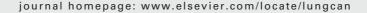# Nodule management protocol of the NELSON randomised lung cancer screening trial

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Summary   In December 2003, the Dutch—Belgian NELSON trial, a Dutch acronym for ''Nederlands-Leuvens Longkanker Screenings ONderzoek'', has been launched. Primary objective of the NELSON trial is to investigate whether screening for lung cancer by 16-detector multi-slice CT with 16 mm × 0.75 mm collimation and 15 mm table feed per rotation (pitch = 1.5) in year 1, 2 and 4 will lead to a decrease in lung cancer mortality in high risk subjects of at least 25% compared to a control group which receives no screening. In this paper, the screening regimen and the classification and management of the screen-detected nodules at baseline and incidence screening is presented. This is the first large lung cancer screening trial in which the

nodule management protocol is based on volumetric nodule assessment and the presence or absence of growth. Furthermore, the quality assurance measures and the NELSON management system (NMS) are presented.

1. Introduction

Lung cancer is currently a serious public health problem. In Europe alone, an estimated 375,000 people die from lung cancer every year and worldwide 1.4 million per year [1]. At the time of diagnosis, over 75% of persons with lung cancer have loco-regional spread or distant metastases, substantially reducing the chances of survival [2]. Theoretically, primary prevention, quitting smoking or more importantly, measures to reduce starting smoking may totally eliminate the disease, but although several such measures have been successful, the number of lung cancer deaths each year is still unacceptably high. One of the most promising recent preventive measures is early detection using multi-detector low-dose computed tomography (MDCT) screening. Cohort studies have shown that lung cancer can be detected in a much earlier disease stage, but it is yet unknown if earlier detection will eventually reduce lung cancer mortality [2]. To address this question, in the US the National Lung Screening trial (NLST) has been launched in 2002. It is a very large multi-center trial with 53,476 participants in 46 institutes across the US, comparing CT screening with Chest X-ray screening in the control arm [3]. In Europe, the only large randomised trial is the Dutch—Belgian NELSON trial with 15,523 males and to a lesser extent females participants in four institutes, which have been launched in December 2003 [4]. Primary objective of the NELSON trial is to investigate whether screening for lung cancer by MDCTs in year 1, 2 and 4 will lead to a decrease in lung cancer mortality in high risk subjects of at least 25% compared to a control group which receives no screening, and to estimate the cost-effectiveness of this screening programme. In collaboration with a single institute in Copenhagen Denmark where 4104 participants have been enrolled in a randomised MDCT screening trial with almost the same design as NELSON, the target of 20,000 participants has almost been reached.

Screening is not merely a radiological technique, but instead a complex process of identification and selection of the target population, call and recall of participants, work-up and evaluation of positive screenees and adequate communication of the test results to the participants and all involved health care professionals. The recruitment procedure, the selection criteria and the power calculation used in the NELSON trial have been described elsewhere [4]. This paper deals with the screening algorithm and the classification and management of screen-detected nodules at baseline and incidence screening.

The management of persons with pulmonary nodules detected in a screening context differs markedly from usual clinical practice. Screening deals with asymptomatic 'healthy' individuals, approached by a letter of invitation and health care professionals participating in a screening programme carry thus extra responsibility for the information and safety of the individuals included in such a programme. Therefore, in this paper, also attention will be paid to quality assurance aspects and the role of the NELSON management system (NMS) in it. Given the fact that more and more advanced multi-detector CT scanner with smaller collimations are being used, also outside screening programmes, clinicians are more and more faced with the problem of small non-calcified pulmonary nodules. Prevalence rates up to 50% have been reported [5]. New software tools to assess volumes and volume doubling times become rapidly and widely available. Therefore, this management protocol could also be useful for the non-screening setting and provide new tools on how to deal with pulmonary nodules by using volumetric software.

2. NELSON management system (NMS)

To conduct this logistically complex multi-center study, the NELSON management system (NMS) has been developed. It is a web-based interactive database application used for data collection and management of all study related processes such as the selection and randomisation of participants, electronic storage of questionnaires and informed consent forms, completely trackable data collection, study monitoring, reporting of scan results and scheduling of appointments for follow-up scans. Because the system works with action dates, it provides us with a complete overview and control of the planned actions, such as the planning of follow-up scans, sending of invitations to participants, test results and work-up and evaluation of suspicious nodules.

3. Screens

The participants randomised to the screen arm were invited by an invitation letter to one of the four screening sites (University Hospital Groningen, University Hospital Utrecht and Kennemer Gasthuis Haarlem in the Netherlands, and University Hospital Gasthuisberg Leuven in Belgium. The CT scans used were all 16 detector MSCT scanners (M×8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH, USA, or Sensation-16, Siemens Medical Solutions, Forchheim, Germany). All scans were realised in about 12 s in spiral mode with 16 mm × 0.75 mm collimation and 15 mm table feed per rotation (pitch = 1.5), in a cranial—caudal scan direction, without contrast in low-dose setting. Depending on the body weight (<50, 50—80 and >80 kg) the kVp settings were 80—90, 120 and 140 kVp, respectively and to achieve a CTDI-vol of 0.8, 1.6 and 3.2 mGy, respectively, the mAs settings were adjusted accordingly dependent on the machine used. To minimise breathing artefacts, scans were performed in inspiration after appropriate instruction of the participants.

4. Image reading

Images were read on Siemens workstations using the Syngo Lungcare software package (Version Somaris/5 VB 10A-W)

for multi-dimensional image processing and computer viewing. Lung windows were assessed at a width of 1500 and a level of −650 Hounsfield Units. After a first reading, the data were stored locally on the PACS system, and sent overnight via a protected Internet connection to Groningen for second reading and central storage in the radiological database. The second readers were unaware of the conclusion of the first reader and read the images within 3 weeks after the first reading. In case of a discrepancy, a third reader (M.P. and M.O.) made the final decision. One of the second readers was trained for 3 weeks in lung cancer screening at the Department of Radiology Weill Medical College, Cornell University New York (Prof. C. Henschke), the others trained themselves by means of the ELCAP teaching file.

A nodule was defined as a small approximately spherical, non-linear circumscribed focus of abnormal tissue [6]. A non-calcified nodule (NCN) was classified as non-calcified if it did not show a benign pattern of calcification [6]. For all NCNs found at baseline and annual repeat scan the maximum dimensions in x, y and z direction, minimum, maximum and mean diameter, size, volume, density, location (central versus peripheral, lung segment, slice number) were recorded, as well as the surface characteristics (smooth, spiculated or other).

During CT evaluation, for each evaluable nodule, the surface characteristics, distance to the pleura and the aspect of the nodule (i.e. solid, partial-solid or non-solid) was entered by the radiologist in an electronic data collection form customized for the Lungcare Siemens workstation. Nodules were classified as peripheral if the distance to the thoracic wall was less than one third of the total distance to the lung hilum. Together with the calculated sizes and volumes generated by the Siemens software, these data were automatically uploaded in NMS immediately after completion of the reading for an unlimited number of evaluated nodules per scan. In case of consecutive CT scans, nodules were matched with the same nodules documented on previous scans in order to determine changes in volume and to estimate the volume doubling time (VDT). This could be done either automatically — a matching algorithm in NMS resulted in the most probable match of nodules based on the combination of consistency, size and location — or manually, or both automatically and manually. Based on the matching of nodules, NMS detected whether a nodule was new or already existing, and automatic determination of the nodule category (1—4) and/or growth category (A, B or C) was reported (Tables 1 and 3). After the second reading of the CT-scan and after reaching consensus about the screen result and the planned actions to be taken, the NMS generated the appropriate standard letter in order to inform both the participant and the general practitioner within 3 weeks after the CT scan. Discrepancies were identified when there was no auto-matching achieved or when the second reader disagreed on nodule number, location or volume.

For solid nodules and for the solid component of partial-solid nodules, volume was calculated by three-dimensional (3-D) volumetric computer assessment. In case of inappropriate segmentation, the radiologist was able to enter manual measurements as well, which then overruled the automatically generated volume calculations. For solid pleural-based nodules, the diameter perpendicular to the costal pleura was taken because the volumetric software used was not accurate enough for pleural-based lesions, due to inappropriate segmentation. Also for non-solid lesions, size had to be determined based on two-dimensional (2-D) manual measurements, and was defined as the average of length and width (d_{mean}). Length was measured in the X/Y-axis on a single CT image that showed the maximum length. Width was defined as the longest diameter perpendicular to length on the same CT image. For partial-solid lesions, both the volume (solid part) and d_{mean} (overall size of the nodule) were recorded. Throughout the study, the definition of growth was kept constant, and was defined as a percent volume change (PVC) of 25% or more after at least a 3 months interval according to the following formula:

$$PVC(\%) = 100 \times \frac{(V_2 - V_2)}{V_2} \qquad (1)$$

Also for NCNs in which only 2-D size parameters (d_{min} or d_{mean}) were available, volume and PVC could be estimated based on formula (3) (see below).

5. Baseline screen protocol

NCNs were classified in four nodule categories (NODCAT) based on size, either 3-D (solid and partial solid lesions) or 2-D (solid pleural lesions and non-solid lesions) or based on growth (GROWCAT) according to formula (1) (Table 1). NODCAT 1 was defined as benign, NODCAT 2 as non-significantly small, NODCAT 3 as indeterminate and NODCAT 4 as potentially malignant. Based on the highest nodule category found, participants with NODCATs 1 and 2 received a negative test result, and were invited for an annual repeat scan (first incidence screen) 1 year later because the likelihood of malignancy in a NODCAT 2 nodule at baseline is less than 1% (Table 2) [7]. NODCAT 3 was defined as an indeterminate test result which required a repeat scan 3—4 months later to assess growth. If there was no significant growth on the repeat scan, the test result was called negative and participants were scheduled for an annual repeat CT scan 8—9 months later. If there was significant growth, the test result was positive (GROWCAT C), which means that a histologi-

Table 1 NELSON classification of the different non-calcified nodules according to size at baseline screening

NODCAT baseline	Definition
I	Benign nodule (fat/benign calcifications) or other benign characteristics
II	Any nodule, smaller than NODCAT III and no characteristics of NODCAT I
III	Solid: 50—500 mm^3 Solid, pleural based: 5—10 mm d_{min} Partial solid, non-solid component: $\geq$8 mm d_{mean} Partial solid, solid component: 50—500 mm^3 Non-solid: $\geq$8 mm d_{mean}
IV	Solid: >500 mm^3 Solid, pleural based: >10 mm d_{min} Partial solid, solid component: >500 mm^3

Table 2 NELSON management protocol for non-calcified nodules at baseline screening

Nodule type	NODCAT I	NODCAT II	NODCAT III	NODCAT IV	GROWCAT C
Solid	Negative test Annual CT	Negative test Annual CT	Indeterminate test 3 month follow-up CT	Positive test Refer to pulmonologist for work-up and diagnosis	Positive test Histological diagnosis required
Partial solid	Negative test Annual CT	Negative test Annual CT	Indeterminate test 3 month follow-up CT	Positive test Refer to pulmonologist for work-up and diagnosis	Positive test Histological diagnosis required
Solid-pleural based	Negative test Annual CT	Negative test Annual CT	Indeterminate test 3 month follow-up CT	Positive test Refer to pulmonologist for work-up and diagnosis	Positive test Histological diagnosis required
Non-solid	Negative test Annual CT	Negative test Annual CT	Indeterminate test 3 month follow-up CT	Non-existing category	Positive test Histological diagnosis required

cal diagnosis had to be obtained (Table 2). Also NODCAT 4 was a positive test result which required referral to a pulmonologist for work-up and diagnosis. In case of NODCAT 4 and GROWCAT C, the general practitioner was first of all informed by the radiologist of the screening site by phone about the test results and its consequences, followed by a letter to the participant and the general practitioner.

6. Incidence screen protocol

At annual repeat screening (incidence screening), there are two possibilities: either an NCN is existing, and comparison with baseline screening is possible, or the NCN is new. For the new nodules, the same classification according to size was made as for the baseline screening round. Follow-up was different, however, because at incidence screen new nodules are supposed to have a relatively higher growth rate (Table 4).

For all existing nodules, except for NODCAT 1, always a comparison with the baseline screening round was made. If in solid nodules or solid components of partial solid nodules the PVC was 25% or more (Table 3), the volume doubling time based on changes in calculated volumes over time (VDT_v) was determined according the formula (2) [8]:

$$VDT_v(days) = \frac{[\ln 2 \times \Delta t]}{[\ln(V_2/V_1)]} \quad (2)$$

In situations in which a reliable volume estimate could not be made due to software limitations and/or manual measurement was preferred in either one of the two evaluations, changes in volumes based on changes in estimated diameter over time (VDT_d) was determined according the formula (3):

$$VDT_d(days) = \frac{[\ln 2 \times \Delta t]}{[3 \ln(MaxDiamXY2/MaxDiamXY1]} \quad (3)$$

where MaxDiamXY1 and MaxDiamXY2 are maximum diameters in X/Y-axis at first and second evaluation.

However, if *both* scans had to be evaluated by manual measurements, such as for pleural-based solid nodules or non-solid nodules, the following formula for growth deter-

mination was applicable:

$$VDT_d = \frac{[\ln 2 \times \Delta t]}{[\ln((MaxDiamXY2 \times PerpDiamXY2 \times MaxDiamZ2)/(MaxDiamXY1 \times PerpDiamXY1 \times MaxDiamZ1)]} \quad (4)$$

where MaxDiamXY is the maximum diameter in X/Y-axis, PerpdiamXY the maximum diameter perpendicular to MaxDiamXY and MaxDiamZ is the maximum diameter in Z-axis. If MaxDiamZ was missing, then MaxDiamZ equalled $0.7 \times |$caudal slicenumber $-$ cranial slicenumber$|$.

According to the VDT, growing NCNs were classified in three growth categories; GROWCAT A with a VDT > 600 days, GROWCAT B with a VDT between 400−600 days and GROWCAT C with a VDT < 400 days. Non-solid nodules in which a new solid component appeared were also classified GROWCAT C (Table 3).

During incidence screening, the test result (negative, indeterminate, positive) was based on the highest GROWCAT or the highest NODCAT in case of a new nodule. Subjects with no growth or GROWCAT A received a negative test result, and they were re-scheduled for a CT scan in year 4. For subjects with GROWCAT B or a new NODCAT 2, the test result was indeterminate and a repeat scan was made 1 year later (year 3) (Table 4). A new NODCAT 3 was also an indeterminate test result which, however, required a repeat scan 6−8 weeks later. Participants with GROWCAT C or a new NODCAT 4 had a positive test result and were referred to a chest physician for work-up and diagnostic assessment.

7. Management of NODCAT 4 and GROWCAT C nodules

Before describing the work-up and staging procedures for the different nodule categories, it is important to realise that especially in a screening setting unnecessary surgery for benign nodules should be avoided as much as possible. This imposes special problems for the diagnostic strategy. In general, non-invasive diagnostic procedures should be applied before invasive ones if possible, so that the latter can be reserved for lesions with a high probability of

Table 3 NELSON follow-up protocol for non-calcified nodules at annual repeat screening

	Year 1	Year 2	Year 3	Year 4
Volume	V_1	V_2	V_3	V_4
Percentage volume change: PVC (%) (solid nodules only)		$100 \times (V_2 - V_1)/V_2$	$100 \times (V_3 - V_1)/V_1$	$100 \times (V_4 - V_1)/V_1$
Growth		PVC <25%: no; PVC ≥25%: yes	PVC <25%: no; PVC ≥25%: yes	PVC <25%: no; PVC ≥25%: yes
If growth: determined volume doubling time (VDT)				
Volume (solid): VDT_v (days)		$VDT_v = [\ln 2 \times \Delta t]/[\ln (V_2/V_1)]$	$VDT_v = [\ln 2 \times \Delta t]/[\ln (V_3/V_1)]$	$VDT_v = [\ln 2 \times \Delta t]/[\ln (V_4/V_1)]$
Diameter (part solid, non solid, pleural based, manual measurements): VDT_d (days)		$VDT_d = [\ln 2 \times \Delta t]/[3 \ln (D_2/D_1)]$	$VDT_d = [\ln 2 \times \Delta t]/[3 \ln (D_3/D_1)]$	$VDT_d = [\ln 2 \times \Delta t]/[3 \ln (D_4/D_1)]$
Select lowest VDT (either VDT_v or VDT_d)				
VDT >600 days: GROWCAT A		Annual CT year 4	Annual CT year 4	Stop
VDT 400–600 days: GROWCAT B		Annual CT year 3	Annual CT year 4	Stop
VDT <400 days or new solid component in non-solid lesion: GROWCAT C		Refer to pulmonologist	Refer to pulmonologist	Refer to pulmonologist

malignancy and resources can be used most economically. Another problem is that the national CBO guideline for non-small cell lung cancer only deals with nodules larger than 1 cm, because sub-centimeter lung cancer lesions have been almost non-existing so far. Even though our standard work-up protocol and the national CBO guideline are available and approved by all participating centers [9], all clinical management decisions were taken at an individual level at regular (weekly) multi-disciplinary oncology meetings at the four screening sites. In some rare cases, the team decided to deviate from the management protocol described below in particular circumstances, but this was always after consensus of the whole team was obtained.

8. Baseline: NODCAT 4

If the highest category was a NODCAT 4, the participant was referred to the chest physician of choice via the general practitioner, usually the chest physician associated with the screening center. Primary objective was to confirm the presence of malignancy by performing routine physical examinations, routine laboratory tests and a bronchoscopy (bronchial washing for cytology and culture, and transbronchial biopsy or brushing on indication). A percutaneous CT-guided fine needle aspirate (FNA) to obtain histology or cytology of the lesion is not a routine procedure in the Netherlands and Belgium, and if the FNA technique is used, it is only for larger peripheral nodules with good access. The FNA result can be malignant, specific benign or non-specific benign. Specific benign diagnosis include tuberculosis, mycoses, nocardia, hamartoma or a benign lymph node. If malignancy was proven, the patient was further staged (see below), followed by surgical resection. A definitively specified benign diagnosis required treatment or just observation, but if no diagnosis or a non-specific benign diagnosis was obtained, the follow-up strategy was based on the assessment of nodule growth similar as to NODCAT 3, i.e. a repeat scan after 3—4 months. If at that time there was no growth, the test result was negative and participants were scheduled for an annual repeat CT scan 8—9 months later. If there was growth, the test results was positive (GROW-CAT C), which meant that a definitive histological diagnosis had to be obtained. Actually, this work-up was according to our national CBO guidelines for the diagnosis and treatment of non-small cell lung cancer [9], with the exception that a FDG-positron emission tomography (PET) scan was not routinely included in the work-up of a NODCAT 4, primarily because our NELSON trial is a CT screening trial, in which the presence or absence of growth of the nodule is leading, and not the outcome of the PET scan. Furthermore, the pre-test probability of malignancy in this population of current and former smokers is very high, and a substantial proportion of the PET scans is false negative because of bronchiolo-alveolar cell carcinomas (BAC) or adenocarcinomas with BAC features, limiting the diagnostic value of the PET in the context of this CT screening trial [10—12].

9. Baseline or incidfence: GROWCAT C

The work-up for participants with growing lesions (GROW-CAT C) was essentially the same as for NODCAT 4, except

Table 4 NELSON management protocol for non-calcified nodules at incidence screening

Nodule type	NODCAT I	NODCAT II	NODCAT III	NODCAT IV	GROWCAT C
Solid	Negative test CT in year 4	Indeterminate test CT in year 3	Indeterminate test CT after 6—8 weeks	Positive test Refer to pulmonologist for work-up and diagnosis	Positive test Histological diagnosis required
Partial solid	Negative test CT in year 4	Indeterminate test CT in year 3	Indeterminate test CT after 6—8 weeks	Positive test Refer to pulmonologist for work-up and diagnosis	Positive test Histological diagnosis required
Solid-pleural based	Negative test CT in year 4	Indeterminate test CT in year 3	Indeterminate test CT after 6—8 weeks	Positive test Refer to pulmonologist for work-up and diagnosis	Positive test Histological diagnosis required
Non-solid	Negative test CT in year 4	Indeterminate test CT in year 3	Indeterminate test CT after 6—8 weeks	Non-existing category	Positive test Histological diagnosis required

that for these nodules a final histological diagnosis had to be obtained either by FNA, video-assisted thoracoscopic surgery (VATS), or wedge resection and examination on frozen section, and that further observation by follow-up CT scans was no longer allowed. If malignant, the nodule had to be surgically removed after appropriate staging. If the outcome of the investigation(s) was that the lesion was benign, the participant was re-scheduled for the next regular annual CT scan.

10. Staging

Staging included a standard CT with intravenous contrast of the chest and upper abdomen including the liver and adrenal glands. A bone scintigraphy and MRI brain were only made on clinical indication. If the nodule was a NODCAT 4 or GROWCAT C larger than 500 mm^3, a mediastinoscopy was only performed if the PET scan showed positive mediastinal lymph nodes, if there were enlarged lymph nodes on CT (short axis > 1 cm), and in the presence of a peripheral adenocarcinoma or a centrally located tumor. For nodules between 50—500 mm^3, the role of routine FDG-PET and mediastinoscopy is not yet established and were therefore not routinely recommended.

11. Surgical resection

The treatment of small malignant lesions (T1) found at screening is according to standard practice [9], i.e. if possible at least a lobectomy should be performed due to a high frequency of local recurrence after more limited resections. Only in patients with poor pulmonary function who are judged by the surgeon not to tolerate a lobectomy, a segmentectomy or wedge resection could be performed. This may in some cases be performed as a minimal invasive VATS procedure. Because the small ground glass lesions have turned out to have an excellent prognosis (Noguchi A and B) for these lesions a more limited resection is allowed [13]. During surgery staging of the tumor by systematic lymph node dissection is mandatory. In medically inoperable patients, curative stereotactic 4D radiotherapy is allowed.

12. Quality assurance

In order to promote the expertise of the investigators and to ensure the lung cancer screening trial's compliance with the quality demands of the National Health Council, several measures were taken. All radiological images are interpreted as well locally as centrally in Groningen for second reading, with the intention to promote the quality and to optimise the sensitivity of the screening. To this end, two full-time dedicated radiologists were appointed in Groningen, and a third one joined later. Annual site visits, central quarterly monitoring meetings and an annual investigators' meeting were organised. Taking into account the quality requirements with which the NELSON project must comply, these site visits and monitoring meetings led to specific adjustments in the approach and the formulation of specific areas of attention. Finally, a national panel for pathology review was established, constituted by relevant pathologists at the different screening sites and an international pathology review panel formed by seven pathologists from the United States and Europe (Dr. Flieder (USA), Prof. Franklin (USA), Prof. Westra (USA), Prof. Brambilla (FR), Dr. Thunnissen (NL), Dr. Kerr and Dr. Guldhammer (DK)).

13. Discussion

With the advent of high resolution CT screening, physicians are faced now with the very early stages of lung cancer among large numbers of insignificant, benign nodules. What the optimal management protocol is to discriminate between malignant and benign lesions is yet unknown. Several differences exist between the various nodule management protocols used world-wide and also the definitions used vary or are undefined, as for example, what should be regarded as an indeterminate nodule and what the definition of growth is. Both retrospective evaluation and future harmonisation of the ongoing nodule management protocols is needed, and will be of great importance for the further evolution and the clinical implementation of MDCT screening for lung cancer.

Our nodule management protocol is primarily based on the Early Lung Cancer Action Project (ELCAP) protocol [14—16], but there are several differences. First of all, the nodules detected at baseline and the new nodules detected at incidence screening are classified and managed according to volume. At (annual) repeat CT scanning, the first assessement is whether there is growth or not, and if so, they are subsequently classified in three growth categories based on VDT. As such, NELSON is the first large lung cancer screening trial in which automated, volumetric nodule assessment is routinely applied and forms part of the nodule management protocol. Hopefully, this will provide an answer to the question what the predictive value of VDT is for the likelihood of malignancy in the pre-operative evaluation of screen-detected lung nodules with the current available software. New software versions for automated nodule detection and improved nodules segmentation and volume assessment will soon be released, so that the volume of non-solid nodules can also be estimated. At least in the Netherlands, FNA of a small pulmonary nodule <10 mm is not part of the routine practice and not only requires a skilled interventional radiologist, but, ideally, also a cyto-pathologist on site. Reliance on VDT alone might therefore be an attractive option, but although 90% of all solid and part-solid nodules have a VDT of less than 400 days, several open questions remain. Growth may not always be linear, but instead be sigmoid-shaped. Although data are scarce, lung cancer, and especially lung adenocarcinoma precursor lesions, may suddenly change towards a rapid growth phase with invasive characteristics [17]. On the other hand, also benign lesions may demonstrate growth. These factors may potentially limit the value of using VDT in stratifying nodules in potentially benign or malignant.

Another major difference compared to other lung cancer screening protocols [18—20] is that we tried to limit the number of additional radiological investigations in between the planned annual CT scans to only a repeat scan after 3—4 months or 6—8 weeks for indeterminate nodules at baseline or incidence screening, respectively, not only to reduce the work load, costs and radiation exposure, but also to enable us to conclude that a reduction in lung cancer mortality is due to annual CT screening and not the result of a combined effect of annual screening and numerous repeat scans. A 3—4 months interval seems at least long enough for nodules of infectious origin to resolve. Therefore also, we decided not to prescribe broad-spectrum antibiotics routinely for inde-terminate nodules. A screening protocol is of course never ''once and forever'' and certain changes might be needed after evaluation of final trial results, but the NELSON board decided to keep the protocol unchanged for the duration of the trial in order to be able to evaluate the results retro-spectively.

In conclusion, taking into account the ongoing technological evolution, the widespread introduction of multi-slice CT scanners capable of producing extremely thin slices and the application of volumetric analysis systems, the specific management recommendations for screen-detected lung nodules are likely to change. The NELSON nodule management protocol presented is the first lung cancer screening protocol based on volumetry and designed for a large scale population-based screening programme without the standard use of FNA.

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