examinations are some of the necessary investigations regarding the diagnostic and therapeutic attitude (11).

The Baseline Results of a French Prospective Study show that Over a 2.5-year period, 1307 subjects were recruited. Screening was negative in 733 cases (77.2%), positive in 54 (5.7%), and indeterminate in 162 (17.1%). After the 3-month scans, 57 subjects screened positive: 26 patients exhibited 31 lung cancers (67.7% of stage 0 to I), of whom 76.9% underwent surgical resection, and 29 had no cancer (false-positive rate = 3.1%). The prevalence of lung cancer was 2.7% (12). These results strengthen the hypothesis of using low dose CT scan in lung cancer screening.

Screening programs are designed to help detect bronchopulmonary cancer at an early stage, while it is still curable. The second largest study is a collaboration between Belgian and Dutch researchers, NELSON, a 10-year study for men in the UK with increased risk for lung cancer, which showed a 24% reduction in deaths using low-radiation CT scans (13).

A meta-analyze LDCT lung cancer screening trials, identifying studies by searching PubMed, Google Scholar, the Cochrane Registry, Clinical Trials.gov, said that LDCT screening significantly increased the detection of stage I LC, RR = 2.93

(95% CI, 2.16-3.98), $I^2 = 19\%$, and reduced LC mortality, RR = 0.84 (95% CI, 0.75-0.93), $I^2 = 0\%$. The number needed to screen to prevent an LC death was 265. Women had a lower risk of LC death (RR = 0.69, 95% CI, 0.40-1.21) than men (RR = 0.86, 95% CI, 0.66-1.13), p value for interaction = 0.11. LDCT screening significantly reduced LC mortality, though not overall mortality, with women appearing to benefit more than men. The estimated risks for false positive results, screening complications, overdiagnosis, and incidental findings were low. Long-term survival data were available only for North American and European studies limiting generalizability (14).

b) Chest radiograph/sputum cytology

Not recommended !

One study recruited a total of 3,318 heavy or long-term smokers who were not participants in the PLCO trial and randomized them to receive either a screening LDCT scan 1,660 participants, or screening posteroanterior view chest radiograph (CXR) 1,658 participants. The screens were completed on 96% of subjects in the LDCT scan arm and 93% of subjects in the CXR arm. A total of 20.5% of screened subjects in the LDCT scan arm and 9.8% of those in the CXR arm had findings that were suspicious for lung cancer (15).

Another screening with 5991 (8.9%) of all chest radiographs were abnormal, ranging from 11 percent in current smokers to 8 percent in never-smokers. After up to three rounds of annual screening (non-smokers did not participate in the third screening round), participants were followed through 13 years, with a screening adherence of 86.6% at baseline and 79 to 84% during years 1 to 3 (16). After 13 years of follow-up, there was no significant difference in lung cancer incidence rates between the screening and usual care groups and no difference in lung cancer mortality rates or stage of disease. Screening for lung cancer by chest radiograph and/or sputum cytology is not recommended.

c) Tumor markers

Although molecular markers for the early detection of lung cancer are still in the research phase, expectations are high and thought to facilitate the selection process of high-risk individuals who are already undergoing screening for bronchopulmonary cancer and will also improve the specificity of undetermined lung nodules.

According to a study from January 2022, a new blood biomarker in combination with lung cancer prediction models was more sensitive – 88.4% vs 78.5%, and more specific – 56.2% vs 49.3% than the extended 2021 criteria developed by USPSTF, which lowered the age limit (55 to 50 years) and smoking history (30 to 20 BP) for lung

cancer screening, eligibility criteria, and who can benefit from screening.

This study showed that for 10 packages-years smokers, the combined model identified 9,2% more lung cancers annually and reduced the non-case referral by 13,7% compared to the USPSTF 2021 criteria (17).

The need for such a marker arose from the desire to have an easier screening opportunity, namely by blood collection, and because CT scans are not yet valid in many countries.

At present, no liquid biopsy or breath exhalate-derived biomarkers exist that could be efficiently used and reliably implemented in a routine LDCT screening program (18).

d) Autofluorescence bronchoscopy

Bronchoscopy is a helpful diagnostic tool for lesions close to central airways, however there is ongoing dispute over how well these procedures work for PPLs, or peripheral pulmonary lesions (19).

Similar to how aberrant gastroesophageal or cervical mucosa is seen and biopsied by esophagogastroduodenoscopy or colposcopy, respectively, the detection of these pre-invasive bronchial lesions (PBL) has up to now relied on direct bronchoscopic observation and sampling. Long-standing interest in additional bronchoscopic technologies suitable for this purpose has resulted from the limits of traditional white-light bronchoscopy (WLB) in the identification of PBLs. One such technique is autofluorescence bronchoscopy (AFB), which depends on variations in the wavelength of visible light emitted between healthy and sick mucosa, namely the latter's lesser green autofluorescence (20).

In a study conducted by Tremblay et al. (21) results found that a total of 56 lung malignancies were found by LDCT (4.3%), a prevalence comparable to that found in the NLCST, but only 5 of the 69 participants with pathologic abnormalities in the AFB were found to have cancer. A case of CIS and a typical carcinoid tumor of unreported size, the latter of which is a neoplasm that is frequently quite apparent bronchoscopically without AF, were the only two patients in whom the lesion was missed by LDCT, giving an overall rate of 0.15% for the bronchoscopic detection of cancer.

e) Smoking and smoking cessation in screening cancer

The prevalence of smoking is declining in Western Europe, but it remains a major preventable risk factor. The WHO estimates that cigarette smoking is responsible for 7 million deaths annually. Passive smoking is also associated with an increased incidence of lung cancer.

Polycyclic aromatic hydrocarbons and nitrosamines are potent carcinogens. Smokers have a significant inflammation in the airways, rich in neutrophils and macrophages, which release proteases capable of destroying lung tissue. Since pulmonary

epithelial permeability is affected, carcinogens are allowed to enter the bloodstream.

The effect on health would be enormous if the entire population could be persuaded to quit smoking. Banning smoking in public places and at work helped. Nicotine replacement therapy and bupropion should only be used for smokers who achieve a target, but there is no evidence that these therapies combined would have an effect.

Varencycline is an oral nicotine receptor agonist that can reduce the urge to smoke, especially with a 12-week treatment which is presumed to double the chances of quitting. Electronic cigarettes and vaping may also be effective, but there is no evidence for the long-term safety of these products (22).

f) Atmospheric pollution and lung cancer

Although cigarette smoking accounts for most lung cancers, substantial numbers of lung cancer cases are observed among never-smokers. Outdoor ambient air pollution and exposure to other inhalable agents, such as household burning of solid fuels, residential radon, second-hand tobacco smoke, asbestos, certain metals and organic chemicals, and work in rubber manufacturing, paving, roofing, painting, or chimney sweeping, and other occupational exposures have also been associated with lung cancer risk. household burning of coal as a Group 1 human carcinogen and household burning of biomass fuel as Group 2A (probably carcinogenic) for lung cancer. Household burning of solid fuels, both coal and biomass, contribute significantly to high levels of outdoor air pollution, and thus to the burden of disease, in low-income and middle-income countries (23).

Potential harm of screening

While screening for lung cancer has the potential benefits of decreased morbidity and mortality from lung cancer, it also has potential harms, which include:

A) Overdiagnosis

The overestimation of the diagnosis in cancer screening is obvious and involves the identification of precancerous lesions in asymptomatic patients, which otherwise would not have been clinically apparent.

Overdiagnosis could be expected to have greater impact in screening programs where subjects are at increased risk for other potentially life-threatening comorbidities, as is the case for smokers (24).

The risk for unnecessary invasive studies and therapy for “overdiagnosed” lung cancer might be greatest in this population. Observational studies of screening for lung cancer with LDCT have estimated the extent of overdiagnosis to range between 13 and 27 percent (25, 26, 27).

B) Patient distress

The screening process is not psychologically straightforward for the patient, even the slightest discovery, regardless of the tumour substrate, can cause an inner state of panic, especially when lung nodules that are discovered require follow-up over several months/year, the patient's stress level increases due to the fear of developing lung cancer. In the NLST in which participants were asked to complete questionnaires regarding anxiety at 1 month and 6 months of screening, showed that anxiety was substantially higher among those in the true-positive group compared with the false positive, SIF, and negative groups in crude and adjusted analyses (28).

C) Radiation exposure

An independent risk factor that contributes to the development of cancer is radiation exposure, although a deterministic effect between radiation from imaging techniques and cancer would undoubtedly be difficult to demonstrate. Several hypotheses have been provided based on the events that took place in Japan due to atomic bombs in 1945 (29), but given that the doses in medical imaging are below 100 mSv, it is considered that radiosensitivity is strongly dependent on age and exposure time.

Conclusions

The way patients are approached is very important for any screening program, especially when it comes to male patients, the likelihood that they will consider the medical consultation is much lower. It is very important that the bronchopulmonary cancer screening algorithm allows for timely monitoring and re-evaluation of selected patients.

To get the most out of screening, people with low levels of education and poor socioeconomic status should also be considered, as this category of patients is often at increased risk of developing lung cancer and how to approach literacy. Health is the key to reaching this kind of audience. A patient-friendly language is especially important in the therapeutic approach when it comes to smoking cessation. Information about the screening process should be discussed and explained with the patient, the public and health experts. Thus, the patient must be informed both about the potential risk and benefits through a personalized communication by the medical team, as well as about the possible therapeutic decisions regarding the screening (30).

Researchers argue that screening for bronchopulmonary cancer is more effective when smoking cessation is being pursued in parallel. However, current data to guide clinicians in the choice of smoking cessation interventions

in this specific context are limited due to the small number of randomized studies that have been carried out. The optimal approach to smoking cessation during lung cancer screening needs to be clarified by new studies comparing different motivation strategies, establishing the ideal moment to propose stopping smoking and the most effective therapies to use (31).

Visits to the hospital are not pleasant and generally offer a significant degree of anxiety to patients (11), which is why in this attempt to co-opt the population to participate in screening, vans, containers, or health caravans that will promote this approach, preferably located in more friendly or recreational environments, such as parks, malls or parking lots of supermarkets, to facilitate the faster, more active and easier participation of these people.

There is currently no national bronchopulmonary cancer screening program in Europe, although there is a high level of evidence in favor of this strategy.

Authors contributions

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Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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