EDITORIAL

Low-dose computed-tomography lung cancer screening: the first European recommendations from the European Society of Radiology and European Respiratory Society

Comment on Kauczor HU, Bonomo L, Gaga M, et al. ESR/ERS white paper on lung cancer screening. Eur Respir J. 2015; 46: 28-39

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The annual death toll of lung cancer is impossible to ignore. It amounts to 1.37 million deaths worldwide and 266 000 deaths in the European Union. Unlike other major cancer killers, the 5-year survival in lung cancer has not been measurably altered over the past 25 years, despite all novel diagnostic methods and advances in treatment modalities. Radical surgery remains the most effective treatment option for lung cancer. Moreover, it has exhaustively been documented that a longer survival time strongly correlates with a smaller cancer lesion, that is, an early stage of the disease.

While awaiting the results of the NELSON trial,[1] which are expected to be conclusive with regard to the European population, the first European Union recommendations for low-dose computed tomography (LDCT) screening were proposed by a multinational team on April 30, 2015. The authors present a joint standpoint of the European Society of Radiology and European Respiratory Society, exploiting the knowledge accumulated until now.

The recommendations are comprehensive and most likely reflect the hypothesis that the European population is more heterogeneous than the American one.

The minimum requirements to perform LDCT lung cancer screening are as follows:[1]

1 a longitudinal program with fixed eligibility criteria, offering a complete protocol that includes screening intervals, workup, and follow-up; single-round screening is not recommended
2 designated medical centers having multidisciplinary expertise plus standardized technical, software, and medical procedures
3 population target: healthy individuals aged from 55 to 80 years, with a smoking history of at least 30 pack-years, including exsmokers who quitted smoking within the past 15 years; exclusion criteria: comorbidities precluding curative treatment or lack of consent to undergo radical therapy
4 smoking cessation program integrated with screening
5 multidetector CT yielding at least 1-mm spatial resolution and effective radiation dose around 1 mSv for normally-sized individuals with preference for submillisievert scans
6 software-assisted nodule evaluation; volumetric-based assessment is preferred over diameter-based
7 creation of screening registry as the first step to a pan-European biobank and image bank.

In the early 1990s, Henschke et al[2] initiated the use of computed tomography (CT) to screen for lung cancer. From 1993 to 2005, more than

31 000 of at-risk individuals were screened. The repeat screen was offered within 7 to 18 months to all participants. More than 27 000 individuals returned for the second screen round. The study demonstrated that 88% of patients with lung cancer stage I survived more than 10 years.

Inherently, each screening results are distorted by lead-time bias, length-time bias, and overdiagnosis. They are related to patient selection and monitoring process. In the case of lead-time bias, the sooner diagnosis seems to prolong survival although the death time is not delayed. Length-time bias is screening distortion manifested in favoring detection of slow-growing tumors. When screening detects cancers that would remain subclinical before death from other causes, it is referred to as overdiagnosis and constitutes the extreme form of length-time bias. The best way to minimize these biases to influence screening results is to choose mortality reduction as a reliable endpoint. Additionally, randomization would act as a measure to exclude the other type of bias. The first trial designed to achieve this goal was the National Lung Screening Trial (NLST), which began in 2002 and was halted in 2010.[3]

LDCT screening has targeted lung cancer at--risk individuals who fulfilled 2 criteria at the time of randomization: they were 55 to 74 years old and had a smoking history of at least 30 pack--years. The trial enrolled 53 454 eligible individuals, who were randomized either to low-dose CT or posteroanterior chest radiography. All participants were offered a baseline screen (T0) and 2 annual repeat screens (T1, T2). In addition to 3 LDCT examinations, all participants were followed up for the next 4 years. The NLST showed a survival benefit for the LDCT arm, with a reduction of 20% in lung cancer-related mortality. All-cause mortality in the LDCT subgroup was reduced by 7%.

An erroneous interpretation of the NLST results has widely been dispersed among medical professionals by scientific bodies. For instance, the American College of Chest Physicians (ACCP) and American Society of Clinical Oncology (ASCO) stated that a reduction in mortality by 20% in the LDCT arm shows the number of lives saved, that is, 4 of 5 people will die of lung cancer even though they are screened. In fact, the NLST's aim was to demonstrate, with sufficient statistical power, the proof of concept that lives can be saved. In addition, its primary goal was to find out whether treatment of smaller cancers diagnosed by CT had an advantage in comparison to more bulky lesions revealed by chest X-ray screening. The trial has been successful in testing these questions.[4]

Data from the NLST have fueled extensive research, assessment, and reanalyses, which, over the past 4 years, have prompted the major medical societies in the United States to issue their guidelines and recommendations regarding LDCT lung cancer screening.[5]

The National Cancer Comprehensive Network (NCCN), ACCP, ASCO, American Association for Thoracic Surgery (AATS), US Preventive Services Task Force, to list only a few, recommend to target at-risk population of 55- to 74-year olds, with an extension to 79-year olds, proposed by the AATS, and a history of smoking of at least 30 pack-years. In the presence of 1 additional risk factor, the NCCN and AATS have lowered the age to 50 years and smoking history to 20 pack-years.[5]

Apart from the recognition of a live-saving capability by medical societies, there has been ongoing and untiring advocacy, with the Lung Cancer Alliance as the leading charity. Under its leadership, the American College of Radiology and the Society of Thoracic Surgeons, which included nearly 100 other professional societies, public health organizations, medical centers, and patient groups, in a genuinely allied action have successfully lobbied the Center for Medicare and Medicaid services (CMS) to announce a decision of covering annual lung cancer screening for former or current heavy smokers (**FIGURE 1**). The positive decision was reached on February 5, 2015, even though the advisory board voted against the coverage.

LDCT screening still raises some major concerns including a high rate of false-positive results, exposure to radiation, and patients' anxiety evoked by screening. There are various ways to eliminate false-positive results, thereby increasing a positive prediction value of LDCT screening:

1 advances in imaging techniques

2 proteomic or genomic biomarker clusters[6,7]

3 sputum cytology analysis – multiparametric morphology – cell CT.[8]

Owing to constant advancements in the hardware and software of CT scanners, LDCT can be currently regarded as a submillisievert CT, with virtually no evidence on exerted harms. According to estimates, in the case of an effective CT radiation dose equal to 1.3 mSv for women and 1.0 mSv for men, the increased cancer risk was calculated to be 0.05% in female and 0.02% in male smokers for 3 annual rounds of screening. Considering a 3- to 5-fold decrease in a radiation dose in new scanners, to the level of 0.2 mSv, it seems evident that screening benefit outweighs the risk related to radiation exposure.[9]

Although LDCT screening is associated with exposure to radiation, which may evoke anxiety in patients or discourage them from quitting smoking, it has some additional benefits that should be noted, such as detection and assessment of comorbidities (eg, emphysema, interstitial lung disease, tuberculosis, coronary artery calcium, calcification of heart valves, or aortic aneurysms).

Finally, the reduction in all-cause mortality by 7% in the CT arm of the NLST trial remains inexplicable. Although it is highly speculative, perhaps we are witnessing here an added value to a general health benefit.

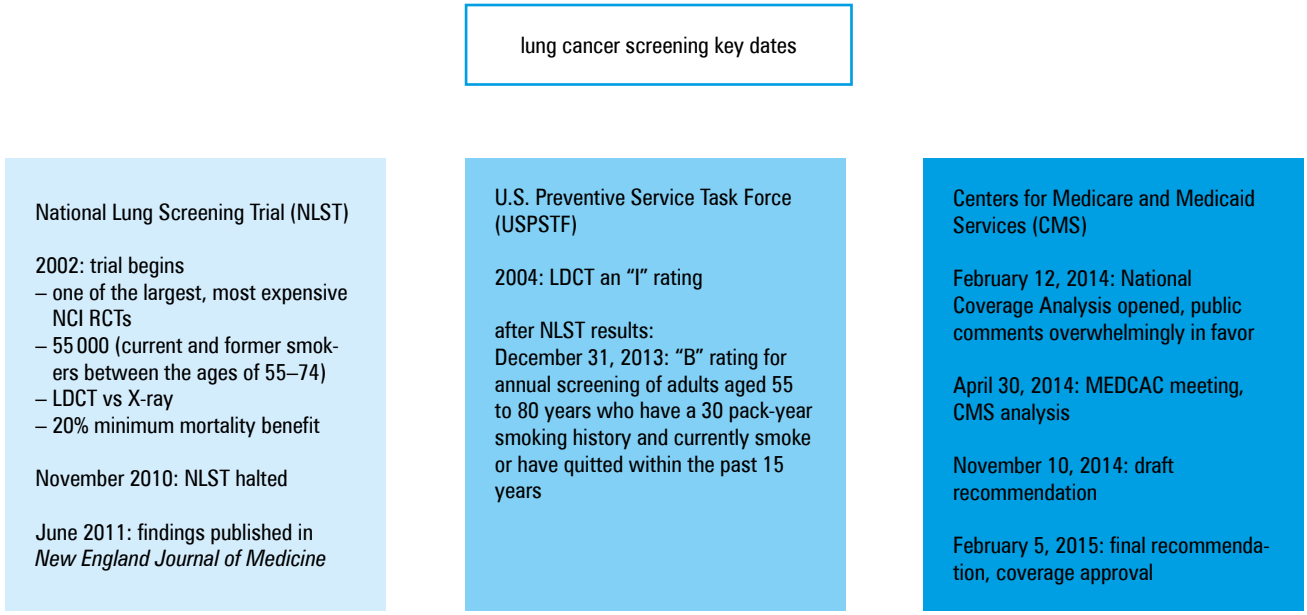

FIGURE 1 Overview of a 13-year period of advancement in lung cancer screening (courtesy of Lung Cancer Alliance; www.lungcanceralliance.org; www.rakpluca.edu.pl) Abbreviations: LDCT, low-dose computed tomography; MEDCAC, Medicare Evidence Development & Coverage Advisory Committee; RCT, randomized controlled trial

Kauczor et al[1] published their paper during great scientific turmoil and heated discussions on whether we have sufficient data in favor of screening, whether the benefits outweigh harms, whether there is anything to confirm we are on the right track, and how to orchestrate the whole complex machinery comprising multiple medical professionals to ensure the appropriate quality of screening.

It seems fair to suggest that the long-lasting scientific effort has matured enough to initiate a nationwide debate on what practical actions would ensure an efficacious implementation of LDCT lung cancer screening within the available health care resources. The bottom line is that without an opportunity to gain experience, we will not be able to learn from that experience. We may find ourselves in a constant indecisive standstill.

Quite recently, in July 2015, there was a meeting of regional consultants headed by a national consultant in thoracic surgery. It was estimated that more than 34 000 at-risk individuals had been screened in Poland between the years 2008 and 2012. They were recruited to local open-access programs in Gdańsk,[10] Szczecin, Poznań, and Warsaw. The positive LDCT result, whatever the definition, ranged between 43% to 58%, and the lung cancer detection rate, for a baseline screen in all centers, was close to 1%, in accordance with the worldwide data. The majority of detected lung cancers (70%) were in stage I or II. While this is a substantial accomplishment, a considerable challenge now is to integrate these regional efforts into a single national program with regulated and unified procedures ensuring an adequate use of the health care resources.

Implications from LDCT screening are potentially remarkable. For the first time, we may have a tool capable of decreasing mortality from lung cancer. The question is no longer whether we can diminish the lung cancer burden, but how to do it avoiding the known and yet unknown limitations. There should be a strict distinction between a longitudinal lung cancer screening program and a single-round screening. The latter is discouraged by the authors of the consensus.[1] Researchers together with policymakers and resource managers should carefully consider the pros and cons of paving the way to an affordable LDCT lung cancer screening in the near future.

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