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ERS International Congress, Madrid, 2019: highlights from the Thoracic Oncology Assembly

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ABSTRACT Lung cancer is a devastating disease affecting hundreds of thousands of patients in Europe. Despite recent advances in treatment, its prognosis remains poor. This is mainly attributed to the late stages that diagnoses are usually established at, consequently excluding curative treatment options. During the 2019 European Respiratory Society International Congress in Madrid, Spain, lung cancer experts presented the most recent aspects of lung cancer early detection with low-dose computed tomography.

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Introduction

Lung cancer is the third most common cancer in Europe. Despite substantial progress in its diagnosis and management it remains the most lethal [1]. Contrary to cancer mortality projections anticipating a downward trend in most cancer types in both sexes, lung cancer mortality is expected to rise, especially in women [2] In 2018, over 387 000 deaths in Europe were attributable to lung cancer [3]. This high toll in human lives but also in related direct and indirect costs burdening national healthcare systems is linked to the late stage at which lung cancer is symptomatic and thus diagnosed. During the 2019 European Respiratory Society (ERS) international Congress in Madrid, Spain, thoracic oncology experts presented the most recent aspects of lung cancer early detection with low-dose computed tomography (LDCT). The aim of this article is to offer a summary of the presented data.

Lung cancer screening, evidence and advantages

In 1992, the Early Lung Cancer Action Program (ELCAP) began to assess the benefit of annual computed tomography (CT) screening for lung cancer. It showed a high proportion of patients diagnosed at stage I, triggering more research on lung cancer screening [4]. The expansion of ELCAP and the development of a multi-institutional protocol provided robust data supporting the beneficial role of lung cancer screening in the survival of the participating individuals [5]. The cure rate, estimated by the 10-year Kaplan–Meier survival rate of 484 patients, was 88% (95% CI 84–91%), regardless of the cancer stage or treatment. As for patients diagnosed with clinical stage I lung cancer and resected within 1 month of diagnosis, they had a higher estimated cure rate (92% (95% CI 88–95%)) [6].

The National Lung Screening Trial (NLST) [7] was the first randomised controlled trial to show the effectiveness of lung cancer screening by LDCT compared to chest radiography with a lung cancer mortality reduction of 20% in at-risk individuals. The risk population targeted in the NLST was composed of active smokers with a history of at least 30 pack-years, aged 55–74 years or those who had quit within the last 15 years.

The strong NLST evidence favouring lung cancer screening programmes resulted in their approval in 2015 by Centers for Medicare & Medicaid Services, followed by other private insurers. The eligibility criteria include age 55–77 years, current or former smokers who quit within the last 15 years, with a minimum smoking history of 30 pack-years, no signs or symptoms of lung cancer, and no chest CT in the prior 12 months.

Other positive implications are possible, such as increased smoking cessation rates. This was underlined in the UK Lung Cancer Screening (UKLS) study [8] with a 2-year quit rate of 22% in patients participating in the study compared to the 4% population quit rate. Furthermore, in the study population, the smoking cessation risk went up two-fold when further investigations were suggested. A summary of the pivotal lung cancer screening trials is presented in table 1.

Past, present and future difficulties encountered with lung cancer screening

False-positives

Although it did show reduction in lung cancer mortality, one of the limitations raised in the NLST was the high number of false-positive findings leading to unnecessary secondary referrals and their related avoidable harms and costs. In the NELSON trial [10], 86–90% of participants effectively got screened and only 2.1% of the screened got a positive test requiring further testing. 9.2% percent had an indeterminate test result necessitating repeat scanning. The latter result seems far more reasonable regarding harm within a lung cancer screening programme.

This raises the issue of defining a positive screen. In NLST [7] the threshold used was 4 mm and this resulted in a large number of false-positive tests. When comparing the false-positive rate between the different screening studies, it ranged from 23.1% in NLST [7] to 1.2% in NELSON [8] and 3.6% in UKLS [7]. It has also been suggested that a positive screen be defined using a combination of the American College of Radiology Lung-RADS [11] and the British Thoracic Society criteria [12].

When faced with a pulmonary nodule on a chest CT, one of the main difficulties will be to determine its risk of being malignant. In order to do so, it needs to be classified as either low risk, intermediate risk or high risk. This first step is crucial as the implications for the patients significantly differ depending on this initial classification. If the nodule is deemed to be of low or intermediate risk, the implications are quite reasonable: some increased anxiety for the patient and a follow-up LDCT scan. However, nodules classified as high risk will lead to more invasive procedures such as high-dose CT, endoscopy, biopsies, positron emission tomography scans and surgery. As such, the initial classification of the nodule is important and elements such as size (<5 mm), aspect (smooth, spherical) and location within the lung

TABLE 1 Summary of the main screening trials

Study	Patients n	Inclusion criteria	Screening modalities	Main results
National Lung Screening Trial [7]	53 454	Age: 55–74 years Sex: male and female Smoking status: history of cigarette smoking of at least 30 pack-years, and, if former smokers, had quit within the previous 15 years Country: USA	Three annual screenings with LDCT OR three annual screenings with single view postero-anterior chest radiography	Relative reduction in mortality from lung cancer with LDCT screening of 20.0% (95% CI 6.8–26.7; p=0.004) Reduction of death from any cause in the LDCT group, as compared with the radiography group, by 6.7% (95% CI 1.2–13.6; p=0.02)
UK Lung Cancer Screening [8]	4055	Age: 50–75 years Sex: male and female Smoking status: 5-year lung cancer risk ⩾5%, based on the LLPv2 risk prediction model[#] Country: UK	Single thoracic LDCT scan OR usual care	Pilot study concluding that lung cancer screening is feasible in the UK in the target population
Lung Cancer Screening Intervention [9]	4052	Age: 50–69 years Sex: male and female Smoking status: at least 25 years smoking of at least 15 cigarettes per day, or at least 30 years smoking of at least 10 cigarettes per day, including ex-smokers who had stopped smoking ⩽10 years Country: Germany	Five annual screenings with LDCT OR no screening	HR for lung cancer mortality 0.74 (95% CI 0.46–1.19; p=0.21) among men and women combined Modelling by sex: statistically significant 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)
NELSON [10]	13 195	Age: 50–74 years Sex: male Smoking status: current or former smokers (those who had quit ⩽10 years ago) who had smoked >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years Countries: Netherlands, Belgium	Four screens with LDCT at baseline, year 1, year 3 and year 5.5 OR no screening	Cumulative rate ratio for death from lung cancer at 10 years 0.76 (95% CI 0.61–0.94; p=0.01) in the screening group as compared with the control group

LDCT: low-dose computed tomography. [#]: LLPv2 risk model includes age, sex, smoking duration (cigarettes, pipe and cigars), previous history of respiratory diseases (COPD, emphysema, bronchitis, pneumonia, tuberculosis), history of previous cancer, family history (early/late onset) and exposure to asbestos.

(attached to a fissure, the pleura and veins) are all markers indicating a nodule is of low risk of malignancy.

Another future challenges will be cost effectiveness, and one option could be to lengthen the interval between the two scans [13]. There is currently little data backing this approach and a new randomised controlled trial would be required to provide sufficient evidence. Similarly, there is also a challenge to provide sufficient capacities for screening and subsequent management of abnormal findings requiring further referral.

Missing patients

Some patients defined as hard to reach might not be reached by screening programmes and there is also concern regarding whether there are high-risk populations currently excluded from screening. The correct characterisation of high-risk populations remains an issue. For instance the National Comprehensive Cancer Network (NCCN) criteria, used by some insurers, distinguishes two different groups: 1) based on the NLST eligibility criteria; and 2) age ⩾50 years with an active smoking status and at least 20 pack-years, as well as one additional risk factor (history of lung cancer in first-degree relatives, occupational exposures, residential radon exposures, chronic lung disease, personal history of smoking related cancer or radiation exposure). However, in a study assessing the performance of these two distinct NCCN high-risk groups, both appeared to be equally effective [14].

Regarding age and quit years, in a cohort that prospectively evaluated 5-year survival in patients aged 50–80 years with lung cancer, with a smoking history of ⩾30 pack-years, and included both current smokers and former smokers who quit within the past 30 years, the 5-year overall survival yielded similar results between long-term quitters and the US Preventive Services Task Force (USPSTF) group in both cohorts [15].

Identifying high-risk individuals is a key component of running a successful lung cancer screening programme. The PLCOm2012 model estimates the 6-year risk of developing and dying from lung cancer. It estimates risk including multiple parameters such as age, sex, race, body mass index, lower socioeconomic status, self-reported history of COPD, personal history of cancer, family history of lung cancer, smoking intensity and duration and, in former smokers, time since quitting. This model recommends CT screening for patients if they have a 6-year risk of >1.5% [16]. In a prospective study comparing USPSTF and PLCOm2012, the PLCOm2012 outperformed the USPSTF criteria in lung cancer detection. Participants in the International Lung Screening Trial (ILST) received two annual screens and were followed for 6 years for lung cancer outcomes. Of the 5013 patients screened, 110 were found to have lung cancer. The PLCOm2012 prediction showed significantly higher sensitivity and a higher positive predictive value than the USPSTF criteria. More precisely, 99% of the cancers were found using PLCOm2012 compared to 77% using USPSTF criteria. Furthermore, 21.8% of cancers were found by PLCOm2012 alone while only 0.9% were found by USPSTF criteria alone [17].

It also remains debatable who should not be screened. The USPSTF criteria explicitly exclude patients unable to tolerate surgical resection, while other guidelines generally recommend screening those in reasonably good health, making eligibility decisions far from straight forward. The impact of comorbidities is another important consideration. They need to be balanced against the risk of lung cancer, since their severity may significantly impact possible treatment and survival outcomes.

Messaging

Most screening programmes have low turnouts, in part, due to inappropriate messaging. Clear targeted messaging is essential in order to reach the appropriate population. Furthermore, appropriate messaging around the general lung cancer screening process should also be encouraged as patients often have worries that are not always well perceived by healthcare professionals. Improved communication around screening programmes would not only help screen people but it would also help ease anxiety associated to the CT scan and its results.

How to properly implement lung cancer screening programmes

The optimal strategy for implementing lung cancer screening programmes was discussed based on the results of NLST and NELSON but also on those from the German Lung Cancer Screening Intervention (LUSI) trial [9]. To effectively implement lung cancer screening, the following aspects should be considered: age for initiating and ending screening as well as smoking history. The optimal age would be 60–79 years for individuals considered as high risk (current smokers having smoked for ⩾40 pack-years or former smokers having quit in the last 10 years with the same amount of pack-years). Once the patient is included in the screening programme, an annual screening interval would be recommended. These might seem like stringent criteria, but they would allow high-quality screening which could be expanded in a second step. Also, the use of pack-years might be replaced by the use of risk calculators which could detect more lung cancers during screens.

However, a large-scale implementation of lung cancer screening in European countries would require particular dispositions. An initial screening phase would use stringent criteria to select patients. These criteria would then be loosened in order to screen a larger number of people. Risk stratification could be used after the initial CT scan in order to rank patients depending on risk and the screening interval would then be adapted appropriately. Future research on implementation strategies is still needed so that population based lung cancer screening programmes can be appropriately deployed.

Future directions

A binary strategy could be suggested where low-risk nodules return to screening or LDCT follow-up and high-risk nodules require work-up with the objective of minimal harm.

Morphology patterns of nodules could be of use by differentiating pure ground-glass nodules, sub-solid and solid nodules. These nodule types have particular characteristics. In the former pattern growth is usually indolent and the prognosis is good, while in the latter two nodules may need resection and all need prolonged surveillance. In general, treatment should be suggested in the case of the presence of a solid component and growth.

The reduction of the number of false positives requires the use of new radiological techniques such as volumetry and potentially sophisticated artificial intelligence. Furthermore, shorter CT intervals to evaluate nodules should be reserved for high-risk nodules only. The management of nodules should be patient based. The possible distress caused by cancer workup, the risk of malignancy, the impact on prognosis but also fitness, age and patient wishes should all be taken into consideration.

Following the 2015 white paper [18], an upcoming European Society of Radiology (ESR)/ERS statement on LDCT lung cancer screening was also presented by the two societies. The principal aim was to produce a statement on pivotal points in lung cancer screening and emphasise the quality that such a programme requires. Multiple topics were addressed such as ways to reach out to potential participants, optimal communication and shared decision making, standards for the infrastructure and quality assurance, incorporation of tobacco cessation programmes, benefits and harms, radiation exposure, management of positive screens and cost-effectiveness.

According to European Union (EU) statistics, there are approximately 192 million current smokers, while lung cancer is responsible for 387 000 lung cancer deaths per year [3]. However, no organised nationwide lung cancer screening programme exists in Europe. In some cases, there are pilot projects and screening through private services.

In order to have a successful lung cancer screening programme it is necessary to choose who to screen. There are a number of risk prediction models, all with a similar rationale. Duration and intensity of screening has also been discussed, with annual repetition over two decades after 55 years of age; however this subject has to be revisited with regards to risk profiles, although there is tendency to suggest biannual screening for low risk patients with a negative first scan.

The providers need to offer accessible and well-targeted information, using clear language and terminology, but also actively involve patients and patient advocacy organisations. Decisions regarding follow-up, intervention and treatment should be taken after informative discussions on potential benefits and harm, and always taking into account participant's preferences and values.

Tobacco cessation is another important component of a well-organised lung cancer screening programme. There is evidence supporting higher success of cessation among the participants, possibly related to higher motivation. Intensive intervention has shown greater efficacy and sustained abstinence will reduce lung cancer mortality so it is important to incorporate tobacco cessation into lung cancer screening [19, 20]

Lung cancer screening programmes also need state of the art CT protocols to ensure sufficient diagnostic quality. Volumetric evaluation offers better characterisation and follow-up of possible findings. Computer-assisted diagnostics may also offer optimum nodule detection and discrimination of malignancy, while maintaining a low radiation dose.

Furthermore, the use of risk prediction models not only for patients but also for nodules could also be highly effective. Radiologist expertise training is also a key feature, and for that purpose a certification programme is run by ESR.

Lung cancer screening is often criticised for overdiagnosis and unnecessary invasive procedures which could potentially lead to harm. In order to minimise this, priority should be given on production and application of risk stratification strategies, including risk models for participant's and for nodules, conservative management of subsolid nodules, quantification of volume doubling time, and longer interval of screening especially for negative screens of low risk. It is also important to develop clear algorithms and specific recommendations for incidental findings. Psychosocial consequences should also be addressed. Cost-effectiveness is also discussed, and although it is extremely heterogeneous across EU countries, lung cancer screening proves to be more effective in high-risk individuals and women.

Lung cancer screening should be viewed as a lung prevention programme not just for lung cancer. It also detects a number of smoking-related lung disease (COPD, emphysema, fibrosis) and cardiovascular diseases, potentially leading to a total reduction of overall mortality and increase of cost-effectiveness.

The ESR/ERS statement paper concludes that there is a need for an action plan to be implemented on a European, national and local level. Advocacy is needed by relevant European medical societies and organisations (*e.g.* ESR, ERS and European Alliance for Personalised Medicine) and in collaboration with respective national societies, but also European patient organisations such as the European Lung Foundation, Lung Cancer Europe and other potential stakeholders at the EU level.

It also calls for the development of a recommendation or even directive by European councils asking for implementation of nationwide population-based LDCT lung cancer screening programmes in EU countries. A minimum of standards and quality assurance, continuous analysis of benefits and harms, regular surveillance of latest evidence and setup of registries are unquestionable prerequisites of

implementation of screening programmes. Another key feature for the success of these programmes is raising public awareness by media and other communication channels.

In summary, lung cancer remains the primary cause of cancer death in Europe with poor long-term survival mainly due to late detection. As demonstrated during this session at the 2019 ERS International Congress, there is now an abundance of scientific data to support lung cancer early detection *via* implementation of national population-based LDCT screening programmes. These may pave the way for more comprehensive lung health preventive programmes in the future. Scientists and clinicians, along with patient advocates, need to raise public awareness and convince policy makers in Europe to take the necessary measure enabling citizens at risk for lung cancer to benefit from its early diagnosis.

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