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Journal club

Lung cancer screening by volume computed tomography: thriving to high performance

Commentary on:
de Koning HJ, *et al*. Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med* 2020; 382: 503–513.

Context

Lung cancer remains the leading cause of cancer-related death worldwide, with an estimated 1.8 million deaths annually [1]. Prognosis is poor given the advanced stage diagnosis resulting in a low 5-year survival rate of 15%. The US National Lung Screening Trial (NLST) showed that computed tomography (CT) screening results in 20% mortality reduction, which has led the US Preventive Services Task Force to recommend annual low-dose CT (LDCT) screening [2]. The most recent recommendation statement advises screening in adults aged 50–80 years who have a 20-pack-year smoking history and currently smoke or have quit within the past 15 years [3]. However, although evidence in favour of developing CT screening programmes is growing, only a few countries (China, Korea and the USA) currently offer nationwide lung cancer screening programmes, while others (the UK and the Netherlands) only have local screening options in place [4, 5]. As adequate evidence of the benefits of lung cancer screening is available, a rapid expansion of its implementation is expected in the near future [5, 6]. Adding to this knowledge, the

goals of this NELSON study by DE KONING *et al.* [7] were to investigate differences in the incidence of lung cancer by screening and to assess whether lung cancer screening by volume LDCT in high-risk subjects leads to a decrease of at least 25% in the 10-year lung cancer mortality rate compared to a control group without screening. A minimum of 17300 participants needed to be included, to obtain this result with a power of 80%.

Methods

This international randomised control trial incorporated four sites that performed LDCT screening of at-risk individuals and collected data on work-up, cancer diagnosis and stage, treatment, vital status and cause of death, if applicable.

Recruitment and screening protocol

A total of 606409 individuals living in Belgium or the Netherlands aged between 50 and 74 years (current or former smokers) were invited to participate, of which 15822 individuals were found to be eligible (84% males; figure 1). After randomisation (1:1) into a screening and a non-screening group, the screening group was invited to undergo LDCT screening at baseline and at years 1, 3 and 5.5. Depending on the presence of nodules and their volume and volume-doubling time, a CT scan was
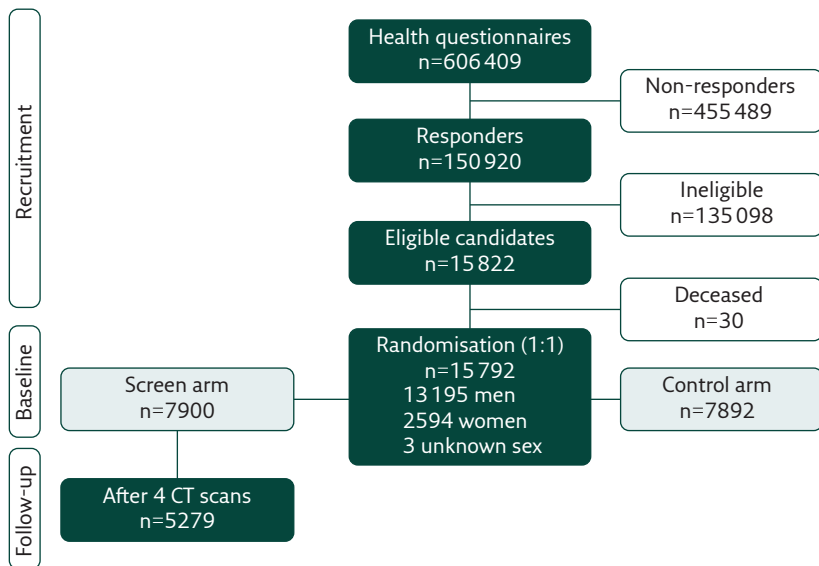
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Figure 1 *Overview of the included participants. Of the 606409 individuals who were contacted, 590617 individuals were excluded due to not responding to the invitation letter (n=455489), ineligibility (n=135098) or death before inclusion (n=30).*

scored as positive, negative or indeterminate. Participants in the control group underwent no screening. All participants were followed-up for 11 years.

Statistical assessment

The primary outcome of the NELSON trial was lung-cancer-specific mortality. Follow-up data were retrieved up to 11 years and the cause of death was retrieved from the official death certificate. As primary analysis, a two-sided t-test was employed to compare the lung cancer mortality rate ratio between the screening and control group. The secondary analysis assessed the all-cause mortality and the incidence of first recorded lung cancer diagnosis.

Main results

Incidence

After 10 years of follow-up in the male subset, a cumulative lung cancer incidence of 5.58 cases per 1000 person-years was detected in the screening group, while 4.91 cases per 1000 person-years were detected in the control group, resulting in a rate ratio of 1.14 (95% CI 0.97–1.33). Although not significantly different, this indicates an increase in lung cancer detection by screening. In the screening group, 467 CT scans (2.1%) out of a total of 22600 were scored as tumour positive, of which 203 were ultimately confirmed as lung cancer (positive predictive value (PPV) of 43.5%). However, 264 (1.2%) out of 22600 scans are false positives, resulting in a false discovery rate of 56.5%.

Cancer-related mortality

A higher number of lung-cancer-related deaths were reported in the control group, leading to a cumulative rate ratio of 0.76 (95% CI 0.61–0.94), showing a significant impact of LDCT screening on lung cancer mortality. When only the subset of participants who also met the more stringent eligibility criteria of the NLST were included, the rate ratio increased to 0.82 (95% CI 0.64–1.05).

All-cause mortality

No major differences in all-cause mortality at 10 years of follow-up were observed between groups (rate ratio 1.01; 95% CI 0.92–1.11). In the very small subset of women, a low rate ratio of 0.67 (95% CI 0.38–1.14) was observed.

Commentary

The NELSON trial showed a relative reduction in lung-cancer-related mortality of 24%, confirming and even outperforming the NLST results. Furthermore, this study proves that volume CT screening leads to a substantial shift in detecting lung cancer at an earlier stage and, therefore, increases the effectiveness of treatments. An enormous advantage of the NELSON trial is the inclusion of a large number of participants who were followed for an extended period of time. Nevertheless, the study is underpowered as the minimum number of participants needed according to the power calculation was not reached, resulting in a lower mortality rate than premised (3.3 deaths per 1000 person-years instead of 3.4 per 1000 person-years) and nonsignificant differences in incidence and female mortality. Only a small subset of women was included in this study due to the low eligibility rate (smoking was less prevalent and intense among women at the time of the study). However, as the use of tobacco products amongst women has been increasing [8], further research in the female population should be performed to establish the true effectiveness of volume LDCT screening, especially since this trial suggests a greater benefit for women compared to men, which is in line with the NLST results [2]. In addition, the effect of vaping of e-cigarettes, which is becoming increasingly more popular, should also be further elucidated and the integration of smoking cessation programmes into lung cancer screening programmes should be considered, as smoking is the number one risk factor for lung cancer. Furthermore, LDCT screening seems biased towards the subtypes with a better prognosis: 50% of nonsmall cell lung cancer cases, which have a 25% 5-year survival rate, were detected by LDCT screening, compared to only 32.5% of small cell lung cancer (SCLC) cases (7% 5-year survival rate), possibly inducing a selection bias

in detecting the subtypes that have in general a better prognosis. This should be kept in mind when the effect of LDCT screening on the overall cancer mortality rate is discussed, as this might skew the results in a positive way (it is not anticipated that earlier detection of SCLC will result in a significant reduction in mortality, making the results from this trial overoptimistic) [9]. However, it is not clear whether LDCT screening detects early-stage SCLC, which could have an impact on patient survival and could affect this skewing, or if it is a random finding, as SCLC is less prevalent and not matched in the screened groups. Therefore, its true outcome on survival should be further investigated [10].

Although LDCT is considered the current standard procedure for lung cancer screening, we also want to highlight some concerns. First, LDCT still uses radiation, although at a limited dose, which can potentially induce cancer. A study investigating the long-term effects of lung cancer screening has shown that the median cumulative effective dose after 10 years of follow-up is roughly between 9 and 13 mSv, which is similar to one standard chest CT scan (7–8 mSv) [11]. Furthermore, this is lower than the average individual environmental exposure (for the USA this is estimated at around 30 mSv after 10 years). However, there is an additional overall risk to develop cancer caused by LDCT radiation of 0.05%, which is why screening protocols should always try and implement the lowest radiation dose possible [11]. Hence, we can conclude that the benefits of lung cancer screening outweigh the drawbacks regarding exposure to radiation [11].

Secondly, quality of life and cost-effectiveness are underrepresented in most studies. The UK Lung Cancer Screening Trial has provided evidence of the cost-effectiveness by reporting an incremental cost-effectiveness ratio of GBP 8466 per gained quality-adjusted life year [12]. However, analysing pooled lung cancer screening data is advised to completely settle this issue, as this is a crucial factor for the global implementation of lung cancer screening programmes in all countries, including developing nations.

Thirdly, only 59% of all lung cancers in the screening group were detected on screening, leaving many cases undetected with the currently applied screening protocol. In addition, LDCT screening results in a large number of false positive results. The NELSON trial reports a PPV of 43.5% and an excess incidence overdiagnosis rate of 19.7%. However, this overdiagnosis reduced by more than half after 11 years of follow-up (excess incidence overdiagnosis rate of 8.9%) compared to 10 years [13]. This is in line with the reported time between the diagnosis by CT screening and when the cancer would have been detected due to symptoms (lead time) of 9–12 years. The immense impact of one additional year of follow-up (prior to the lead time) clearly favours the need for longer follow-up post screening. Ideally, the NELSON trial would have included a longer follow-up, which might have further reduced the false positive findings, and the overdiagnosis rate of 8.9% should therefore be interpreted as the upper limit of overdiagnosis. Screening protocols should therefore implement a follow-up period of at least 12 years to account for the lead time.

Overdiagnosis due to a high number of incidental nodules can lead to unnecessary (invasive) follow-up procedures, thereby causing additional stress and anxiety to the patient [14]. A correct classification and follow-up of the identified nodule is therefore crucial. One way to lower overdiagnosis is by refining the post-screening work-up of incidental nodules. Particularly, the classification of indeterminate nodules deserves specific interest to determine nodule malignancy. The (post-)screening protocol can be improved by addressing the following four points (figure 2).
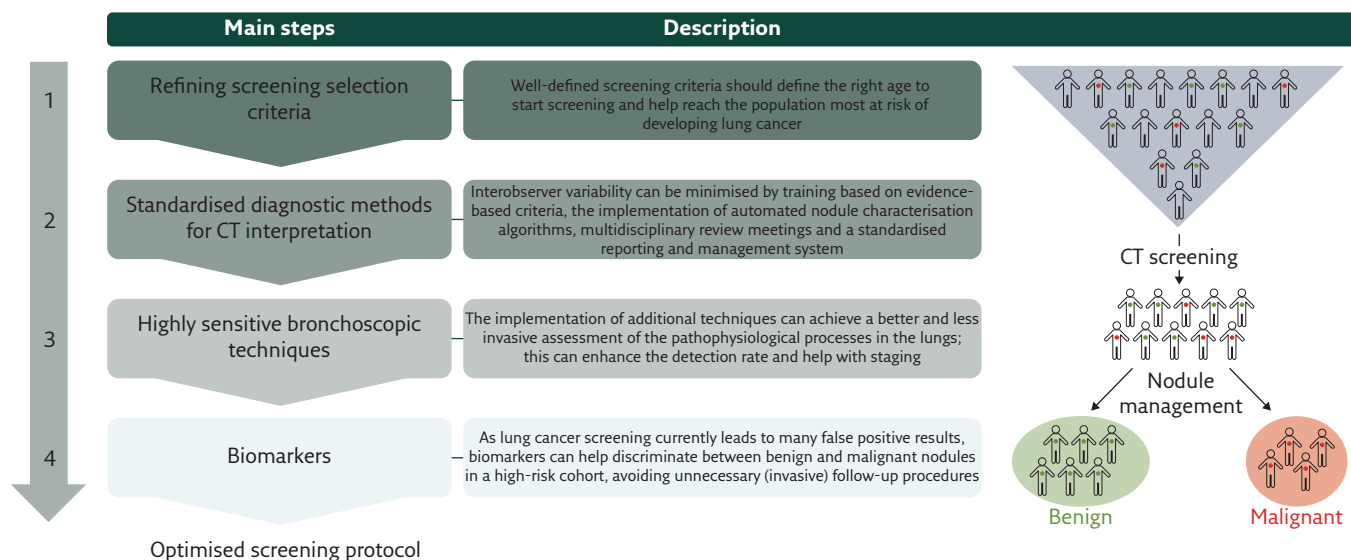

Main steps	Description
1 Refining screening selection criteria	Well-defined screening criteria should define the right age to start screening and help reach the population most at risk of developing lung cancer
2 Standardised diagnostic methods for CT interpretation	Interobserver variability can be minimised by training based on evidence-based criteria, the implementation of automated nodule characterisation algorithms, multidisciplinary review meetings and a standardised reporting and management system
3 Highly sensitive bronchoscopic techniques	The implementation of additional techniques can achieve a better and less invasive assessment of the pathophysiological processes in the lungs; this can enhance the detection rate and help with staging
4 Biomarkers	As lung cancer screening currently leads to many false positive results, biomarkers can help discriminate between benign and malignant nodules in a high-risk cohort, avoiding unnecessary (invasive) follow-up procedures

Optimised screening protocol

Figure 2 *General overview of how the LDCT screening protocol can be further optimised.*

First, the screening selection criteria should be refined. This will be key to determine the right age to start screening and to select the target population that fully benefits from lung cancer screening [6]. Since this group is often less likely to participate in screening programmes, more likely to have a lower socioeconomic background, and be current smokers [6, 15], the set-up of screening programmes should implement a strategy to reach these patient groups.

Secondly, there should be a focus on training and developing standardised methods for CT interpretation. As different centres and specialists will be involved in assessing the CT scans, the risk of interobserver variability is substantial [16]. It is therefore important that all sites interpret the scans in the same way, suggesting rigorous training based on evidence-based criteria and the implementation of automated nodule characterisation algorithms to help standardise nodule management. Together with multidisciplinary review meetings, and a standardised screening CT reporting and management system, this will assure the highest quality for lung cancer screening [6, 16].

Thirdly, highly sensitive bronchoscopic techniques should be used to enhance the detection rate and help with staging. Many recent advancements in bronchoscopic diagnostic techniques have led to new tools, such as autofluorescence imaging, navigational bronchoscopy, narrow band imaging and endobronchial ultrasound. These techniques can achieve a better and less invasive assessment of the pathophysiological processes of the lung [17].

Fourthly, biomarkers to classify lung nodules should be developed. Brown et al. [18] already showed an association of markers such as interferon-γ, interleukin (IL)-12/IL-23p40, IL-6, IL-8 and C-reactive protein with lung cancer, but there is currently no evidence that these proteins can distinguish benign from malignant nodules. Furthermore, breath analysis is being explored as breath profiles have already proven to be able to discriminate between benign and malignant nodules in a high-risk cohort [19]. As individual markers or tests often prove to be insufficient, a risk classifier model combining different markers and clinical risk factors is expected to exceed the discriminatory capacity of the individual parameters [20].

Implications for practice

A key clinical aspect in lung cancer management and survival is its early diagnosis, offering earlier and better treatment options. The NELSON study clearly showed a substantial shift to early-stage diagnosis in the screening group (58.6%) compared to the control group (13.5%) using volume LDCT screening. However, this comes at the price of a high false discovery rate, making subsequent nodule management crucial to minimise morbidity of patients undergoing unnecessary invasive diagnostic procedures and to further improve the cost-effectiveness of LDCT screening. This warrants the implementation of a standardised post-CT screening protocol aiming to optimise nodule identification. Next to improved cost-effectiveness, this will also reduce stress from not knowing if or when the nodule will transform to lung cancer in patients with an indeterminate nodule [14, 21]. However, clinicians could help alleviate part of this stress by clear communication and a thorough explanation [22]. In addition, the integration of smoking cessation trajectories into lung cancer screening programmes is advised.

In conclusion, the implementation of a lung cancer screening programme with a follow-up of at least 12 years is advised for individuals aged between 50 and 80 years who have a 20-pack-year smoking history and currently smoke or have quit within the past 15 years. However, in order to reach its full potential, further research should look into the optimisation of the post-screening protocol.

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References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209–249.

2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011; 365: 395–409.

3. US Preventive Services Task Force, Krist AH, Davidson KW, *et al.* Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA* 2021; 325: 962–970.

4. European Lung Foundation. Lung Cancer Screening. https://europeanlung.org/en/information-hub/factsheets/lung-cancer-screening/ Date last updated: 25 October 2021. Date last accessed: 10 November 2021.

5. Kauczor HU, Baird AM, Blum TG, *et al.* ESR/ERS statement paper on lung cancer screening. *Eur Respir J* 2020; 55: 1900506.

6. Field JK, de Koning H, Oudkerk M, *et al.* Implementation of lung cancer screening in Europe: challenges and potential solutions: summary of a multidisciplinary roundtable discussion. *ESMO Open* 2019; 4: e000577.

7. de Koning HJ, van der Aalst CM, de Jong PA, *et al.* Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N Engl J Med* 2020; 382: 503–513.

8. World Health Organization. 10 Facts on Gender and Tobacco. Geneva, World Health Organization, 2010. Available from: www.who.int/gender/documents/10facts_gender_tobacco_en.pdf

9. Swensen SJ. CT screening for lung cancer. *AJR Am J Roentgenol* 2002; 179: 833–836.

10. Thomas A, Pattanayak P, Szabo E, *et al.* Characteristics and outcomes of small cell lung cancer detected by CT screening. *Chest* 2018; 154: 1284–1290.

11. Rampinelli C, De Marco P, Origgi D, *et al.* Exposure to low dose computed tomography for lung cancer screening and risk of cancer: secondary analysis of trial data and risk-benefit analysis. *BMJ* 2017; 356: j347.

12. Field JK, Duffy SW, Baldwin DR, *et al.* The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. *Health Technol Assess* 2016; 20: 1–146.

13. Ten Haaf K, de Koning HJ. Overdiagnosis in lung cancer screening: why modelling is essential. *J Epidemiol Community Health* 2015; 69: 1035–1039.

14. Jeffers CD, Pandey T, Jambhekar K, *et al.* Effective use of low-dose computed tomography lung cancer screening. *Curr Probl Diagn Radiol* 2013; 42: 220–230.

15. Ghimire B, Maroni R, Vulkan D, *et al.* Evaluation of a health service adopting proactive approach to reduce high risk of lung cancer: the Liverpool Healthy Lung Programme. *Lung Cancer* 2019; 134: 66–71.

16. Martini K, Ottilinger T, Serrallach B, *et al.* Lung cancer screening with submillisievert chest CT: potential pitfalls of pulmonary findings in different readers with various experience levels. *Eur J Radiol* 2019; 121: 108720.

17. Zaric B, Stojsic V, Sarcev T, *et al.* Advanced bronchoscopic techniques in diagnosis and staging of lung cancer. *J Thorac Dis* 2013; 5: Suppl. 4, S359–S370.

18. Brown D, Zingone A, Yu Y, *et al.* Relationship between circulating inflammation proteins and lung cancer diagnosis in the National Lung Screening Trial. *Cancer Epidemiol Biomarkers Prev* 2019; 28: 110–118.

19. Peled N, Hakim M, Bunn PA Jr, *et al.* Non-invasive breath analysis of pulmonary nodules. *J Thorac Oncol* 2012; 7: 1528–1533.

20. Kearney P, Hunsucker SW, Li XJ, *et al.* An integrated risk predictor for pulmonary nodules. *PLoS One* 2017; 12: e0177635.

21. de Koning HJ, Meza R, Plevritis SK, *et al.* Benefits and harms of computed tomography lung cancer screening strategies: a comparative modeling study for the U.S. Preventive Services Task Force. *Ann Intern Med* 2014; 160: 311–320.

22. Freiman MR, Clark JA, Slatore CG, *et al.* Patients' knowledge, beliefs, and distress associated with detection and evaluation of incidental pulmonary nodules for cancer: results from a multicenter survey. *J Thorac Oncol* 2016; 11: 700–708.