EDITORIALS

Mortality Reduction with Low-Dose CT Screening for Lung Cancer

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Since the publication of the first mortality results from the National Lung Screening Trial (NLST), which showed a 20% reduction in lung-cancer mortality with low-dose computed tomographic (CT) screening,[1] the intervention has been adopted as policy in the United States, and there has been considerable discussion of the possibilities for its adoption in Europe.[2,3] Policy decisions are still awaited in many countries, despite the unequivocal nature of the original NLST results.[1] This is likely to be partly due to doubts fostered by the early publication of inconclusive results of a number of smaller trials in Europe.[4,5]

These doubts should be laid to rest by the results of the Dutch–Belgian lung-cancer screening trial (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]) reported in this issue of the *Journal* by de Koning et al.[6] In this trial, arguably the only adequately powered trial other than the NLST, 15,792 participants (84% male) were randomly assigned to periodic low-dose CT screening or no screening. At 10 years of follow-up, lung-cancer mortality was lower in the screening group that in the control group, both among men (lower by 24%) and among women (lower by 33%). The researchers estimate that approximately 60 deaths from lung cancer were prevented as a result of four offered rounds of screening in 7900 participants.

These results bear out the NLST finding that low-dose CT screening reduces lung-cancer mortality. Four further observations may be made. First, the intervals between the four screenings were 1 year, 2 years, and 2.5 years, as compared with strict 1-year intervals in the NLST. This suggests that a 2-year interval between screenings would be safe and effective, as has been speculated in the past.[3] Moreover, Figure 1B in the article by de Koning et al. suggests that the trajectories of lung-cancer mortality in the two trial groups became parallel at 8 years after randomization, approximately 2.5 years after the final screening in the trial. The NLST results suggest the same phenomenon occurring approximately 3.5 years after the final trial screening.[7] These findings imply that the protection afforded by a screening lasts between 2.5 and 3.5 years. A review of all the trials should further clarify this issue. The U.K. Lung Cancer Screening Trial, in which a single screening was offered to the participants in the screening group, may yield information of relevance here.[8]

Second, the inclusion of a small sample of women, seemingly as an afterthought, yielded the interesting suggestion of a greater relative benefit in women than in men. This too has been observed in the NLST and in another trial.[9,10] Further examination of this question is needed in the results of the other European trials to ascertain whether this is a general phenomenon and, more importantly, why it occurs.

Third, the NELSON results suggest overdiagnosis of approximately 10% at worst and considerably smaller numbers of overdiagnoses than of lives saved. Although there is no room for complacency in this regard (there is no "good" way to receive a diagnosis of lung cancer), the balance of overdiagnosis and mortality reduction is likely to be acceptable.

Fourth, an important observation relates to

the numbers of screened participants undergoing further investigation. Results in the past have indicated that approximately 20% of participants screened then undergo at least one additional scan to check for tumor growth or regression. In the NELSON trial, this level of additional testing was observed only at the first screening, with percentages of 1.9 to 6.7% at subsequent screenings and an average over all four screenings of less than 10%.

A previous article by the NELSON investigators provided an insight into the use of nodule volume and the doubling time of the nodule volume to identify highly suspicious malignant nodules.[11] Recently, the NELSON investigators evaluated both diameter and volume measurement to estimate lung-nodule size as an imaging biomarker for nodule management; this provided evidence that using mean or maximum axial diameter to assess nodule volume led to a substantial overestimation of nodule volume.[12] The approach to nodule-volume management described by de Koning et al. resulted in a substantial number of early-stage cancers identified at the time of diagnosis and avoided false positives from the overestimation incurred by management based on diameter.[6]

The lung-nodule management system used in the NELSON trial has been advocated in the European position statement on lung-cancer screening.[2] This will improve the acceptability of the intervention, because the rate of further investigation has been a major concern in lung-cancer screening.[2]

So what are the implications of the NELSON results? Most important, there can no longer be any doubt as to the efficacy of periodic low-dose CT screening in reducing mortality from lung cancer. The task for evaluation is now to estimate the cost-effectiveness of this screening. The latter, of course, does not have a single value and is country-specific. It will depend crucially on the interval between screenings and more crucially on the population targeted. Selecting high-risk persons with the use of validated models for predicting lung-cancer risk is considered essential.[2] In an era when most lung cancers in developed countries are diagnosed in ex-smokers, accurate estimation of individual risk becomes more important.

With the NELSON results, the efficacy of low-dose CT screening for lung cancer is confirmed. Our job is no longer to assess whether low-dose CT screening for lung cancer works: it does. Our job is to identify the target population in which it will be acceptable and cost-effective.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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