New Fissure-attached Nodules in Lung Cancer Screening: A Brief Report from The NELSON Study

Daiwei Han[a]
Marjolein A Heuvelmans[b,c]
Carlijn M van der Aalst[d]
Lisa H van Smoorenburg[a]
Monique D Dorrius[a]
Mieneke Rook[a, e]
Kristiaan Nackaerts[f]
Joan E Walter[b]
Harry J M Groen[g]
Rozemarijn Vliegenthart[a]
Harry J de Koning[d]
Matthijs Oudkerk[h,j]

[a] University of Groningen, University Medical Center Groningen, Department of Radiology, Groningen, The Netherlands

[b] University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, The Netherlands

[c] Medisch Spectrum Twente, Department of Pulmonology, Enschede, The Netherlands

[d] Erasmus MC - University Medical Center Rotterdam, Department of Public Health, Rotterdam, The Netherlands

[e] Martini Ziekenhuis, Department of Radiology, Groningen, The Netherlands

[f] KU Leuven, University Hospitals Leuven, Department of Pulmonary Medicine, Leuven, Belgium.

[g] University of Groningen, University Medical Center Groningen, Department of Pulmonology, Groningen, The Netherlands

[h] University of Groningen, Faculty of Medical Sciences, Groningen the Netherlands

[i] Institute for Diagnostic Accuracy Research, Groningen, the Netherlands

Disclosures:

Prof. Oudkerk discloses that he holds a financial interest in iDNA – the Institute for Diagnostic Accuracy Research BV, an organization that aims to speed up the global implementation of the early detection of lung cancer (with comorbidities in cardiovascular diseases and COPD).

Abstract

Introduction

In incidence lung cancer screening rounds, new pulmonary nodules are regular findings. They have a higher lung cancer probability than baseline nodules. Previous studies showed that baseline perifissural nodules (PFNs) represent benign lesions. Whether this is also the case for incident PFNs is unknown. This study evaluated newly detected nodules in the Dutch-Belgian randomized-controlled NELSON study with respect to incidence of fissure-attached nodules, their classification, and lung cancer probability.

Method

Within the NELSON trial, 7,557 participants underwent baseline screening between April 2004 and December 2006. Participants with new nodules detected after baseline were included. Nodules were classified based on location and attachment. Fissure-attached nodules were re-evaluated to be classified as typical, atypical or non-PFN by two radiologists without knowledge of participant lung cancer status.

Result

1,484 new nodules were detected in 949 participants (77.4% male, median age 59 [interquartile range: 55-63]) in the second, third and final NELSON screening round. Based on 2-year follow-up or pathology, 1,393 nodules (93.8%) were benign. In total, 97 (6.5%) were fissure-attached, including 10 malignant nodules. None of the new fissure-attached malignant nodules was classified as a typical or atypical PFN.

Conclusion

In the NELSON study, 6.5% of incident lung nodules were fissure-attached. None of the lung cancers that originated from a new fissure-attached nodule in the incidence lung cancer screening rounds was classified as a typical or atypical PFN. Our results suggest that also in the case of a new PFN, it is highly unlikely that these PFNs will be diagnosed as lung cancer.

INTRODUCTION (max 200 words)

Pulmonary nodules are common findings in lung cancer screening and in clinical settings (1–3). To increase the efficiency of lung cancer screening, it is key to timely and adequately identify high-risk nodules while preventing overdiagnosis and overtreatment. Nodule follow-up and management are mainly determined based on nodule size and growth rate (4-6). Recently, it was shown that new solid pulmonary nodules detected in incidence lung cancer screening rounds comprise a higher lung cancer probability compared with baseline nodules , and require more stringent follow-up of smaller nodules (7).

Twenty to thirty percent of screen-detected nodules from baseline is classified as perifissural nodule (PFN) (8–10). Previous studies showed that baseline PFNs and PFNs in clinical settings represent non-malignant lesions such as intrapulmonary lymph nodes (11–13). Whether this also applies for new incident PFNs is unknown. To investigate this, we evaluated newly detected nodules in the Dutch-Belgian randomized-controlled NELSON study with respect to incidence of perifissural nodules, their classification and lung cancer probability.

MATERIAL AND METHODS (max 350 words)

The NELSON trial (trial registration number, ISRCTN63545820) was authorized by the Dutch Health Care Committee and approved by Ethics Committees of all participating centers in the Netherlands and Belgium. Written informed consent was obtained from all participants. The study protocol has been published before (14,15). In brief, 15,792 participants between 50 and 75 years of age, who had daily smoked >15 cigarettes for >25 years or >10 cigarettes for >30 years and were still smoking or had stopped smoking less than 10 years previously were randomized (1:1). The 'screen' group (N=7,900) received low-dose CT scans in year 1 (baseline), 2, 4 and 6.5.

For the current analyses, all participants with a new nodule $\geq 15mm^3$ in one of the three incidence screening rounds were included. A three month follow up scan was performed for newly found pulmonary nodules. Nodules that have suspicious appearance and rapid growth were referred to pulmonologist for further workup. Confirmation of malignancy was done using histology, or in case when histology was not possible confirmation was done based on their appearance, growth rate, and PET-CT results. Details regarding imaging acquisition/analysis and nodule measurements are provided in the Supplementary Methods section, and Supplementary References.

Based on attachment, nodules were classified as vessel-attached, fissure-attached or intraparenchymal by the NELSON radiologists. All screening CT scans of participants with newly detected lung cancer were re-evaluated in retrospect by two radiologists (4 and 6 years of experience) to assess fissure attachment. Furthermore, benign and malignant fissure-attached nodules were re-evaluated by classifying them as typical, atypical or non-PFN. The definition of these nodule classifications were previously given by de Hoop et al. Shortly,

typical PFNs were defined as fissure-attached, homogenous, solid nodule that had smooth margins and lentiform triangular shape. Atypical PFNs were nodules that either met all features but were not attached to a visible fissure or were fissure-attached nodules with convex on one side and round on the other side. All other fissure-attached nodules with shape that does not appear to be influenced by the fissure were defined as non-PFN (16). During the evaluation, the radiologists were blinded with regards to outcome of the nodules (either based on histology, or stability in nodule size during two-year follow-up). In case of disagreement, a third radiologist (13 years of experience) arbitrated.

Statistical analysis

Normally distributed variables are described as mean and standard deviation. Otherwise, the median and interquartile range are presented. Mann-Whitney U test was used to analyze continuous, non-parametric independent data. Chi-Square test was used for the analysis of categorical data. Statistical significance was considered for $p < 0.05$ and all tests were 2-tailed. For the statistical analysis, SPSS version 25 was used.

RESULTS (max 350 words)

In the three NELSON incidence screening rounds, 1,484 new solid nodules were detected in 949 participants. Of these, 107 (7%) nodules in 104 participants were registered as fissure-attached by the NELSON radiologists, and these were selected for re-evaluation. Because CT images from four participants were not retrievable, and six nodules were rated as not fissure-attached in the re-evaluation, the final number of re-evaluated fissure-attached nodules was 97, from 95 participants (Figure 1).

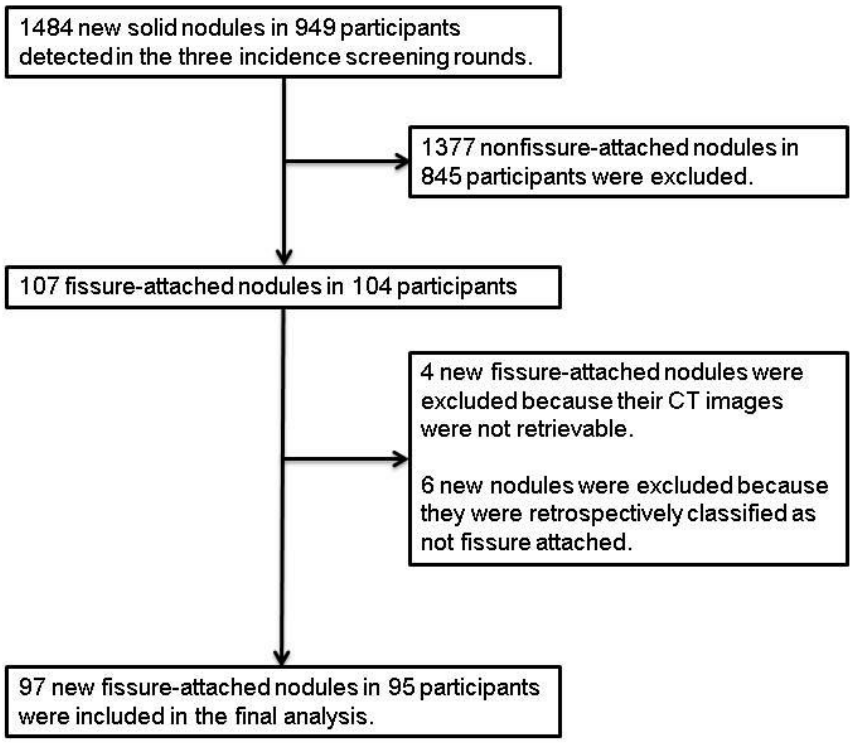

Figure 1. Flowchart of new fissure-attached nodules in the NELSON trial

Median age of the participants with new fissure-attached nodules was 58 years (IQR, 63-55) and 67 (71%) were male. Overall, 55 (58%) participants were current smoker with a median of 38 pack-years (IQR: 49-28). Of the new fissure-attached nodules, 32 (33%) were detected

in the second screening round, 44 (45%) were detected in the third screening round and 21 (22%) nodules were detected in the final screening round.

Table 1. Size, location, and appearance of fissure-attached nodules

	PFNs (all benign)	**Benign non-PFNs**	**Malignant non-PFNs**	**P value** [a]
Total (n)	58 (60%)	29 (30%)	10 (10%)	
Nodule size [b]				
Volume (IQR)	19 mm^3 (14)	51 mm^3 (250)	108 mm^3 (1128)	< 0.03
Mean diameter (IQR)	4 mm (1)	5 mm (5)	6 mm (9)	< 0.01
Location (n)				
Right oblique	16 (28%)	11 (38%)	5 (50%)	
Horizontal	13 (22%)	6 (21%)	1 (10%)	0.423
Left oblique	26 (45%)	10 (34%)	3 (30%)	
Accessory	3 (5%)	2 (7%)	1 (10%)	
Appearance (n)				
Lentiform	12 (21%)	0	0	
Triangular	30 (52%)	0	0	< 0.01
Other	16 (27%)	29 (100%)	10 (100%)	

n, number of nodules; IQR, interquartile range; PFN, perifissural nodule (including both typical and atypical perifissural nodules).
[a] Comparison between PFNs and Malignant non-PFNs
[b] Missing values were excluded from the analysis

In the 97 fissure-attached nodules that were re-evaluated, 42 (43%) were typical PFNs and 16 (17%) were atypical PFNs. Thirty-nine (40%) nodules were classified as non-PFN. Among the non-PFNs, 10 (10%) were malignant (Table 1). Both malignant nodules and non-PFNs were not lentiform or triangular in appearance. There was no malignant nodule classified as PFN (Figure 2).

Of the 10 malignant fissure-attached nodules, seven were located in the right lung. Four malignant nodules were located in the upper lobe, one in the middle lobe, and five were located in the lower lobe. The median volume was 108 mm^3 (IQR, 1183-55; range, 37-2793) and median diameter was 6 mm (IQR, 14-5; range, 5-20). Two of the malignant nodules were large cell carcinomas, four were adenocarcinomas and one was small cell carcinoma, the malignancy of the other three nodules did not have histological diagnosis, but were regarded as malignant in nature based on their suspicious appearance, fast growth and positive PET-CT.

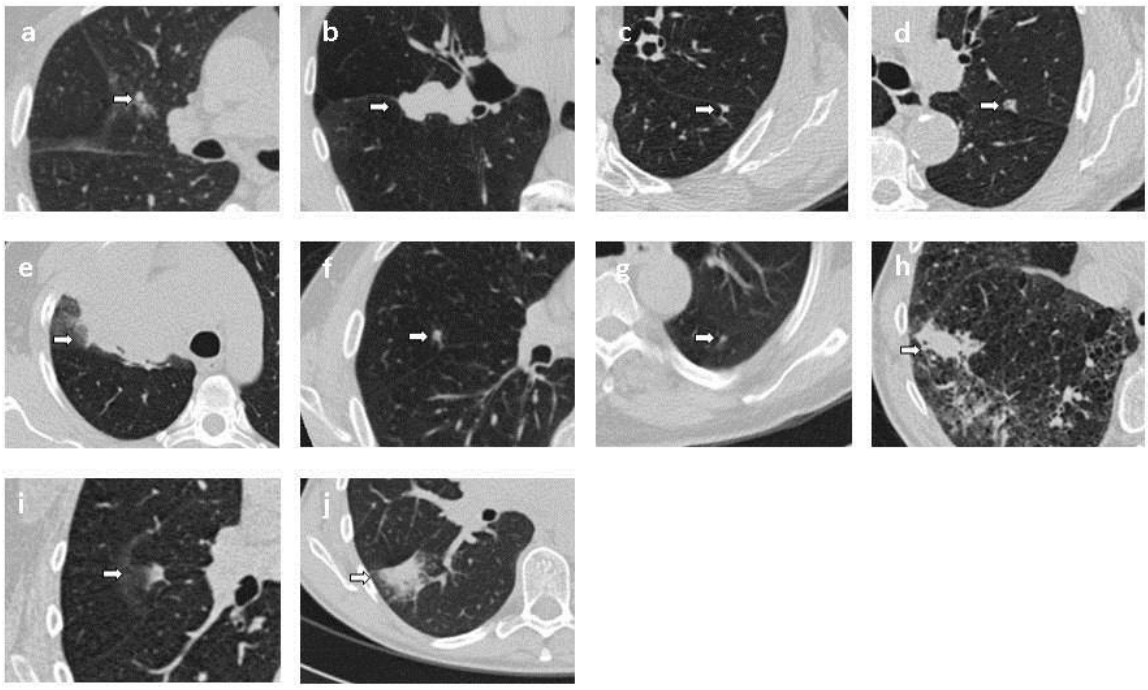

Figure 2. Transverse images of new malignant fissure-attached nodules. Nodule (a) and (g) were large cell carcinomas. Nodule (d), (f), (i), and (j) were adenocarcinomas. Nodule (e) was a small cell carcinoma. (b), (c), and (h) were treated as lung cancers (without histological diagnosis) with stereotactic radiotherapy because of suspicious appearance, fast growth and positive PET-CT.

DISCUSSION (max 450 words)

To the best of our knowledge, this is the first study focusing on new perifissural nodules detected in CT lung cancer screening. A total of 97 new solid fissure-attached nodules were identified, 6.5% of all incident screen-detected lung nodules. Sixty percent of all new fissure-attached nodules met the criteria of PFN. None of the malignant nodules were classified as PFN. This suggests that PFNs, even in the case of newly developed nodules, are benign findings.

The prevalence of PFN nodules from the total number of new solid nodules in the NELSON study was 4% (58/1484). This percentage is considerably lower compared to the previously reported prevalence of baseline PFNs detected in a lung cancer screening setting. De Hoop et al. reported that 20% of all baseline nodules were typical PFNs and 3% were atypical, Ahn et al. reported that 28% of non-calcified nodules (NCN) were PFNs (8), and more recently Mets et al. reported that outside a lung cancer screening setting, PFNs represent 21% of the non-calcified nodules (10). All these studies showed a 0% risk of malignancy in PFNs. Since PFNs are likely to be intrapulmonary lymph nodes, they may appear less frequently as new nodule in incidence screening rounds than in the baseline round.

Although in our study none of the nodules classified as PFNs turned out to be lung cancer, Scheurder et al. have reported that 0.9% of nodules (five of 533) classified as typical PFNs were lung cancers. Moreover, 4.8% of atypical PFNs (16 of 332) were lung cancers (17). The difference with our result may be explained by the fact that their dataset from the NLST was enriched with malignant nodules (70 cancers and 246 benign nodules) therefore the true misclassification rate could be far lower than the reported values. Moreover, the difference in the study designs, as they did not limit their study to only fissure attached nodules, could have

further contributed to the misclassification of malignant nodules as PFN. Finally, in the NELSON study, the first MDCT systems with isotropic volume reconstruction were used, which could also explain the superior display of nodule morphology and location.

The size of PFNs found in our study (median 4 mm) is in line with previous studies where the mean maximum diameter of PFNs were reported to be 3.2-5.5 mm (16,18,19). A significant size difference between PFNs and non-PFNs was found which is similar compared to the results reported by Scheuder et al.

A limitation of our study is the relatively small number of new fissure-attached nodules detected, although our study represents one of the largest lung cancer screening trials worldwide. Furthermore, although all malignant new nodules have been re-evaluated, a small number of benign perifissural nodules could not be re-classified into typical, atypical or non-PFN since the CT scans were not retrievable.

In conclusion, in the NELSON study, none of the lung cancers originating from a new nodule was classified as a typical or atypical PFN. Our results suggest that also in the case of a new PFN, it is highly unlikely that it will be diagnosed as lung cancer. This implies that short-term follow-up for these nodules might be superfluous.

Acknowledgements

The NELSON study is funded by the Dutch Organisation for Health Research and Development (ZonMw); Dutch Cancer Society Koningin Wilhemina Fonds (KWF); Stichting Centraal Fonds Reserves van Voormalig Vrijwillige Ziekenfondsverzekeringen (RvvZ);

Siemens Germany; Rotterdam Oncologic Thoracic Steering committee (ROTS);

G.Ph.Verhagen Trust, Flemish League Against Cancer, Foundation Against Cancer, and the Erasmus Trust Fund. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011 Aug 4;365(5):395–409.

2. Horeweg N, van Rosmalen J, Heuvelmans MA, van der Aalst CM, Vliegenthart R, Scholten ET, 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 Nov;15(12):1332–41.

3. Zhao YR, Xie X, de Koning HJ, Mali WP, Vliegenthart R, Oudkerk M. NELSON lung cancer screening study. Cancer Imaging. 2011 Oct 3;11(1A):S79–84.

4. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017 Feb 23;161659.

5. Margolis ML. Lung Cancer Screening Kit with LUNG-RADS, Version 3.0. Ann Am Thorac Soc. 2016 Jan;13(1):145.

6. BTS Guidelines for the Investigation and Management of Pulmonary Nodules | British Thoracic Society | Better lung health for all [Internet]. [cited 2018 Apr 9]. Available from: https://www.brit-thoracic.org.uk/standards-of-care/guidelines/bts-guidelines-for-the-investigation-and-management-of-pulmonary-nodules/

7. Walter JE, Heuvelmans MA, Jong PA de, Vliegenthart R, Ooijen PMA van, Peters RB, et al. Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT: analysis of data from the randomised, controlled NELSON trial. The Lancet Oncology. 2016 Jul 1;17(7):907–16.

8. Ahn MI, Gleeson TG, Chan IH, McWilliams AM, MacDonald SL, Lam S, et al. Perifissural Nodules Seen at CT Screening for Lung Cancer. Radiology. 2010 Feb 8;254(3):949–56.

9. de Hoop B, van Ginneken B, Gietema H, Prokop M. Pulmonary Perifissural Nodules on CT Scans: Rapid Growth Is Not a Predictor of Malignancy. Radiology. 2012 Nov 1;265(2):611–6.

10. Mets OM, Chung K, Scholten ETh, Veldhuis WB, Prokop M, van Ginneken B, et al. Incidental perifissural nodules on routine chest computed tomography: lung cancer or not? Eur Radiol. 2018 Mar 1;28(3):1095–101.

11. Ishikawa H, Koizumi N, Morita T, Tsuchida M, Umezu H, Sasai K. Ultrasmall Intrapulmonary Lymph Node: Usual High-resolution Computed Tomographic Findings With Histopathologic Correlation. Journal of Computer Assisted Tomography. 2007 May 1;31(3):409–13.

12. Honma K, Nelson G, Murray J. Intrapulmonary lymph nodes in South African miners—an autopsy survey. American Journal of Industrial Medicine. 2007 Apr 1;50(4):261–4.

13. Wang C-W, Teng Y-H, Huang C-C, Wu Y-C, Chao Y-K, Wu C-T. Intrapulmonary lymph nodes: computed tomography findings with histopathologic correlations. Clinical Imaging. 2013 May 1;37(3):487–92.

14. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, et al. Management of Lung Nodules Detected by Volume CT Scanning. New England Journal of Medicine. 2009 Dec 3;361(23):2221–9.

15. van Iersel CA, de Koning HJ, Draisma G, Mali WPTM, Scholten ET, Nackaerts K, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomised lung cancer multi-slice CT screening trial (NELSON). Int J Cancer. 2007 Feb 15;120(4):868–74.

16. de Hoop B, van Ginneken B, Gietema H, Prokop M. Pulmonary Perifissural Nodules on CT Scans: Rapid Growth Is Not a Predictor of Malignancy. Radiology. 2012 Nov 1;265(2):611–6.

17. Schreuder A, van Ginneken B, Scholten ET, Jacobs C, Prokop M, Sverzellati N, et al. Classification of CT Pulmonary Opacities as Perifissural Nodules: Reader Variability. Radiology. 2018 Jul 3;288(3):867–75.

18. Ahn MI, Gleeson TG, Chan IH, McWilliams AM, MacDonald SL, Lam S, et al. Perifissural Nodules Seen at CT Screening for Lung Cancer. Radiology. 2010 Feb 8;254(3):949–56.

19. Schreuder A, van Ginneken B, Scholten ET, Jacobs C, Prokop M, Sverzellati N, et al. Classification of CT Pulmonary Opacities as Perifissural Nodules: Reader Variability. Radiology. 2018 Jul 3;288(3):867–75.