Lung cancer screening

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General outline

In this part of the ECCO education book, a historical perspective of lung cancer screening will be given, from the first randomised trials in the 1970s with chest X-ray followed by 20 years of no interest and the revival after the introduction of computed tomography (CT) in the 1990s. The CT scan, as a screening tool for lung cancer, will be described, as well as its diagnostic performance in terms of its sensitivity, specificity and the ability to detect lung cancer at an early stage. Subsequently, information will be provided on the reason for the high rate of test positives in most CT screening trials, the as yet unresolved issue of overdiagnosis and the most recent exciting data on the mortality reduction demonstrated by the largest randomised CT screening trial in the USA. The effects of CT screening for lung cancer on quality of life and smoking behavioural changes will be addressed as well as the available cost-effectiveness data based on modelling. Finally, an overview will be given on the open issues around lung cancer screening that have to be addressed in coordinated demonstration projects in the next five years.

Historical background

Lung cancer is a health problem of global proportions. It is the most important cause of cancer death in the world, with a disproportionate proportion of cases occurring in the developed world. Despite intensive research over many years, the prognosis is still very poor, with less than 15% of the patients surviving five years after primary diagnosis. The poor survival is mainly attributable to the lack of effective treatment for systemic disease, and the fact that over two-thirds of patients present with regional or distant metastases. Theoretically, primary prevention, quitting smoking or more importantly measures to reduce starting smoking may almost totally eliminate the disease, but although several such measures have been successful, the number of lung cancer deaths each year is still unacceptably high. Even after stopping smoking, the long-term smokers remain at high risk of lung cancer. In the USA more ex-smokers now develop lung cancer than current smokers. As a result, 80% of all lung cancer cases occur in former smokers. At the same time, the risk of lung cancer is increasing rapidly for women as is smoking in adolescents. More than two-thirds of these people are diagnosed with locally advanced or metastatic disease. Their prognosis is poor due to the late diagnosis and lack of effective treatment of metastatic disease. Less than 15% of the patients are surviving for five years, and in several European countries the percentage of patients with five-year survival is far lower.

Lung cancer screening (secondary prevention) might, therefore, play an important role in reducing lung cancer mortality.

Between 1951 and 1975 ten prospective screening studies were performed with chest X-ray (CXR). Only four of them had a prospective randomised controlled design. Two of them investigated the benefit of adding sputum cytology to CXR screening and two others, the Mayo Lung Project (MLP) and the Czechoslovak study (CS) investigated the effect of CXR screening versus no screening. The MLP was a randomised, controlled clinical trial of lung cancer screening conducted in 9,211 male smokers between 1971 and 1983. The intervention arm was offered screening by CXR and sputum cytology every four months for six years; the usual-care arm was advised at trial entry to receive the same tests annually. No lung cancer mortality benefit was evident at the end of the study. The CS study also failed to demonstrate a mortality benefit. Based on these two negative trials the American Cancer Society (ACS) recommended at that time not to screen for lung cancer, but to focus on primary prevention, and that people with signs and symptoms should consult their physician. Within the context of this no-screening policy the vast majority of lung cancer patients are symptomatic at the time of their diagnosis today.

After a silent period of almost 20 years, the conclusions of the MLP and CS were increasingly

criticised. Lack of statistical power was recognised as one of the major shortcomings of these trials, and contamination of the control arm was high. In addition, a CXR appeared not sensitive enough to detect lung cancer at a very early stage. To increase the statistical power the follow-up of the MLP was extended. After extended follow-up through 1996 the median follow-up time was 20.5 years. Lung cancer mortality was 4.4 (95% confidence interval [CI] = 3.9–4.9) deaths per 1000 person-years in the intervention arm versus 3.9 (95% CI = 3.5–4.4) in the usual-care arm (two-sided P for difference: 0.09). For participants diagnosed with lung cancer before 1 July 1983, survival was better in the intervention arm (two-sided P: 0.0039). The median survival for patients with resected early-stage disease was 16.0 years in the intervention arm versus 5.0 years in the usual-care arm. Conclusion was that extended follow-up did not reveal a lung cancer mortality reduction for the intervention arm. Similar mortality, but better survival for individuals in the intervention arm indicated that some lesions with limited clinical relevance may have been identified in the intervention arm. This was the first evidence that over-diagnosis might play a role in lung cancer screening.

Because of the lack of power of the MLP and CS studies, in 1993 the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial was initiated in the USA to determine whether screening would reduce mortality rates from these cancers including lung cancer. People in the screen arm were invited for five annual rounds of CXR screening. Final mortality results are anticipated at the end of 2015.

Description of the screening tool

With the advent of low-dose multi-detector CT technology in the 1990s interest in lung cancer screening has gained enormous momentum. Advantage of this technique is that it is well suited for high-throughput screening programmes because of its advance in scan speed (the lungs can be scanned within one breath hold), improved spatial resolution and the capacity to reconstruct multiple series from a single data acquisition. The low-dose technique results in an effective radiation dose of approximately 0.65 mSv, as opposed to 3.5–7.0 mSv for standard diagnostic CT. In addition, no intravenous contrast medium is used. In some trials, such as the International-Early Lung Cancer Action Project (I-ELCAP), screen-detected pulmonary nodules were evaluated by semi-automated volumetric software. This software offers the possibility of providing, in addition to the standard nodule characteristics, information on the nodule volume and the volume doubling time (VDT).

The concept of growth is based on the observation that benign lesions vanish or grow very slowly or very rapidly over time, while malignant lesions show rapid growth. Within the range of malignant growth, the speed of growth may be related to the degree of malignancy. This volumetric software offers the possibility of using VDT as a biomarker for malignancy and to discriminate between benign and malignant nodules. Based on the first I-ELCAP experience, the Dutch–Belgian lung cancer screening trial (NELSON) investigators evaluated for the first time all screen-detected nodules according to their volume and VDT, the so-called NELSON nodule management strategy. Nodules were classified according to their volume and VDT only, without the need for PET, evaluation after antibiotics or FNA. Several other European trials have adopted this approach, such as the Danish Lung Cancer Screening Trial (DLCST), the German screening trial (LUSI) and the recently started UK screening trial (UKLS).

Diagnostic performance of CT screening

The diagnostic performance of lung cancer screening can be expressed both by the proportion of early stage I disease detected and by the sensitivity of CT screening. The sensitivity of CT screening is the ratio between the number of screen-detected lung cancer cases and the number of screen-detected cases plus those missed by screening. The group of missed lung cancer cases consists of those identified by symptoms between the regular screening rounds (so-called interval cancers) and those missed by CT screening because they are centrally located in the larger airways and picked up by other diagnostic procedures, for example, a bronchoscopy or sputum cytology.

From a large number of non-randomised studies that are currently running or have been completed, information can be obtained on the diagnostic performance of CT screening. These data appear to be very consistent. In a first pooled analysis of five large observational studies including the Anti Lung Cancer association (ALCA) and the Hitachi Health Center study from Japan, the Early Lung Cancer Action Project (ELCAP), the Mayo Clinic Study from the USA and the lung cancer screening study from Milan in Italy, 13,122 baseline and 10,245 annual follow-up scans were evaluated. Fifty-five to 85% of the lung cancers were detected at baseline and

60–100% of the cancers detected at annual repeat screening were stage I tumours. This is markedly better than in the current clinical practice where only 15–20% of all newly diagnosed lung cancer cases are stage I disease. The lung cancer detection rate varied between 0.4% and 2.7% in these trials at baseline and 0.07–1.1% at annual repeat screening. Subsequently, several review papers have been published on the diagnostic performance of lung cancer low-dose CT screening. They showed that the proportion of early-stage disease ranged between 38% and 66%. The reported median sensitivity, specificity, positive predictive value and negative predictive values were 81%, 81%, 8% and 99%, respectively.

Positive test results

Approximately 50% of those who undergo screening have at least one non-calcified pulmonary nodule on their CT scan, and this number is expected to rise with the use of more advanced CT scanners and the use of thinner reconstruction intervals. In certain geographic regions where fungal infections are endemic the proportion of people with at least one non-calcified pulmonary nodule can be even higher. Because of the different definitions used to define what a positive test result is, the proportion of participants with a positive test result varied widely in the different trials, and, consequently, so did the rate of false-positive test results. The test positivity rate has a large impact on the proportion of those who undergo one or more subsequent recall CT scans and further work-up of the suspicious nodule(s) for diagnosis. Although not yet investigated, it might be expected that the higher the test positivity rate, the more people will also experience discomfort and anxiety as a result of screening. In the NLST trial, 27% of the baseline and second round CT screen arm participants had a positive test result, while this was only 2.6% and 1.8% respectively, in the NELSON trial. In NLST any new nodule $\geqslant$4 mm was defined as test-positive, while in NELSON this was defined as any new nodule $>500\,mm^3$ (>9.6 mm in diameter) or any growing nodule (percentage volume change $\geqslant$25%) with a VDT <400 days. Although the CT recall rate was 19% for baseline screening in NELSON, it was only 4% for the second round. This illustrates that the advantages of volumetric measurement become only fully apparent when a volumetric comparison can be made with a previous CT scan. Because no previous CT scans are available at round one, the first-round recall rate in NELSON was almost as high as in other trials, but much lower in subsequent rounds. Most trials did not report on their second-round recall rates, but values up to 41% have been reported by the PLuSS study investigators. These data suggest that the efficiency of diagnostic work-up can be improved by integrating the measurement of volume growth of lung nodules as an indicator of clinically significant lung cancer, while limiting the need for additional costly or potentially harmful diagnostic procedures.

The proportion of invasive procedures that revealed benign disease was 27% at baseline and 19% at the second screening round in the NELSON trial. These figures are within the same range as those reported by others for baseline screening (0–43%, median 19%). Although there is no consensus on what an acceptable resection rate for benign disease is, a rate between 10% and 20% can be regarded as acceptable. This means that the resection rate for benign disease in the CT screening trials is still too high and that future research efforts should be directed at bringing this number down with, for example, the use of biomarkers.

Overdiagnosis in lung cancer screening

Overdiagnosis, or the detection of lung cancer cases that would not lead to an individual's death because of a slow growth rate or competing age-related risks for death, remains an important concern as CT resolution continues to find smaller and smaller primary lung cancers. So far, no firm evidence exists to allow a reliable estimate of its influence in lung cancer screening trials because of the lack of long-term follow-up and the unavailability of adjustment for the lead time, as a true estimate of the lead time for CT screening is as yet unknown. Review of the lung cancer cases detected in the ELCAP trial revealed that the histopathology was consistent with the invasive characteristics of conventionally detected lung cancers. In addition, the gene expression profiles of lung cancer cases detected in the Milan MILD trial by cDNA microarray analyses were compared with matched series of symptom-detected lung cancers in addition to quantitative real-time PCR and immuno-histochemistry. The results suggest that the aggressive biological behaviour of CT-detected cancers is similar to that of symptom-detected ones. In NELSON and I-ELACP only 8–10% of all lung cancer cases had pure bronchiolo-alveolar carcinoma (BAC) histology. These BAC cases may represent overdiagnosed cancer cases because it is well known that they have a very favourable 10-year survival rate after resection, although this is only a very rough estimate for the magnitude of

overdiagnosis in lung cancer screening. VDT could also be used as a first indication of the proportion of overdiagnosed cases. Assuming that overdiagnosed cancer cases have a volume doubling time (VDT) of >400 days, in the Mayo Clinic CT screening trial 27% of all cancers detected were overdiagnosed cases. Eighty-five percent of the tumours with a VDT >400 days were in female patients and only 15% in male patients. This can be explained by length-biased sampling in female patients for more slowly-growing adenocarcinomas. The nodules with ground-glass or part-solid attenuation comprised only a slight majority of the tumours with a VDT >400 days. From Japan, overdiagnosis rates of around 40% have been reported. In NELSON and I-ELCAP 8–10% of the cancers detected had a VDT >400 days. In NELSON, nodules with a VDT >600 days were left in situ and watched closely. This volumetry approach used in the NELSON nodule management strategy, which filters for biological indolent tumours, might therefore reduce the risk of overdiagnosis in lung cancer screening.

Effectiveness of lung cancer screening

I-ELCAP investigators were the first to report on their long-term survival data of this non-randomised screening cohort in which world-wide over 32,000 subjects have undergone baseline and a large fraction of them serial annual follow-up screening. They showed that patients with screen-diagnosed early stage I disease had an 88% 10-year survival rate, which is much higher than the five-year survival rates of between 60% and 70% for stage I disease. Based on these data, the authors concluded that the disease is curable and that spiral CT screening is ready for implementation on a large scale. The authors also demonstrated that all the 484 cancers detected were genuine invasive cancers except for 20 adenocarcinomas of BAC subtype. Even after exclusion of the BACs from the analysis – they are known to have a very good prognosis and are probably overdiagnosed cases – the 10-year survival rates remained very high. These results should be interpreted with caution, however, because five- and ten-year survival rates are well known to be subject to different kinds of screening bias. Similar observations have been made in Japan: since the introduction of spiral CT screening in the 1990s, 5-year survival rates of all stages of lung cancer have improved to 76.2%. Sone and colleagues reported on similar long-term follow-up survival data of the mass screening programme for lung cancer that has been conducted between 1996 and 1998. A total of 13,037 annual CT scans were made in 5,480 subjects (2,969 men, 2,511 women) between 40 and 74 years of age. Median follow-up was 101 months (range 70–117 months) after surgery. The 10-year overall survival rate was 83.1% and the lung cancer-specific survival was 86.2%. Fifty-five percent of all participants were non-smokers and especially in this group BAC and well-differentiated adenocarcinomas have been found (Noguchi's A and B) with excellent prognosis. The mean VDT of the tumours detected in non-smokers was 607 days, which was nearly twice as long as those for smokers (292 days). The authors suggest that the very high 10-year survival rate observed for the whole group might partly be due to length-time bias and overdiagnosis. Indirect evidence of effectiveness also came from a study by Henschke and colleagues. They found a clear relationship between tumour size and lymph node status. The percentages of cases without lymph node metastases was 91%, 83%, 68% and 55% for tumour size categories of <15 mm, 16–25 mm, 26–35 mm and >35 mm, respectively. The percentages of N0M0 cases in screen-diagnosed lung cancers are much higher than those previously reported in the Surveillance, Epidemiology, and End Results (SEER) registry, which gives indirect support to the hypothesis that the smaller the cancer detected, the better the prognosis. Again, all previously mentioned biases also apply to this study. Only prospectively randomised studies can ascertain whether CT screening is effective or not.

In Europe, six randomised trials in which CT screening was compared with no-screening were launched to address the question whether CT screening will reduce lung cancer mortality. In total more than 32,000 high-risk current and former smokers have been enrolled so far. The six trials include the Dutch–Belgian Nederlands–Leuvens Longkanker Screenings Onderzoek (NELSON), the Danish Lung Cancer Screening Trial (DLCST), the MILD trial, the Italian Lung cancer Computer Tomography screening trial (ITALUNG), the Detection And screening of early lung cancer by Novel imaging Technology and molecular Essays (DANTE), and the German Lung Cancer Screening Intervention Study (LUSI). In the UK a randomised pilot study with 4,000 participants has been initiated very recently. This pilot will probably be followed by one single screening round for 32,000 participants if the pilot demonstrates that the recruiting of participants and the logistics of the CT screening process are feasible. In the NELSON trial, in which 15,750 participants have been enrolled, the first, second and third screening rounds have been completed and the fourth round will be completed in 2011. The first screening interval is one year, the

second two years and the third two and a half years. The DLCST randomised 4,104 participants and all five annual screening rounds have been completed. The DANTE trial enrolled 1,276 participants to the screen arm and 1,196 to the control arm; also in this trial all five annual screening rounds have been completed. ITALUNGCT randomised 1,613 participants to the screen arm and 1,593 to the control arm; all four annual screening rounds have been completed. The LUSI trial has enrolled 3,551 of the planned 4,000 participants who will undergo five annual screening rounds. The MILD trial randomised almost 3,000 subjects so far between a screen-dense arm (10 annual screening rounds) and an arm with five screening rounds with a two-year interval. Even with the 32,000 subjects enrolled so far, we have to wait until 2015 until a sufficient number of events have taken place.

The National Lung Screening Trial (NLST), a randomised national trial among current and former heavy smokers aged 55 to 74 years, compared the effects of two screening procedures for lung cancer – low-dose helical CT and standard CXR – on lung cancer mortality. Starting in August 2002, the NLST enrolled about 53,500 men and women at 33 trial sites in the USA over a 20-month period. Participants were required to have a smoking history of at least 30 pack-years and were either current or former smokers without signs, symptoms, or history of lung cancer. Participants were randomly assigned to receive three annual screens with either low-dose helical CT or standard CXR. Participants were followed up for five years; all deaths were documented, with special attention given to the verification of lung cancer as a cause of death. In October 2010, a total of 354 deaths from lung cancer had occurred among participants in the CT arm of the study, whereas a significantly larger number, 442, of lung cancer deaths had occurred among those in the CXR arm. The data-monitoring committee concluded that based on this 20.3% reduction in lung cancer mortality and a 7% overall mortality reduction, which met the standard for statistical significance, the study had to be ended and was considered positive. This was the first time that clear evidence of a significant reduction in lung cancer mortality was demonstrated with a screening test in a randomised controlled trial. The fact that low-dose helical CT provides a decided benefit is unprecedented, and it is expected that these results will have major implications for lung cancer screening and the management of lung cancer for many years to come.

At the press release NLST trial investigators did not expect that if the trial had been closed prematurely the mortality reduction would have been larger. If a screening trial is continued without continuing to screen, the ability to pick up cancers diminishes and the screen effect will be more and more diluted. On the other hand, there is evidence that randomised controlled trials that are stopped early for benefit, the outcome effect that precipitated early termination (i.e. lung cancer mortality) is systematically overestimated, and the true effect of CT screening may thus potentially also be smaller than the reported 20% mortality reduction. Even though it was recognised that the news of the positive NLST trial result was a breakthrough in the early detection and treatment of lung cancer, there remain several major questions to be answered within the next five years before national implementation can be considered in Europe. Key issues to be addressed are the true magnitude of the disease-specific and overall mortality reduction that can be achieved by CT screening, the number of screening rounds needed, the optimal duration of the screen interval, and the optimal target population to be invited for screening. Answers to these questions are critical elements for a solid cost-effectiveness analysis based on which health care providers and national health care policy makers can and will decide on reimbursement and national implementation.

So far, it is unknown what the effect of CT screening is compared with no screening. NLST investigators stated that when the chest X-ray groups of the NLST and PLCO were compared (PLCO and NLST participants have comparable background characteristics with regard to lung cancer risk), lung cancer mortality was comparable in the two studies. When subsequently the PLCO CXR arm was compared with community care no benefit of CXR screening was found, which suggests that the mortality benefit that can be achieved by CT screening for lung cancer will not be larger in screening trials with a no-screen arm.

Also from modelling studies, there is evidence that lung cancer screening will reduce lung cancer mortality, but the number of screening rounds and the duration of follow-up needed to demonstrate the mortality reduction in these studies varied widely. With a NELSON-like screening programme (three rounds with one- and two-year intervals) a mortality reduction of only 15% after ten years of follow-up was found. Others reported a 23% mortality reduction with annual screening after ten years of follow-up and a 28% mortality reduction after five annual screening rounds and six years of follow-up. ELCAP investigators also used a validated TSCE microsimulation model for the observed versus predicted lung cancer death rate in the New York-ELCAP state cohort (n = 7,995)

who underwent two annual screening rounds. They even found a 45% mortality reduction (95% CI 34.7–54.0%) compared with no screening after ten years of follow-up. Also, Bach and colleagues modelled the effect of CT screening. They estimated the effect of CT screening based on a combined cohort of three single-arm studies of 3,246 participants, and compared the observed numbers of lung cancer outcomes with the expected numbers from a validated lung cancer prediction model. They observed a three-fold increase in the number of new lung cancer cases detected and a ten-fold increase in the number of lung cancer cases resected, but no decrease in advanced-stage disease (42 observed versus 38.8 expected) or in lung cancer deaths (38 observed versus 38.8 expected). The investigators acknowledge that within a median 3.7-year follow-up period only a 30% mortality reduction could have been observed, and that prolonged follow-up or more screening rounds could have led to a difference in mortality. Also, the accuracy of the Bach model is of concern because it might have underestimated the expected number of lung cancer cases in the screen cohort, which biases against CT screening, while the population of Bach's study probably had a higher cancer risk because of a stronger smoking history and prevalence of COPD, although adjustments for the increased cancer risk with COPD have been made.

When a historical comparison was made between the New York-ELCAP CT screen cohort with age, sex and tobacco exposure-matched individuals from two well-described cohorts including the Beta-Carotene and Retinol Efficacy Trial (CARET) and the Cancer Prevention Study II (CPS II) the authors generated an estimated lung cancer mortality reduction for current smokers of 36% and for former smokers of 64% after two screening rounds and four years' follow-up. Therefore, European randomised trial data will not only be important to confirm the NLST trial results, but will also provide information on the mortality benefit compared with no screening. Only Chien and Chen modelled the number needed to screen (NNS) per one death from lung cancer averted by CT screening. They reported a NNS of 208, much lower than for breast and prostate cancer screening. This is very close to the NNS of 300 reported by NLST investigators.

Effect of screening on quality of life and behavioural changes

In general, the population health benefits of lung cancer CT screening should always be weighed against the potential physical and psychological harm caused by the test, diagnostic follow-up and over-treatment. Benefits will only apply to a small group of participants, whereas the majority are subjected to the potentially unfavourable side-effects of the screening process such as discomfort, anxiety and distress associated with undergoing a CT scan and waiting for the test result.

In most studies, however, the impact of CT screening on quality of life (QOL) appeared to be very limited and not of clinical relevance. Factors that influenced QOL were especially related to the CT test result and the level of the affective lung cancer risk perception of the participant. In addition, waiting for the test result was found to be discomforting.

The high 14.5% smoking abstinence rate observed among participants in NELSON has also been reported by several other investigators. This abstinence rate is very encouraging in comparison to the quit rates of 3–7% observed in adults of the general population after minimal smoking cessation interventions, because trial participants are usually elderly people with a long and intense smoking history for whom it is difficult to make an attempt to quit. Furthermore, higher education, contemplating quitting in the near future and participation in the control arm were associated with prolonged smoking abstinence after two years of follow-up in the NELSON trial. Lung cancer screening may thus be regarded as a teachable moment to improve smoking behaviour. Compared with a normal test result an indeterminate test result had a similar impact on future smoking abstinence in high-risk male smokers after two years' follow-up in the NELSON trial.

Cost-effectiveness analyses

As the true magnitude of the mortality reduction of CT screening compared with no screening, the number needed to screen (NNS) to save one life and the QOL-adjusted life-years gained by CT screening are as yet unknown, no firm conclusion can be drawn with regard to the cost-effectiveness of CT screening for lung cancer. So far, only high-risk current and former smokers have been invited, but it is well known that only an estimated 11% of female smokers and 17% of male smokers will be diagnosed with lung cancer in their lifetimes. Lung cancer risk stratification may help to increase the cost-effectiveness of lung cancer screening by stratifying people for subsequent screens, for the length of the interval between the screening rounds and to reduce the rate of false-positive test results. Several lung cancer risk models have already

been developed, but their discriminative power has only been modest so far. Identification of potential new epidemiological lung cancer risk factors and the incorporation of genetic and serum biomarkers may help to improve these models. Research is also needed to understand better the natural history and epidemiology of screen-detected lung cancers, particularly small, well-differentiated adenocarcinomas, as well as the impacts on quality of life. Cost-effectiveness ratios based on modelling vary widely. Data from ELCAP were incorporated into a decision analysis model comparing low-dose CT screening of high-risk participants with no screening. The incremental cost-effectiveness ratio of a single baseline low-dose CT scan was only 2,500 US dollars per year of life saved. Only when the likelihood of overdiagnosis was >50% did the cost effectiveness ratio exceed 50,000 US dollars per year of life saved. In contrast, an Australian cost-effectiveness model for men aged 60–64 years, with an annual incidence of lung cancer of 552 per 100,000, showed that the incremental cost-effectiveness ratio was 57,325 AU dollars per life-year saved and 105,090 AU dollars per QALY saved. For female patients aged 60–64 years with the same annual incidence of lung cancer, the cost-effectiveness ratio was 51,001 AU dollars per life-year saved and 88,583 AU dollars per QALY saved.

Future perspectives

In 1998 the *International Conference on Prevention and Early Diagnosis of Lung Cancer* was held in Varese, Italy. Its consensus statement was published in 2000 and recognised the potential of early detection in improving outcome in lung cancer. However, no consensus was reached about offering screening for lung cancer outside the context of an experimental trial because CT screening for lung cancer was regarded as experimental. Because of ambiguities in the data, the consensus statement concluded at that time that "existing studies provide us with an imperfect basis for health policy". Based on recommendations from the Varese Conference, the ACS did not recommend lung cancer screening either, but at the same time offered the possibility for individuals at a high risk of lung cancer who wanted to be screened for lung cancer of being informed about the options for early detection and the risks, benefits and problems, so that they could make an informed decision. The ACS also stressed the importance of quality control and appropriate follow-up. The primary objective of the Como Conference, which was held in 2005, was to re-consider whether there was sufficient scientific evidence to advise screening for lung cancer among asymptomatic individuals outside the context of a clinical trial. The conclusion of this conference was, again, that whenever possible, high-risk individuals should be encouraged to participate in ongoing trials. For subjects who, although eligible, did not have access to such trials, a process of shared decision-making between physicians and at-risk individuals was recommended. In March 2011, more than five years after the Como conference, European trial investigators met in Pisa, Italy. The primary objective of this meeting was to provide an update on the ongoing European Randomised lung cancer screening trials and to provide a position statement with regard to the national implementation of CT screening for lung cancer and a recommendation with regard to CT screening outside clinical trials in Europe after the release of the positive NLST trial results. Following the public announcement of the mortality benefit obtained in the NLST in the USA, it is to be expected that there will be an increased demand for the introduction of more widespread CT screening for lung cancer. A decision to initiate national CT screening programmes will require an evaluation of both the positive and negative effects of such a programme. Such evaluations are under way from the screening trials in Europe as well as from the NLST. The decision will ultimately depend on many factors including national issues, for example, resources. The conclusion of this meeting was that the European trial investigators recognised that even though the news of the positive NLST trial result is a breakthrough in the early detection and treatment of lung cancer, there remain several major questions to be answered within the next five years before national implementation can be considered in Europe. The open questions include the optimal number of rounds and the optimal screen interval.

Another unresolved question is whether all heavy current and former smokers should be invited at least once, or that people should be stratified according to their lung cancer risk. So far, only age and smoking history have been used as selection criteria for enrolment in screening trials, but it is well known that even though over 80% of all lung cancer cases are directly related to smoking, only 11% of female smokers and 17% of male smokers will be diagnosed with lung cancer during their lifetimes. Therefore, lung cancer risk stratification may help to increase the cost-effectiveness of a lung cancer screening programme, not only by enrichment of the population at risk, but also by reducing the

high rate of false-positives that trigger unnecessary surgery and the need for recall CT scans to improve the specificity. Biomarkers could potentially play a role in the process of risk stratification. Although several papers have reported on biomarkers for lung cancer early detection, most of them lack independent validation. One of the approaches is auto-antibody profiling, which could be a powerful tool for early detection when incorporated into a comprehensive screening strategy. An increasing number of reports describe the presence of a humoral immune response in the form of autoantibodies to tumour-associated antigens (TAAs) in lung cancer and other solid tumours. Tumours are thought to induce the release of many TAAs into the blood. They can be overexpressed, aberrantly expressed, mutated, misfolded or aberrantly degraded such that an auto-reactive immune response is induced. Post-translational modifications could also induce an immune response by generating a neo-epitope or by enhancing self-epitope presentation and affinity to the major histocompatibility complex or T-cell receptor. Diagnosing cancer based on serum profiling is therefore an attractive concept especially because cancer auto-antibodies can be detectable up to five years before radiological detection. Second, auto-antibodies are inherently stable and persist in serum for a relatively long period of time at considerable higher concentrations than TAAs because they are usually not subject to proteolysis.

Automated volumetric software development and nodule management algorithms are needed as these will play a crucial role in the management of the large number of screen-detected nodules. Based on this additional information evidence-based cost-effectiveness analyses can be performed. Until then, CT screening should only be recommended as part of well-designed screening trials. Well co-ordinated and strategic planned research efforts are needed in order to be able to provide these answers once the final mortality data from the European trials become available in 2015. The European trial group investigators expressed their support for the IASLC efforts in taking the lead in this process and in participating in the different international task forces (radiology, pathology, clinical care, surgery) that have been formed.

Conflict of interest statement

The author has no conflict of interest to declare.

Further reading

1 Mulshine JL, Sullivan DC. Clinical Practice. Lung Cancer Screening. *N Engl J Med* 2005;**352**:2714–20.
2 Henschke CI, Yankelevitz DF, Libby DM, et al. Survival of patients with stage I lung cancer detected on CT screening. *N Engl J Med* 2006;**355**:1763–71.
3 Henschke CI, Yankelevitz DF, Meittinen OS. Computed tomography screening for lung cancer: the relationship of disease stage to tumor size. *Arch Int Med* 2006;**166**:321–5.
4 Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. *Radiology* 2005;**235**: 259–65.
5 van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer Multi-slice CT screening trial (NELSON). *Int J Cancer* 2007;**120**:868–74.
6 Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. *JAMA* 2007;**297**:953–61.
7 van Klaveren R, et al. Management of lung nodules detected by volume CT scanning. *N Engl J Med* 2009;**361**:2221–9.
8 NLST-website: http://www.cancer.gov/clinicaltrials/noteworthy-trials/nlst.
9 The International Early Lung Cancer Action Program Investigators. Survival of patients with Stage I lung cancer detected on CT screening. *N Engl J Med* 2006;**355**:1763–71.
10 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;**55**(2):74–108.
11 Marcus P, Bergstrahl EJ, Fagerstrom RM, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. *J Natl Cancer Inst* 2000;**92**:1308–16.
12 Manser RL, Irving LB, Byrnes G, Abramson MJ, Stone CA, Campbell DA. Screening for lung cancer: a systematic review and meta-analysis of controlled trials. *Thorax* 2003;**58**:784–9.
13 Black W. Overdiagnosis: an underrecognised cause of confusion and harm in cancer screening. *J Natl Cancer Inst* 2000;**92**: 1280–2.
14 Hocking WG, Hu P, Oken MM, et al.; PLCO team. Lung cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. *J Natl Cancer Inst* 2010; **102**(10):722.
15 Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. *Lancet* 2003;**362**:593–7.
16 Blanchon T, Bréchot JM, Grenier PA, et al.; Dépiscan Group. Baseline results of the Depiscan study: a French randomized pilot trial of lung cancer screening comparing low dose CT scan (LDCT) and chest X-ray (CXR). *Lung Cancer* 2007;**58**:50–8.
17 Infante M, Lutman FR, Cavuto S, et al.; for the DANTE Study Group. Lung cancer screening with spiral CT: baseline results of the randomized DANTE trial. *Lung Cancer* 2008;**59**:355–63.
18 Lopez Pegna A, Picozzi G, Mascalchi M, et al. Design, recruitment and baseline results of the ITALUNG trial for lung cancer screening with low-dose CT. *Lung Cancer* 2009;**64**:34–40.
19 Pedersen JH, Ashraf H, Dirksen A, et al. The Danish randomized lung cancer CT screening trial – overall design and results of the prevalence round. *J Thorac Oncol* 2009;**4**(5):608–14.
20 Becker N. Epidemiology of lung cancer. *Radiologe* 2010;**50**: 654–61.
21 Baldwin DR, Duffy SW, Wald NJ, Page R, Hansell DM, Field JK. UK Lung Screen (UKLS) nodule management

protocol: modelling of a single screen randomised controlled trial of a low-dose CT screening for lung cancer. *Thorax* 2011;**66**(4):308–13.
22 Strauss GM, Dominioni L, Jett JR, Freedman M, Grannis FW. Como International Conference position statement: lung cancer screening for early diagnosis 5 years after the 1998 Varese conference. *Chest* 2005;**127**(4):1146–51.
23 Chien, CR, Chen TH. Mean sojourn time and effectiveness of mortality reduction for lung cancer screening with computed tomography. *Int J Cancer* 2008;**122**:2594–9.
24 McMahon PM, Kong CY, Johnson BE, et al. Estimating long-term effectiveness of lung cancer screening in the Mayo CT screening study. *Radiology* 2008;**248**:278–87.
25 Foy M, Yip R, Chen X, Kimmel M, Gorlova O, Henschke CI. Modeling the mortality reduction due to computed tomography screening for lung cancer. *Cancer* 2011;**117**(12):2703–8.
26 Henschke CI, Bofetta P, Gorlova O, Yip R, Delancey J, Foy M. Assessment of lung cancer mortality reduction from CT screening. *Lung Cancer* 2011;**71**(3):328–32.
27 Yau G, Lock M, Rodrigues G. Systematic review of baseline low-dose CT lung cancer screening. *Lung Cancer* 2007;**58**:161–70.
28 Black WC. Computed tomography screening for lung cancer: review of screening principles and update on current status. *Cancer* 2007;**110**:2370–84.
29 Black C, de Verteuil R, Walker S. Population screening for lung cancer using computed tomography, is there evidence of clinical effectiveness? A systematic review of the literature. *Thorax* 2007; **62**:131–8.
30 Sone S, Nakayama T, Honda T et al. Long-term follow-up study of a population-based 1996–1998 mass screening programme for lung cancer using mobile low-dose spiral computed tomography. *Lung Cancer* 2007;**58**:329–41.
31 Brenner DJ, Hall EJ. Computed tomography – an increasing source of radiation exposure. *N Engl J Med* 2007;**357**:2277–84.
32 Lindell RM, Hartman TE, Swensen SJ, et al. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. *Radiology* 2007;**242**:555–62.
33 Yankelevitz DG. Quantifying "overdiagnosis" in lung cancer screening. *Radiology* 2008;**246**:332–3.
34 van der Aalst CM, van Klaveren RJ, van den Bergh KA, Willemsen MC, de Koning HJ. The impact of a lung cancer CT screening result on smoking abstinence. *Eur Respir J* 2011;**37**(6):1466–73.
35 van den Bergh KA, Essink-Bot ML, Borsboom GJ, Scholten ET, van Klaveren RJ, de Koning HJ. Long-term effects of lung cancer CT screening on health-related quality of life (NELSON). *Eur Respir J* 2010; doi: 10.1183/09031936.00123410.
36 van der Aalst CM, van den Bergh KA, Willemsen MC, de Koning HJ, van Klaveren RJ. Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch–Belgian randomised controlled lung cancer screening trial. *Thorax* 2010;**65**(7):600–5.
37 van den Bergh KA, Essink-Bot ML, van Klaveren RJ, de Koning HJ. Informed decision making does not affect health-related quality of life in lung cancer screening (NELSON trial). *Eur J Cancer* 2010;**46**(18):3300–6.
38 van den Bergh KA, Essink-Bot ML, Borsboom GJ, et al. Short-term health-related quality of life consequences in a lung cancer CT screening trial (NELSON). *Br J Cancer* 2010;**102**(1):27–34.
39 van den Bergh KA, Essink-Bot ML, van Klaveren RJ, de Koning HJ. Informed participation in a randomised controlled trial of computed tomography screening for lung cancer. *Eur Respir J* 2009;**34**(3):711–20.
40 van den Bergh KA, Essink-Bot ML, Bunge EM, et al. Impact of computed tomography screening for lung cancer on participants in a randomized controlled trial (NELSON trial). *Cancer* 2008; **113**(2):396–404.
41 Bunge EM, van den Bergh KA, Essink-Bot ML, van Klaveren RJ, de Koning HJ. High affective risk perception is associated with more lung cancer-specific distress in CT screening for lung cancer. *Lung Cancer* 2008;**62**(3):385–90.