

Semi-automated volumetric analysis in the NELSON trial for lung cancer screening: is there room for diagnostic experience yet?

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The reliability of lung cancer screening based on low-dose computed tomography (LDCT) instead of X-ray is supported by a reduction of lung cancer mortality by 20% for high-risk subjects (1). As a consequence, this approach is recommended in heavy smokers.

However, some questions about the modality of screening have not been answered yet. Among these some issues appear more relevant:

- (I) What subjects should be considered at high risk?
- (II) How long time should elapse between screening rounds?
- (III) What patterns of nodules should be considered as suspicious for lung cancer?
- (IV) What nodule size would induce a greater suspicion of malignancy?

The NELSON trial has just addressed the attention partially to these topics. It randomized high-risk subjects to screening with LDCT or no screening (2). To be enrolled in this trial, participants should be current smokers who have smoked at least 15 cigarettes per day for 25 years or more or 10 cigarettes per day for 30 years or more. Former smokers could also be included if had quit smoking less than 10 years before.

This study aimed to investigate the growth rate of nodules through incidence screening rounds. A volumetric software with semi-automated measurement was used. Two-dimensional measure of nodule diameters did not achieve enough reliability to assess the growth rate, because the manual measurement of diameters cannot be reproducible for lack of precision. Different results are almost always obtained (3).

This volumetric analysis led to the conclusion that a large volume in new solid nodules is the strongest predictor for lung cancer independently from other variables: sex, age, number of smoked cigarettes, nodule features, time elapsing between CT scans. Indeed 95% sensitivity was achieved through a cutoff of 27 mm³.

This trial met its goal because the prevalence of lung nodules is quite high in this selected high-risk population. It's about 50% with overall lung cancer risk by about 3% in 5 years. So the investigators could observe that the maximum volume doubling time was significantly lower in new solid nodules diagnosed as malignant than in those diagnosed as benign. Nodules with volume change less than 25% were not considered for the calculation of volume doubling time. Even though the volumetric analysis in this study currently represents the most precise method to detect growth rate, the NELSON trial holds some limitations:

- (I) Nodule size less than 15 mm³ was not reported by the radiologists because of a detection method in the software;
- (II) Irregular shapes or margins of the nodule caused variability because of incomplete segmentation performed by the software;
- (III) The volumetric analysis was only applied to solid nodules with exclusion of non-solid nodules, which could comprise some lung cancers;
- (IV) The approach of maximum volumetric doubling time has not been validated yet for new nodules detected by LDCT.

To understand the complexity of early lung cancer

presentation some issues have to be taken into account, including the different kinds of suspicious lung nodules, unusual forms and specific location of some of them (4). The detection of lung nodules with a high diagnostic quality can be achieved by means of low radiation dose in CT scans because of the high contrast between air and nodules. A find on LDCT is defined as lung nodule if it is characterized by a rounded opacity, well or poorly defined, less than 3 cm in diameter (5).

Lung nodules can be classified according to their different attenuation as solid, part-solid and ground-glass nodules. Solid nodules display a complete X-ray attenuation that obscures the pulmonary parenchyma within its volume. Ground-glass nodules hold a lesser attenuation so that vessels and airways structures are displayed. Part-solid nodules present both characteristics (6). Part-solid nodules could be the presentation of lung cancer in more than 60% of cases. And the suspicion of malignancy raises if solid components appear or increase at the subsequent follow-up evaluation. These considerations support the idea that only size evaluation is not sufficient in lung cancer screening, even though it is assisted by a highly precise semi-automated volumetric analysis.

Furthermore the presence of air spaces, such as cysts, bullae and blebs could be the basis on which lung cancer can arise (7,8). Some lung cancers can appear as a wall thickening within a bulla. About 20% of these unusual forms are missed on LDCT, even because they often grow slowly (9).

The revision of images from patients with a recent lung cancer diagnosis led some authors to conclude that some cancerous lesions were recognized, but these were considered to be benign because of non-nodular shape or slow growth rate (10).

Further challenges in lung cancer detection via LDCT-based screening are the location as endobronchial lesions or its rise as lymph node in the mediastinum or hilum. In this case the use of a comparison between images in lung and mediastinal window settings could help the radiologist to not miss lung cancer (11). Similarly apical fibrotic scars could favor to miss lung cancer. So new lesions on an apical fibrosis, or an enlargement after one year from the previous LDCT round of screening, are the only elements that can push cancer suspicion.

For all these reasons, we can consider the semi-automated volumetric analysis an accurate and precise method to evaluate the grow rate of solid nodules. However, a comprehensive assessment of the various presentations of early lung cancer

is needed for clinicians. So, the semi-automated technique should always support the experience by a radiologist. Indeed, the NELSON trial required that at least two radiologists evaluated the images if they had an experience in thoracic CT ranging from 1 to more than 20 years.

Anyway, a long experience by the radiologist, who will evaluate screening LDCT scans, is not always available. So, Bayesian analysis could help to objectify the reasoning of a radiologist in the process leading to lung cancer suspicion. The Bayesian method is a way to summarize evidence in the form of probability. It estimates the final probability of an event by combination of a pre-test probability with derived probabilities for each feature (12). A Bayesian calculator has been developed also for lung cancer screening. When information is available about patient's characteristics, patient's history, volume, shape and location of lung opacity, and dynamic changes (volume doubling time, HU value, CT contrast enhancement, FDG-PET SUV changes), a reliable prediction of malignancy can be achieved (13).

When a single lung nodule is detected on LDCT screening, the largest possible number of data should be gathered and described by the radiologist and also quantitative evaluation by semi-automated methods must be taken into account if available. The decision-making about a bioptic ascertainment on a suspicious lung nodule should be based on a quantitative estimation for probability of malignancy. We think that the Bayesian method can represent the more accurate way to let diagnostic experience get closer to precision medicine.

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Footnote

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