impactfactor

CT screening for lung cancer – do we have an answer?

UGO PASTORINO & NICOLA SVERZELLATI

Concerns still exist regarding the best use of low-dose CT screening for lung cancer and how to select high-risk individuals who will benefit most from participation in screening programmes. Two studies now indicate factors that may reduce the false-positive rate of lung cancer screening with low-dose CT.

The decision of the US Preventive Services Task Force to recommend low-dose CT screening for all individuals aged 55–79 with ≥30 pack/year smoking history, based on the outcomes from the National Lung Screening Trial (NLST), has not eliminated the scepticism that still affects the scientific community concerning the cost–benefit profile of lung cancer screening. A number of major concerns still exist regarding the best use of low-dose CT for lung cancer screening, including how to identify individuals at high risk of developing lung cancer, the optimal diagnostic algorithm and management of lung nodules, high false-positive rates, and potential harm from overdiagnosis. The recent report on the results of incidence screenings with low-dose CT in the NLST highlights some favourable prospects, and also the current limitations, for lung cancer screening.[1]

Ideally, an effective screening programme should identify all malignant lesions while reducing, as much as possible, the probability of false-positive results. Reducing the number of false-positive results in screening programmes is important because of the risks and costs related to follow-up with low-dose CT scans, and the potential for unnecessary invasive diagnostic and surgical procedures. The NLST is the largest randomised study of lung cancer screening in a high-risk population to date. The NLST enrolled 53,454 current or former smokers between the ages of 55 and 74 years with a smoking history of a minimum of 30 pack-years from 33 sites. Participants were randomly assigned to screening with low-dose CT (n=26,722) or chest radiography (n=26,732). The NLST showed a 20% relative reduction in mortality from lung cancer with three rounds of low-dose CT screening (rounds T0, T1, and T2) compared with radiography.[1] However, in the incidence screenings (T1 and T2) of the NLST the positive predictive value (below 5%) seems far too low to encourage the use of a similar diagnostic protocol for future large-scale screening programmes. As suggested by the authors of the study, the simple increase of the lung nodule size threshold above 6 mm for positive low-dose CT would reduce the false-positive rate by over 50%, with only a minimal loss in lung cancer detection. In agreement with this concept, Henschke et al.[2] have recently suggested that using a nodule size threshold of 7 mm or 8 mm to define positive results in the low-dose CT baseline

round might substantially reduce the frequency of the diagnostic work-up without significantly delaying a diagnosis of lung cancer. Moreover, the decrease in late-stage lung cancers in the low-dose CT group as compared to the chest radiography group at both T1 and T2 reported by Aberle et al.[1] should be perceived as a very promising outcome.

The outcome of a study by McWilliams et al.[3] represents another important step forward in the optimisation of lung cancer screening strategies. In this study, data from two cohorts of participants, which totalled 2,961 individuals undergoing low-dose CT screening, was analysed to identify factors that could predict the probability that lung nodules detected on the first screening low-dose CT scans were malignant or would be confirmed as malignant on follow-up. Using simple predictive tools based on patient and nodule characteristics, a predictive model was developed that accurately distinguished malignant from benign nodules. This type of multiparametric model should be regarded as a reference tool to be validated further and, perhaps, improved by other ongoing trials. The exclusion of forced expiratory volume in one second (FEV_1) from the model developed by McWilliams et al.[3] seems to be in contrast to findings reported by other studies, which showed that decreased FEV_1 is a robust risk factor for lung cancer development, and an easy index to improve the management of nodules detected by low-dose CT.[4,5] It should be noted that the simple visual score of emphysema, as performed in the study by McWilliams et al.,[3] could be an over-simplistic way to measure this factor, and an automated assessment – that is, by using low-dose CT densitometric analysis – might be more appropriate.[6,7]

Since nodule size was the most relevant risk factor in the model tested by McWilliams et al.,[3] any technological development that is able to optimise and standardise measurement of nodules should be adopted in screening programmes. The analyses in both the PanCan and NLST studies were based on the maximum diameter of the nodules, which are associated with major limitations. For example, nodules may grow along an axis different than that of the maximum diameter, and also the minimal diameter variation of small nodules could be difficult to assess.[1,3]

By contrast, a study investigating the use of nodule volume and volume-doubling time as the main criteria for deciding on further action in 7,557 patients in the NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek) lung cancer screening trial[8] showed that nodule volumetry in the low-dose CT arm obtained a much higher positive predictive value (42.2%) than observed in the NLST, where nodule diameter on low-dose CT gave lower predictive values than chest radiography in the incidence screenings (2.4% vs 4.4% at T1; 5.2% vs 6.7% at T2).[1] Although data comparison needs to be interpreted with caution at this stage, as it depends on the contexts of the specific cohorts undergoing screening, the 3D volumetric measurements of lung nodules have, so far, proven superior to 2D

> **Incidence screenings ... in the NLST highlights some favourable prospects ... for lung cancer screening**

Key points

- Lung nodule size is the strongest predictor of malignancy in low-dose CT screening
- Positive predictive value of low-dose CT can be increased by volumetric assessment and higher cut-off for positive screenings
- Lung cancer risk can be stratified by a multiparametric model

diameter measurements in terms of accuracy – because the whole nodule is analysed, regardless of its irregular shape – and reproducibility.

The majority of ongoing European randomised screening trials have adopted volumetric assessment for the management of screen-detected pulmonary nodules, and have selected volume doubling time as the most reliable predictive index to distinguish true-positive screenings (requiring additional diagnostic procedures) from false-positive low-dose CT screening results.

Refinement of volumetric assessment of lung nodules will bring further improvement to future screening strategies. This has been demonstrated by Heuvelmans et al.[9] who, through a retrospective analysis of participants in the NELSON study, demonstrated that optimising the volume doubling time cut-off (≤232 days) reduced the false-positive referrals by 33% at a three-month follow-up.

In the studies by McWilliams et al.[3] and Aberle et al.,[1] neither addressed another fundamental problem of lung cancer screening: optimising the identification of high-risk populations. In an attempt to ensure that individuals at high-risk of developing

lung cancer are selected for screening programmes, the American Association for Thoracic Surgery has recommended low-dose CT screening for individuals from the age of 50 with a 20 pack-year history and a minimum lung cancer risk of 5% over the following 5 years.[10]

However, combining the new screening-generated risk prediction models with measurements of pulmonary damage (as indicated by the FEV_1 levels), and possibly with a few validated blood biomarkers, could identify individuals with a cancer risk greater than 10%, on whom future screening research can be focused.

Until the results of ongoing European randomised trials are available (possibly by the end of 2016), it seems unlikely that European countries will be able to follow the US guidelines. However, in the meantime, all efforts should be made to include volunteers at high risk of developing lung cancer in prospective demonstration studies to improve the efficacy of low-dose CT screening, reduce the burden of false-positive findings and prevent unnecessary surgery for nonmalignant pulmonary nodules. ■

References

1. DR Aberle et al. (2013) Results of the two incidence screenings in the National Lung Screening Trial. *NEJM* 369:920–931
2. CI Henschke et al. (2013) Definition of a positive test result in computed tomography screening for lung cancer: a cohort study. *Ann Intern Med* 158:246–252
3. A McWilliams et al. (2013) Probability of cancer in pulmonary nodules detected on first screening CT. *NEJM* 369:910–919
4. AK Greenberg et al. (2012) CT scan screening for lung cancer: risk factors for nodules and malignancy in a high-risk urban cohort. PLoS ONE 7:e39403
5. N Sverzellati et al. (2013) Increased mean lung density: another independent predictor of lung cancer? *Eur J Radiol* 82:1325–31
6. DS Gierada et al. (2011) Quantitative CT assessment of emphysema and airways in relation to lung cancer risk. *Radiology* 261:950–959
7. JK Field, M Oudkerk, JH Pedersen et al. (2013) Prospects for population screening and diagnosis of lung cancer. *Lancet* 382:732–741
8. RJ van Klaveren et al. (2009) Management of lung nodules detected by volume CT scanning. *NEJM* 361:2221–29
9. MA Heuvelmans et al. (2013) Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals. *Eur Radiol* 23:1836–45
10. MT Jaklitsch et al. (2012) The American Association for Thoracic Surgery guidelines for lung cancer screening using low-dose computed tomography scans for lung cancer survivors and other high-risk groups. *J Thorac Cardiovasc Surg* 144:33–38

Author affiliations

Ugo Pastorino, Director of Thoracic Surgery, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Nicola Sverzellati, Department of Surgical Sciences, Section of Radiology, University of Parma, Parma, Italy