short review

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Lung cancer screening from the oncologist's perspective

How does lung cancer treatment benefit from the NELSON trial

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Summary With the release of the survival results from the NELSON lung cancer screening trial there is now additional evidence that low-dose computed tomography (LDCT) screening leads to a reduction of lung cancer mortality in high-risk individuals. These results clearly show that LDCT screening has to be implemented in daily routine. However some questions like the most efficient screening intervals, duration of screening or the most appropriate participant selection are still not finally answered. This article provides a view on lung cancer screening from an oncologist's perspective.

Keywords Lung cancer · Low-dose computed tomography · Screening · Survival · NLST

Take-home message

- The NELSON lung cancer screening trial is the so far second largest randomised trial showing that low-dose computed tomography (CT) screening reduces lung-cancer specific mortality in high-risk individuals.
- From an oncologist's perspective there is now enough evidence to implement screening programs in the clinical routine.
- It seems reasonable to first set up regional pilot-screening programs offering the possibility to collect experience regarding feasibility questions according to the local requirements.
- Questions like the most efficient screening intervals, duration of screening or the most appropriate participant selection are still not finally answered.
- Keeping the dramatic stage shift observed in NELSON and NLST in mind, studies evaluating adjuvant and neoadjuvant therapeutic concepts have to be prioritized.

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Introduction

Lung cancer remains the leading cause of cancer related death worldwide, mainly due to the presence of advanced disease in the majority of patients at the time of diagnosis [1]. As early disease stages can be treated with curative intent and due to some other clinical characteristics (smoking as the major risk factor, prolonged asymptomatic interval before diagnosis, high morbidity and mortality), screening for lung cancer in populations at risk, in theory, is an attractive approach [2].

In the past, several observational studies suggested that low-dose CT (LDCT) screening might be effective in identifying early stage asymptomatic lung cancer [3–6]. Nevertheless, robust data from prospective, randomised trials evaluating the clinically most important endpoint of overall survival were lacking until in 2011 the National Lung Cancer Screening Trial (NLST) reported that annual LDCT screening over a period of three years leads to a 20% reduction of lung-cancer-specific mortality compared to individuals undergoing annual screening by chest x-ray [7]. Based on these results, several North American expert groups recommended lung cancer screening using LDCT in high-risk individuals, as defined in the NLST [8–10]. The European Society of Medical Oncology (ESMO), in turn, did not recommend large-scale implementation of lung cancer screening due to the

Table 1 Main characteristics and results of the NELSON lung cancer screening trial and the NLST

	NELSON	NLST
Participants randomised (*n*)	15,792	53,545
Randomisation	LDCT vs. usual care (no screening)	LDCT vs. chest X-ray
Main inclusion criteria	Aged 50–74 years Smoking history – ≥10 cig/day for ≥30 years – ≥15 cig/day for ≥25 years – Smoking cessation ≤10 years or current smoker	Aged 55–74 years Smoking history – ≥30 pack–years – Smoking cessation ≤15 years or current smoker
Screening rounds	4 (randomisation, 1 year, 2 years, 4 years, 6.5 years)	3 (randomisation, 1 year, 2 years)
Definition of a positive/indeterminate* screening result	Positive: newly detected nodule >500 mm^3 or volume growth ≥25% and volume doubling time <400 days Indeterminate: newly detected nodule 50–500 mm^3 or volume growth ≥25% and volume doubling time 400–600 days (assessed by semiautomated software)	Noncalcified nodule ≥4 mm in any diameter (assessed by radiologist)
Results		
Adherence to screening (%)	86	95 vs. 93
Positive results (%)	2.2 (indeterminate 9.2)	24.2 vs. 6.9
Lung cancer detected (%)	0.9	1.1 vs. 0.7
Positive predictive value of a positive screening (%)	41	3.8 vs. 70.2
Lung-cancer-specific mortality reduction (%)	26	20

NA not applicable, *LDCT* low-dose computed tomography, *cig* cigarettes
*indeterminate: only in NELSON

lack of confirmatory results [11]. Recently, survival results of the Dutch/Belgian randomised lung cancer screening trial (NELSON) were released at the World Conference on Lung Cancer 2018, adding further evidence in favour of LDCT screening in high-risk individuals.

NELSON lung cancer screening trial

The NELSON trial is the so far second largest randomised trial evaluating the benefit of LDCT lung cancer screening compared to a control group undergoing no screening at all. The study was sufficiently powered to detect a ≥ 25% mortality reduction after 10 years compared to the no-screening cohort. Eligible patients were selected after completion of questionnaires about general health status, lifestyle and smoking habits. Individuals with an age between 50–75 years, who had smoked ≥15 cigarettes per day for ≥25 years or ≥10 cigarettes per day for ≥30 years and were current smokers or former smokers with cessation ≤10 years were invited to participate in the trial. Finally 15,792 individuals were randomised in the LDCT arm ($n=7892$) and the observational arm ($n=7900$). Screening was performed in 4 rounds following different intervals (after randomisation, year 1, year 2, year 4 and year 6.5) which allowed the evaluation of different screening timeframes. Images were analysed using semiautomated software. Screening tests were classified as negative, indeterminate, or positive according to a prespecified nodule management protocol, depending on the presence of nodules, nodule volume and volume doubling time. Participants with indeterminate results were invited to an additional scan 6–8 weeks or 12 months later depending on the nodule size and outcome of previous screening rounds. In case of positive results, participants were referred to a pulmonologist for further diagnostic work-up. Overall 27,000 screens were performed with 2503 (9.3%) indeterminate and 598 (2.2%) positive results. Finally, lung cancer was detected in 243 participants in the screening arm (0.9%). This corresponds to a positive predictive value of positive LDCT results of 41%. In the screening arm 69% of lung cancer cases were detected in stage IA or IB, whereas in the control arm about 70% were detected in stage III/IV. After 10 years of follow-up, a 26% reduction of lung-cancer-associated deaths in men and an even more favourable risk reduction in women (39%) compared to the control arm was reported. Table 1 summarizes the main characteristics and results of the NELSON lung cancer screening trial and the NLST.

Oncologist's perspective

With the now released survival results of the NELSON lung cancer screening study a second, well-designed and sufficiently powered randomised trial is supporting the concept that lung cancer screening by LDCT decreases lung cancer mortality. From the oncologist's perspective the body of evidence now seems sufficient to implement screening into daily clinical practice. The introduction of such programs will hopefully have a more sustainable impact on our success in fighting the lung cancer epidemic than the recent advances in the treatment of metastatic disease. Currently, the main focus of research is set on novel therapeutic con-

cepts for the treatment of advanced disease. However, with the regular implementation of lung cancer screening it can be assumed that a certain stage-shift in lung cancer might become apparent, with, fewer patients in advanced stages and a growing number of early stage lung cancer cases. Such trends should also have an impact on the study landscape. According to the clinical trials registry (accessed February 20, 2019, clinicaltrials.gov) 114 interventional studies are currently recruiting patients with stage IV NSCLC. In contrast only 55 recruiting studies are listed for patients with stage I NSCLC. Keeping the dramatic stage shift observed in NELSON and NLST in mind, studies evaluating adjuvant and neoadjuvant therapeutic concepts have to be prioritized. Currently numerous phase II and III trials are enrolling early stage NSCLC patients for different investigational therapies including adjuvant checkpoint blockade, stereotactic radiotherapy in combination with checkpoint inhibitors, targeted therapies as adjuvant therapy or chemotherapeutic combinations. Results of these trials will certainly have an even greater clinical impact in regions with implemented screening programmes.

Even though screening provides a survival benefit, the risk of overdiagnosis is an incremental aspect to consider as some of the detected lung cancers might not affect morbidity or mortality. It can be expected that the risk of overdiagnosis is especially increased in patients with additional life-threatening comorbidities or in the elderly. According to observational studies, the extent of overdiagnosis due to LDCT screening seems to range between 13 and 27% [12, 13]. An analysis of the NLST data has estimated that 18.5% of cancers detected by LDCT seem to be indolent and therefore might be considered overdiagnosed. However this model has been criticized for not accounting length or lead time bias [2]. At the moment the optimal duration of LDCT screening is uncertain. With prolonged screening, patients in those cohorts will become older and therefore an augmented risk of overdiagnosis might appear. Future studies and long term follow-up data will hopefully delineate the true risk of overdiagnosis and the optimal duration of screening. With prolonged screening the potential induction of secondary lung cancer due LDCT radiation exposure is an important point to address. In the Italian COSMOS study individuals >50 years with a smoking history of ≥20 pack years were included and underwent annual LDCT over a time span of 10 years. A secondary analysis of the COSMOS study, evaluating the harms of LDCT, estimated that for every 108 lung cancers detected by screening, one cancer was induced by radiation [14]. Even though the risk of LDCT screening-induced lung cancer is not negligible, it might be of minor relevance considering the substantial survival benefit in patients undergoing of LDCT screening.

Patients who receive curative treatment for early stage lung cancer are at substantial risk for recurrence or the development of second primaries. Up to now, there is still no clear evidence-based recommendation regarding the modalities of follow-up for this patient group. According to the only randomised study of follow-up in resected NSCLC (IFCT-0302 study) the use of contrast-enhanced CT scans of the thorax and upper abdomen (6-monthly for the first two years, afterwards yearly until year 5) did not lead to improved survival when compared with surveillance using x-ray only [15]. However, after long-term follow-up a late advantage in the CT arm seemed to emerge. It can be speculated that this effect is caused by early detection of second primaries supporting the concept of screening in this patient group by using 12-monthly LDCT in the long-term follow-up.

Conclusion

With the release of the survival results from the NELSON lung cancer screening trial there is now additional evidence that LDCT screening leads to a reduction of lung cancer mortality in high-risk individuals. From an oncologist's perspective, these results clearly show that LDCT screening has to be implemented in daily routine. In our opinion it seems reasonable to first set up regional pilot-screening programs (like the right now designed ITOG TyrolungScreen; www.itog.at), offering the possibility to collect experience regarding feasibility questions according to the local requirements. Questions like the most efficient screening intervals, duration of screening or the most appropriate participant selection are still not finally answered. An optimization of these tasks might improve effectiveness and cost–benefit ratio of LDCT screening in the future. With regard to interpretation of screening results, the algorithm used in NELSON seems to be more appropriate, keeping in mind the substantially higher positive predictive value compared to the NLST. Bringing such screening initiatives to life will be challenging and will require a multidisciplinary collaboration of medical professionals (radiologists, pneumologists, thoracic surgeons), health care providers and federal institutions.

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Conflict of interest F. Kocher and G. Pall declare that they have no competing interests.

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