Editorial

Radiologic features of small pulmonary nodules detected in initially negative screening CT examinations: a step towards personalized screening strategies?

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Results of the National Lung Screening Trial (NLST) have invigorated the discussion around performing lung cancer screening using low-dose computed tomography (LDCT) of the chest. The NLST trial demonstrated a clear benefit of LDCT screening in reducing lung cancer and all-cause mortality, by showing reduced lung cancer mortality in high-risk individuals by about 20%, and all-cause mortality by 6.7%, compared to a control group of subjects receiving chest radiographs (1). There is, however, concern about different aspects on lung cancer screening that require further research. For example, everyone would agree that implementation of programs that would facilitate smoking cessation would be the most valuable action to reduce not only the incidence of lung cancer, but also the incidence of other tobacco-related cancers, as well as the incidence cardiovascular and respiratory diseases (2). On the other hand, definition of specific target populations that would benefit most from a lung cancer screening program need to be defined. In this sense, there are several clinical risk factors that are well known to be related to a higher risk to develop lung cancer, such as age, exposure to tobacco smoke, respiratory diseases as chronic obstructive pulmonary disease (COPD) and emphysema, family history of lung cancer, previous malignancy, and exposure to asbestos, which have been used to develop risk prediction models to select individuals for lung cancer screening (3,4). Clinical implementation of those models remains scarce (5). From the perspective of early lung cancer detectability, LDCT of the chest has consistently demonstrated its superiority over other imaging techniques, i.e., chest X-ray, to detect potentially curable small lung cancers and it is therefore considered the imaging modality of choice as a screening method (1,6,7).

LDCT-based lung cancer screening is not without limitations. As with any other type of tumor, the benefits of lung cancer screening must overcome possible harms before its implementation. It is well recognized that lung cancer screening with LDCT may lead to undesirable effects such as radiation exposure, cancer overdiagnosis, invasive procedures for benign lesions, and psychological harm, mostly derived from false positive results (8). The high rate of false-positive results is, in fact, one the major drawbacks of using CT for lung cancer screening, and different pulmonary nodule management strategies have been suggested to minimize its effects (7). Further, to address this issue, imaging improvements and peripheral specimen biomarkers have been suggested (9). On the other hand, frequency of screening rounds needs to be established (10). Traditionally, annual repeat LDCT has been performed in all high-risk individuals, although increasing the interval between screens in participants with a negative baseline scan has been recently suggested (11). This requires, of course, correct identification of the population that may benefit from this action, and would definitely lead to more efficient lung cancer screening.

One interesting observation from the NLST trial is that

participants with incident lung cancers detected in follow-up screening have poorer overall survival and progression-free survival and higher lung cancer mortality rates than patients with screening-detected incident cancers that had baseline positive screenings (11,12). With this observation in mind, Liu *et al.* (13) used data and images from the NLST and evaluated small pulmonary nodules (SPNs) not suspicious for lung cancer in the initially negative screening examination in order to identify radiologic features associated with lung cancer risk. These authors found five clinically relevant features that were significantly associated with lung cancer risk, including pulmonary emphysema, vessel-attached nodules, upper lobe nodule location, a poorly define nodule border, and concavity (13). The relationship of pulmonary emphysema and increased lung-cancer risk is not new. A decade ago, de Torres *et al.* (14) and Wilson *et al.* (15) showed that the presence of visually detected emphysema on LDCT but not airway obstruction was associated with increased risk of lung cancer. This observation was later confirmed on a systematic literature review (16). Further, as Liu and colleagues state (13), a pulmonary nodule may modify its morphology and appear concave when surrounded by emphysema, thus mimicking benignity. The rest of the imaging features described in this publication are acknowledged imaging biomarkers of potentially malignant pulmonary nodules (17). Vessel attachment may translate a more vascular and angiogenic nature, whereas poor definition of margins is a classic sign that may raise the suspicion for malignancy in indeterminate SPNs (18). Finally, primary lung cancers are commonly located in the upper lobes (19).

The strength of the study conducted by Liu *et al.* (13) is that the identified radiologic features can be easily scored in the setting of lung cancer screening, without the need of additional post-processing or sophisticated software tools. Recent recommendations for the management of solid nodules emphasize the use of software for semi-automated segmentation in preference to diameter measurements so as to more accurately estimate nodule size and its growth over time (7). This, however, requires improvement and widespread availability of software technology.

As previously mentioned, clearly defining the target population for lung cancer screening is key to achieving greater efficacy in a lung cancer screening program. In most studies, including the NLST trial, baseline screening inclusion and exclusion criteria are well-defined and include clinical and demographic features that may classify individuals at high-risk to develop lung cancer. Less attention is paid to imaging findings present on initially negative screening examinations so as to select individuals at high-risk to develop incident lung cancers that may benefit from more intensive surveillance. The study by Liu *et al.* (13) demonstrates that SPNs present on this type of examinations may possess unique features that may reflect more rapidly growing and aggressive nature and therefore may be used as imaging biomarkers to determine lung cancer risk. If proven in other screening cohorts, these findings may help discriminate participants who need more intensive follow-up from those who require less frequent screening. This would provide a step forward towards personalized and individually tailored lung cancer screening strategies.

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Footnote

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