European position statement on lung cancer screening

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Introduction

Lung cancer screening with low dose computed tomography (LDCT) saves lives and it is only a matter of time before it is embraced by national health organisations throughout Europe. The evidence from the NLST trial on reduction in mortality and from seven pilot trials within Europe on other aspects of screening, have provided sufficient evidence for Europe to start planning for lung cancer screening now; whilst mortality data from NELSON are awaited.

This is the rationale for an EU Position Statement (EUPS) that describes the current status and sets out the essential elements needed to ensure the development of effective European screening programmes. The EUPS expert group comprises individuals from eight European countries who have been actively engaged in the planning and execution of the randomised controlled European screening trials, those actively engaged with the clinical management of patients with lung cancer and lung nodules, and those that have developed relevant clinical guidelines; they represent all the specialties and professions involved in delivering successful lung cancer screening programmes in Europe. The emphasis for this EU position statement focuses on the actual implementation of CT lung cancer screening programmes in Europe by radiologists supported by epidemiologists, pulmonologists and thoracic surgeons, in the full context of clinical lung cancer diagnosis and treatment. We performed a comprehensive literature search for papers on lung cancer screening and through in-depth discussions developed this EUPS consensus.

The structure of the EUPS document reflects the evidence addressing the major questions concerning the delivery of a successful screening intervention but also highlights the issues that still need to be resolved. The contributions to the EUPS were provided by a team of clinicians and scientists expert in CT as the method of choice for lung cancer screening. The requirement for a EUPS stems from the need to provide European recommendations on CT screening that will assist the EU commission and national health agencies in starting planning implementation of lung cancer screening within the next two years and to avoid opportunistic uncontrolled screening. Since the publication of the NLST results in 2011, it is now crucial that we have a EUPS consensus.

The focus of the EUPS is limited to lung cancer screening with LDCT and early detection of lung nodules prior to clinical work-up, but does not address the entirety of work-up and treatment choices. It is highly unlikely that there will be any new randomized controlled LDCT screening trials powered to allow conclusions about mortality reduction, so recommendations are based on the current evidence. Existing evidence provided by a number of studies is sufficient to make recommendations concerning the minimization of false positive results in both screen-detected nodules and for clinically detected nodules identified in a non-screen environment. The need for non-contrast-enhanced low-dose interval imaging should not be considered a false positive test, as the individual is not undergoing an invasive clinical workup and therefore the chance of physical harm is very low. Furthermore the evidence shows that psychological distress is transient and smoking cessation rates are higher amongst subjects requiring interval imaging.

The position statement represents a balance of the available evidence and therefore reflects (a) what we have good evidence for, (b) where further evidence is needed to implement effective screening programmes, and (c) where practical implications for lung cancer screening can already be drawn from current knowledge and state of the art.

1. Current diagnostic tests for lung cancer detection

Computed tomography is the only early detection method suitable for national lung cancer screening programmes.

Computed tomography has evolved as the prime method for lung cancer screening. Evidence from previous lung cancer screening trials in the 1980's on chest X-ray with and without sputum cytology demonstrated that there was no survival advantage,[1,2] and resulted in inactivity in this field of research for more than two decades. The first publication in 1999 on lung CT screening ignited this modality of lung cancer screening again.[3] Other diagnostic methods may have a future potential in lung cancer screening but currently there no trials to support them.[4]

Earlier trials using CT provided evidence, not only for the likely effectiveness, but also a great deal about the natural history of the disease. The debate continued about the ability of CT screening to reduce mortality until the US National Lung Cancer Screening Trial (NLST), that randomized 53454 subjects was stopped one year earlier than planned because the stop criteria of a 20% reduction in lung cancer mortality rate compared with that achieved by screening with chest X-ray had been reached in a periodic planned interim analysis; the trial also showed a 6.7% reduction in all-cause mortality.[5]

There is increasing evidence of the effectiveness of CT screening from several pilot trials in Europe and from the current NELSON publications, Table 1. However, we need to remain aware of the implications and problems associated with the work-up of suspicious nodules (i.e. invasiveness of biopsies, waiting time until final decision etc.).

The high false-positive rates both in the initial screening and subsequent screening rounds, as reported in the NLST, need to be reduced to ensure minimal harmful impact on the screenees. This is best achieved by accurate interval imaging using the latest and most accurate methods, particularly semi-automated volumetric analysis rather than manual maximum diameter measurements as already implemented by a number of trials.[6–8] Furthermore, the definition of false positives also has a major bearing on how we interpret false-positive data. NELSON,[9] MILD,[10] and UKLS[7] define false positives from their baseline data, as those requiring referral to the pulmonologist and further diagnostic investigation (3.5%), but who subsequently did not have lung cancer This is in contrast to the NLST, where every individual with a repeat CT scan prior to a repeat annual screen, was considered positive (24%, of which 96% were false positive with unnecessary CT examinations and a related radiation burden). In NLST, a positive screen included all CTs that showed a nodule 4mm or more in diameter and since publication of NLST, the NELSON study has shown that nodules smaller than 5mm (or $100mm^3$) do not confer a greater risk of malignancy at baseline.

No other technology is currently available that can replace CT screening. Emerging technologies need to undergo the same scrutiny that has been applied to CT screening. However, if a new emerging technology is considered, it must be compared to CT screening in a randomized controlled trial (RCT) and the negative predictive value (NPV) should be near 100% and positive predictive value (PPV) should be higher than CT screening. Some technologies might be applied as an adjunct to CT screening (see section 3).

2. Outcomes of lung cancer screening trials

The outcomes of lung CT screening trials have impact on implementation.

The outcomes of a wide variety of lung cancer screening trials give insight as to how to implement lung cancer screening in differing countries in Europe and the optimal set-up for population as well as single centre screening in Europe. We have learnt a great deal about each stage of the lung cancer CT screening pathway and the management decisions required.[11] Current trials have provided us with an insight into risk assessment, CT screen nodule management, multidisciplinary team (MDT) work-up, surgical interventions, as well as psychological impact on the participants and cost effectiveness.

Several nationally funded randomized studies have already been undertaken in Europe (DANTE,[12] DLCST,[13] ITALUNG,[14] LUSI,[8] MILD,[15] NELSON,[6] and UKLS.[7,16] Their results, individually and when pooled, will all contribute to the implementation of CT screening in Europe. The only European fully powered RCT that will provide mortality and cost effectiveness data is NELSON, although we do have sufficient data to start planning; the results from NLST alone have been sufficient for LDCT screening to start in the US and Canada.

The incorporation of coronary artery calcification (CAC) score and emphysema assessment on LDCT imaging, may enhance the cost-effectiveness and attractiveness LDCT lung cancer screening.[17] COPD and emphysema are the strongest lung cancer risk predictors and together with cardiovascular disease all three imaging biomarkers have a substantial impact not only on morbidity but also, independently, on overall mortality.[18,19]

3. Lung cancer risk prediction modelling

Future Lung cancer CT screening programmes should embrace the use of risk prediction modelling to select high risk populations.

The concept of clearly defining the target population for lung cancer screening is gaining weight, as selection based only on age, as in most other cancer screening scenarios (e.g. breast, colon) is insufficient in lung cancer because of other powerful risk factors, the most important of which is exposure to tobacco smoke. The other major risk factors which are now also taken into account include; History of respiratory diseases (COPD, emphysema, bronchitis, pneumonia and TB), history of previous malignancy, family history of lung cancer (first degree relative greater or less than 60 years), exposure to asbestos. There are several published multivariable risk prediction models, but only two have so far been used to select subjects for screening in a clinical trial. Risk prediction models have been tested in the NLST dataset, demonstrating that the NLST selection criteria could have been improved, including the USPSTF recommendations, if a risk model had been implemented.[20–22] The LLP risk model ($LLPv_2$) is the only risk model used to date to select subjects for a lung cancer screening RCT. A higher percentage of participants were identified with lung cancer at baseline compared to baseline NLST and NELSON. The cut-off of the LLP_{v2} model of 5% over 5 years is currently being validated in the Liverpool Health Lung Project (LHLP).[7,23–25] The LLP previously compared favourably with the Spitz and Bach models.[26] The LLP was validated in the UK LLPC cohort with an AUC of 0.82 (CI, 0.80 to 0.85).[24] The Bach, Spitz, LLP and $PLCO_{m2012}$ risk models were externally validated in the EPIC-German cohort of 20,700 ever smokers. The $PLCO_{M2012}$ model showed the best performance in external validation (C-index: 0.81; 95% CI, 0.76-0.86) and the highest sensitivity, specificity, and PPV, however, the superiority over the Bach model and the LLP model was considered modest by the authors.[27]

Recently, five different risk models have been compared utilising data from the PLCO and NLST datasets.[28] Even though a number of sophisticated models have utilised a range of risk variables (i.e. family history, previous malignancy, previous respiratory disease, exposure to asbestos), the Bach model still proved to have a good sensitivity and specificity,[29] and it only uses age and smoking history in calculating the risk score, emphasizing the dominance of these two risk factors. The $PLCO_{2012}$ model also provided good results, however, one of the limitations of the analysis, is that this model was developed using the PLCO data set, so potentially there may be issues of over-fitting. However, all of the models were superior to the NLST selection criteria and the current USPSTF recommendations. The predicted risk of lung cancer was analysed in 95,882 ever-smokers aged 45 years in the Australian Up Study (2006–2009), was calculated using $PLCO_{m2012}$ applied to baseline data, which showed good discrimination (AUC 0.80, 95% CI 0.78–0.81) and excellent calibration.[30] Thus, it is essential that risk prediction models are used to select subjects for lung cancer screening. Cost effectiveness was shown to be improved in the higher risk groups so it follows that better risk prediction should also improve costs per life saved. There is no information on related cost effectiveness.[28] We recognise that the aforementioned risk prediction models were based on non-European populations, realizing that lung cancer risk prediction may be influenced by loco regional differences. The EUPS does not recommend any specific risk prediction model, however either the $PLCO_{2012}$ or the LLP_{v2} would suffice if screening was implemented today.

We have to be aware of the different European healthcare systems and the issues of utilising a risk stratification approach (i.e. Germany), where all individuals have a legal right of access to the available diagnostic and therapeutic techniques. However, it should be argued that it would be unethical to screen low risk patients, based on the harm-benefit considerations.

The risk profile of subjects is a valuable and cost-effective tool to identify those with preclinical disease that are eligible for screening.[7,20] Integration of the risk profile with biomarker(s) or susceptibility genes could potentially improve the selection of subjects at higher level of risk for screening and/or for the management of the disease.[31,32] Predictive biomarkers, such as microRNA, have been shown as potentially effective tools for the identification of susceptible subjects and future lung cancer cases,[33–35] whilst bronchial-airway gene-expression classifier possibly could improve the diagnostic performance of bronchoscopy.[34] Breath tests for lung cancer have to be considered a strong possibility and are currently being tested in a clinical trial.[35,36]

Identification of new biomarkers for screening will be a reason to implement cooperative research; the availability of large, high quality biobanks embedded in screening trials together with the radiomics analysis is a future opportunity.

4. **Harms and benefits associated with lung cancer screening**

There are more benefits than harms from lung cancer screening, when screening is undertaken in those with sufficiently high risk

Before implementation of lung cancer screening it should be beyond any doubt that the harms associated with lung cancer screening, such as over-diagnosis, surgery for benign lesions, psychological harm and radiation exposure are at acceptable levels.

Minimizing harms in CT screening is essential in order to maximize the clinical effectiveness of the intervention. Harms may be considered as physical or psychological. The ways in which physical harms can be reduced are by (i) ensuring that only those who are at sufficiently high risk to benefit are screened, (ii) reducing screening radiation dose to a minimum, (iii) effective management of abnormal findings, including nodules, suspected lung cancer and incidental findings. This is predicated on ensuring that there is a high level of clinical expertise available so that all aspects of CT screening and management of findings are completed to the highest standard. Thus, lung cancer screening should only be undertaken according to protocol and screening units and centres should be in a position to ensure rigorous quality control.

"LDCT screening can be carried out outside a clinical trial, provided it is offered within a dedicated program with quality control, in a centre with experience in CT screening, a large volume of thoracic oncology activity and multidisciplinary management of suspicious findings" and a well-developed minimally invasive thoracic surgery program. This approach is according to the ESMO and ESTS guidelines.[37,38]

Potential psychological harms can be reduced by the provision of information about CT screening presented in a language that is understood by the screenees, as well as detailed information concerning abnormal findings, with accurate information about the probability of cancer, especially where findings are likely to be benign.

The potential physical harms should be provided to screenees in a clear manner, including radiation exposure,[39] and harms from biopsy or resection of a benign lesion. However, radiation risk is likely to be overestimated, and will in the future be lower with the latest CT platforms with ultra-low dose technology. The European trials will provide data which will allow for a direct quantification of overdiagnosis. Rates of benign resection vary in clinical trials from 10% to at least 25% of total operations.[7,10] The consensus is that we should be working towards a 10% figure or even lower, however, an optimal percentage has not established to date. It should be considered that the patient/physician dynamic is altered in the lung cancer screening setting compared to symptomatic individuals who present themselves to healthcare institutions.

Effective management includes the benefits of maximizing smoking cessation within CT screening programmes. Thus, it is important to inform current smokers of the dangers of continuing to smoke for the own general health and to ensure they are offered suitable support.[40–42]

5. **CT methodologies for early lung cancer detection.**

Volume methodology should be utilised for the detection of early lung cancer by CT.

In the NLST trial, a CT screen was regarded as positive if it showed any non-calcified nodule at least 4 mm in diameter. The American College of Radiology set up a Lung Cancer Screening Committee subgroup to develop Lung-RADS,[43,44] in-order to have a quality assurance tool to standardize lung cancer screening CT reporting and also provide management recommendations. The rationale behind this initiative was the hope that it would assist in lung cancer screening CT nodule scan interpretation.

LungRADS performance was compared to the NLST screening trial data,[45] which indicated that LungRADS substantially reduced the false positive result rate but also the sensitivity level decreased. Recently it has been recommended by Mehta et al. indicated that the LungRADS system needs to be revised and they faulted the system on the basis that it has never been studied in a prospective fashion. In addition, Li et al. have recently analysed the size and growth of pulmonary nodules, as a consequence of 'rounding ' methodology used in LungRADS.[46] They concluded that rounding up the mean nodule diameter, which was used in LungRADS, increases the frequency of positive results and has a detrimental effect on the efficiency of lung cancer screening. Furthermore, LungRADS does not provide guidance on risk prediction models. The Brock score[47] has been shown to be more accurate than baseline LungRADS criteria.[48]

An alternative method is to determine nodule volume using software for semi-automated segmentation, which enables an accurate estimation of nodule size after three-dimensional reconstruction (Figure 1). Volumetric analysis of CT detected nodules was initially recommended by Henschke et al in 1999,[3] and has been further developed and validated within the NELSON and the UKLS trial. A recent comparative analysis on both the diameter and volume has been undertaken on the NELSON baseline participants with 2,240 non-calcified nodules. Minimum and maximum diameter within a single nodule varied by a median of 2.8mm, which is larger than the LungRADS cut off for nodule growth (increase in mean diameter >1.5mm). Nodules with a diameter between 8 to 10mm were represented in each of the five differing nodule volume categories (Figure 2).[49]

The recommendation for the future management of CT screen solid nodules is that semi-automatically derived volume and volume-doubling time should be used in preference to diameter measurements; the latter should only be used where volumetry is not technically possible.

6. Lung cancer population screening prerequisites

National clinical screening standards are required for future lung cancer CT screening programmes.

Accreditation for institutions and radiologists participating in lung cancer CT screening should include training and participation in quality assurance.

A central national registry for participants ensures that inclusion criteria are met. In this registry, other screening modalities, i.e. CT manufacturer dose, and results together with work-up results should be collected, which ensures that previous screens are available and quality control can be assured. The institutions providing a lung cancer screening service should be registered, have access to a participant registry as well as previous screens, providing a certified nodule evaluation software, and will deliver screening results and recommendations to the central participant registry. It is recommended that the European lung cancer community develop national registries, which potentially could be linked on a hub and spoke format, thus enabling international quality control and utilising the data to improve the provision of lung cancer screening throughout Europe over time.

National quality assurance boards should be set up which monitors the adherence to minimum technical standards and to standardized diagnostic criteria for screen-detected lung nodules, similar to the UK and European breast screening programmes,[50–52] and are entitled to advise /intervene whenever basic requirements are not met. The lung cancer community should consider following the example of the Dutch breast screening service by organising national 'Central Reading Centres' of all CT screening programmes;[52] as the local reading of CT screen scans would potentially have a major impact on routine radiology service delivery. This would also enable ongoing national quality assurance and the introduction of the forefront automated pulmonary nodule reading software.

Institutions participating in screening programmes require MDTs to be available providing access to all relevant specialities (pulmonologist, thoracic surgeon, radiologist, lung cancer nurse etc.) in which suspicious screening results may be discussed. They should regularly demonstrate to a quality assurance board that they continue to meet basic standards, similar to those proposed by RSNA.[53]

7. Lung nodule management at baseline CT screening

Baseline CT screening programmes should be targeted to prevalent lung nodules.

Management of prevalent lung nodules will largely depend on size criteria. Volumetry is essential, but diameter cut-offs will also need to be provided for cases where segmentation is not possible. Minimum standards will need to be met for lung cancer screening CT acquisition parameters to ensure the standardization of volumetric analysis (i.e. acquisition protocol regarding slice thickness, reconstruction interval and image reconstruction algorithm (kernel) as well as, clearly defining the low-radiation dose parameters).

Management should be based on the evidence from screening trials that have used volumetry such as the NELSON trial. In the original NELSON nodule management protocol, cut-offs for negative and positive screen results were 50 and 500mm^3, respectively. Nodules within volume range of 50-500mm^3 were classified as indeterminate. Based on lung cancer probability outcome results of the first two screening round of the NELSON study, these cut-offs could be optimized.[54] E.g. for solid nodules <100mm^3 return to annual screen (based on an annual screening programme), 100-300mm^3 for repeat study in 3 months, >300mm^3 for referral to MDT (Figure 3a).[54] Detailed risk profiles have been provided by the NELSON group for both nodule volume and volume doubling time (<400 and 400-600 days - increased risk described in Figure 3b; no significant increased risk, >600 days), on lung cancer probability over a two year period (Figure 4),[54] which provides guidance of the future follow–up interval for specific screenees. Recently, in-vivo evidence for growth patterns of screen-detected lung cancers demonstrated an exponential growth pattern which can be described by the VDT.[55] Acknowledging that software packages give different estimates of solid nodule volume, commonly of the order of 20%, (Corresponding to a non-measurable 7% error in nodule diameter; absolute 0.4mm error,[56] there may be merit in reducing the nodule threshold for a repeat study at 3 months to 80 mm^3 if the software is not phantom validated (Figure 3c).

For sub-solid nodules, surveillance should be favoured over intervention to avoid over-diagnosis. For all pure ground glass nodules and most partial solid nodules, return to annual screening will be the most likely recommendation. (Figure 3d).[57] Knowledge and data from ongoing lung cancer screening projects will also be important for future optimization and refinement of nodule management protocols.

It should be noted that morphology assessment will also play a role in the management of solid nodules, e.g. clustered ill-defined nodules, which are more in keeping with inflammatory aetiology, or smooth peri-fissural nodules or intrapulmonary lymph nodes, which will require management not based purely on size criteria.[58] There are a number of alternative work-up methods of screen-detected suspicious nodules >300mm^3 at baseline: i.e. core needle biopsy, PET/CT and primary resection.

The management of the patient should be according to the risk of malignancy. As we have discussed, lower risk nodules, say those with a <10% risk of malignancy can be followed up with interval imaging but those with higher risk need further work-up, provided this is in line with the patient's wishes after an informed discussion. Management options are, broadly, further surveillance, biopsy or treatment as the risk of malignancy increases.

The recent ESMO guidelines indicate that the cornerstone of treatment of potentially resectable lung cancer is surgical removal of the tumour.[37] For those who are not willing to accept the risks, or are at very high risk, non-surgical curative therapy should be offered, either SABR, hypofractionated high-dose RT or image guided ablative therapy.[37]

8. Incident screening rounds

The management of lung nodules at incident screening rounds.

Although incident screening rounds will comprise the majority of the work in the early detection of lung cancer, until recently, research did not focus on incident nodules and their definition. The definition of incident lung nodules has varied widely between LDCT lung cancer screening trials.[16,59–61] Incident nodules detected in high-risk individuals after baseline screening were either missed previously, or develop *de novo* in the time interval since the prior scan. In the case of a missed nodule, calculation of the volume doubling time is advised for further risk stratification. Newly developed nodules, on the other hand, entail a specific group of pulmonary nodules distinct from baseline nodules. With an annual incidence between 3% and 13% of participants, these nodules are regularly encountered in LDCT lung cancer screening.[62–65] Contrary to baseline nodules, which may have been present for years before detection, new incident nodules are potentially fast-growing.[66–69] This is reflected in a high cancer risk of 2-8% for participants with a new incident nodule.[62,63,65,66] Because these nodules have comparably less time to grow before detected, baseline cut-off values are not applicable.[66] This previously theoretical concept, that led to an adjustment of cut-off values for new incident nodules in several trials,[45,63,69] has recently been confirmed for new solid incident nodules by the NELSON trial.[66] Considering that a large proportion (37-57%) of new incident nodules are very small (below 50mm^3 volume),[62,65,66] volume measurement should be preferred since diameter measurements are far less precise and reproducible. Data from the NELSON trial suggest that new solid incident nodules <27mm^3 volume (<1% lung cancer probability) represent a low risk group and may return to annual screen (based on an annual screening programme), new solid incident nodules 27-207mm^3 volume (3% lung cancer probability) form an intermediate risk group requiring repeat LDCT in 3 months, and new non-calcified solid incident nodules ≥208mm^3 volume (17% lung cancer probability) form a high risk group requiring referral to MDT.[66] We suggest simplifying these categories to <30mm^3, 30 to 200mm^3 and ≥200mm^3 (Figure 3b). The existing data indicates that the majority (68-86%) of lung cancers found in new incident nodules during lung cancer screening are detected at stage I,[63,66] volume doubling time assessment at follow-up scans appears appropriate, such as outlined in the BTS guidelines.[61] However, the current evidence body regarding new incident nodules is insufficient and a more standardized manner of reporting, for instance strictly separating baseline and incident nodules, could simplify the translation to routine clinical management of incidentally detected pulmonary nodules. If a previous CT scan <2 years ago is available, recommendations for screen detected new incidence nodules could be extrapolated to routine clinical practice in a high-risk patient population, similar to the NELSON trial. This has now been adopted from the BTS guideline nodule management,[70] and in the BTS Quality Standard on Lung Nodule management (Thorax, 2017 in press). In a lower risk patient population, management should follow the BTS guidelines.

9. Clinical workup of CT detected lung nodules in clinical practice.

In clinical practice the preferred initial and subsequent management should be based on the lung cancer probability of the CT detected lung nodules.

Incidentally detected lung nodules are an increasingly common clinical problem arising from the increased use of cross-sectional imaging in clinical practice. The British Thoracic Society (BTS) has undertaken an in-depth piece of work developing guidelines on the management of pulmonary nodules in a clinical context and not in the context of population screening.[61] This work has been based on extensive review of the literature and the utilisation of recent publications from a number of lung cancer CT screening trials and in-depth analysis of the data. The Guideline Development Group (GDG) used methodology compliant with AGREE Collaboration criteria and standards set by NHS Evidence. The evidence review was comprehensive, conducted in November 2012 and updated in June 2014. The guidelines provide four management algorithms and two malignancy prediction tools.[61] The Brock risk prediction tool to calculate malignancy in solid pulmonary nodules ≥5 mm, which are unchanged at three months[47] and the Herder prediction tool to be used after PET-CT[71] (Figure 3c).

Furthermore, volumetry has been recommended by BTS as the preferred measurement method of CT detected nodules. The guideline also provides recommendations for the management of nodules with extended volume doubling times.

The BTS guidelines provide recommendations on the use of further imaging, and the use of PET-CT information which can be incorporated into pulmonary risk models (Herder model), as well as advice on biopsy and the threshold for treatment without histological confirmation. BTS provides advice on the information which should be given to patients on the management of pulmonary nodules in a non-screening context. The EUPS recommends keeping a database of all nodules that can facilitate future refinement of nodule management in line with new evidence.

10. Optimal timing of lung cancer screening intervals

Screen interval depends on the baseline and subsequent risk of lung cancer.

The US Preventive Services Task Force (USPSTF) on CT screening has recommended screening yearly from the age of 55 to 80 years.[72] In a recent NELSON publication, a 2.5 year screening interval resulted in a significant increase in interval cancers in the fourth screening round, thus arguing against using such an interval in a future screening programme.[73] There were significantly more interval cancers in the 2 year time frame and still a trend towards less early stage disease and detailed cost effectiveness of various screening scenarios has demonstrated that almost all scenarios are most cost effective when screens are annual.[74] However, in the NELSON trial, in half of the included participants no pulmonary nodules were detected and their 2-year probability of developing lung cancer was 0·4%, thereby indicating that a screening interval of up to 2 years, could be considered for similar individuals in future screening programmes, a risk stratified approach. The only trial to test annual and biennial screening was the MILD trial, where no difference was found in terms of mortality when comparing these two screening intervals.[75]

Screening intervals have been modelled by both the ULKS and IELCAP.[76,77] Duffy et al. acknowledged the risk of increasing the number of interval cancers but potentially providing a more cost-effective approach. Yankelevitz at al.[77] argued that we have to move beyond hypothesis-testing and on to quantification. We need to learn how the length of the interval between screens affects the diagnostic distribution before we consider changing annual screening intervals.

Currently we only have trial evidence for annual screening. Recent studies have shown that previous negative screening results may provide directions for further risk stratification.[78,79] Future decisions regarding the screen interval timing should be based on risk, psychosocial impact,[80] cost-effectiveness and the feasibility of implementation,[81] but these areas require further investigations. However, with newer, ultra-low dose CT techniques, the radiation dose for repeated CT screenings over a 30-year period, may not be a major issue for the screenees. New developments such as deep learning will assist us in the automation of pulmonary nodule management of lung cancer screening.[82]

In the future, there will be an issue for screening high risk individuals every year, over a 25 year period. We should be considering precision medicine in the field of lung cancer screening and whether an individual who has had a negative baseline and year one scan, should be moved into biennial screening, until their risk profile changes. Lung cancer screening is still in an embryonic stage of implementation in Europe and thus we have an opportunity to plan to develop an optimal lung cancer LDCT screening strategy.[83]

Conclusions

The EUPS describes the current status of lung cancer screening in Europe. Through consensus discussions with experts from the eight European countries undertaking RCT lung cancer CT screening trials, we have developed nine recommendations to guide the implementation of lung cancer screening in Europe. It is recognised that there remain specific areas which require further development and consideration (i.e. integrating smoking cessation and selection of the screening population), however, the weight of evidence clearly points to the imperative for Europe to start planning for implementation within the next 18 months as outlined in the EUPS ‘Call for Action’. During this planning period, the focus for each country will be to decide on the best risk prediction methodology to identify and recruit the high-risk population and also to set up the required infrastructure for quality controlled CT scans, utilising volumetric analysis. The EUPS has provided detailed recommendations on the management of lung nodules by lung cancer MDTs, with the aim to minimise harm and ensure patients receive the optimal diagnosis and therapy.

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Figure Legends

Figure 1

Upper figure legend

A volume growth of 26 % , defined as growth by NELSON criteria, is hardly appreciable by diameter measurement (8 % diameter increase which is NO growth by current criteria)

Lower figure legend.

A 25% diameter increase i.e. threshold for the current growth definition reflects almost a doubling in volume (95%). It reflects the insensitivity for growth of diameter measurement

Reproduced from :

Field et al. Prospects for population screening and diagnosis of lung cancer. Lancet. 2013;382(9893):732-41.

Figure 2. Range in mean axial nodule diameter per nodule category. Nodules with mean diameter between 8 and 10 mm (coloured zone) are represented in each volume category. These nodules represent the category with highest uncertainty about nodule nature. The data in this figure is based on intermediate-sized baseline nodules only.

Figure 3 Nodule Management Protocol

Fig 3a Nodule management protocol for screen detected solid nodules at baseline.

For nodules with volume-doubling time (VDT) between 400 and 600 days (intermediate cancer risk of ~4%), a second repeat CT in 3 months should be considered as an initial workup option.

Fig 3b Nodule management protocol for screen detected incidental solid nodules at follow-up.

Fig 3c Nodule management protocol for clinically detected solid nodules

Fig 3d Nodule management protocol for subsolid nodules for both screen detected and clinically detected

Figure 3c an 3d reproduced from :

Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules. Thorax. 2015;70 Suppl 2:ii1-ii54.

Figure 4

Contour plot of the effect of the combined effect of nodule volume and volume doubling times on 2-year lung cancer probability.

Reproduced from:

Horeweg et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol. 2014;15(12):1332-41.

Search strategy and selection criteria

Data for this EU Position Statement were identified searches of PubMed, Medline, and references from relevant articles using search terms lung cancer CT screening trial', 'lung screen detected nodules', 'lung cancer CT screening recommendations', 'lung cancer CT screening cost effectiveness'. Abstracts and reports from meetings were included only when they related directly to previous published work. Only articles published in English between 1999 and 2017 were included.

Authors Conflict of Interest Statements

Dr. Bastarrika reports other from BAYER, other from GENERAL ELECTRIC, other from SIEMENS HEALTHCARE, outside the submitted work.

Dr.D. R. Baldwin reports personal fees from Astra Zeneca, outside the submitted work.

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Dr Rzyman reports he has a patent protein marker signature of early lung cancer pending and a patent miRNA signature of early lung cancer.

The other authors declared no conflicts of interest

Authors contribution:

Matthijs Oudkerk & John K. Field developed the concept and design of the EU Position Statement on Lung Cancer Screening

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