

Journal club

Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial

Commentary on:

Black WC, *et al.* Lung cancer incidence and mortality with extended follow-up in the National Lung Screening Trial. *J Thorac Oncol* 2019; 14: 1732–1742.

Context

Since lung cancer (LC) is still the leading cause of cancer deaths worldwide [1], early detection through screening represents an important opportunity to improve LC survival and is a priority area for cancer care. The National Lung Screening Trial (NLST) aimed to compare low-dose helical computed tomography (LDCT) with chest radiography in LC screening of current or former heavy smokers. The trial found a relative reduction in mortality from LC of 20% in those who had undergone LDCT screening. LC screening has regained prominence in the thoracic oncology literature with the completion of NELSON and other European trials, which support the role of LC screening in achieving early diagnosis and reducing mortality. A growing number of implementation pilots are providing an impetus towards organised, national programmes for LC screening, which are in need of long-term follow-up data such as those presented in this study.

Methods

This multicentre, randomised controlled trial assessed incidence and mortality in an extended follow-up of the original NLST. Inclusion and exclusion criteria remained consistent with the previously published NLST study design [2]. Briefly, men and women aged 55–74 years who had a positive history of cigarette smoking (≥ 30 pack-years and current smokers, or former smokers who had quit within the previous 15 years) were enrolled from 2002 to 2004 at 33 medical institutions across the USA. Participants were randomised to an LDCT or single-view chest radiography arm, which comprised of three annual screens for each modality. They were actively followed for LC incidence and mortality until 31 December 2009, corresponding to the time point of the final analysis of the initial NLST, and covering a median follow-up duration of 6.5 years. For the extended follow-up thereafter, participants were followed only passively through state cancer registries and the National Death Index for an additional 6 years. For most of the participating centres, follow-up of LC incidence and mortality was until the end of 2014 or 2015, respectively. This was the first study to achieve an extended follow-up in lung LC screening and to assess whether screening was not only able to delay LC death but also to prevent it.

The primary endpoint of the extended follow-up was to report LC incidence and LC-specific mortality given as rates and rate ratios (RRs). The secondary

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The extended follow-up of the NLST represents a timely and important update to the NLST data, alongside full results of the NELSON and the LUSI trials, as Europe begins to set out a vision for lung cancer screening. <http://bit.ly/2MYXedl>



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endpoint was to assess overdiagnosis due to LDCT screening. The number needed to screen (NNS) to prevent one LC death was assessed and compared to prior data.

Since the case ascertainment period is far beyond the three yearly screening rounds, potential issues arise towards dilution of screening effects [3, 4]. Thus, to correct LC mortality RRs for such dilution, the cut-off time for cancer diagnosis was determined, and cancer death solely in that period were included in the RR analysis. This method leads to a balanced number of cancer deaths across the two arms.

For the dilution-adjusted analysis, bronchioloalveolar carcinoma (BAC) cases, which represented most of the overdiagnosed cases, were excluded and the cut-off time for cancer diagnosis was defined as the earliest study year for which there was no significant difference in cumulative incidence across the LDCT and chest radiography arm. Thus, only deaths with a corresponding LC diagnosis within 6 years of randomisation were included.

Main results

After an extended median follow-up of 11.3 years for incidence and 12.3 years for mortality, 1701 and 1681 LC diagnoses were established in the LDCT (n=26722) and in the chest radiography arm (n=26730), respectively. In the extended follow-up analysis, an increase in LC incidence was no longer observed (RR 1.01). Death from LC was observed in 1147 cases with LDCT and 1236 cases with chest radiography leading to an unadjusted RR of 0.92 (p=0.05) and after adjusting for dilution to a significantly reduced RR of 0.89 (p=0.043). Despite correction for the dilution effect of an extended follow-up, there was a smaller reduction in LC-related mortality compared to the prior NLST analysis. The extended analysis also did not show a significant reduction in the overall mortality in the LDCT arm compared to the chest radiography arm (RR 0.97), which the authors attributed to the methodological challenges of dilution.

The NNS with LDCT to prevent one death from LC was 303. Based on the similar NNS values found in the earlier NLST analysis (320) and six additional years of mortality follow-up, the authors concluded that LDCT screening was able to prevent LC deaths or at least delay death for more than a decade.

LDCT helped diagnose more early- and fewer late-stage LC compared to chest radiography, and the number of stage IV incidences of LC in the LDCT arm continued to decrease compared to the chest radiography arm into the long-term follow-up window.

Commentary

From a general point of view, screening for cancer is performed in individuals without any

signs or symptoms of cancer so that disease can be detected as early as possible, which allows for early treatment to reduce the mortality and morbidity associated with the disease [5]. An optimal screening programme should have an interval during which there is a low likelihood of developing cancer, and it should be cost-effective based on the duration of risk reduction following an initial negative screen [6].

This study represents a timely and important update to the NLST data, alongside full results of the NELSON [7] and the LUSI trials [8], as Europe begins to set out a vision for LC screening. Although 10 years have passed since the publication of the first results of this landmark study, the USA still encounters the difficulties of implementation and the challenges of screening uptake by high-risk populations. Following important updates to the literature with trials based in the Netherlands (NELSON), the UK (UKLS), Germany (LUSI), Italy (ITALUNG, DANTE and MILD) and Denmark (DLST), and evolving implementation pilots, Europe is about to embark on a similar journey.

The extended follow-up data presented in this study allowed the authors to assess if the screening benefit seen in the NLST was sustained in long-term follow-up against potential diminutive factors such as overdiagnosis. Overdiagnosis was a criticism of early diagnosis approaches where the overrepresentation of additional early stage cancers detected by a more sensitive technique than chest radiography would not have come to added harm if detected a short interval later by chest radiography. The LC mortality reduction data previously published for the NLST are supported by this long-term follow-up but with a smaller effect size and nonsignificance for all-cause mortality. However, the data need careful interpretation in view of the effects of dilution.

The authors acknowledge that the study design is problematic in terms of comparing the effect size between the groups: subsequent deaths from cancers developed after the screening window and other causes of death appeared, which will cause a trend towards a reduced difference between the groups (reduced RR) and lead to diminishing levels of significance. Similarly, there are no data on whether participants went on to have further screening. This may have been more likely for those familiar with its process and potential benefits, and would have served to accentuate the mortality benefit beyond that of the NLST itself.

Whilst the mortality benefit is sustained, with NNS of 303, the resultant 3.3 deaths avoided per 1000 participants is comparatively small relative to other interventions, although this is not incomparable to other screening approaches. In mitigation of this, significantly more stage I and fewer stage IV LC diagnoses were made by LDCT *versus* chest radiography. The accompanying “stage shift” will result in a cohort that is more treatable with both radical and curative intent, which will

not only improve treatment accessibility but also reduce symptom burden.

Comparing the NNS in the NLST to those found in screening programmes for other tumour entities, it is noteworthy that the randomised controlled screening trials such as for colorectal cancer (*via* flexible sigmoidoscopy) and breast cancer (*via* mammography) reported a NNS of 871 or 1366, respectively, to prevent one death [9, 10]. It has to be taken into account that there are considerable differences in tumour biology (*e.g.* lethality), tumour incidence and accuracy of screening modality as well as the screening modality itself among these three entities.

The NLST also supports evidence implied by the European screening trials that there is a sex difference in the benefit of LC screening in favour of females, which the NELSON trial could not fully address given most participants were male [7]. In addition, the German LUSI trial found that LDCT screening led to a statistically significant reduction in LC mortality among women (hazard ratio (HR) 0.31, $p=0.04$), but not among men (HR 0.94, $p=0.81$) [8]. This is an area that future studies will need to address to determine whether LC screening needs to be stratified by sex.

Implications for practice

Despite a decade passing since the results of NLST were first published, Europe lags behind the USA in implementation of LC screening. The wide variation in healthcare systems and resources as well as variation in patient access to healthcare services are only few of the issues raised that can be potential obstacles in pan-European implementation of LDCT screening. The lack of such an implementation strategy deepens the aforementioned gap. A number of European countries have seen RCTs and implementation research studies that are supportive of NLST data, and we are now seeing the start of national implementation pilots. One such pilot in the UK will invite 600 000 participants for “lung health checks”, which in some will lead to LDCT. Since the 2018 updated German guidelines on LC include a weak recommendation on the early detection of LC with LDCT, the German Radiological Society and the German Respiratory Society published a joint statement about LC screening including quality assurance processes for the early detection of LC with LDCT in Germany [11].

Policy documents across Europe have set specifications and consensus statements for LC screening that will aim to bring LDCT with the goal of reduced mortality to a wider European population. In this context, the European Society of Radiology and the European Respiratory Society recently published a joint white paper that favours LC screening as part of organised, comprehensive, quality-assured, longitudinal programmes within a clinical trial or in routine clinical practice at certified multidisciplinary medical centres [12]. However, one of the main challenges is the low LC screening uptake by the high-risk population, which was highlighted in the USA and may soon become a problem in Europe. Interestingly, there currently seems to be a gap in strategies to target high-risk populations and prompt their engagement with the LC screening programme. Current strategies are limited to selecting regions of known LC mortality for implementation pilots and placing mobile scanning units within these areas of need.

Overdiagnosis is a significant concern in early diagnosis and screening that requires careful design of research studies and clinical services. The goal is to maximise the opportunities of finding earlier stage disease without bring undue harm to those who would never have needed a given intervention. In LC screening, much enthusiasm has arisen from our new ability to find cancer at a stage when it can be treated in large numbers when late-stage presentations are the norm. In some other cancer types, diagnostic pathways seek to exclude less significant disease. This study provides some reassurance in defence of the ability of LC screening to diagnose the right patients for true effect and is one of many important pieces of data that will be required in the route to national implementation of LC screening in other European countries.

BAC lesions remained stable and were found in significant excess in the LDCT group as compared with the chest radiography group, even after 10 years. These lesions will need a specific follow-up protocol that does not overinvestigate such lesions.

The extended follow-up analysis of the NLST confirms the reduction in LC mortality in the LDCT arm, albeit to a lower degree, but does not confirm a reduction in all-cause mortality. Although it highlights the importance of extended follow-up, there are no set standards regarding its actual duration in a pragmatic clinical setting as well as its actual implication on survival data analysis.

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Conflict of interest

A. Frille has nothing to disclose. G. Hardavella has nothing to disclose. R. Lee reports funding for conference attendance from Cancer Research UK, and that he is employed as a clinical lead for the UK NHS England Targeted Lung Health Check Programme and has been funded by an NHS England grant (Cancer Alliance funding) for Lung Health Check Research.

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