Optimum low dose CT screening interval for lung cancer: the answer from NELSON?

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The Dutch–Belgium randomised controlled trial of low dose CT screening (NELSON) is nearing the time it will report on the primary outcome of lung cancer mortality. The research team has published unique and influential data on the probability of malignancy in indeterminate pulmonary nodules according to their volume, growth as measured by volume doubling time and whether they are newly detected on incident screens.[1 2] The NELSON investigators address another important factor influencing effective low radiation dose computed tomography (LDCT) screening: the maximum time interval allowable between screens before there is an unfavourable stage shift in cancers detected by screening and the rate of missed 'interval' cancers increases.[3] In NELSON, subjects were screened at baseline, and then 1, 3 and 5.5 years from baseline. This gave intervals of 1, 2 and 2.5 years. Following an interval of 2.5 years, there were significantly more late-stage screen-detected cancers than for the 1-year interval and there were more interval cancers (5 during 1 year, 19 during 2 years and 28 during 2.5 years), with more than half appearing in the last 6 months of the 2.5-year interval (figure 3).[3] The authors make the specific conclusion that a 2.5-year interval after two incident screening rounds is likely to reduce the effectiveness of screening but are more circumspect about recommending a 1-year or 2-year interval.

In the paper, table 3 shows how the number of screen-detected early-stage cancers falls as the screening interval increases, with statistical significance reached for the 2.5-year interval versus the 1-year interval. It could be argued that there is a trend across the 1, 2 and 2.5-year intervals (stage I–IIa cancers 82.8%, 76.6% and 67.4%, respectively) and that if larger numbers were screened, a 2-year interval screen may also show significantly less early stage cancers. This is intuitively what would be expected if the cancer rate were constant between screens. In fact the rate will be modified by the advancing age of the screened population (increasing incidence due to age and accumulated pack-years for continuing smokers), the effect of the previous screen (reducing incidence by removing early, slower growing cancers that might otherwise have been detected at a later stage by the subsequent screen) and the screen interval. In fact less cancers were detected at the final NELSON screen, 2.5 years after the two incident screening rounds. The authors point out that they have previously shown no significant difference in stage of screen-detected cancers between a 1-year and 2-year interval, implying that a 2-year interval may be acceptable, although they were not able to comment on the effect on mortality. There are also deterministic models that show relatively small differences in outcomes, importantly including mortality, between annual and biennial screening strategies.[4] In contrast, work from the NELSON group using a microsimulation model based on National Lung Screening Trial (NLST) and Prostate Lung Colorectal and Ovarian (PLCO) screening trial data showed clear dominance of annual strategies in terms of mortality benefit.[5] Disadvantages of annual screening were more screening examinations per death prevented, more false positives and greater overdiagnosis.

The Multicentric Italian Lung Detection trial remains the only one to have randomised subjects to either control, annual or biennial screens. This study was small with only 1152 and 1151 randomised into the annual and biennial arms respectively and only 29 lung cancers detected by screening in the annual arm and 21 in the biennial arm. No differences in detection rate or interval cancer rate were found between the groups, after seven annual screens and four biennial screens.[6] The recall rate for further CT and further work-up were also similar in the annual and biennial arms. The only clear difference was in the total number of LDCTs performed—6893 in the annual arm and 4715 in the biennial.

One of the major issues raised in the Yousaf-Khan *et al* paper, which could impact on future international screening programmes, is whether a maximum of a 2-year interval should be recommended for future screening programmes, or should annual screening be the standard as currently recommended in the US[7] and Canada.[8] At first sight it may seem to be a simple matter of cost effectiveness—a trade-off between the increased cost of annual screening and the reduced cancer detection rate with biennial screening. In the UK,[9] as ever concerned with cost, annual or biennial screening has been suggested with the latter favoured for economic reasons. Perhaps a more refined approach is to adjust screen frequency according to risk, with people at higher risk undergoing more frequent screens. This is the approach taken in the UK breast cancer screening programme where the normal 3-year interval is reduced to annual if there is a strong family history or mutations (TP53 or BRCA 1/2).[10] There are several multivariate risk prediction models that have been proposed to select people for lung cancer screening, but only one, the Liverpool Lung Project model has been used to select subjects for screening in the UK, as part of the UK Lung Screen trial, where the same cancer detection rate was achieved in a single screen as that achieved in the NLST after three rounds.[9 11] Using risk prediction models has been shown to improve efficiency of screening: using the $PLCO_{m2012}$ instead of NLST selection criteria would have screened 8.8% less people with 12.4% more cancers detected.[12] Thus it may be possible to vary the screening interval according to risk, with higher risk individuals being offered more frequent screening thus reducing numbers of missed cancers whilst expecting the minimal effect on stage shift in people eligible for a biennial screen. Further work on accuracy of models at different risk thresholds and the thresholds for changing intervals is needed, along with further analyses of the trials stratified by risk status.

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Another approach might be to vary the screening frequency according to the presence of lung nodules, with closer follow-up of smaller lesions compared to less frequent scanning for individuals without nodules. However the available evidence does not support this. In UKLS, where a more aggressive approach to smaller nodules (≥15 mm^3 to <50 mm^3) was taken because of the single screen design, only 1 cancer was detected from 479 repeat scans at 1 year.[9] In NELSON, nodules <100 mm^3 have been shown to confer no greater risk of development of lung cancer over 2 years than the baseline risk without nodules.[1] Furthermore even though 'new' nodules (those not seen or below 15 mm^3 on a previous screen) were more likely to be malignant, they were almost all early stage disease when detected either 1 or 2 years later.[2] Other factors may also be important: the proportion of participants with indeterminate nodules requiring interval imaging was lower in the final screening round of NELSON (1.9%) compared to earlier screens (19.2%, 6.6% and 6.8% in rounds 1, 2 and 3 respectively).[13] This may reflect radiologists' improving confidence in ignoring stable, longstanding nodules as screening progresses and has implications for calculating cost-effectiveness. Given the growing evidence on the nature of indeterminate nodules, much of it provided by NELSON, it may be possible to substantially reduce the proportion requiring interval CTs thereby improving both cost-effectiveness and acceptability of CT screening.

The NELSON trial has provided firm evidence that the interval between screens should not be extended beyond 2 years but has only added to the debate about annual versus biennial screening by providing some quantification: a 2-year interval is associated with minimal stage shift but 3–4 times more interval cancers which must, surely, represent missed opportunities to save lives. The ultimate decision should ideally be made according to a balance of risk of lung cancer and benefit but for some healthcare systems, cost may be an overriding influence.

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