Article

EU Policy on Lung Cancer CT Screening 2017

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Abstract
Background: Lung cancer kills more Europeans than any other cancer. In 2013, 269,000 citizens of the EU-28 died from this disease. Lung cancer CT screening has the potential to detect lung cancer at an early stage and improve mortality. All of the randomised controlled trials and cohort low-dose CT (LDCT) screening trials across the world have identified very early stage disease (~70%); the majority of these LDCT trial patients were suitable for surgical interventions and had a good clinical outcome. The 10-year survival in CT screen-detected cancer was shown to be even higher than the 5-year survival for early stage disease in clinical practice at 88%. ***Methods:*** Setting up of an EU Commission expert group can be done under Article 168(2) of the Treaty on the Functioning of the European Union, to develop policy and recommendation for Lung cancer CT screening. The Expert Group would undertake: (a) assist the Commission in the drawing up policy documents, including guidelines and recommendations; (b) advise the Commission in the implementation of Union actions on screening and suggest improvements to the measures taken; (c) advise the Commission in the monitoring, evaluation and dissemination of the results of measures taken at Union and national level.

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Results: This EU Expert Group on lung cancer screening should be set up by the EU Commission to support the implementation and suggest recommendations for the lung cancer screening policy by 2019/2020. **Conclusion:** Reduce lung cancer in Europe by undertaking a well-organised lung cancer CT screening programme.

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Background: The European Burden of Lung Cancer

Lung cancer kills more Europeans than any other cancer. In 2013, 269,000 citizens of the EU-28 died from this disease. Age-standardized cancer rates are falling in Europe for all of the major cancers, although mortality rate in women is predicted to rise to 14.6/100,000 in 2017 (+5.1% since 2012, corresponding to 92,300 predicted deaths) [1]. However, crude lung cancer incidence is rising, largely due to the ageing population, and so the burden on healthcare services is becoming greater. Early-stage lung cancer has a very good prognosis over a 5-year period (~73%) [2], whilst late-stage disease outcome is extremely poor (~7% over 5 years). Unfortunately, almost three-quarters of lung cancer patients present with late-stage disease when treatment has little effect on mortality. Thus, screening has the potential to detect lung cancer at an early stage and improve mortality.

CT Lung Cancer Screening Trials: Current Status

All of the randomised controlled trials (RCT) and cohort low-dose CT (LDCT) screening trials across the world have identified very early stage disease (~70%), the majority of these LDCT trial patients were suitable for surgical interventions and had a good clinical outcome. The 10-year survival in CT screen-detected cancer was shown to be even higher than the 5-year survival for early stage disease in clinical practice at 88% [3].

However, it was not until publication of the largest extant RCT of LDCT screening that it was proved beyond doubt that CT screening saves lives: the US National Lung cancer Screening Trial, NLST, which randomized 53,454 subjects, demonstrated a 20% reduction in lung cancer mortality rate 6 years after 3 annual screens with LDCT compared with 3 annual chest radiographs [4]. The data from the non-randomised I-ELCAP CT screening study provides further support for lung cancer screening [3, 5]. There are 7 randomised controlled lung cancer LDCT trials in Europe but the total number of subjects randomized in these is only just over half those randomized in NLST. Indeed, the only trial in Europe powered to detect a mortality difference is expected to publish results soon. The result from this trial, the NELSON trial in the Netherlands and Belgium, is eagerly awaited [6]. However, there is consensus that LDCT screening reduces lung cancer mortality; the debate is more concerning the way in which to conduct CT screening to ensure maximum cost effectiveness. The following recommendations address this consideration.

Correct Selection Criteria: Europe Should Focus on Screening Individuals with a High Risk of Developing Lung Cancer

For screening to be cost effective, it has to be applied to the population at risk. For lung cancer, this is not simply based on age and sex, as in the majority of breast or colon cancer screening. The well-defined risk factors for lung cancer provide the opportunity to target

those at high risk, and there are risk prediction tools that identify those at high enough risk of developing lung cancer to benefit from cost-effective CT screening. The opportunity to introduce precision medicine into lung cancer screening extends further into management of indeterminate findings such as suspicious nodules. Screening trials have shown us how to minimize the clinical implications of these. Lung cancer risk prediction models have been shown to be easily applied in the population at risk [7–9].

Pulmonary Nodule Management Algorithm: Europe Should Adopt a Common Management Protocol for Nodule Management, with Innovative Tools

Reduction of false positive cases is a key element in reducing the economic and human costs of a large-scale lung cancer screening. Dedicated training and educational programmes directed to European radiologists, radiology technicians, pulmonologists, and thoracic surgeons focused on the best way to manage indeterminate lung nodules and indolent screen detected tumours will be critical to minimise invasive procedures, risks for healthy subjects, costs, and overtreatments. To this end, a common management protocol should be adopted based on the most innovative imaging software (volumetry and volume doubling time) together with recent knowledge from clinical experience [6, 10–12]. Nodule size thresholds and in surveillance, the volume doubling time are useful methods to differentiate malignant dangerous lung lesions from benign or premalignant indolent tumours as shown by the investigators of the NELSON study [6, 11], combined with selective use of PET scan [13, 14]. New guidelines show how a combination of nodule size, risk prediction models, and PET-CT scanning can accurately predict malignancy and guide management [15–17].

Quality Assurance: Europe Should Set Up a Central Registry for CT-Screened Individuals – Assists with Training, Manpower, and Quality Assurance

Successful implementation of lung cancer LDCT screening requires quality assurance to ensure that the CT images are undertaken, recorded, and reported to a uniform high standard. This objective can be assisted by the EU Commission by supporting National and a linked Central European Registry for all LDCT-screened individuals. Furthermore, this will enable training of radiologists involved in LDCT screening and provide them with the latest methodologies in undertaking volumetric measurements of CT-detected nodules. It will also facilitate Europe-wide analysis of the efficacy of screening programmes.

The professional groups in Europe who have a specialist interest in LDCT screening should be engaged in the process of developing recommendations for implementation, adapted according to the healthcare landscape of individual nations.

Currently, lung cancer screening utilises LDCT, and participants in lung cancer screening trials have been shown to receive no more than the equivalent of 6 months of average background radiation dose (<1.5 mSv) [15]. Future LDCT platforms are being designed with even lower radiation exposure, equivalent to 1/10th of annual background radiation effective dose. The quality assurance aspects of radiation exposure will be an important aspect of the National and EU Central Registries responsibilities.

Key Steps in the Implementation of a Cost-Effective Lung Cancer Screening Programme in Europe

a   Undertake a literature search in order to identify alternative approaches to lung cancer screening, which will be considered in the fully developed EU Policy document – to include references such as [10, 11, 18–22].

b   Identification of high-risk populations. In Europe we have accumulated sufficient evidence to identify individuals with a high risk of developing lung cancer based on epidemiological modelling [7, 9, 22–24] and clinical trials [10, 20].

c   Cost effectiveness of lung cancer screening. We currently have evidence from European modelling that lung cancer screening can be cost effective, if one bases this on individuals with specific high-risk profiles in individuals 55–75 years of age [10, 25]. The Danish study on cost effectiveness demonstrated low-dose lung cancer CT screening increases healthcare costs compared with no screening; however, this difference was attributable to the costs of the CT screening programme [26]. Currently, we await the cost effectiveness data from the NELSON trial.

d   Participation of the population in CT screening programmes and equity across all social groups. The majority of clinical trials in lung cancer screening have utilised postal approaches and thus a bias in the selection of "health aware" population. However, recently an innovative programme in the UK called Accelerate, Coordinate, Evaluate (ACE) [27], has stimulated over 5 independent groups to develop CT screening demonstration projects to focus on the access to the "hard to reach population." These ACE projects have been extremely successful in encouraging people in disadvantaged groups to participate [28, 29].

e   The optimal screening intervals. The current evidence on screening intervals is based on trials with annual screening and, at this time, one would recommend that high risk individuals 55–75 years were screened annually. However, recent evidence from the NELSON and NLST trials indicates that one could potentially work towards precision medicine; where a baseline screen and first found screen is negative (no nodules detected), the risk reduces to 0.4% of the population; thus, biennial screening could be considered for this subset of individuals.

f   Quality control in lung cancer screening. The lung cancer community has developed robust guidelines for the management of screen detected nodules, when implemented in an accredited clinical centre. The proposal is to set up National CT screening reading centres, which are in time integrated into a "European Central CT Imaging Centre" and would monitor quality and reporting standards. This is a specific area the EU Commission could assist in funding. Appropriate registries should be set up to monitor radiation dose and use approved CT protocols.

Resource Allocation, Which Maximizes the EU Commission Action in Enabling Lung Cancer Screening in Europe

The lung cancer screening community in Europe are requesting specific funding to assist in the planning for implementation, as well as in supporting future programmes in Europe, through Regional Development funding [30].

This builds on the initiatives of the European Guide on Quality Improvement in Comprehensive Cancer Control (CANCON) which followed in the wake of European Partnership for Action Against Cancer (EPAAC). This is led mainly by Member States with the support of the EU, and also involves other stakeholders including NGOs working across Europe. CANCON has the goal of reducing cancer incidence by 15% by 2020. Its objectives include: (a) improv-

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ing quality of cancer care across Member States; (b) improving the quality of life of cancer patients and survivors; (c) bringing down inequalities in various areas of cancer care; (d) creating a European Guide on Quality Improvement in Comprehensive Cancer Control.

There is evidence that the resources spent on lung cancer CT screening would have more of an impact, than the allocation of the same resources on other areas.

a   Policies to incorporate smoking cessation are needed as we know that this is substantially greater in the context of CT screening and contributes to a reduction in lung cancer mortality that has been shown to be twice that of the effect of CT screening alone. This has a major effect on cost effectiveness [23].

b   Major benefits in terms of reduction of other smoking-related diseases; the potential to utilise lung CT screening to diagnose coronary artery calcification, COPD [31–33], and potentially in breast cancer and spinal stenosis. Further research is required to direct EU policy on these added benefits.

c   The new innovative treatments for lung cancer will potentially be available to individuals developing recurrences or metastasis, post-CT screening, and potentially have a much better outcome.

d   Detection of early-stage lung cancer with successful surgical intervention, improves the quality of life for these patients.

e   The stage shift related to screening will allow the EU member states to reduce costs of treatment of lung cancer patients as the treatment of early stage lung cancer is half that of treatment of advanced stage.

The Decision to Implement Lung Cancer Screening

Each country in Europe will consider the decision to implement lung cancer screening within their own health service mechanisms/procedures and based on the implementation of current screening programmes in breast, colon, and cervical cancer. This has been previously undertaken individually by each country. This aligns with Decision No. 1350/2007/EC of the European Parliament and of the Council of 23 October 2007 establishing a second programme of Community action in the field of health (2008–2013)(2) while reiterating that health services are primarily the responsibility of Member States, and stresses that cooperation at Community level can benefit both patients and health systems. According to Article 7(2) and to the Annex to that Decision, the actions in the field of generation and dissemination of health information and knowledge shall be implemented in close cooperation with Member States developing consultation mechanisms and participatory processes.

EU Expert Group on Lung Cancer Screening

There should be an EU Council recommendation initiating the work on a EU Expert Group on lung cancer screening that reflects the experience with the existing recommendations and guidelines for the three other cancers. It should leverage on the experience made with the EU actions aiming at harmonizing the access for patients to such early detection programmes in the Member States. The expert group on screening should, at the request of a group of Member States and facilitated by the Commission, provide advice and expertise to the Commission in formulating and implementing the Union's activities in the field of lung cancer screening and early detection and foster exchanges of relevant experience, policies, and practices between the Member States and the various parties involved. These European Recommendations should be developed in association with professional groups involved in CT screening in Europe.

The setting up of an EU Commission expert group can be done under Article 168(2) of the Treaty on the Functioning of the European Union; Member States are required, in liaison with the Commission, to coordinate among themselves their policies and programmes in the areas referred to in paragraph 1. The Commission may, in close contact with the Member States, take any useful initiative to promote such coordination, initiatives aiming at the establishment of guidelines and indicators, the organisation of exchange of best practice, and the preparation of the necessary elements for periodic monitoring and evaluation.

Expert Group Tasks

The Expert Group would:

- assist the Commission in the drawing up policy documents, including guidelines and recommendations;
- advise the Commission in the implementation of Union actions on screening and suggest improvements to the measures taken;
- advise the Commission in the monitoring, evaluation, and dissemination of the results of measures taken at Union and national level;
- advise the Commission on international cooperation;
- provide an overview on Union and national policies;
- foster exchanges of relevant experience, policies, and practices between the Member States and the various parties involved.

Expert Group Members

The expert group shall be composed of the following members:

- Member States' competent authorities;
- patients' organisations;
- European associations of producers of products or service providers relevant for patients affected;
- European professional associations or scientific societies acting in the field;
- individuals appointed in a personal capacity as experts having public health or scientific expertise at Union level.

In agreement with the Commission, the expert group may set up subgroups to examine specific questions on the basis of terms of reference defined by the group. Such subgroups shall be disbanded as soon as their mandate is fulfilled.

Timeline Proposed

i   The EU action on guidelines and recommendations for lung cancer CT screening should be proposed and initiated at the EU Congress entitled "Personalising Your Health: A Global Imperative" in Belfast in November 2017. This should include a set of recommendations for action with the establishment of an EU Expert Group on LCS.

ii   This EU Expert Group on lung cancer screening should be set up by the EU Commission to support the implementation and suggest recommendation of the lung cancer screening policy by 2019/2020.

iii Member States should agree to start implementation planning of LDCT screening immediately, with the long-term objective to initiate lung cancer screening, in the full knowledge that this will take 18 months. This will also allow time for the NELSON trial to report. The Commission can facilitate coordination with input from the Expert Group.

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Disclosure Statement

Dr. Javier Zulueta declares that he is a part-time employee and has shares in Vision-Gate Inc.

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