

## REVIEW

# A practical approach to radiological evaluation of CT lung cancer screening examinations

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### Abstract

Lung cancer is the most common cause of cancer-related death in the world. The Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON) was launched to investigate whether screening for lung cancer by low-dose multidetector computed tomography (CT) in high-risk patients will lead to a decrease in lung cancer mortality. The NELSON lung nodule management is based on nodule volumetry and volume doubling time assessment. Evaluation of CT examinations in lung cancer screening can also include assessment of coronary calcification, emphysema and airway wall thickness, biomarkers for major diseases that share risk factors with lung cancer. In this review, a practical approach to the radiological evaluation of CT lung cancer screening examinations is described.

**Keywords:** Lung cancer; screening; multidetector computed tomography; population; pulmonary nodule; volume measurement.

## Introduction

Lung cancer is the primary cancer in males and the second in females, accounting for 18% of the total number of deaths<sup>[1]</sup>. Despite advances in treatment, the 5-year survival rate is still only 15% or even less, as many lung cancers are found at a relatively late stage<sup>[2]</sup>. Low-dose computed tomography (CT) was proposed as a promising screening method for early detection of lung cancer.

The Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON) was launched in 2003. The hypothesis of the NELSON trial is that lung cancer screening by low-dose spiral CT will reduce 10-year lung cancer mortality by 25% in a high-risk population. Details on participant recruitment and the CT acquisition protocol are described elsewhere<sup>[3]</sup>. In short, heavy (ex-)smokers between 50 and 75 years of age underwent four rounds of low-dose CT screening in years 1, 2, 4, and 7. The NELSON lung nodule management is based on volumetry and volume doubling time assessment. Thin-slice thoracic CT images were acquired with a slice thickness of 1 mm, and a slice interval of 0.7 mm,

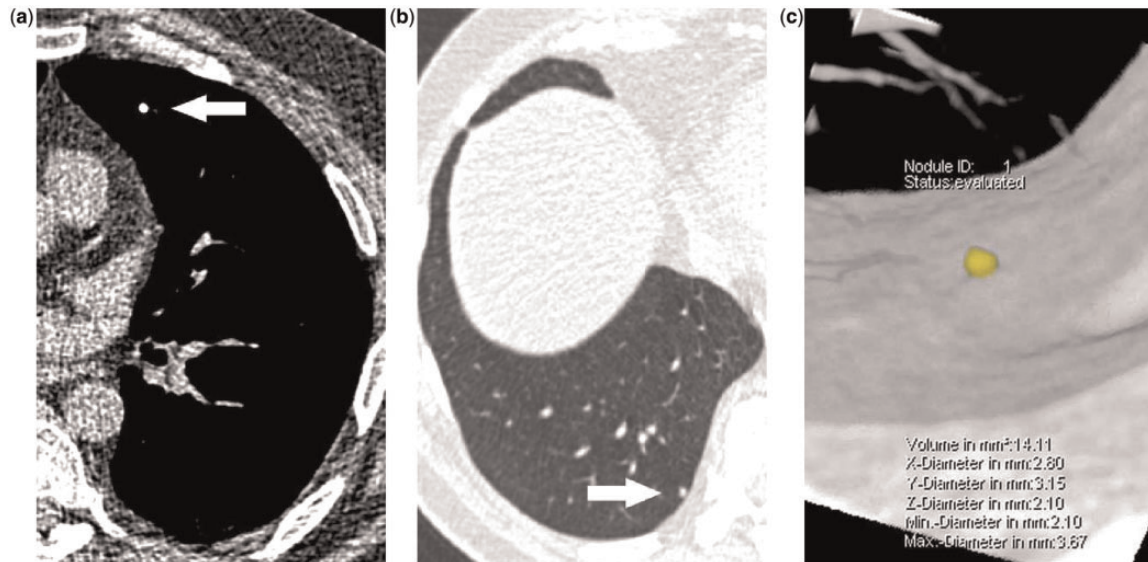
allowing for volume measurements of pulmonary nodules.

Evaluation of CT examinations in lung cancer screening can also include assessment of coronary calcification, emphysema and the airway wall, markers for major diseases that share risk factors with lung cancer<sup>[4]</sup>. In this review, a practical approach to the radiological evaluation of CT lung cancer screening examinations is described, including assessment of pulmonary nodules and non-nodular diseases.

## Pulmonary nodule evaluation

### Initial assessment

The assessment starts with evaluating whether a newly detected nodule has purely benign characteristics such as benign calcifications or is very small ( $<15 \text{ mm}^3$ ) (Fig. 1). If so, the nodule can be categorized as benign, and needs no further evaluation. If the nodule cannot be directly defined as benign, the nodule is further



**Figure 1** A complete calcified nodule is considered as benign on a transverse thin-slice CT image in the soft tissue setting (a). A very small ( $14 \text{ mm}^3$ ) nodule is not further evaluated (b, transverse thin-slice CT image in the lung setting). The volume-rendered image of this small nodule is shown in (c).

evaluated. Next, the density of the lung nodule is assessed. A nodule can be solid, partial-solid, or non-solid.

### *Size-based evaluation*

Evaluation of nodule size is essential to determine nodule growth. Evaluation methods for solid, partial-solid and non-solid nodules are different.

Semi-automated volumetry measurements are used for segmentable nodules (Fig. 2), e.g., solid nodules and the solid part of partial-solid nodules. In the NELSON study, approximately 98% of the nodules were solid, and thus could be assessed using semi-automated software<sup>[5]</sup>. In cases of inappropriate segmentation, the reader is allowed to manually modify the segmentation for more accurate segmentation, which then overrules the automatically generated volumetry.

Manual measurement of diameters is performed in cases of non-segmentable nodules (Fig. 3), e.g., non-solid nodules and the non-solid part of partial-solid nodules. Although partial-solid and non-solid nodules constitute the minority of nodules that are detected, the frequency of malignancy is higher<sup>[6,7]</sup>.

Interscan variability in nodule size evaluation is inevitable. Based on validation studies with repeated low-dose CT on the same day, in which the measurement error was maximally 25%, nodule growth is defined as a change in volume of at least 25% between two subsequent examinations<sup>[8]</sup>.

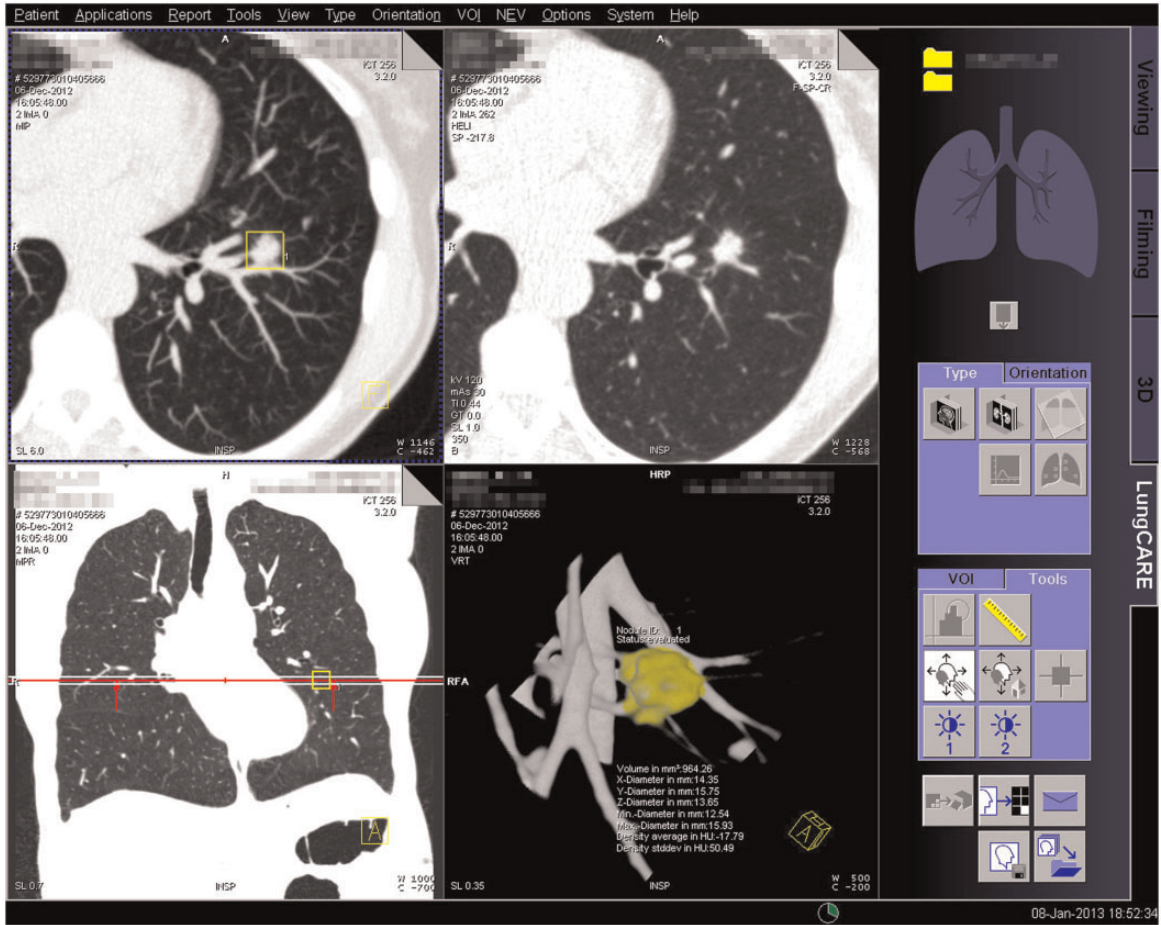
### *Additional non-size-based evaluation*

Beside nodule density, attachment type, shape, margin and location should be taken into account when

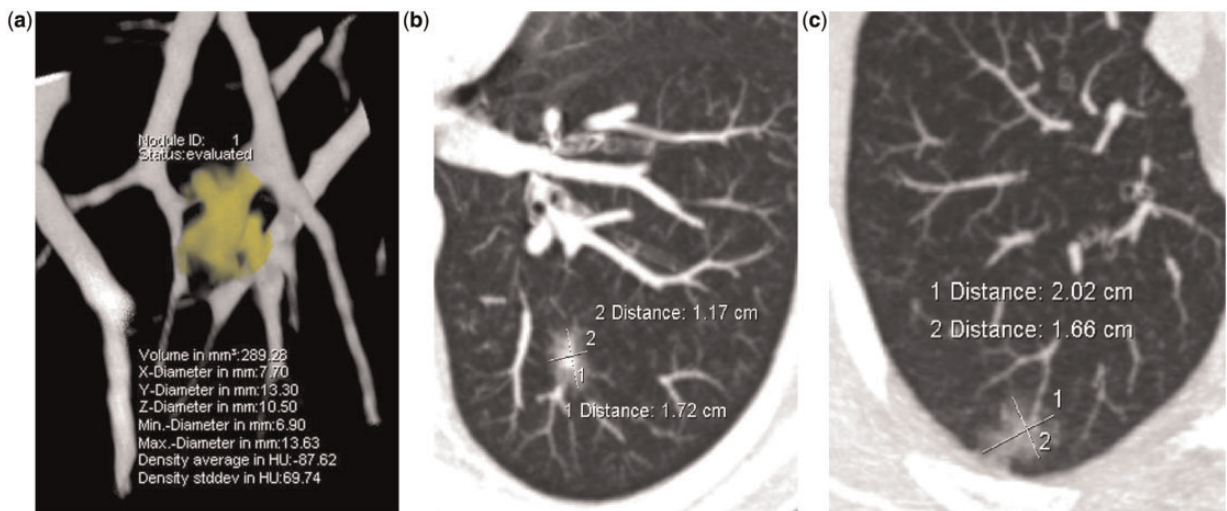
evaluating a pulmonary nodule (Fig. 4). First, the attachment of nodules (peri-fissural, vessel-attached, pleural-based and intraparenchymal) is evaluated. Although peri-fissural nodules may show growth at follow-up CT, the malignancy potential of peri-fissural nodules is low<sup>[9,10]</sup>. In addition, a previous study showed negligible cancer risk in fast-growing vessel-attached and pleural-based nodules 1 year after baseline<sup>[11]</sup>. Second, the shape of nodules (spherical and non-spherical) is evaluated. Non-spherical shape has been found to increase the likelihood of malignancy, rather than spherical shape<sup>[12]</sup>. Third, the margin of nodules (smooth, lobulated, spiculated or other) is assessed. In a subgroup of NELSON with 469 solid intraparenchymal nodules, a lobulated or spiculated margin increased the likelihood for malignancy compared with a smooth margin<sup>[13]</sup>. Fourth, nodule location is defined by the pulmonary segment and according to distance to pleura: peripheral nodules are defined as  $<1/3$  from total distance between hilus-costal pleura, and central nodules are defined as  $>2/3$  from this distance. In-between nodules are defined as between  $1/3$  to  $2/3$  from total distance between hilus-costal pleura.

### *Reading*

A single CT lung cancer screening evaluation by an experienced reader seems sufficient. In the first three rounds of the NELSON trial, images were evaluated twice. The second reader was unaware of the conclusion of the first reader. In cases of discrepancy, a third reader made the final decision. However, based on the results from these rounds, no statistically significant benefit was found for consensus double reading for detection of lung cancer

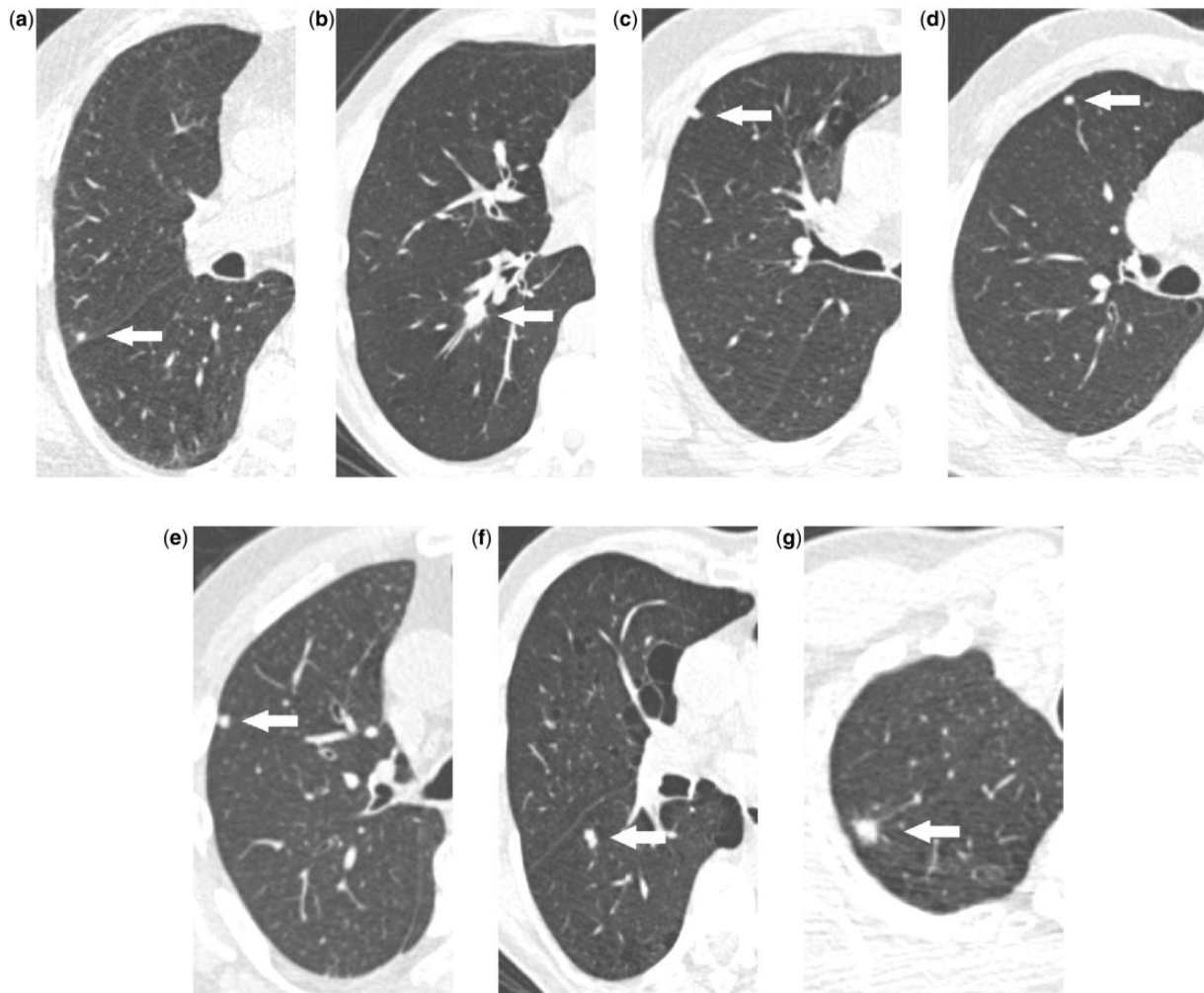


**Figure 2** Screen capture of dedicated software to semi-automatically measure the volume of a solid nodule (LungCare, Siemens, Forchheim, Germany). At the top left section, a thin maximum intensity projection is shown; in the yellow box, the nodule of interest selected by the radiologist. The top right section shows a transverse thin-slice image. On the bottom left, a coronal thin-slice image is shown, and a volume-rendered image of the selected nodule is shown bottom right.



**Figure 3** Semi-automated volumetry for the solid part of a partial-solid nodule (a), and manual measurement of the diameter for the non-solid part of this partial-solid nodule (b). Manual measurement of diameters is performed for a non-solid nodule (c). (a) is a volume-rendered image; (b) and (c) are maximum intensity projection images.





**Figure 4** Example images of four nodule attachment types: peri-fissural (a), vessel-attached (b), pleural-based (c) and intraparenchymal (d). Example images of three margin types: smooth (e), lobulated (f) and spiculated (g). All images are transverse thin-slice CT slices.

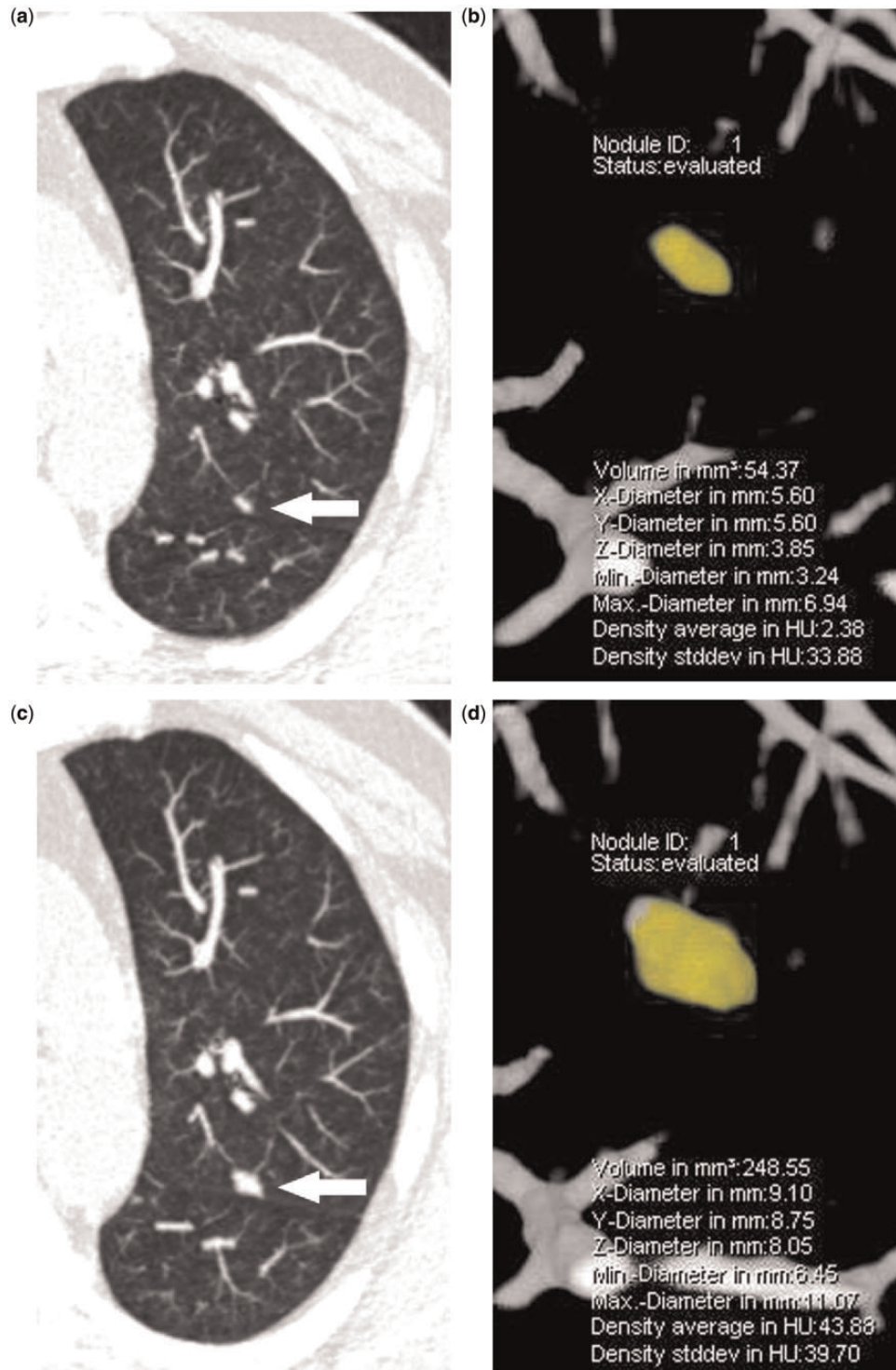
with the use of a nodule management strategy based on semi-automated volumetry measurements<sup>[14]</sup>. Thereafter, in the fourth round, only one reading was performed by one of the two radiologists with at least 8 years of experience in thoracic imaging.

Images are interpreted on a workstation for evaluation of pulmonary nodules and non-nodular diseases (in the NELSON trial: Leonardo, Siemens, Forchheim, Germany), both at lung window and mediastinal settings. When a pulmonary nodule is identified, a dedicated software package (in the NELSON trial: LungCare, Siemens, Forchheim, Germany) is used for semi-automated volumetric measurement. In cases of non-segmentable nodules, the reader should manually measure the diameter of the lesion. In the LungCare software package, previous and current images are displayed simultaneously on the same screen for comparison. Besides the evaluation of nodule size, nodule characteristics (attachment type, margin, etc.) are then also evaluated and reported.

#### *Lung nodule decision management*

Newly detected lung nodules are divided into four categories (NODCAT 1 to 4), based on nodule density and size. In subsequent screening rounds, preexisting nodules are defined as three categories (GROWCAT A to C), based on nodule growth in terms of volume doubling time (Table 1). For newly detected nodules, the test result (negative, indeterminate and positive) is based on the highest NODCAT. For preexisting nodules, the test result is based on the highest GROWCAT. A negative result indicates that no further workup is needed. The participant is then invited to undergo the regular next-round CT. An indeterminate result requires a follow-up examination after 6 weeks (for incidence screening) to 3 months (for baseline screening). A positive result necessitates referral to a pulmonologist for workup and diagnosis. The decision tree for baseline, second, third and fourth rounds are shown in Figs. 5 and 6. An example of a growing nodule that turned out to be lung cancer is shown in Fig. 7.





**Figure 7** New pulmonary nodule in the apicoposterior segment of the left superior lobe in the third round (a and b), non-spherical, lobulated and solid, with volume of 54 mm<sup>3</sup> (NODCAT 3). In the fourth round, 3 years after the third round (c and d), the volume had increased to 249 mm<sup>3</sup>, and the volume doubling time was 284 days (GROWCAT C). Thus, this was considered to be a positive case; the participant was referred to a pulmonologist. Lung cancer was confirmed. (a) and (c) are thin maximum intensity projection images; (b) and (d) are volume-rendered images.



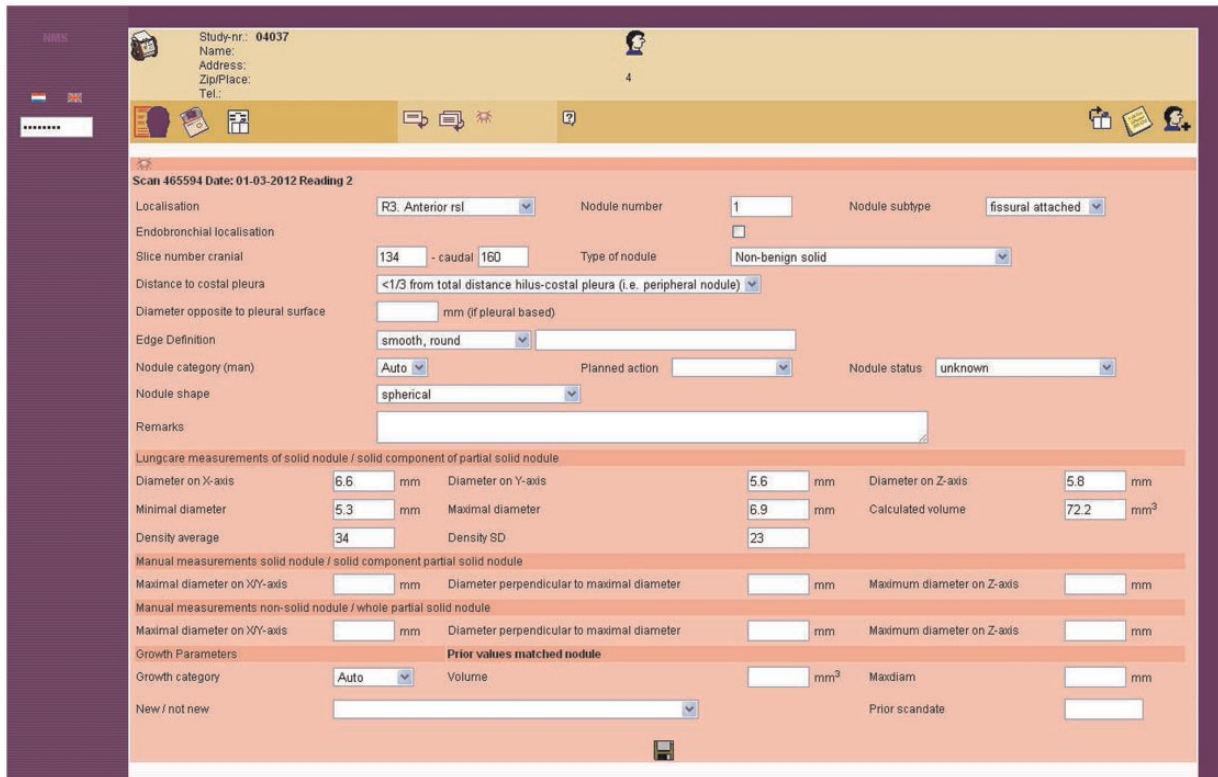


Figure 8 Screen capture of the web-based NELSON management system.

*NELSON management system*

In the NELSON trial, evaluation results are exported into the web-based NELSON management system (Fig. 8). Nodule characteristics, volume and diameter are recorded. Nodule volume is automatically compared with the previous data to calculate the percentage volume change and the volume doubling time in days. The system then makes a suggestion for categorization of pulmonary nodules.

**Non-nodular diseases**

Beside lung cancer originating from pulmonary nodules, over 14% of participants in lung cancer screening have other diseases, such as cardiovascular disease and other pulmonary disease<sup>[15]</sup>. Aging and smoking, the two major risk factors for lung cancer, are also main contributors in the development and progression of coronary calcification and emphysema<sup>[16,17]</sup>. It is important to review the CT screening examination for coronary artery calcification and emphysema. These thoracic biomarkers can be evaluated quantitatively.

A list of non-nodular findings that were initially reported in the NELSON trial is given in Table 2. The screening population of (ex-)smokers frequently shows findings such as pleural plaques to a certain extent, without having high clinical relevance. Thus, these were not

Table 2 Non-nodule radiological findings in lung cancer CT screening

Clinical relevance too low to report to GP	Clinically significant and reported to GP
Aortic calcium	Aortic aneurysm
Adrenal lesion ≤10 HU	Adrenal lesion >10 HU
Pleural calcifications	Bone destruction
Pleural plaques	Liver lesions
Pulmonary fibrosis	Mass (thyroid, breast, abdominal, etc.)
Bronchiectasis	Pleural fluid
Lymph node enlargement	Pneumonia
	Segmental or larger atelectasis

GP, general practitioner.

reported to the general practitioner, to prevent unnecessary costs and patient anxiety. Some severe diseases were detected in the NELSON screening group that led to clinical referral, e.g., abdominal aortic aneurysm and renal cancer. However, the prevalence of these other potentially significant findings in the NELSON trial is only 1%, and the benefit for systematically searching for these additional findings has been found to be negligible<sup>[18]</sup>.

*Coronary calcification*

Coronary calcification is a frequent finding in the NELSON screening group, with a prevalence of over 70%<sup>[19]</sup>. Calcium scoring as part of low-dose CT lung

**Table 3** A 10-step approach to evaluate a participant in the NELSON trial

Step	Practical approach
1	Evaluate the presence of nodules (new or existing)
2	Exclude nodules with benign calcifications and nodules <15 mm <sup>3</sup>
3	Determine the nodule density (solid, partial-solid, or non-solid)
4	Measure the nodule (volume and diameters)
5	Determine the nodule characteristics (morphology, margin, location, lung segment)
6	In case of an existing nodule: compare with the previous examination and determine volume doubling time
7	Categorize the nodule (for a new nodule based on size, for an existing nodule based on growth)
8	Repeat steps 3–7 for each additional nodule
9	Review for coronary calcification, emphysema, and other findings
10	Derive screening result (negative, indeterminate or positive)

cancer screening can be used as an independent predictor of cardiovascular death and events<sup>[19,20]</sup>. For the analysis of coronary calcification, the raw data should be reconstructed into 3-mm thickness to improve interscan reproducibility and make the settings more comparable with the dedicated coronary calcium examination<sup>[21,22]</sup>. Then, calcium scoring can be performed using the method developed by Agatston<sup>[23]</sup>.

### *Emphysema and airway wall*

Emphysema is also a frequent finding in lung cancer screening. The two primary causes of chronic obstructive pulmonary disease (COPD) are emphysema and airway remodelling<sup>[24]</sup>. In a meta-analysis, CT-measured emphysema and airway wall thickness correlated with airflow obstruction in COPD<sup>[25]</sup>. CT examinations obtained for lung cancer screening can identify participants with COPD, with a sensitivity of 63% and a specificity of 88%<sup>[26]</sup>. Among the parameters that can be used to quantify emphysema, percentage of lung attenuation area under –950 HU, mean lung density and 15 percentile point for lung density are the most commonly used. Among the parameters to quantify airway wall thickness, wall area percentage and wall thickness are the most commonly used<sup>[25]</sup>. Dedicated software is needed to obtain quantitative emphysema and airway wall measures.

### **Conclusion**

The NELSON trial is the first lung cancer screening trial in which nodule management is based on semi-automated volumetric measurements. High-resolution images acquired in low-dose thin-slice CT result in accurate evaluation of nodule volume and volume doubling time. Nodule volume and volume doubling time are used to categorize a lung nodule according to risk of lung cancer, and recommend adequate nodule management. A 10-step practical approach to evaluate a CT lung cancer screening examination is provided in Table 3.

Cardiovascular disease and COPD share risk factors with lung cancer, such as aging and smoking. The

prevalence of these diseases in a lung cancer screening population is high. Besides the evaluation of lung nodules, low-dose thoracic CT can be used to evaluate coronary calcification, emphysema and airway wall thickness, and thereby estimate the risk of cardiovascular disease and COPD. An integrated evaluation of quantitative biomarkers of these diseases can potentially enhance the benefit of CT lung cancer screening.

### **Conflict of interest**

The authors have no conflicts of interest to declare.

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