Lung cancer CT screening: are we ready to consider screening biennially in a subgroup of low-risk individuals?

John K Field,[1] Stephen W Duffy[2]

Most published research on low-dose CT screening for lung cancer pertains to annual screening.[1] Schreuder and colleagues explore the possibilities for extending the interscreening interval on an individual basis.[2] Using data from the US National Lung Screening Trial,[3] they build up a logistic regression model of risk of a lung cancer at the second annual screen or in the year following it, based on subject characteristics and radiological observations including nodule attributes at the first screen. The logistic model incorporates polynomial regression coefficients where appropriate. They compare their model with other possible prediction models for this specific endpoint and find it to be superior.

The authors conclude that there is scope for extending the interval for some screenees. From their model, they project that for different risk thresholds, at the second screen, 2558 (10.4%), 7544 (30.7%), 10 947 (44.6%), 16 710 (68.1%) and 20 023 (81.6%) of the 24 368 screens could have been omitted, at the cost of delayed diagnosis of 0 (0.0%), 8 (4.6%), 17 (9.8%), 44 (25.3%) and 70 (40.2%) of the 174 lung cancers, respectively.

These observations need to be validated prospectively and evaluated in terms of cost-effectiveness, but they are certainly interesting and potentially very important. Another question which remains is, for the cancers whose diagnosis would be delayed as a result of postponing the second screen to 2 years after the first, what is lost in terms of stage of disease at diagnosis and the consequent effect on mortality?

The authors report the (actual, observed) stage at diagnosis of the cancers which would be missed for the various thresholds. Apart from the lowest risk threshold, for which 10% of screens could be avoided with an estimated zero loss in terms of later diagnosis, for any given threshold, the majority of tumours which would have had their diagnosis delayed were diagnosed at stage I or II. Thus, the delay might well mean a substantial proportion having a good prognosis replaced by a poor one. This will be an important ingredient in a cost-effectiveness analysis. A future modelling exercise might target the issue of screening those whose tumours are most likely to benefit from early diagnosis, while not screening those destined either not to develop the disease or to be diagnosed at late stage despite our best efforts at early detection.

We reiterate that the results here will need validation. However, they are important and will stimulate further work to improve the process of early detection of lung cancer for both provider and public.

In the European position statement on lung cancer screening (EUPS),[4] the management of prevalent lung nodules is discussed in detail and it was argued that nodule management will largely depend on size criteria; however, volumetry is now considered essential, but diameter cut-offs will also need to be provided for cases where segmentation is not possible.

The Nelson trial group have analysed volume, volume doubling time and volumetry-based diameter of 9681 non-calcified nodules detected by CT screening in 7155 participants and provided a very compelling argument to consider screening a subgroup of individuals on a biennial basis.

They found that the Lung cancer probability was not significantly different between the participants who had nodules $<100\,mm^3$ in volume and those participants who had no detected nodules (0.6% (95% CI 0.4 to 0.8) vs 0.4% (0.3 to 0.6); p=0.17). The participants who had nodules between 100 and $300\,mm^3$ had a significantly greater probability of developing lung cancer compared with participants with no screening-detected nodules (2.4% (95% CI 1.7 to 3.5); p<0.0001) and were considered ‘indeterminate’ and requiring 3 or 12 months follow-up CT scan, while nodules of $300\,mm^3$[3] or greater had a significantly greater chance of developing lung cancer.

However, in about half of the NELSON participants, no pulmonary nodules were detected and their 2-year probability of developing a lung cancer was 0.4%. Thus, it may be argued that they could have a screening interval of at least 2 years.[5]

There have been two major publications based on modelling screening intervals from the UKLS[6 7] and the International Early Lung Cancer Action Program.[7] While Duffy *et al* estimated that 2 yearly screening could potentially be more cost effective, Yankelevitz *et al* argued that we should focus on how the interval between screens affects the stage distribution prior to thinking about changing from annual screening intervals.

Patz *et al* examined the NLST participants who had a negative prevalence screen and found that they had a substantially lower risk of developing lung cancer compared with individuals with a positive prevalence screen[8] thereby providing further support for the argument to consider biennial screening.

The cost effectiveness of lung cancer screening has been analysed using microsimulation modelling by ten Haaf *et al*.[9] Their results indicate that we have to seriously consider a range of screening scenarios and especially the interactions between the smoking eligibility criteria as well as the screening interval, both of which influence the cost-effectiveness of each scenario.

The EUPS argued that future decisions on interval timing should be based on risk, psychosocial effects, cost-effectiveness and the feasibility of implementation, all of which require further investigation. While we would argue that this remains the case, the results of Schreuder *et al* give valuable food for thought.

[1]Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK
[2]Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Correspondence to Professor John K Field, Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool L69 3BX, UK; j.k.field@liverpool.ac.uk and Professor Stephen W Duffy, Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London EC1M 6BQ, UK; s.w.duffy@qmul.ac.uk

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Provenance and peer review Commissioned; externally peer reviewed.

To cite Field JK, Duffy SW. *Thorax* 2018;**73**:1006–1007.

Accepted 11 June 2018
Published Online First 28 June 2018

Linked

► http://dx.doi.org/10.1136/thoraxjnl-2017-211107

Thorax 2018;**73**:1006–1007.
doi:10.1136/thoraxjnl-2018-211814

REFERENCES

1 Field JK, Duffy SW. Lung cancer CT screening: is annual screening necessary? *Lancet Oncol* 2016;17:543–4.
2 Schreuder A, Schaefer-Prokop CM, Scholten ET, *et al*. Lung cancer risk to personalise annual and biennial follow-up computed tomography screening. *Thorax* 2018:626–33.
3 National Lung Screening Trial Research T, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
4 Oudkerk M, Devaraj A, Vliegenthart R, *et al*. European position statement on lung cancer screening. *Lancet Oncol* 2017;18:e754–e766.
5 Horeweg N, van Rosmalen J, Heuvelmans MA, *et al*. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. *Lancet Oncol* 2014;15:1332–41.
6 Duffy SW, Field JK, Allgood PC, *et al*. Translation of research results to simple estimates of the likely effect of a lung cancer screening programme in the United Kingdom. *Br J Cancer* 2014;110:1834–40.
7 Yankelevitz D, Henschke C. Lung cancer: Low-dose CT screening - determining the right interval. *Nat Rev Clin Oncol* 2016;13:533–4.
8 Patz EF, Greco E, Gatsonis C, *et al*. Lung cancer incidence and mortality in National Lung Screening Trial participants who underwent low-dose CT prevalence screening: a retrospective cohort analysis of a randomised, multicentre, diagnostic screening trial. *Lancet Oncol* 2016;17:590–9.
9 Ten Haaf K, Tammemägi MC, Bondy SJ, *et al*. Performance and cost-effectiveness of computed tomography lung cancer screening scenarios in a population-based setting: a microsimulation modeling analysis in Ontario, Canada. *PLoS Med* 2017;14:e1002225.