Perifissural nodules: ready for application into lung cancer CT screening?

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The National Lung Screening Trial (NLST) was the first multicentered randomized controlled trial which showed that chest CT scans for early lung cancer detection in a high-risk population significantly reduced lung cancer mortality by 20% compared to a control group (1). Though these results were groundbreaking, 24% of all screening results were false positives; their definition for a positive outcome was the presence of a solid nodule ≥4 mm in diameter. Nine years after the NLST results were published, the Dutch-Belgian Lung Cancer Screening Trial (NELSON) reported a lung cancer mortality reduction of 24% and a false-positive rate to 2% (2). This false-positive reduction was achieved by volumetrically reassessing indeterminate nodules for growth instead of immediate referral to the pulmonologist. With nodule growth being the best visual predictor of malignancy, this implies that new nodules (not visible in prior scans) have a higher lung cancer probability than those found in the baseline scan (3).

Han et al. (4) investigated the incidence of perifissural nodules (PFN) exclusively among new nodules detected in NELSON’s follow-up CTs (2nd, 3rd, and 4th screening rounds at 1, 3, and 5.5 years after the baseline scan, respectively) (4). Seven percent (107/1,484) were recorded as fissure-attached nodules by NELSON radiologists. Blinded to the outcomes, two radiologists independently reassessed the nodules for fissural attachment and classified them as typical PFNs, atypical PFNs, or non-PFNs according to the definitions by de Hoop et al. (6); a third radiologist arbitrated disagreements. Ninety-seven new fissure-attached nodules were included in the

determined that nodules classified as PFNs by radiologists or trained readers did not turn out to be cancerous, even when the PFN exhibited size changes in a subsequent scan (6). The added value of categorizing nodules as PFNs is hereby to reduce the unnecessary follow-up of nodules guaranteed to be benign. However, two studies have reported that there is an unlikely but not impossible chance that some lung cancer nodules may be classified as PFNs (7,20). Being a relatively new and underinvestigated topic, more research is required to recommend a new nodule category which can be used to downgrade risk management. Han et al. (4) observed that none of the new nodules which were classified as PFNs were malignancies within the follow-up time. This finding that PFNs can reliably be considered benign among nodules with a higher a priori malignancy probability is a welcome addition to the literature.

Han et al. (4) included all 1,484 new solid nodules ≥15 mm³ detected in NELSON’s follow-up CTs (2nd, 3rd, and 4th screening rounds at 1, 3, and 5.5 years after the baseline scan, respectively) (4). Seven percent (107/1,484) were recorded as fissure-attached nodules by NELSON radiologists. Blinded to the outcomes, two radiologists independently reassessed the nodules for fissural attachment and classified them as typical PFNs, atypical PFNs, or non-PFNs according to the definitions by de Hoop et al. (6); a third radiologist arbitrated disagreements. Ninety-seven new fissure-attached nodules were included in the
analysis, of which 43% (42/97) and 17% (16/97) were classified as typical and atypical PFNs, respectively. All 10 malignancies in this study cohort (10%) were among the remaining nodules classified as non-PFNs (40%, 39/97). Other unsurprising but important findings are that nodules classified as PFNs are typically smaller than non-PFN malignancies and that none of the malignancies had a lentiform or triangular shape.

The authors mentioned two limitations: one was that some CT scans were not retrievable. The other was that the sample size was small (n=97); the justification was that the full data set of new nodules from the second-largest randomized controlled lung cancer screening study was used. Furthermore, the CTs were all of 1 mm slice thickness while most from the NSCLC are at least 2 mm thick. It is therefore likely that the largest collection of thin-slice chest CT scans from an individual lung cancer screening trial is from the NELSON. Higher quality scans are especially important for being able to assess nodules <10 mm. However, the sample size would have been considerably larger had the nodule selection criteria been less strict regarding fissure attachment.

It was mentioned that the prevalence of PFNs among new solid nodules (4%, 58/1,484) was much lower than that reported in other studies (20% to 28%) (5,6,8), but no reasons were discussed. The most likely explanation is that the proportion of benign nodules among new nodules is lower than at baseline. A second contributing factor is that—unlike other PFN studies—fissure attachment was an inclusion criterion. The decision to exclusively reassess fissure-attached nodules is only partially justifiable: an ongoing issue of classifying nodules as PFNs is the lack of a clear definition as to what a PFN is. Four different definitions have been used to date (5-8). However, one of the common criteria among all definitions is that nodules which are not fissure-attached but still within at least 5 mm from a major, minor, or accessory fissure are still eligible for classification as PFNs. Han et al. (4) applied the definition from de Hoop et al. (6) which states that typical PFNs must be fissure-attached but atypical PFNs have no restrictions regarding fissure distance. This means that the reported (atypical) PFN prevalence rate is an underestimation.

A replacement nodule selection criterion which may have been considered is a size limit: the malignant fissure-attached nodules (a), (b), (e), (h), (i), and (j) in Figure 2 appear to have diameters ≥15 mm (not reported) which would often justify a PET/CT or biopsy. Also considering that intrapulmonary lymph nodes ≥12 mm are rare (9-19), only nodules classified as PFNs within an indeterminate size range should have their risk management downgraded (e.g., approximately 6 to 10 mm (21-23); lower for new nodules). Assuming that the vast majority of benign nodules in the study were <10 mm, the probability that a lung cancer is misclassified as a PFN was low to begin with. The proportion of malignant nodules included in Ahn et al. (5) and de Hoop et al. (6) were also small [≤2%, exact frequency not provided by de Hoop et al. (6)]; Schreuder et al. (7) and Mets et al. (8) used a malignancy-enriched sample to compensate.

Acknowledging that brief reports only have a 1,500 word limit, it is understandable that Han et al. (4) did not report the kappa of agreement between readers in the reassessment of fissure-attached nodules. Schreuder et al. (7) demonstrated (using a different PFN definition) that there is only a fair to moderate agreement among experienced radiologists when classifying nodules as PFNs, leading to some variation in the misclassification rate of cancer nodules. It would therefore be informative to know the number of nodules which required arbitrage and whether any of those were malignancies.

It also remains unclear whether nodules were assessed in other directions besides the axial plane because each nodule was only labelled with a two-dimensional shape (i.e., lentiform, triangular, or other). This is the common practice in all other imaging studies on intrapulmonary lymph nodes and PFNs (5,6,8-19,24). Especially with the improvements in scan quality, future PFN studies should report nodule shapes in all three orthogonal planes. This would reduce the chance of overlooking suspicious morphology in the sagittal or coronal planes. Though the misclassification of cancers as PFNs is not completely avoidable, this new practice would work towards keeping this to a minimum.

With the effectiveness of CT screening in reducing lung cancer mortality having been demonstrated in two large randomized controlled trials (1,2), strategies to improve efficiency need to be investigated. One facet is to reduce the unnecessary workup of benign nodules (false positives) without delaying the diagnosis of malignancies (false negatives). Omitting nodules classified as PFNs from additional diagnostic tests appears to be a highly reliable and effective strategy for contributing towards this goal. This approach had indicated trustworthiness in screening (5,6) and clinical settings (8) and in pediatric cohorts (25,26); even PFNs which grew or shrunk in a follow-up scan were not found to be cancerous (6). Han et al. (4) expand the range of evidence to include new nodules. Future research
needs to work towards a standardized definition of PFNs and its validation in a sufficiently cancer-rich and high-quality CT cohort.

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**Footnote**

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