Editorial

Determination of the optimal screen interval in low-dose CT lung cancer screening: are we there yet?

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Introduction

In view of the prospective results of the largest randomized controlled lung cancer screening trial worldwide, the National Lung Screening Trial (NLST), and baseline results of other trials, interest in low-dose chest CT for lung cancer screening in high-risk individuals is increasing. In 2011, the U.S. NLST demonstrated that screening using annual low-dose chest CT reduces lung cancer mortality by 15–20% compared to screening by chest radiography (1). This result was translated by several U.S. medical associations, including the U.S. Preventive Services Task Force, into a recommendation to screen subjects at high-risk for developing lung cancer by annual low-dose chest CT (2-5). According to the recommendation of the U.S. Preventive Services Task Force, all individuals between 55 and 80 years old who smoked at least 30 pack-years and quit not longer than 15 years ago are eligible for lung cancer screening. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery (5).

A drawback of CT screening is the high prevalence of small to intermediate-sized (<500 mm^3 or <10 mm) lung nodules, most of which are benign. Up to 66% of participants enrolled in CT screening trials has at least one pulmonary nodule (6). Additionally, about 5–7% of lung cancer screening participants develop a new nodule each year (7). Accurate nodule management is required to differentiate between benign and malignant lung nodules, as over 99% of all screen-detected lung nodules are benign.

Determination of the optimal screen interval plays an important role in the balance between harms for the patients, costs, and benefits of CT lung cancer screening. It is not said that a screening protocol should be uniform for all screening participants over the whole 25-year period of screening. If participants with higher and lower risk of developing lung cancer can be identified during screening, the screening protocol might need to be adjusted for those screenees. Currently, lung cancer screening is being implemented in routine clinical care in the United States, via annual low-dose CTs based on the screening regime as used in the previously mentioned NLST. In the Dutch-Belgian lung cancer screening trial (NELSON trial, a Dutch acronym for Nederlands-Leuvens Longkanker Screening Onderzoek), the largest randomized lung cancer screening trial in which lung cancer screening by low-dose chest CT is compared to no screening, screenees were invited for four screens by low-dose chest CT: at baseline, one year later (round 2), two years later (round 3), and another two-and-a-half years later (fourth round). The mortality results of this trial are awaited. The NELSON strategy with prolonged screen intervals provides a unique opportunity for evaluation of the influence of the screen interval length on screening characteristics like sensitivity and specificity (8). A second European study that looked into the influence of prolonged screen interval is the Multicentre Italian Lung Detection Trial (MILD). Participants

were randomized to no screening, or annual or biannual screening. Overall, the study showed no mortality benefit for the CT screen group compared to the non-screen group after five years of follow-up, possibly due to the limited sample size (9).

Optimal screen interval

The NLST used three annual screening rounds. Recently, a retrospective cohort analysis was published in which the necessity of annual screening for all eligible screening individuals was evaluated (10). Patz *et al*. looked into all NLST participants, N=26,231, who received a baseline (T0) screen. The T0 screen was negative (no nodules with diameter over 4 mm or other suspicious findings) in 73% of participants. Special interest was directed to this group of screenees, and the authors found that a prolonged screen interval after a negative T0 screen might be a reasonable option. Both lung cancer incidence and lung cancer mortality were significantly lower for participants with a negative T0 compared to all T0 participants. Furthermore, the yield of screen-detected lung cancer at the T1 screen (first annual screen after baseline) in the negative T0 group (0.34%), was far less than the yield in all T0-screened participants (1.0%). If the negative T0 group would not have received an annual screen, 62 screen-detected lung cancers (3.2 per 1,000 screenees with negative T0) would have been diagnosed by delay. However, even in case all these persons would have died because of lung cancer, lung cancer mortality in the negative T0 group would be lower compared to lung cancer mortality in all T0 participants, suggesting that annual CT might not be needed in case of a negative baseline screen.

Two European studies actually used different screen intervals in their screening protocol, and could thereby directly compare screen characteristics when using an annual, biannual or even 2.5-years screen interval. In contrary to the NLST, this comparison did not include lung cancer mortality data. The MILD trial concluded that biannual screening may save about one third of LDCT scans compared with annual screens, with similar lung cancer detection rate, specificity, sensitivity, positive predictive value, and negative predictive value (11). In the NELSON study, nodule management was based on semi-automatically measured nodule volume instead of manually measured nodule diameter (12). In 2014, Horeweg *et al*. published the results of an in-depth analysis on lung cancer probability based on the presence and size of lung nodules. In more than half of participants, no baseline nodules were found. Furthermore, the 2-years lung cancer probability of screenees with largest lung nodule with volume of less than 100 mm^3 (proposed as new cut-off value for a negative baseline screen) was equally low as compared to screenees with no baseline nodules at all [0.6% *vs*. 0.4%, respectively (P=0.17)]. These results suggest that a screen interval of at least two years might be safe to apply after a negative baseline screen (13). However, in depth analysis of the fourth screening round, 2.5-years after the third round, showed that the interval cancer rate in the last screening round was significantly higher compared with the annual and biannual screen (8). Moreover, the proportion of advanced staged disease in this round was higher compared with the previous rounds. Therefore, a 2.5-year screen interval seems to be too long, at least when not considering the final screen result (positive or negative) of previous screens.

Conclusions

What are we to conclude from these studies? For participants with a negative baseline screen result, which comprises the majority of screen participants, annual screening might not be necessary. Question remains which screen interval will be the best. The study of Patz *et al*. suggests that the optimal screen interval differs for participants with different baseline screen results: A negative result may lead to safe extension of the screen interval beyond 1 year (10). Yousaf-Khan *et al*. showed that a screen-interval of 2.5 years is too long (8). Probably, the optimal screen interval for participants with a negative screen lies somewhere between 1 and 2 years. Further (modeling) studies need to be performed to confirm these results.

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Footnote

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