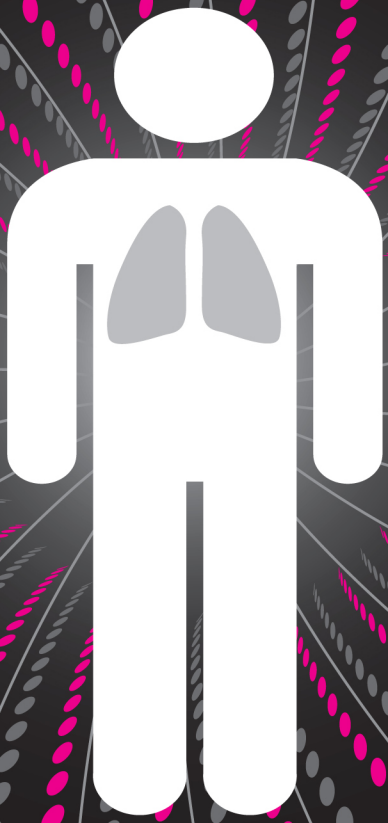
LUNG CANCER SCREENING

clinical implications



SUSAN VAN 'T WESTEINDE

Lung Cancer Screening

Clinical Implications

Susan van ‘t Westeinde

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Lung Cancer Screening and Clinical Implications

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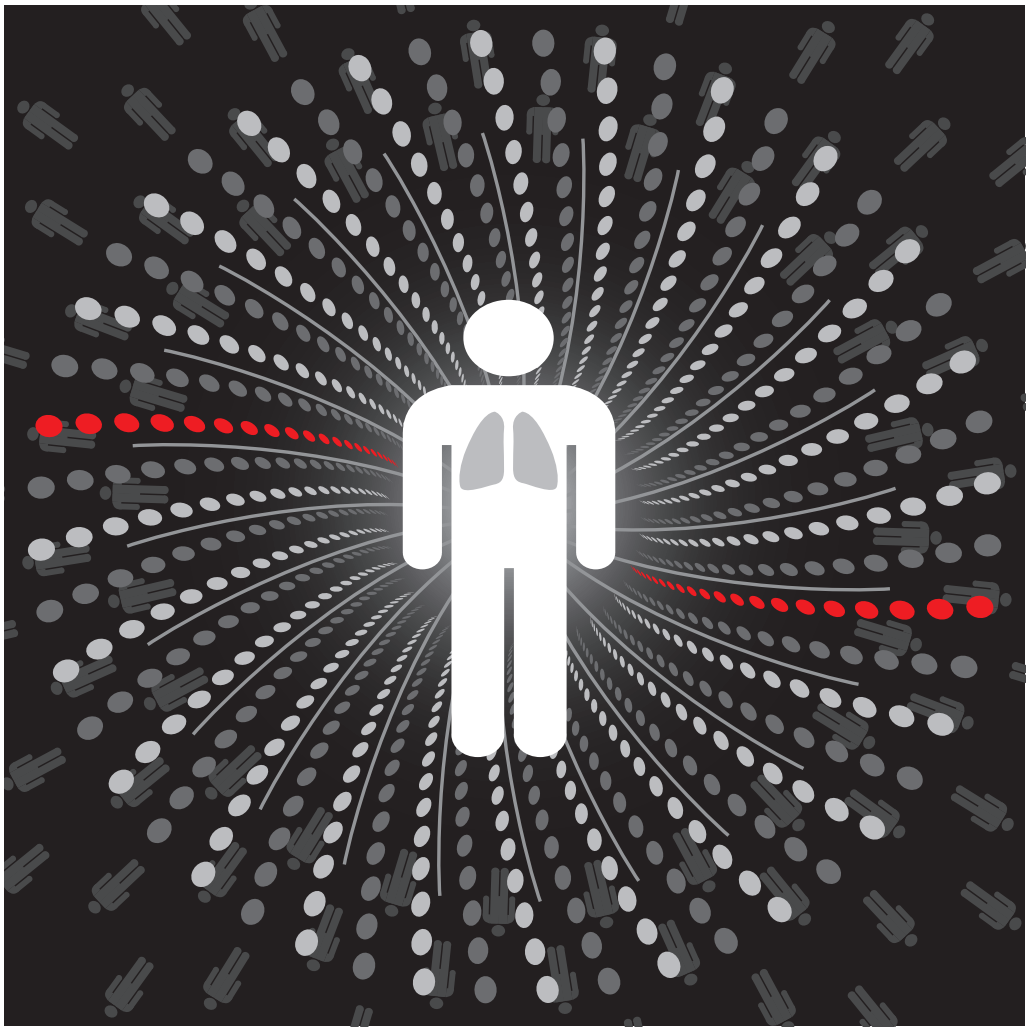


General introduction

Lung cancer

Lung cancer is the most frequently diagnosed major cancer worldwide and the leading cause of death from cancer.[1] Lung cancer is divided into two subgroups: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), accounting for 10-20% and 75% of lung cancer cases, respectively.[2, 3] The most common NSCLC histological subtypes are: adenocarcinoma (~35%), squamous cell carcinoma (~30%) and, large cell carcinoma (~10%). The separation in subgroups is essential with regard to treatment and prognosis. The majority of NSCLC patients only present with symptoms when the tumor reaches an advanced stage. The signs and symptoms in patients with lung cancer depend on the histology of the tumor, the extent of locoregional invasion as well as the location, size, and number of distant metastases. A minority of patients, about 15% present with an asymptomatic localized lesion discovered incidentally on chest radiography or CT scan.[4] For localized NSCLC the 5-year survival rate is 70-85%, whereas for metastasized disease the 5-year survival rate is about 10%.[5, 6]

Epidemiology

In the 19th century lung cancer was an extremely rare disease. In 1878, malignant lung tumors represented only 1% of all cancers seen at autopsy in the Institute of Pathology of the University of Dresden in Germany.[7] By 1918, the percentage had risen to almost 10% and by 1927 to more than 14%.[7] During the 19th century much tobacco was smoked in pipes or cigars and little was smoked as cigarettes, while during the first two decades of the 20th century the consumption of manufactured cigarettes increased greatly.[8] Throughout the first half of the 20th century the hazards of smoking had remained largely unsuspected.[8] Several case control studies on lung cancer and smoking were published in Western Europe.[9-11] In the early fifties the detrimental health effects of smoking were published.[12]

Pathology

Throughout the 1960s, the predominant type of non-small-cell carcinoma was squamous cell carcinoma. Although the overall incidence of lung cancer has dramatically increased during the past 30 years, the relative incidence of squamous cell carcinoma has decreased, and adenocarcinoma has become the dominant type, a phenomenon that has been associated with the changes in tobacco blends and the use of filters in cigarettes.[13] Furthermore, the incidence of small cell lung cancer is decreasing.[2] Small cell lung cancer was historically divided in limited disease and extensive disease stages, aimed at identifying patients in whom surgical resection may be beneficial. Limited disease was defined as restricted to one hemi thorax with regional lymph node metastases. Within the 7th edition of the TNM classification of lung tumors, the distinction between localized and extensive disease is no longer made and it is recommended to use the TNM classification for all SCLC cases.[14]

Solitary pulmonary nodules

Solitary pulmonary nodules (SPN) are are defined as being <30 mm in size, usually >10 mm, completely surrounded by pulmonary parenchyma and not associated with

lymphadenopathy, atelectasis, or pneumonia.[15] The prevalence of pulmonary nodules range between 17 and 51% in various CT-screening programs[16-19] and, malignancy rates between 1 and 18% have been reported.[17, 20, 21] In pulmonary nodules with a benign calcification pattern, the risk of cancer is neglectable (Figure 1).

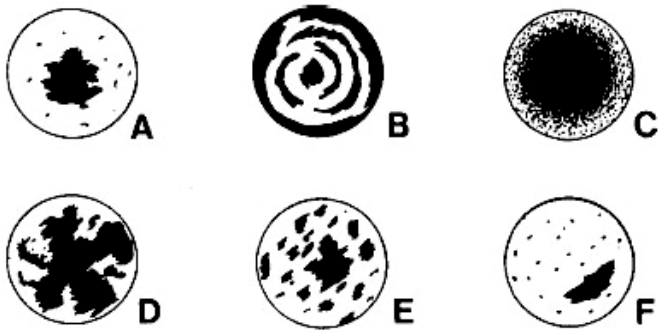


Figure 1. *Patterns of calcification in solitary pulmonary nodules. A, central; B, laminated; C, diffuse; D, popcorn; E, stippled, and F, eccentric. Patterns A through D are virtually always indicative of benignity. Patterns E and F may occur in benign or malignant nodules.*

The risk of lung cancer depends on nodule characteristics such as size, nodule growth as established by volume doubling time (VDT) and, nodule border characteristics. In addition patient characteristics as age, medical history and pack-years are of importance. Based on information obtained from lung cancer screening studies several diagnostic algorithms for pulmonary nodules have been developed. The probability of malignancy in a non-calcified pulmonary nodule can be calculated based on patient related characteristics and nodule parameters (Figure 2).[22, 23]

Probability of malignancy
$= 1/(1 + e^{-X})$

X = -6.8272 + (0.0391 * Age) + (0.7917 * Cigarettes) + (1.3388 * Cancer) + (0.1274 * Diameter) + (1.0407 * Spiculation) + (0.7838 * Upper lobe)

e = the base of natural logarithms
Age = patient age in years
Cigarettes = 1 if the patient is a current or former smoker, otherwise 0
Cancer = 1 if the patient has a history of extrathoracic cancer that had been diagnosed > 5 years ago (otherwise, 0).
Diameter = the diameter of the SPN (mm)
Spiculation = 1 if the edge of the SPN has spicula (otherwise, 0).
Upper lobe = 1 if the SPN is located in an upper lobe (otherwise, 0).

Figure 2. *Probability of malignancy in non-calcified nodules. This equation is not applicable to patients with a diagnosis of cancer that has been made within the previous 5 years or to patients with previous lung cancer.*[23, 24]

SPN with a benign calcification pattern need no further investigation, the same is the case for small nodules (<4 mm) in a low-risk patient (Figure 3). Swensen et al[24] developed a risk-model to calculate the risk of lung cancer, and his risk model was successfully used by others.[25] However, in daily practice it may be difficult to translate an odds ratio into management of a given nodule. Therefore, guidelines with recommendations for follow-up are easier to use in daily practice. In addition, the risk-calculator may not be as useful in areas with endemic granulomatous lung diseases. For small pulmonary nodules measuring <8 mm follow-up with serial high-resolution CT is recommended.[26, 27] For nodules measuring 8-30 mm which are classified as low, intermediate or high probability for harboring lung cancer, serial HR-CT, additional testing (FDG-PET, contrast enhanced CT, biopsy) or, VATS with frozen section is recommended (Figure 4).[27-29]

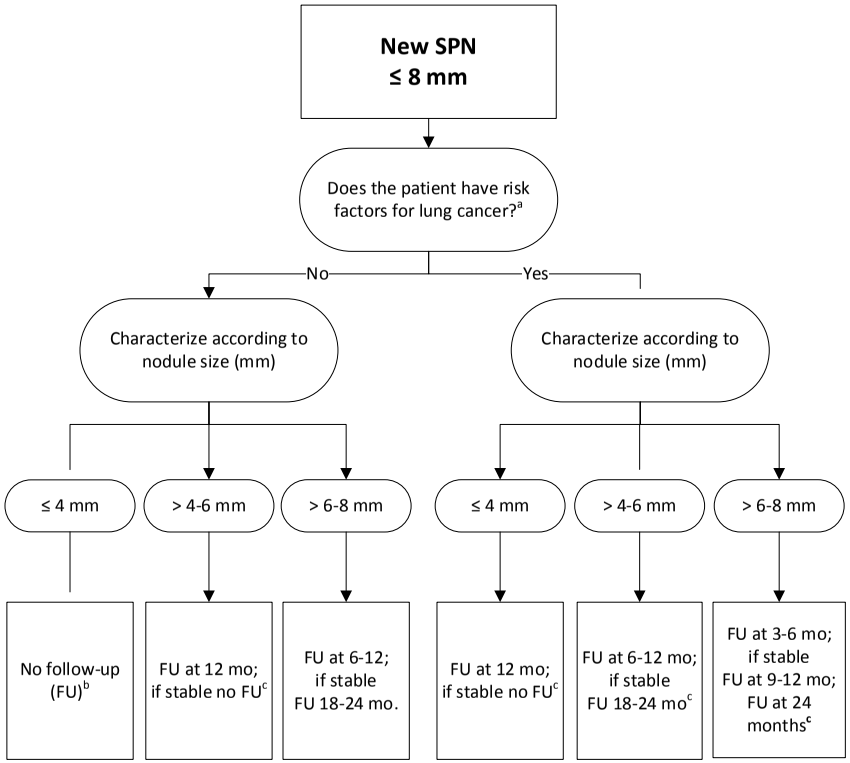


Figure 3. Recommended management algorithm for patients with SPNs that measure ≤8 mm in diameter. Adapted from: Gould *et al.* Chest 2007;132;108S-130S and, McMahon *et al.* Radiology 2005;237(2):395-400. Note: Newly detected indeterminate nodules in persons 35 year of age or older

Clarification of abbreviations and symbols:
FU: follow-up, mo: months
[a] History of smoking and other known risk factors
[B] The risk in this category (< 1 %) is substantially less than that in a baseline CT scan of an an asymptomatic smoker
[C] Nonsolid (ground-glass) or partly solid nodules may require longer follow-up to exclude indolent adenocarcinoma

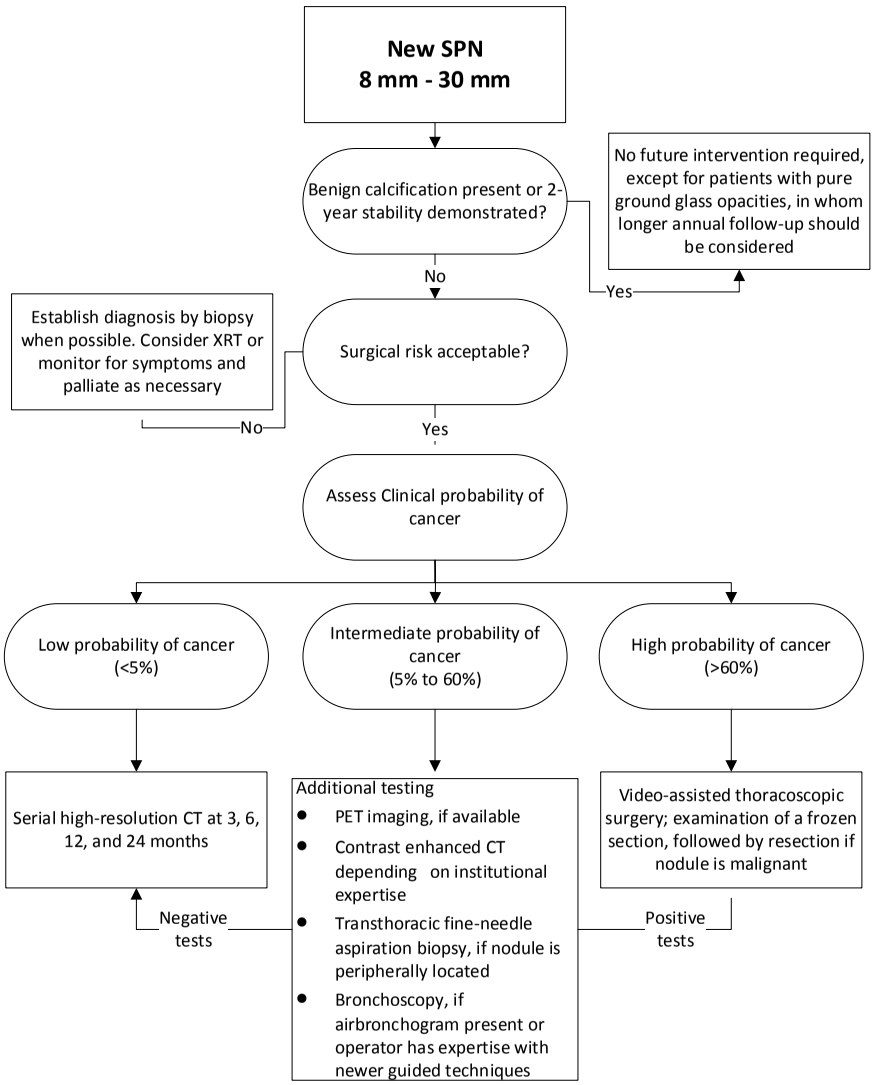


Figure 4. Recommended management algorithm for patients with SPNs that measure 8 to 30 mm in diameter. Adapted from: Gould *et al.* Chest 2007;132;108S-130S and, Ost *et al.* New Engl J Med 2003;348;2535-2542

Lung cancer screening

Primary prevention by promoting abstinence from smoking and preventing people from starting to smoke, is essential. The purpose of lung cancer screening (secondary prevention) is to detect lung cancer in an early stage in which the chance of cure is higher, thus reducing lung cancer mortality. The Dutch Belgian Lung Cancer Screening trial (NELSON) is the second largest randomized lung cancer screening study in the world. The NELSON study is powered to detect a 25% decrease of lung cancer mortality; the final results have to be awaited.[30] Similarly, the mortality results of other randomized lung cancer screening trials are yet to be published. Lung cancer screening studies have shown that lung cancer may be identified in an early stage with detection rates varying between 40-66%.[31, 32] Recently, the largest randomized lung cancer screening trial showed a lung cancer mortality reduction of 20%.[33] It is important to realize that survival rates do not adjust for the effects of lead-time, length-time bias or, overdiagnosis bias. Lead time bias occurs when testing increases the perceived survival time without affecting the course of the disease (Figure 5A). Length time bias occurs because screening is more likely to detect slow-growing cancers, which may give the appearance that screening prolonged life (Figure 5B). This may be due to the hypothesis that screening is more likely to detect slow-growing cancer, which may be less aggressive, giving the appearance that screening prolonged life. Another form of bias is overdiagnosis, which refers to participants diagnosed with lung cancer that would not be lethal even if it remained undiagnosed. With randomized controlled lung cancer screening trials these sources of bias can be overcome.

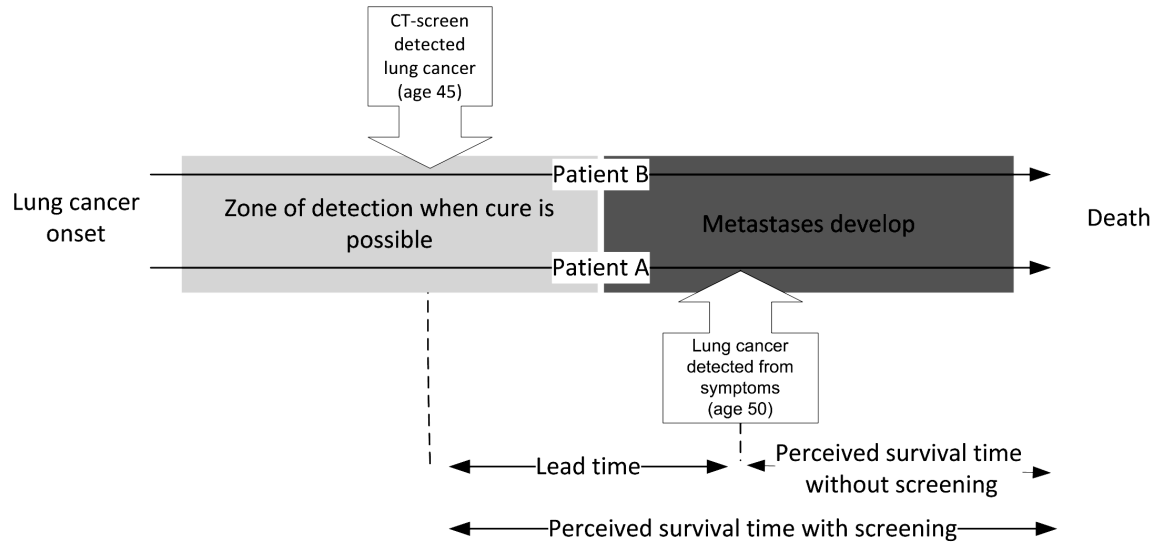


Figure 5A. *Lead time bias occurs when testing increases the perceived survival time without affecting the course of the disease.*

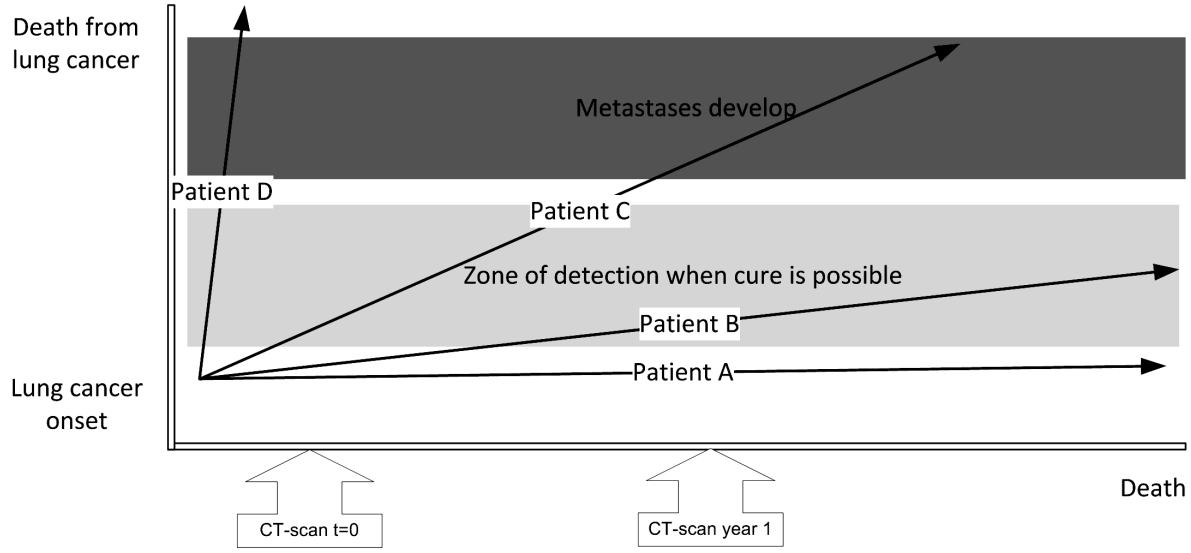


Figure 5B. *Length time bias occurs because screening is more likely to detect slow-growing cancers, which may give the appearance that screening prolonged life.*

The Nelson study

The NELSON study, -the Dutch-Belgian Lung Cancer Screening trial- is a population based randomized lung cancer screening trial, using a novel strategy with semi-automated volumetry software (LungCare®, Siemens Medical Solutions). The NELSON trial started in 2003, its purpose was to investigate whether lung cancer screening leads to a reduction in lung cancer mortality of at least 25%. High risk smokers, subjects aged between 50 and 75 with a smoking history of >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years, were recruited by mail. Subjects with a bad/moderate self-reported health status who were unable to climb two flights of stairs and/or had a body weight over 140 kilograms were excluded. A total of 15,822 people, mainly males, were randomized (1:1) to the screen or control arm. Subjects that received a positive test result were referred to a pulmonologist based on the size and volume doubling time (VDT) of the non-calcified nodule(s) detected. A nodule was classified as non-calcified if it did not meet previously specified criteria for a benign lesion. For solid pleural-based and non-solid pulmonary nodules, the diameter was manually determined and the VDT calculated. For pleural-based nodules, the diameter perpendicular to the costal pleura was taken. For partially solid lesions, only the volume of the solid region was used. The diameter was defined as the average of maximum nodule length and width. Growth was defined as a change in volume between the first and the second scan of $\geq$ 25%. The 25% threshold was based on 3 zero-change datasets in which volume variation of individual nodules was assessed between two low-dose CT scans. In these studies, the volume measurement error varied between 20-25%. Growing nodules were classified into 3 growth categories according to their VDT (<400, 400-600 and >600 days) (Figure 6A). A baseline scan was considered positive if any non-calcified nodule had a solid component > 500 mm^3 (> 9.8 mm in diameter), or indeterminate if the volume of the largest solid nodule or the solid component of a partially solid nodule was 50-500 mm^3 (4.6-9.8 mm in diameter), or > 8 mm in diameter for non-solid nodules (Figure 6A). Subjects with an indeterminate result had a follow-up scan 3 months later to assess growth (Figure 6B). If

at that time the lesion had a VDT < 400 days, the final result was declared positive, otherwise negative. Subjects with positive screening tests were referred to a chest physician for work-up and diagnosis. If lung cancer was diagnosed, the participant was treated for the disease and went off screening; if no lung cancer was found the regular 2nd round CT scan was scheduled 12 months after the baseline scan. For participants with one or more new nodules on the second round scan, the result (positive or negative) was based on size of the nodule as for round one; a follow-up scan for an indeterminate result was performed 6 weeks later. For participants with previously detected nodules, the second round result was based on the VDT. If there was no growth, or if the VDT was > 600 days, the screen was negative. If the VDT was < 400 days or if a new solid component had emerged in a previously non-solid nodule, the scan was considered to be positive. When the VDT was 400-600 days, the test was indeterminate and a follow-up scan was done one year after the second round. With a VDT < 400 days, the final result was considered to be positive, otherwise negative. If both new and existing nodules were present, the nodule with the largest volume or fastest growth determined the test result.

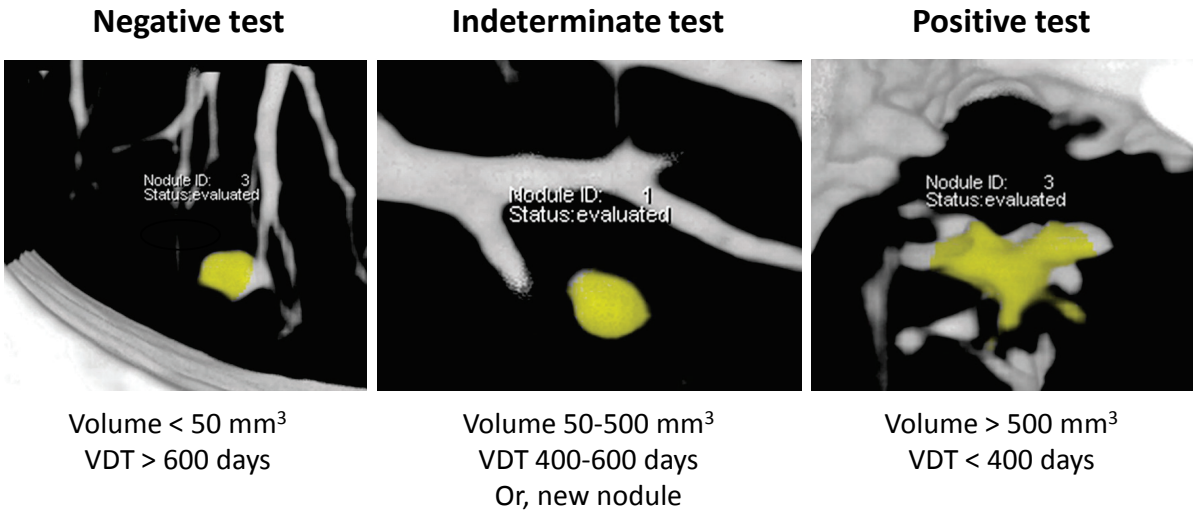


Figure 6A. *The NELSON nodule management system: test result based on volume doubling time (VDT) and nodule volume. The nodule with the largest volume or fastest growth as established by VDT determined the screening result.*

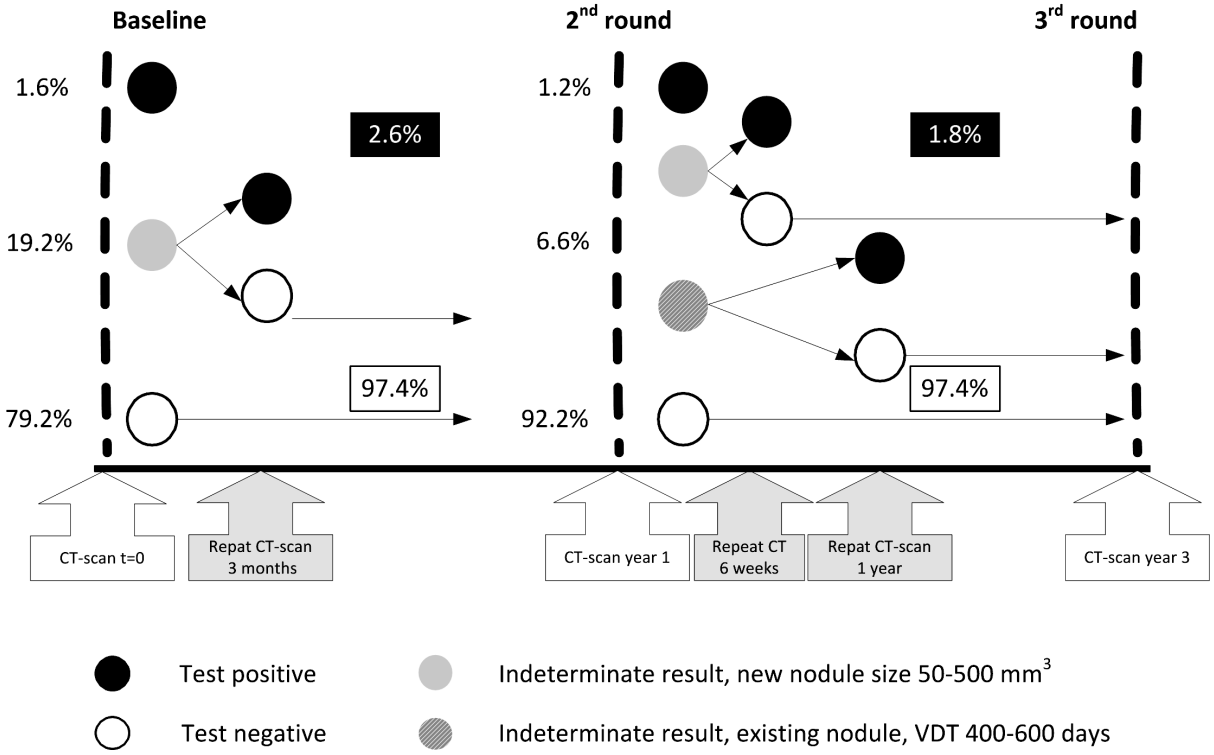


Figure 6B. *The NELSON nodule management system: test result at baseline and 2nd round screening and subsequent management. At baseline 1.6% had a positive test-result and were referred to the pulmonologist for further analysis. In 19.2% the test-result was indeterminate and a repeat scan was made 3 months later, resulting in a total of 2.6% of participants who underwent further analysis by the pulmonologist. Subjects with a negative test-result at baseline (79.2%) underwent screening at 2nd round screening, one year later.*

Staging and diagnosis of suspected lung cancer

Tumor, node and metastases classification (TNM)

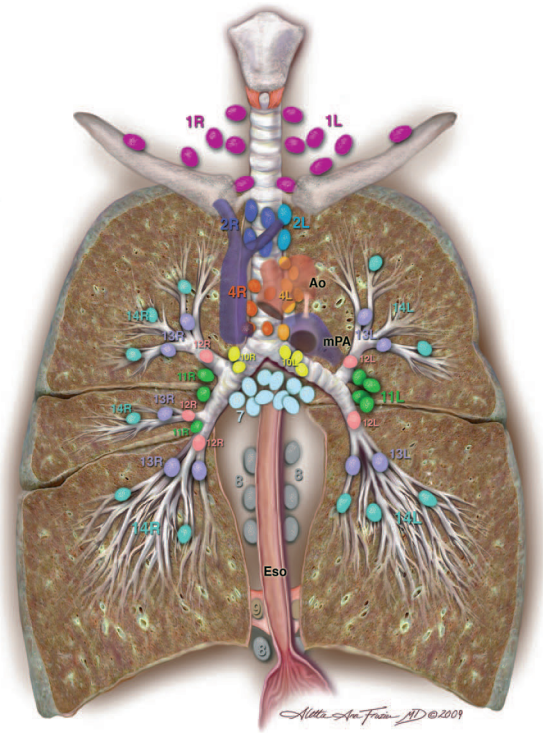
The system for lung cancer staging is based on the 7th revised tumor, node and metastases (TNM) criteria as established by the IASLC (International Associations for the Study of Lung Cancer) (Table 1).[5] The locoregional lymph node map for lung cancer staging is provided in Figure 7. Using the TNM system, four stages of lung cancer have been identified (Table 2) with significant differences in 5-year survival depending on the stage of disease at diagnosis (Table 3). The evaluation of any patient suspected of having lung cancer starts with a detailed history and physical examination. The negative predictive value of the clinical evaluation for brain, abdominal, and bone metastases are ≥ 90%.[34] Once the physical examination has been completed, posteroanterior and lateral chest x-rays as well as CT scans of the chest and upper abdomen should be obtained. In the next section we will describe the different investigations that can be performed for the staging of suspected lung cancer. The clinical TNM stage (cTNM) is based on these studies. When the tumor is resectable and, the patient is medically operable the next step is surgery. Following surgery a definitive TNM stage is made based on the pathological examination of the resection specimen (the pTNM). It is therefore possible that the pTNM stage differs from the cTNM stage.

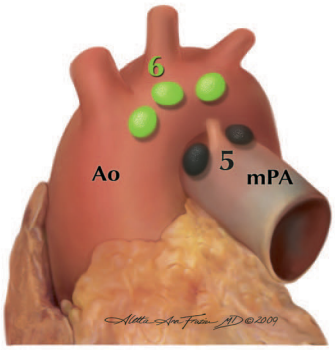
Table 1. *Definitions for T, N, M Descriptor of 7th edition of the TNM classification of lung cancer.*[5]

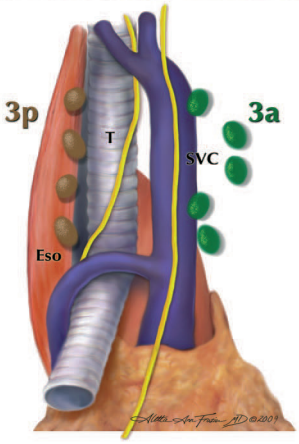
Descriptor	Definitions
T	**Primary tumor**
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No primary tumor
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2 but ≤ 3 cm in greatest dimension
T2	Tumor > 3 but ≤ 7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤ 5 cm) : Involves main bronchus ≤ 2 cm distal to the carina Invades visceral pleura Atelectasis/obstructive pneumonitis extending to the hilar region but not involving the entire lung
T2a	Tumor > 3 but ≤ 5 cm in greatest dimension
T2b	Tumor > 5 but ≤ 7 cm in greatest dimension
T3	Tumor > 7 cm or directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina[a]; or atelectasis/obstructive pneumonitis of entire lung; or separate tumor nodules in the same lobe
T4	Tumor of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; or separate tumor nodules in a different ipsilateral lobe
N	**Regional lymph nodes**
N0	No regional node metastasis
N1	Metastasis in ipsilateral peribronchial and/or perihilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph nodes
M	**Distant metastasis**
M0	No distant metastasis
M1a	Separate tumor nodules in a contralateral lobe; or tumor with pleural nodules or malignant pleural dissemination[b]
M1b	Distant metastasis

[a]The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

[b]Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathological examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is none bloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3 or T4.







Supraclavicular zone
- 1 Low cervical, supraclavicular, and sternal notch nodes

SUPERIOR MEDIASTINAL NODES

Upper zone
- 2R Upper Paratracheal (right)
- 2L Upper Paratracheal (left)
- 3a Prevascular
- 3p Retrotracheal
- 4R Lower Paratracheal (right)
- 4L Lower Paratracheal (left)

AORTIC NODES

AP zone
- 5 Subaortic
- 6 Para-aortic (ascending aorta or phrenic)

INFERIOR MEDIASTINAL NODES

Subcarinal zone
- 7 Subcarinal

Lower zone
- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

N1 NODES

Hilar/Interlobar zone
- 10 Hilar
- 11 Interlobar

Peripheral zone
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

Figure 7. *Locoregional lymph node map for lung cancer staging. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer.*[35]

Table 2. *Stage groups according to TNM descriptor and subgroups.*[36]

T/M	Sub group	N0	N1	N2	N3
T1	T1a	**IA**	**IIA**	**IIIA**	**IIIB**
	T1b	**IA**	**IIA**	**IIIA**	**IIIB**
T2	T2a	**IB**	**IIA**	**IIIA**	**IIIB**
	T2b	**IIA**	**IIB**	**IIIA**	**IIIB**
T3	T3	**IIB**	**IIIA**	**IIIA**	**IIIB**
T4	T4	**IIIA**	**IIIA**	**IIIB**	**IIIB**
M1	M1a	**IV**	**IV**	**IV**	**IV**
	M1b	**IV**	**IV**	**IV**	**IV**

Table 3. *Non-small cell lung cancer and survival according to lung cancer stage.*[5, 6, 37]

Lung cancer stage	Median survival (months)	5-year survival (%)
IA	59	73-85
IB	48	58-75
IIA	30	46-62
IIB	24	36-52
IIIA	14	24-32
IIIB	9	9-15
IV	4	13

CT-chest and CXR

Routine chest-X-ray (CXR) will generally reveal large peripheral lung cancers or central obstructing lesions, a normal chest x-ray does not exclude a primary lung cancer. In fact, conventional chest radiographs fail to detect nearly 80% of the histologically proven CT-detected lung cancers of 2.0 cm or more in diameter.[38] A computer aided detection (CAD) system detected lung cancer with a median size of 11.8 mm with a sensitivity of 61% on CXR; radiologists detected lung cancer with a sensivity of 63%, a figure that was not significant altered by the use of CAD.[39]

CT allows the detection of more and smaller nodules than CXR, however, it is known that very small lung cancers, or central lung cancers may be missed on CT.[40, 41] All subjects with known or suspected lung cancer should undergo a CT with intravenous contrast of the chest and upper abdomen, unless the performance status is too poor and no treatment is planned, or if the patient is unwilling to undergo further evaluation. The pooled diagnostic value of CT scanning for the detection of mediastinal metastasis proved to be limited and showed a sensitivity of 51% and, specificity of 85%.[42] CT-scanning of the chest however is useful to determine anatomical detail and guide further management. Positive CT findings need pathological or radiological confirmation. A limitation of CT-scanning is the reduced diagnostic value for detection of endobronchial lesions, with a sensitivity and specificity of 60 and 80%-90%, respectively.[43, 44] Often CT is inaccurate in defining the type of abnormality seen at bronchoscopy (localized mucosal abnormality, endobronchial mass, or extrinsic compression).[43]

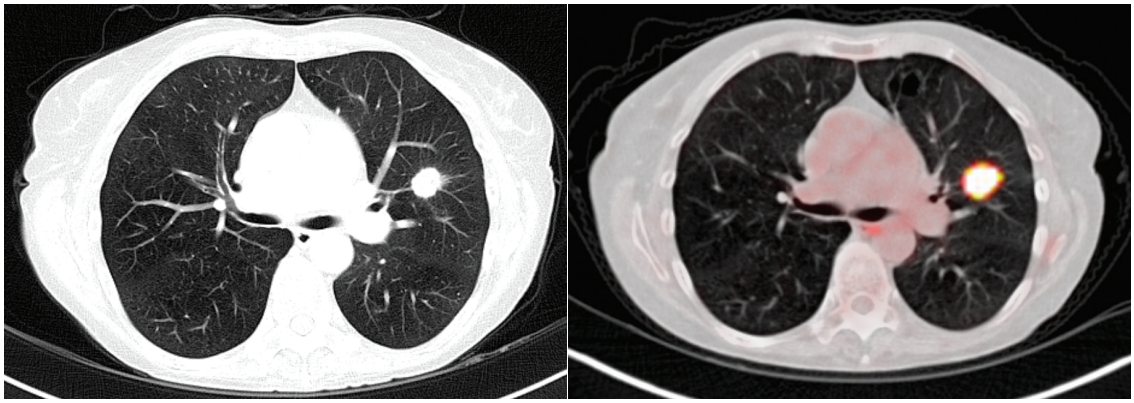


Figure 8. *CT-scan of the chest showing a nodule of the left upper lobe with spiculation 17 x 16 mm (left panel). The correlated PET image shows profound FDG-uptake by the left upper lobe lesion (right panel). The subject was diagnosed with a cT1aN0M0 non-small cell lung cancer.*

FDG-PET scan

A 18-fluorodeoxyglucose positron emission tomography scan (FDG-PET-scan) is a functional noninvasive imaging test that is widely used in clinical oncology for tumor diagnosis, disease staging, and evaluation of tumor response. Increased uptake is seen in cells with high metabolic rates, such as tumors and areas of inflammation (Figure 8). FDG-PET scanning should be performed in all subjects with clinical 1A-IIIB lung cancer for mediastinal and extrathoracic staging.[42, 45] For non-invasive staging of the mediastinum, FDG-PET showed a pooled estimated sensitivity and specificity of 74% and, 85%, respectively.[42] Positive PET-scan findings need pathologic or radiologic confirmation.

Magnetic Resonance Imaging (MRI) of the brain

CT and MRI are computer-based imaging modalities. Unlike CT scans, MRI does not use ionizing radiation. MRI uses a powerful magnetic field and radio frequency pulses to produce detailed pictures. MRI provides good contrast between different soft tissues of the body, which makes it expecially useful in imaging the brain. Currently, MRI is the most sensitive imaging test of the head. The negative predictive value of negative findings for signs of brain metastasis in clinical evaluation is high.[42] However, in a recent study 8.3% of subjects with NSCLC had asymptomatic brain metastasis and, in a Korean study 2% of subjects with stage I lung cancer were diagnosed with brain metastasis on MRI.[46, 47] Therefore, in neurologically asymptomatic patients with NSCLC silent brain metastasis may be more common than previously thought. Currently, in the abcence of neurological symptoms, an MRI of the brain is recommended in subjects with clinical stage III lung cancer and, can be considered in subjects with clinical stage IB-II and in selected cases with stage IV.[45]

Bronchoscopy

All subjects with clinical stage I-III lung cancer should undergo a bronchoscopy to obtain a diagnosis and, for local staging of both central and peripheral lung lesions.[45] In subjects with central lesions and/or massive infiltration of the mediastinum in addition a bronchoscopy is recommended to confirm the diagnosis.[48] Subjects with stage IV lung cancer should undergo a bronchoscopy provided this is the easiest method to obtain a biopsy.[48] For diagnosing of

pulmonary nodules of at least 8 to 10 mm bronchscopy is of limited value, and should only be performed when an air bronchogram is present or in centers with expertise in newer techniques.[27] The use of more advanced bronchoscopic techniques suchs as electromagnetic-navigated, ultrathin bronchoscopy or peripheral endobronchial ultrasound-guided bronchoscopy might play a role in the near future for the evaluation of this type of smaller nodules because of their higher sensitivity for peripherally located lesions.

Mediastinal staging

In case of enlarged mediastinal lymph nodes on CT, FDG-uptake of mediastinal lymph nodes or, a central FDG positive tumor, biopsies of the mediastinal lymph nodes should be obtained. Mediastinal nodal sampling is often necessary and has traditionally been performed by mediastinoscopy. Nowadays most often endoscopic needle aspiration techniques such as endobronchial ultrasound (EBUS) to guide transbronchial needle aspiration (TBNA) and endoscopic ultrasound (EUS) are used. Mediastinoscopy is usually performed in an operating theatre under general anesthesia and may require overnight hospitalization. EBUS and EUS can be performed under local anesthesia and conscious sedation in an outpatient setting.

Pathology

In table 4 an adapted histologic classification of lung tumors is provided. Changes according to the new International Multidisciplinary Classification of Lung Adenocarcinoma are indicated in Italics. The terms bronchoalveolar cell carcinoma (BAC) and mixed subtype adenocarcinoma are no longer used. For resection specimens new concepts are introduced, such as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) for small solitary adenocarcinomas with pure lepidic growth and predominant lepedic growth with ≤ 5 mm invasion, respectively. Lepidic growth is defined as growth along preexisting alveolar structures. The former two types of adenocarcinoma have a 100% or near 100% disease specific survival. For invasive adenocarcinoma several subgroups were defined, based on histological pattern. Invasive growth is one of the hallmarks of cancer malignancy and defined as a complex biological program which instructs cells to dissociate, degrade the surrounding matrix, migrate, proliferate and survive. The new classification provides guidance for small biopsies and cytology specimen. Advanced non small cell lung cancer (NSCLC) should be classified into more specific subtypes because of consequences for the choice of systemic treatment.

Table 4. *World Health Organization (WHO) Histologic Classification of Epithelial Tumors of the lung.*[49, 50]

World Health Organization Histologic Classification of Epithelial Tumors of the Lung	
PREINVASIVE LESIONS	Large cell carcinoma
Squamous dysplasia/carcinoma *in situ*	Large cell neuroendocrine carcinoma
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia	Combined large cell neuroendocrine carcinoma
Atypical adenomatous hyperplasia	Basaloid carcinoma
Adenocarcinoma in situ (≤3 cm, formerly BAC)	Lymphoepithelioma-like carcinoma
Nonmucinous	Clear cell carcinoma
Mucinous	Large cell carcinoma with rhabdoid phenotype
Mixed mucinous/nonmucinous	Adenosquamous carcinoma
Minimally invasive adenocarcinoma (≤3 cm lepidic predominant tumor with ≤ 5 mm invasion)[a]	Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
INVASIVE MALIGNANT LESIONS	Carcinoma with spindle and/or giant cells
Squamous cell carcinoma	Pleomorphic carcinoma
Papillary	Spindle cell carcinoma
Clear cell	Giant cell Carcinoma
Small cell	Carcinosarcoma
Basaloid	Pulmonary blastoma
Small cell carcinoma	Carcinoid tumors
Variant	Typical carcinoid
Combined small cell carcinoma	Atypical carcinoid
Invasive adenocarcinoma	Carcinomas of salivary gland type
Acinar predominant	Mucoepidermoid carcinoma
Papillary predominant	Adenoid cystic carcinoma
Micropapillary predominant	Others
Lepidic predominant (formerly nonmucinous BAC pattern, with >5 mm invasion)	Unclassified carcinoma
Solid predominant with mucin production	
Variants of invasive adenocarcinoma	
Invasive mucinous adenocarcinoma (formerly mucinous BAC)	
Fetal (low and high grade)	
Colloid	
Enteric	

Adapted World Health Organization (WHO) Classification of lung tumors.[49] Cells in *Italic* indicate a change according to the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma.[50]

Initial treatment of lung cancer

In table 5. the treatment options according to lung cancer stage are provided. The determination of resectability should be performed by (thoracic) surgeons who perform lung cancer surgery as a prominent part of their practice.[45] In the preoperative setting the ability to cope with the subsequent reduction of lung volume should be determined. Subjects with significant co-morbidity and increased risk of postoperative complications should be discussed in a multi-disciplinary tumour board and, alternative treatment scenarios should be discussed.[51] In subjects with pulmonary nodules and a high probability of cancer (>60%), surgery is recommended; surgery in addition is recommended in case of indeterminate possibility of lung cancer after positive imaging studies.[27, 52]

Table 5. *Initial treatment of non-small cell lung cancer. Adapted from: National Comprehensive Cancer Network (NCCN).*[45]

Stage	Treatment	Consider adjuvant chemotherapy
Stage IA, IB, IIA Negative lymph nodes (N0) or N1 positive	Surgery	Findings at surgery: • N1/N2 lymph node involvement • Margins positive (R1, R2): resection or RT +/- chemo • Same lobe nodules (T3) • Ipsilateral lobe nodules (T4) High risk-patient: • Poorly differentiated tumors • Neuroendocrine tumors • Vascular invasion • Wedge resection • Tumors > 4 cm • Visceral pleural involvement • Nx.
Stage IIB:		
• **T2bN1**	Surgery	
• **T3 invasion, N0** Invasion chest wall/proximal airway or mediastinum	Surgery (preferred) OR induction chemotherapy +/- radiotherapy	
• **T3 same lobe nodules, N0**	Surgery	
Stage IIIA		
• **T3 invasion, N1** Invasion chest wall/proximal airway or mediastinum	Surgery (preferred) OR induction chemotherapy +/- radiotherapy	
• **T4 extension, N1** Extension in heart, great vessels, trachea etc.	Surgery (preferred) OR induction chemotherapy +/- radiotherapy	
• **T4 ipsilateral lobe nodules, N0**	Surgery	
• **T4 N0-1 unresectable**	Concurrent chemoradiation	
• **T1a-2b, N2**	Concurrent chemoradiation	
Stage IIIB		
• **T1-4, N2-3**	Concurrent chemoradiation	
Stage IV	Chemotherapy EGFR-testing; if positive start Erlotinib	
• **Solitary metastasis**	Local therapy if lung lesion curable	
• **Stage IV (N0, M1A), contralateral lung**	Treat as two primary lung tumors if both curable: surgery	
Clarification of abbreviations and definitions: EGFR: epidermal growth factor receptor; Nx: regional lymph nodes cannot be evaluated; R1: microscopic residual tumor; R2: macroscopic residual tumor; Solitary metastasis: only known metastasis of a tumor in the whole body.		

Aim and outline of the thesis

Aim of the thesis

In the previous section we discussed the management of suspected lung cancer in daily practice. Imaging studies, bronchoscopy and, surgery also were used in screen positive participants in the NELSON lung cancer screening trial. However, the question should be asked, whether these modalities are equally applicable to test-positives of a lung cancer screening trial. This thesis eveluates the role of imaging studies (FDG-PET, both low-dose CT and diagnostic CT with intravenous contrast), bronchoscopy and surgical procedures in test-positives of the NELSON lung cancer screening trial. The aim is to increase the effectivity and efficiency of lung cancer screening. This can be achieved by reducing the number of futile (surgical) diagnostic procedures by determining an optimal strategy of workup of suspicious pulmonary nodules. Knowledge derived from lung cancer screening studies in addition provides guidance for the management of solitary pulmonary nodules in daily practice.

Outline of the thesis

Part I: Lung cancer screening and the NELSON trial

Chapter 2 focusses on early detection and, lung cancer screening with low-dose CT and, the main results of several lung cancer screening trials are provided. In **chapter 3** we report on the baseline and 2nd round screening results of the NELSON lung cancer screening trial.

Part II: Management of suspicious pulmonary nodules: imaging studies and bronchoscopy

In **chapter 4** we discuss the management of pulmonary nodules measuring <1cm in more detail. The natural history of lung cancer is only partly elucidated, conclusions on the impact of overdiagnosis in lung cancer screening are premature, this we discuss in **chapter 5**. The role of standard dose CT with contrast for suspicious screen detected pulmonary nodules in the NELSON trial is discussed in **chapter 6.** In **chapter 7** the diagnostic value of FDG-PET for diagnosing suspicous pulmonary nodules in the NELSON lung cancer screening trial is discussed. The role of bronchoscopy for diagnosing pulmonary nodules in the NELSON trial is reviewed in **chapter 8.**

Part III: Management of suspicious pulmonary nodules: surgical procedures

In **chapter 9** complications following surgery in the NELSON lung cancer screening trial are reviewed and, in **chapter 10** difficulties encountered during surgical procedures for suspcious pulmonary nodules are discussed.

Par IV: Summary and Discussion

Finally, the study results and its interpretation and implication for further research and practice is discussed in **chapter 11**.

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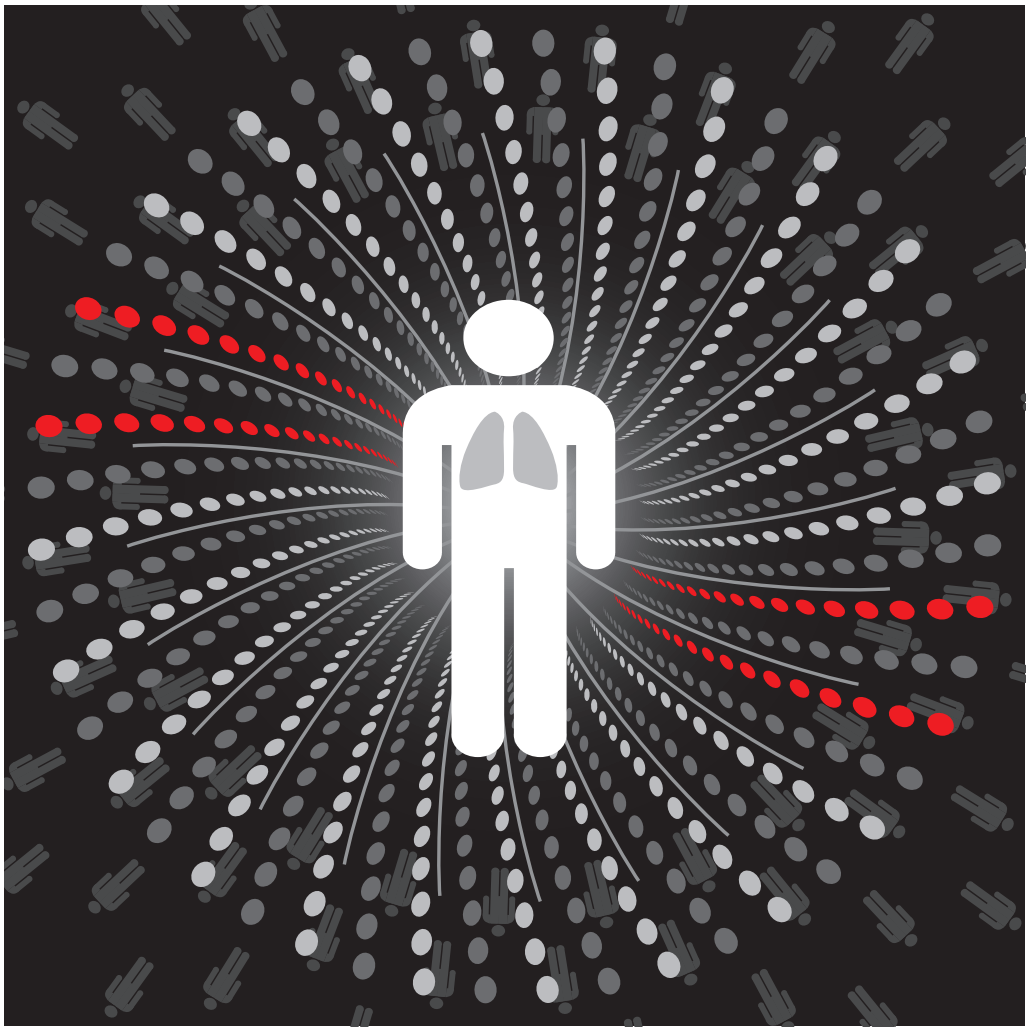
Part I

Lung cancer screening and the NELSON trial

Chapter 2



Screening and early detection of lung cancer

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Abstract

Lung cancer with an estimated 342,000 deaths in 2008 (20% of total) is the most common cause of death from cancer followed by colorectal cancer (12%), breast cancer (8%) and stomach cancer (7%) in Europe. In former smokers the absolute lung cancer risk remains higher than in never-smokers; these data therefore call for effective secondary preventive measures for lung cancer in addition to smoking cessation programs. This review will present and discuss the most recent advances in the early detection and screening of lung cancer. An overview of randomized controlled CT-screening trials is given, the role of bronchoscopy and new techniques are discussed. Finally the approach of (non-invasive) biomarker testing in the blood, exhaled breath, sputum and bronchoscopic specimen is reviewed.

Introduction

Lung cancer with an estimated 342,000 deaths in 2008 (19.9% of total) is the most common cause of death from cancer in Europe, followed by colorectal cancer (12.3%), breast cancer (7.5%) and stomach cancer (6.8%).[1] More than one billion people around the world currently smoke tobacco. The use of tobacco kills more than 5 million of the people yearly. If this trend continues, it is expected that more than 8 million people will die from tobacco related diseases yearly by 2030. The chance that a lifelong smoker will die prematurely from a tobacco related disease is about 50%, and smokers who continued smoking died on average ten years younger compared with lifelong non-smokers. In contrast to other cancers, there has been almost no improvement in the 5-year survival rates of lung cancer in the past 30 years, primarily because lung cancer is detected in the majority of the cases in an advanced stage. Even though people succeed to stop smoking, their absolute cancer risk remains high. As a result, 80% of all lung cancer cases occur in former smokers today. These data call for effective secondary preventive measures for lung cancer in addition to smoking cessation programs. This review will present and discuss the most recent advances in the early detection and screening of lung cancer.

CT-screening

The introduction of low-dose multi-detector helical tomography (CT) has led to a major advance in cross-sectional imaging due to advance scan speed, improved spatial resolution and the capacity to reconstruct multiple series from a single data acquisition. The low-dose technique results in an effective radiation dose of approximately 0.65 mSv[2], as opposed to 3.5-7.0 mSv for diagnostic CTs.[3] In addition, no intravenous contrast is used.

A large number of review studies have been published on lung cancer low-dose CT screening in recent years.[4-15] They all conclude that CT screening will detect lung cancer more often in an early stage with rates varying between 38%[16]-66%.[17] Whether this will translate into a lung cancer mortality reduction was until very recently unknown.[4-15] Therefore, the ACCP guideline does not recommend CT-screening unless as part of a well-designed clinical trial.[18]

Lung cancer and overall mortality data from the randomized controlled lung cancer CT screening trials NELSON, the Danish randomised CT screening trial, ITALUNG CT and LUSI have to be awaited (Table 1). So far, only the DANTE trial investigators reported on the all-cause and lung cancer mortality and stage distribution in both study arms.[19] After a median follow-up of 3 years there was no significant difference between the LDCT group and the control group with respect to the lung cancer specific mortality. However, in a recent press release by the National Cancer Institute Data and Safety Monitoring Board of the NLST trial a 20% lung cancer mortality reduction and a 7% overall mortality reduction was reported after 7 years of follow-up.[20]

One of the concerns about lung cancer screening was the high rate of test positives and the associated high number of work-ups. Investigators from the NELSON study, a population based randomized lung cancer screening trial, demonstrated, however, that this problem could be overcome by using a semi-automated volumetry software (LungCare®, Siemens Medical Solutions).[17]

Table 1. *Overview of randomized controlled CT-based lung cancer screening trials*

Nr	Ref	Year	Author	Study	Design	Round	Participants in screen arm	Test positive (%)	LCA detection rate (%)	Stage I disease (%)	Operations for benign disease/total operations (%)
1	[21]	2004	Gohagan	LSS, USA	CT vs X-ray	Baseline	1,660	20.5	30 (1.8)	16/30 (53)	NA
	[22]	2005	Gohagan	LSS, USA	CT vs X-ray	Incidence	1,398	25.8	8 (0.6)	2/8 (25)	10/18 (55)*
2	[23]	2003	Church	NLST, USA	CT vs X-ray	Baseline, Incidence	53,000	NA	NA	NA	NA
4	[16]	2007	Blanchon	DEPISCAN, France	CT vs X-ray	Baseline	336	8.3	8 (2.3)	3/8 (37.5)	3/8 (37.5)
5	[24]	2008	Becker	LUSI, Germany	CT vs no screening	Baseline	1,780.00	22	18 (1.0)	NA	NA
6	[25]	2008	Infante	Dante, Italy	CT vs no screening	Baseline	1,276	15.6	28 (2.2)	16/28 (57)	6/32 (18.8)
	[19]	2009	Infante	Dante, Italy	CT vs no screening	Incidence	NA	18	46 (3.6)	30/46 (65)	12/66 (20)
7	[26]	2009	Lopes Pegna	ITALUNG, Italy	CT vs no screening	Baseline	1,406	30.3	20 (1.4)	10/20 (50)	1/18 (5.5)
8	[27]	2009	Pedersen	DLCST, Denmark	CT vs no screening	Baseline	2,052	8.7	17 (0.8)	10/17 (58.8)	8/40 (20)
9	[17]	2009	Van Klaveren	NELSON, The Netherlands and Belgium	CT vs no screening	Baseline	7,557	2.6	70 (0.9)	46/70 (65.7)	25/92 (27)
	[17]	2009	Van Klaveren	NELSON	CT vs no screening	Incidence	7,289	1.8	54 (0.7)	42/54 (77.7)	12/62 (19)

* Including surgeries AND biopsies

Definition of abbreviations: DLCST: Danish Lung Cancer Screening Trial; LCA: lung cancer; LSS: Lung Screening Study; NA: not available; NELSON: Dutch-Belgian lung cancer screening trial; NLST: National Lung Screening Trial; Nr: number; Ref: reference.

Subjects received a positive test result and were referred to a pulmonologist based on the size and volume doubling time (VDT) of the non-calcified nodules detected. A nodule was classified as non-calcified if it did not meet previously specified criteria for a benign lesion. For solid pleural-based and non-solid pulmonary nodules, the diameter was manually determined and the VDT calculated as described before.[28] For pleural-based nodules, the diameter perpendicular to the costal pleura was taken. For partially solid lesions, only the volume of the solid region was used. Diameter was defined as the average of maximum nodule length and width. Growth was defined as a change in volume between the first and the second scan of $\geq$ 25%. The 25% threshold was based on 3 zero-change datasets in which volume variation of individual nodules was assessed between two low-dose CT scans. In these studies, the volume measurement error varied between 20-25%.[12,14,15] Growing nodules were classified into 3 growth categories according to their VDT (<400, 400-600 and >600 days).

A baseline scan was considered positive if any non-calcified nodule had a solid component > 500 mm^3 (> 9.8 mm in diameter), or indeterminate if the volume of the largest solid nodule or the solid component of a partially solid nodule was 50-500 mm^3 (4.6-9.8 mm in diameter), or > 8 mm in diameter for non-solid nodules. Subjects with an indeterminate result had a follow-up scan 3 months later to assess growth. If at that time the lesion had a VDT < 400 days, the final result was declared positive, otherwise negative. Subjects with positive screening tests were referred to a chest physician for work-up and diagnosis. If lung cancer was diagnosed, the participant was treated for the disease and went off screening; if no lung cancer was found the regular 2nd round CT scan was scheduled 12 months after the baseline scan. For participants with one or more new nodules on the second round scan, the result (positive or negative) was based on size of the nodule, as for round one; a follow-up scan for an indeterminate result was performed 6 weeks later. For participants with previously detected nodules, the second round result was based on the VDT. If there was no growth, or if the VDT was > 600 days, the screen was negative. If the VDT was less than 400 days, or if a new solid component had emerged in a previously nonsolid nodule, the scan was considered to be positive. When the VDT was 400-600 days, the test was indeterminate and a follow-up scan was done one year after the second round. If both new and existing nodules were present, the nodule with the largest volume or fastest growth determined the test result.

As a result of this NELSON nodule management strategy the rate of test positives during baseline and 2nd round screening dropped from 8.3-30.3%[16, 26] and 18-25.8%[19, 22] to 2.6% and 1.8%, respectively.[17] The NELSON strategy did not compromise the sensitivity (94.6%, 95% CI: 86.5-98.0%) and the negative predictive value increased to 99.9% (95% CI: 99.9-100.0%). Despite a major reduction in the number of test positives, the rate of surgical resections for benign disease (false-positives) remained too high with 27% at baseline and 19% at 2nd round screening, even though this was within the range reported by others (6%-38%).[16] Novel biomarkers (see below) might help to reduce this high rate of false positive test results in the future.

Furthermore, it is yet unknown what proportion of the cancer cases detected are overdiagnosed cases.[29, 30] As no long-term follow-up data are available for lung cancer, this question cannot yet be answered.

Recently, new data have been published on the effect of CT screening on informed decision making, quality of life, and smoking behaviour. The best way to transfer information about lung cancer screening to eligible subjects still needs to be determined as about only half of

the participants showed adequate knowledge on lung cancer screening.[31] Nevertheless, the health related quality of life in subjects with and without adequate knowledge on the subject was similar.[32] Factors that influence quality of life in participants of a CT screening program are related to the CT test result[33] and their affective lung cancer risk perception.[34] In addition, waiting for the test result was reported to be discomforting.[35] Lung cancer screening studies reported that the test result in subjects with negative screening CT did not influence the duration of long-term smoking abstinence.[36, 37] Subjects with a positive test result were reported to have a higher likelihood of point abstinence[37] and in subjects with an indeterminate test a higher number of quit attempts was seen.[36] Lung cancer screening may thus be regarded as a teachable moment to improve smoking behaviour.[38]

Bronchoscopy

As discussed before, multi-detector CT technology enables us to detect lung cancer in a high proportion at an early stage, and they are predominantly adenocarcinomas. Multidetector CT technology is unable to detect pre-invasive lesions and less suited to detect early stage lung cancer in the central airways. Epithelial changes, such as high-grade dysplasia and carcinoma in situ (CIS) in the central airways are early stage squamous cell carcinomas.[39] The most widely used and investigated technique for the detection of this kind of premalignant endobronchial lesions is the light induced fluorescence endoscopy (LIFE), a technique recommended by the American College of Chest Physicians.[40] Limitation of the LIFE system is that it is sensitive to the total mucosal blood volume. As a result it is difficult to discriminate between bronchitis and inflammation on one hand, and premalignant bronchial lesions on the other hand. As a result 2/3 of the LIFE detected suspicious lesions is false positive after correlation with pathology.[41] Because of this low specificity LIFE cannot be used as a screening tool. The modified autofluorescence technique relies on the same technique as LIFE but by using additional filters a red:green ratio is generated which is sensitive to the microvascular pattern instead of the total mucosal blood volume. By using this narrow-band bronchoscopic technique a higher specificity can be achieved up to 80% without significantly compromising the sensitivity.[39] A novel technique currently under investigation is the optical coherence tomography.[42, 43] By this high resolution point imaging technique cross sectional images of the mucosa can be made up to 3 mm in depth. Inflammation can be differentiated from premalignant lesions by measurement of the epithelial thickness. The advantage of this technique is that it is based on real time imaging, the disadvantages the complex interpretation of the images and the high costs. Another novel diagnostic approach is the fibered confocal fluorescence microscopy.[44] The technique is based on the same principle as confocal microscopy. By using a fiberoptic miniprobe (1 mm in diameter) 0-50 µm deep real time cross sectional images of the bronchial epithelium can be obtained. It also increases the specificity as compared to LIFE, but the interpretation is complex and the scopist must know the characteristics of premalignant lesions. Maldonado *et al.*[45] reviewed the use of molecular biological techniques applied to bronchoscopically obtained biopsies. Although not yet implemented in daily practice, the authors expect a role for early diagnosis and clinical guidance for inoperable lung cancer cases with regard to prognosis and expected response to therapy.

Blood Biomarkers

Circulating DNA, epigenetics and transcriptomics

Circulating tumour DNA

Stroun *et al.* were the first to report that cancer patients with malignant disease had extractable amounts of DNA in their plasma.[46] Several case-control studies on circulating DNA have been conducted ever since with cut-of values varying between 2 and 25 ng/ml. Paci *et al.*[47] found a positive predictive value (PPV) of 75% and a negative predictive value (NPV) of 64%. Despite the excellent NPV, varying between 65-95% depending on cut-of value for circulating DNA, reported by Sozzi *et al.*[48] baseline assessment of plasma DNA levels did not improve the accuracy of lung cancer screening by spiral CT.[49] When combining circulating tumour DNA with COX-2 mRNA expression in peripheral blood an excellent diagnostic performance could be achieved with a specificity of 92% and a sensitivity of 91%.[50] Yoon *et al.* reported that the odds ratio for lung cancer detection with circulating DNA levels >20 ng/mL was 50 as compared to healthy controls.[51] In conclusion, cut-off values for circulating DNA value greatly in different studies, and larger studies are necessary to determine an adequate cut-of value for circulating DNA in the blood.

Promotor hypermethylation

Epigenetics refer to modification of genes that are not coded in the DNA sequence itself but by post-translational modifications in DNA. In cancer cells hypermethylation of certain areas is seen, which is associated with silencing of promoter regions of growth controlling genes.[52] In subjects with lung cancer elevated levels of methylated genes in plasma have been found such as RASSFIA, p16 (cell cycle), APC (adhesion), FIHT, RARbeta, MGMT, DAPK (apoptosis), CDH13, TIMP-3, GSTP1 and SOCS1, SOCS3 (cytokine signaling).[53, 54]

In several case-control studies the accuracy of promoter hypermethylation as an early detection marker has been investigated. These studies showed highly variable sensitivities and specificities.[54-57] Ostrow *et al.*[54] used a panel of 4 different genes and found a specificity of 71% in subjects with benign nodules on their CT scan and in 22% the test was false-positive. Therefore, promoter hypermethylation cannot yet be used as a lung cancer early detection biomarker in daily practice.

Transcriptomics: messenger and micro RNA

Messenger RNA has been used for the detection of circulating tumor cells. Xi *et al.* demonstrated that a panel including CK7, EGFR, SCCA, and SFTPB identified all of the 22 lung cancers.[58] MicroRNAs (miRNAs) are a class of small non-coding RNA gene products thought to regulate other genes' expressions. Circulating tumour derived exosomes levels and miRNA patterns appeared to be significantly different in lung cancer patients as compared to controls.[59] MiRNA expression profiles in lung cancer tissues have been used for risk stratification and outcome prediction studies.[60, 61] Downside of serum miRNA profiles in solid cancer is that this approach often fails to identify miRNAs commonly found in lung cancer tissue and that the miRNA profiles found by the different groups are almost non-overlapping, as is the case with gene expression profiling. A possible explanation may be the different techniques and experimental platforms used.[62]

Proteomics

As a result of genomic mutations and subsequent translational changes protein products could be used as potential biomarkers of neoplasia.[63] Examples are CEA (carcinoembryonic antigen), NSE (neuron-specific endolase), Chromogranine, CA125 (carbohydrate antigen 125) and CA19-9 (carbohydrate antigen).[64] The following individual biomarkers have been investigated in case-control studies: Cyfra 21-1 (cytokeratin 19 fragment),[65] CRP,[66] SAA (serum amyloid alpha),[67] adomet,[68] MIF (macrophage migration inhibitory factor),[69] suPAR (soluble urokinase plasminogen activator receptor),[70] soluble E-selectin[71], NNMT (nicotamide N-methyltransferase),[72] cAMP protein kinase,[73] connective tissue-activating peptide III,[74] and TIMP-1 and TIMP-2 (serum tissue inhibitors of metalloproteinase-1 and 2).[75] None of these biomarkers are ideal early detection markers because of their low specificity and/or sensitivity.

In a matched case-control study including 49 lung cancer patients by Patz *et al.*[76] a panel of 4 serum proteins was tested (carcinoembryonic antigen, retinol binding protein, α1-anti-trypsine, and squamous cell carcinoma antigen); a sensitivity of 78% and specificity of 75% was seen. Xiao *et al.* found that a combination of 4 biomarkers had a higher sensitivity and specificity than any single marker, but even then the specificity remained low (53%) at a sensitivity of 86%.[77]

Because lung cancer is a heterogeneous disease it is unlikely that one single marker will be uniformly elevated. Comparative protein profiling is generally acknowledged as a promising way for the detection of specific and predictive protein expression patterns reflecting certain stages of cancer. The advance of new analyzing mass spectrometry techniques as SELDI-TOF-MS (surface-enhanced laser desorption/ionization time-of-flight mass spectrometry) and conventional MALDI-TOF (matrix-assisted laser desorption and ionization time-of-flight mass spectrometry) make it possible to detect multiple protein changes simultaneously.[65]

With MALDI-TOF profiling a sensitivity of 34% for adenocarcinomas, 52% for squamous cell carcinomas at a specificity of 90% was reached.[78] By SELDI-TOF-MS the sensitivity of the marker pattern ranged between 87-93% and the specificity was 80-97%.[79] Ueda *et al*.[80] focused on glycoprotein patterns and found a sensitivity 19% and a specificity of 100%. Lin *et al.* used a novel magnetic bead based MALDI-TOF-MS technique and found a sensitivity of 80% en specificity of 93%.[81]

Limitation of all the studies presented is that independent validation is missing. Despite the discovery of new biomarkers, identification of biomarkers that are superior to those currently used has been proven to be difficult and very few, if any, newly discovered biomarker has entered the clinic in the past 10-years.[82]

Immunomics

From breast but also from lung cancer studies we know that auto-antibodies against cancer-associated antigens can be measured up to 5 years before symptomatic disease.[83] Auto-antibodies to tumour antigens represent a humoral response and are not the product of mutated genes. Different studies have shown that cancer growth and progression are associated with cancer immuno-surveillance and inflammation. Not only in auto-immune diseases like multiple sclerosis but also in cancer, immunoglobulins are released at high levels into blood. The molecular signatures of such immunoglobulins could potentially be used as diagnostic or prognostic biomarkers. Screening for disease related immune responses is generally performed by testing patients' sera against libraries of known

antigens. Although successful, techniques such as serological expression cloning (SEREX) are aimed at detecting the targeted antigens, rather than the reactive immunoglobulins. An alternative strategy is a direct comparison of the amino acid sequences of immunoglobulin molecules between cases and controls using high-resolution Orbitrap mass spectrometry.[84]
Several authors have studied the value of individual auto-antibodies as early detection marker for lung cancer. Brichory *et al.* investigated the protein gene product 9.5 (PGP 9.5); in 14% of the subjects with lung cancer auto-antibodies against PGP 9.5 were detected.[85] In another study they found serum anti-annexins I and II autoantibodies in 30% and 33%, respectively of subjects with lung cancer and, for adenocarcinomas a slightly better performance was seen.[86]
Chapman *et al.*[83] tested 7 auto-antibodies and for a panel based on all 7 auto-antibodies with positivity defined as a raised level of at least one auto-antibody, the best diagnostic values were seen as compared to individual auto-antibody testing or a panel of only 4 auto-antibodies. The 7-auto-antibodies-based panel showed a sensitivity of 76% for all types of lung cancer with a specificity of 92%.[83] Boyle *et al.*[87] investigated the diagnostic performance of the Early CDT-lung TM, a panel of six lung cancer-associated antigens. In a pilot study consisting of 842 lung cancer patients the positivity rate varied between 0-51%, depending on the lung cancer stage and histology; no diagnostic values could be calculated because no controls were included. In another study with 85 cases and 85 matched controls a panel of 3 antigens (Annexin I, LAMR1, and 14-3-3 theta) had a sensitivity to detect lung cancer of 51% and a specificity of 82%.[88] Zhong *et al.*[89] tested a panel of 5 tumour associated-antibodies as markers in a subset of participants of 102 subjects of the Mayo clinic CT screening trial, including 46 cancer cases; they found a sensitivity of 91% and specificity of 91%. Farlow *et al.*[90] used a panel of 6 auto-antibodies which showed only a 7% misclassification rate and an excellent sensitivity and specificity of 95% and 91%, respectively. For diagnosing squamous cell lung cancer (SCC) and healthy controls a panel of 20 antibodies was established which showed a sensitivity and specificity of both 93%.[91] For distinguishing between non-tumour lung pathologies and SCC the panel with the best diagnostic performance was based on 69 antigens, resulting in a sensitivity and specificity of 75% and 94%, respectively.[91] Leidinger *et al.*[92] achieved, with a library of 1,827 peptide clones with reactivity against serum antibodies, an accuracy of 98% in discriminating lung cancer from healthy controls and an 89% accuracy to discriminate lung cancer patients from patients with non-tumour lung pathologies.
Individual auto-antibodies lack sensitivity; auto-antibody signatures are more promising; studies on antibody profiling provide better diagnostic performance as compared to individual auto-antibodies. The identified signatures need replication and independent clinical validation before they can be used in clinical practice. Furthermore, extracting lung cancer cases from non-tumour lung pathologies based on serological essays may even be more challenging, future studies therefore should also focus on this matter.

Biomarkers in exhaled breath and exfoliative materials.

Breath test

Exhaled breath analysis is a novel approach to identify inflammatory and oxidative stress markers involved in the pathogenesis of various respiratory conditions. A frequent used technique is based on exhaled breath condensate (EBC). Drawback of EBC is that the values

obtained from different devices may not be directly comparable, that the markers may reflect each part of the oro-respiratory tract,[93] and that independent validation is missing. Therefore, the ECB approach is still in its experimental phase and cannot be used in clinical practice yet.

The following markers have been studied in exhaled breath condensate: 3-p microsatellite signature,[94] DNA methylation,[95] endothelin,[96] COX-2 and survivin[97] and, angiogenic markers.[98] The afore mentioned studies found significant differences in biomarkers between controls and lung cancer cases, but no diagnostic values were provided. Di Natale used an electronic nose, the analysis of patterns of chromatography were correct in 100% of lung cancer patients and controls were misdiagnosed in 6% of cases.[99] A model based on 16 volatile organic compounds (VOC) had a sensitivity of 85% and specificity of 80%[100] and, a model based on 13 VOCs showed a sensitivity of 72% and a specificity of 94%.[101] Song *et al.* found for the VOCs 3-hydroxy-2-butanone and 1-butanol a sensitivity of 95% and a specificity of 93% and, a sensitivity of 85% and specificity of 93%, respectively.[102]

Bronchoscopy

The role of genomic based markers in bronchial lavage (BAL) samples to distinguish lung cancer from non-cancer cases has been studied by several authors. For promoter hypermethylation of p16 a sensitivity of 64% and specificity of 75% was found.[103] Liloglou *et al.*[104] investigated genomic instability using 4 microsatellite markers and found a sensitivity of 74% and a specificity of 77%. In a study by Kim *et al.*[105] promoter hypermethylation of at least one of the four tested genes was seen in 68% of the lavage samples. However, in cancer free subjects hypermethylation of one of the four genes was seen in 3-28%. A test based on 14 genes from bronchial epithelial cells related to DNA repair, antioxidant activity and DNA transcription showed an AUC of 0.82 and 0.87, respectively, in two small case-control sets including 25 and 18 cases respectively, described by Blomquist et al.[106]

In the next paragraph, studies on the role of biomarkers in both sputum and BAL are discussed. Telomerase activity in sputum had a sensitivity of 82% and a specificity of 100%, whilst for bronchial washings these values were only 68% and 100% respectively, the authors explain this finding by the high number of inflammatory cells found in bronchial washings.[107]. Mecklenburg *et al.*[108] found expression of at least one MAGE gene in 33% (5/15) of the sputum specimens from patients with lung cancer whereas in BAL fluid MAGE expression was observed in 78% (18/23) of the patients with confirmed lung cancer. In the lung cancer screening study of McWilliams *et al,*[109] 18% (4/22) of the lung cancers detected was radio-occult and was detected by LIFE (Lung Imaging Fluorescence Endoscope) bronchoscopy only. Of the subjects with lung cancer 95% (21/22) had sputum atypia on quantitative sputum cytometry, an automatic image analysis of number of (abnormal) nuclear features.[109] However, a large proportion, 75% (423/561) of the screened subjects had sputum atypia, as opposed to only 14 subjects with screen detected lung cancers. Spira *et al.* found an excellent sensitivity and specificity of both 95% when they combined cytopathology with an 80-probe based genetic biomarker on bronchoscopically obtained large airway epithelial cells.[110]

Sputum

To improve the diagnostic accuracy of sputum cytology, the diagnostic value of promoter hypermethylation, fluorescence *in situ* hybridization (FISH) and genetic mutations has been

investigated. Although it is unlikely that early stage lung cancers <1 cm in diameter will exfoliate detectable cancer cells in sputum, it is hypothesized that because of the process of field cancerization genetic or epigenetic changes in exfoliated cells may reflect increased lung cancer risk.[111]

Honario *et al.*[112] reported that the methylation status of a single gene (RASSF1A) had a sensitivity of 28% and, a specificity of 76%. Authors studying methylation status with panels of 3-6 genes found sensitivities varying between 56-64% and specificities between 64-100%.[113-115] Destro *et al.*[116] reported that 48% of the lung cancer cases had either a K-RAS mutation or p-16 hypermethylation, which were almost mutually exclusive seen. Combining the molecular and cytological results increased the sensitivity to 60% and the specificity to 95%. Adding FISH to conventional sputum cytology (HYAL2 or FHT deletions) increased the sensitivity to 76% and a specificity to 92%.[117]

Automated sputum cytometry can be based on aneupolidity (abnormal number of chromosomes), nuclear abnormalities and/or malignancy associated changes (MAC) of cells. Using this technique Kemp *et al.*[118] found improved sensitivity of sputum cytology from 16% to 40% at a specificity of 91%. Using a comparable technique, Li *et al.*[119] found a sensitivity of 75% at a specificity of 50%. A FISH-based panel consisting of 4 DNA targets (epidermal growth factor, MYC, 5p15 and CEP 6) had a sensitivity of 76% to detect lung cancer 18 months prior to diagnosis.[120]

With conventional sputum cytology for all 444 participants with lung cancer a sensitivity of 38% and 20% respectively was found for detecting pre-malignant and cancer cells; of all lung cancer patients with adequate specimens in 75% the sputum was positive for cancer cells.[121] These results are higher than in daily practice; this is due to the labour-intensive study protocol with 3 cytopathologists reviewing 2 sputum specimens per participant (including one induced sputum). The authors suggest a role for automated sputum processing and magnetic-assisted cell sorting to improve efficiency and sensitivity when sputum cytology is to be implemented in a screening setting; in addition, the presence of pre-malignant cells may identify high-risk patients and guide follow-up and imaging intervals.[121] Besides standardization of sputum collection and additional (new) processing techniques of the cytological specimen the addition of biomarkers may improve diagnostic values. Again, larger studies are necessary in order to confirm these results.

Conclusion

The results of ongoing randomised lung cancer CT screening trials have to be awaited before final conclusions can be drawn with regard to the effectiveness and cost-effectiveness of CT screening although preliminary data from the NLST trial are very promising. The final role of lung cancer biomarkers for early detection, risk stratification, or as an adjunct to CT screening to reduce the rate of false positive test results is yet unknown. Although some studies report high sensitivities and/or specificities, most of them lack reproducibility and none of them have been validated in independent large-scale clinical trials.

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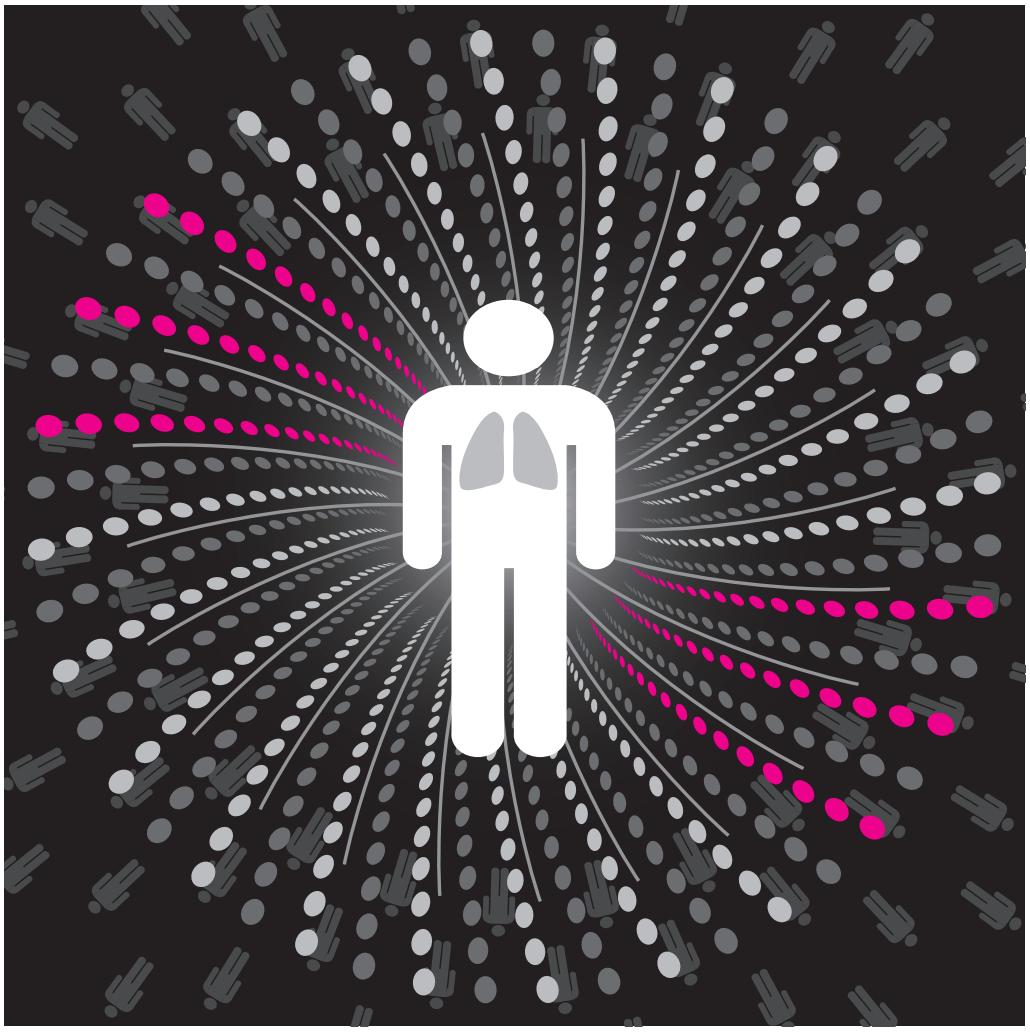
Chapter 3



Management of Lung Nodules Detected by Volume CT Scanning

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ABSTRACT

Background: The use of multidetector computed tomography (CT) in lung-cancer screening trials involving subjects with an increased risk of lung cancer has highlighted the problem for the clinician of deciding on the best course of action when noncalcified pulmonary nodules are detected by CT.

Methods: A total of 7557 participants underwent CT screening in years 1, 2, and 4 of a randomized trial of lung-cancer screening. We used software to evaluate a noncalcified nodule according to its volume or volume-doubling time. Growth was defined as an increase in volume of at least 25% between two scans. The first-round screening test was considered to be negative if the volume of a nodule was less than 50 mm^3, if it was 50 to 500 mm^3 but had not grown by the time of the 3-month follow-up CT, or if, in the case of those that had grown, the volume-doubling time was 400 days or more.

Results: In the first and second rounds of screening, 2.6% and 1.8% of the participants, respectively, had a positive test result. In round one, the sensitivity of the screen was 94.6% (95% confidence interval [CI], 86.5 to 98.0) and the negative predictive value 99.9% (95% CI, 99.9 to 100.0). In the 7361 subjects with a negative screening result in round one, 20 lung cancers were detected after 2 years of follow-up.

Conclusions: Among subjects at high risk for lung cancer who were screened in three rounds of CT scanning and in whom noncalcified pulmonary nodules were evaluated according to volume and volume-doubling time, the chances of finding lung cancer 1 and 2 years after a negative first-round test were 1 in 1000 and 3 in 1000, respectively.

Introduction

The use of multidetector computed tomography (CT) has increased the chance of finding noncalcified pulmonary nodules,[1, 2] and as a result, clinicians often face the problem of deciding on the best course of action with respect to such nodules when they are found in asymptomatic subjects who have an increased risk for lung cancer.[3] This difficulty is especially evident in CT-based screening programs for lung cancer. The current practice is to refer participants in these programs for additional diagnostic evaluation if they have a noncalcified nodule that is larger than 5 mm in diameter.[4-9] In designing the Dutch–Belgian randomized lung cancer screening trial (Nederlands-Leuvens Longkanker Screenings Onderzoek [NELSON], we adopted a strategy that was meant to provide an inexpensive and simple follow-up process without increasing the false negative rate of the screening test.[10] The strategy entailed the use of the volume and volume-doubling time of a noncalcified nodule as the main criteria for deciding on further action. In this article, we report an evaluation of this strategy, which involved the tracking of individual nodules and the collection of 2-year follow-up data from the screened population of the NELSON trial.

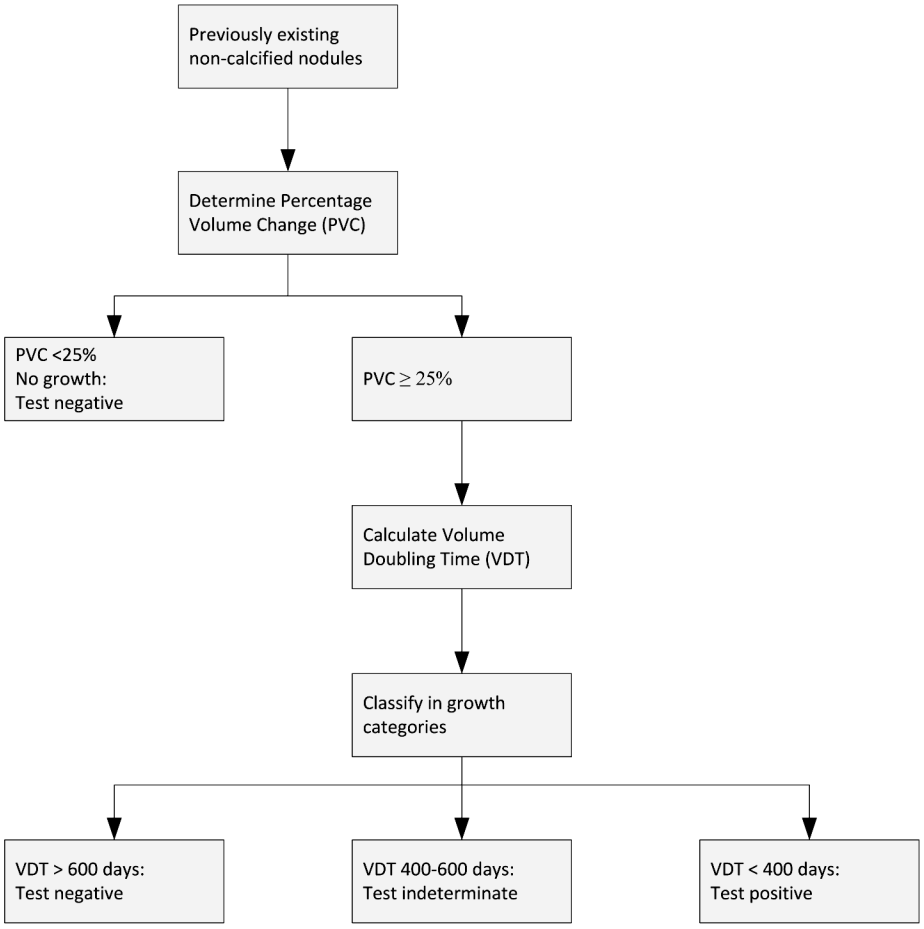
Methods

Participants

We randomly assigned eligible participants in NELSON, who were recruited as described previously,[11] to undergo CT screening at baseline (first round), 1 year later (second round), and 3 years later (third round, 2 years after the second round), or no screening. The purpose of the trial is to determine whether at 10 years after randomization CT screening will have reduced mortality from lung cancer by at least 25%. The trial was approved by the Dutch Minister of Health and the ethics board at each participating center. All participants gave written informed consent.

Screening Strategy

A 16-detector CT scanner (Somatom Sensation 16, Siemens Medical Solutions or, at the screening site in Utrecht, 1x Mx8000 IDT or Brilliance-16P, Philips Medical Systems) was used at each of the screening sites. Data sets were derived from images of the lung with a thickness of 1 mm that were reconstructed at overlapping 0.7-mm intervals. Isotropic data sets allowed for volume measurements with good reproducibility, even in the case of small lesions.[12] Data acquisition and scanning conditions were standard across screening sites and were the same for all rounds of screening.[10] At each site, CT data were analyzed on one type of digital workstation (Leonardo, Siemens Medical Solutions) with the use of software for semiautomated volume measurements (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions).[13, 14] In the case of inappropriate segmentation (i.e., nodules that were attached to a fissure or to a vessel), the radiologist was allowed to enter manual measurements, which overruled the automatically generated volumes. Data generated by the LungCare software were uploaded into the NELSON Management System, which automatically detected whether a nodule was new or had been present previously and which calculated the percentage change in volume and the volume-doubling time in days (Figure 1).



Supplementary Appendix, Figure 1

Formulas
VC (%)= 100*(V2-V1)/V1)
3D: VDTv(days)= [ln2*Δt]/[ln(V2/V2]
4D: VDTd(days)=[ln2*Δt]/[3ln(MaxDiamXY2/MaxDiamXY1)]

Definition of abbreviations:
Vl: volume of the nodule (mm^3) at first detection on CT
V2: volume of the nodule(mm^3) at subsequenCt T evaluation
3D: volume by three-dimensional volumetry software (VDTv)
2D: volume estimate based on two-dimensional measurement(VDTd)
MaxDiamxYl: maximum diameter in X/Y-axis at first detection on CT
MaxDiamXY2: maximum diameter in X/Y-axis at subsequent CT evaluation

Figure 1. *Screening strategy in the NELSON.*

A nodule was classified as noncalcified if it did not meet previously specified criteria for a benign lesion.[4] For solid pleural-based and nonsolid pulmonary nodules, the diameter was determined manually, and the volume-doubling time was calculated as described previously[10] (Figure 1). In the case of pleural-based nodules, the diameter was measured at a point perpendicular to the costal pleura. In the case of partially solid lesions, only the volume of the solid region was used. The diameter was defined as the average of the maximum length and width of the nodule. Growth was defined as a change in volume of at least 25% between the first and second scans or between the second and third scans. The 25% threshold was based on three zero-change data sets in which the variation in volume of individual nodules was assessed between two low-dose CT scans. After the first of these scans, the patient returned to the examining table for the second scan to simulate the

condition of a repeat examination for the follow-up of a pulmonary nodule. In these studies, the volume measurement error varied between 20% and 25%.[12, 14, 15] Growing nodules were classified into three growth categories according to their volume-doubling time (<400, 400 to 600, and >600 days). CT scans were independently read by first and second readers. The experience of the 13 first readers ranged from none to more than 20 years of experience reading thoracic CT scans (median, 6 years); both second readers had 6 years of experience. The second readers matched the nodules they had identified with nodules identified by the first readers according to location and size and compared their results with those of the first readers. If the results were discrepant, the readers reevaluated the scan to reach a consensus. If no consensus was reached, a third radiologist arbitrated the results.

First-Round (Baseline) Scan

A test was considered to be positive if on the CT scan any noncalcified nodule had a solid component that was more than 500 mm^3 (>9.8 mm in diameter) and was considered to be indeterminate if the volume of the largest solid nodule or of the solid component of a partially solid nodule was 50 to 500 mm^3 (4.6 to 9.8 mm in diameter) or if the diameter of a nonsolid nodule was greater than 8 mm. In subjects with an indeterminate result, a follow-up scan was obtained 3 months after the baseline scan to assess the growth of the lesion. If at that time the lesion had a volume-doubling time of less than 400 days, the final result was declared to be positive; otherwise, it was considered to be negative. Subjects with positive screening tests were referred to a chest physician for workup and diagnosis. If lung cancer was diagnosed, the participant was treated for the disease and left the screening trial; if no lung cancer was found, the regular second-round CT scan was scheduled for 12 months after the baseline scan.

Second-Round Scan

When one or more new nodules were found on the second-round scan, the interpretation (positive or negative result) was based on the size of the nodule, as it had been in round one; if the result was indeterminate, a follow-up scan was obtained 6 weeks later. In the case of nodules that had been detected previously, the second round result was based on the volume-doubling time. If there was no growth, or if the volume-doubling time was more than 600 days, the screen was classified as negative. If the volume-doubling time was less than 400 days, or if a new solid component had emerged in a previously nonsolid nodule, the scan was considered to be positive. When the volume-doubling time was 400 to 600 days, the test result was considered to be indeterminate and a follow-up scan was obtained 1 year after the second-round scan. At that time, if the volume-doubling time was less than 400 days, the final result was considered to be positive; otherwise it was considered to be negative. If both new and existing nodules were present, the nodule with the largest volume or fastest growth determined the result. All participants with a negative second-round test result were invited to undergo the third round of screening 2 years after the second round. A cancer detected on screening was classified as a first-round or secondround cancer if it was diagnosed after a workup during the first year after a positive first-round or second-round screen, respectively. Lung cancers that were detected during the first year after a negative first-round or second-round screening test were classified as interval cancers. They were identified through linkage with the national pathology database, information from participants and general practitioners, and, in the case of round-one interval cancers, linkage with the National Cancer Registry. The workup, staging, and treatment were

standard across all screening sites and were performed according to published guidelines.[10, 16, 17] All the authors contributed to the data collection and the decision to submit the manuscript for publication, and all the authors vouch for the accuracy and completeness of the data.

Statistical Analysis

The diagnostic sensitivity was defined as the ratio between the number of true positive results (participants who were diagnosed with lung cancer during the first year after a positive screening test) and the number of true positive results plus the number of false negative results (interval cancers detected during the same time period). Diagnostic sensitivity, specificity, positive predictive value, and negative predictive value were calculated at the participant level, and 95% confidence intervals were determined with the use of SPSS software, version 15.0 (SPSS). The standard for a negative baseline or second-round test result was based on the retrospective information that lung cancer was absent 2 years after the first round of screening and 1 year after the second round. Normally distributed data are shown as means ±SD. P values of less than 0.05 were considered to indicate statistical significance.

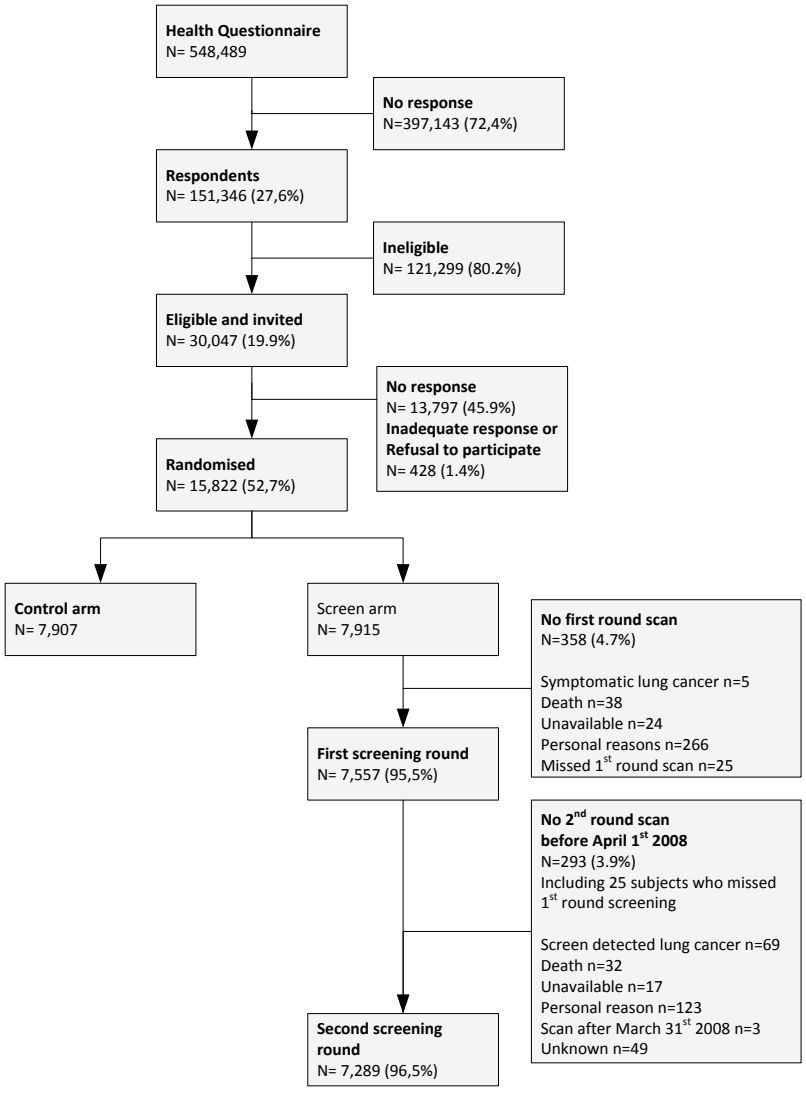


Figure 2. *CONSORT flowchart*

Results

First Round

The mean (±SD) age of the screened participants was 59±6 years, and the mean number of packyears smoked was 42±19; a total of 16% of the participants were women. The first round of screening was conducted from April 2004 through December 2006 (Figure 2). Of the 7557 participants, 50.5% had a total of 8623 noncalcified pulmonary nodules, of which 98.0% were solid.

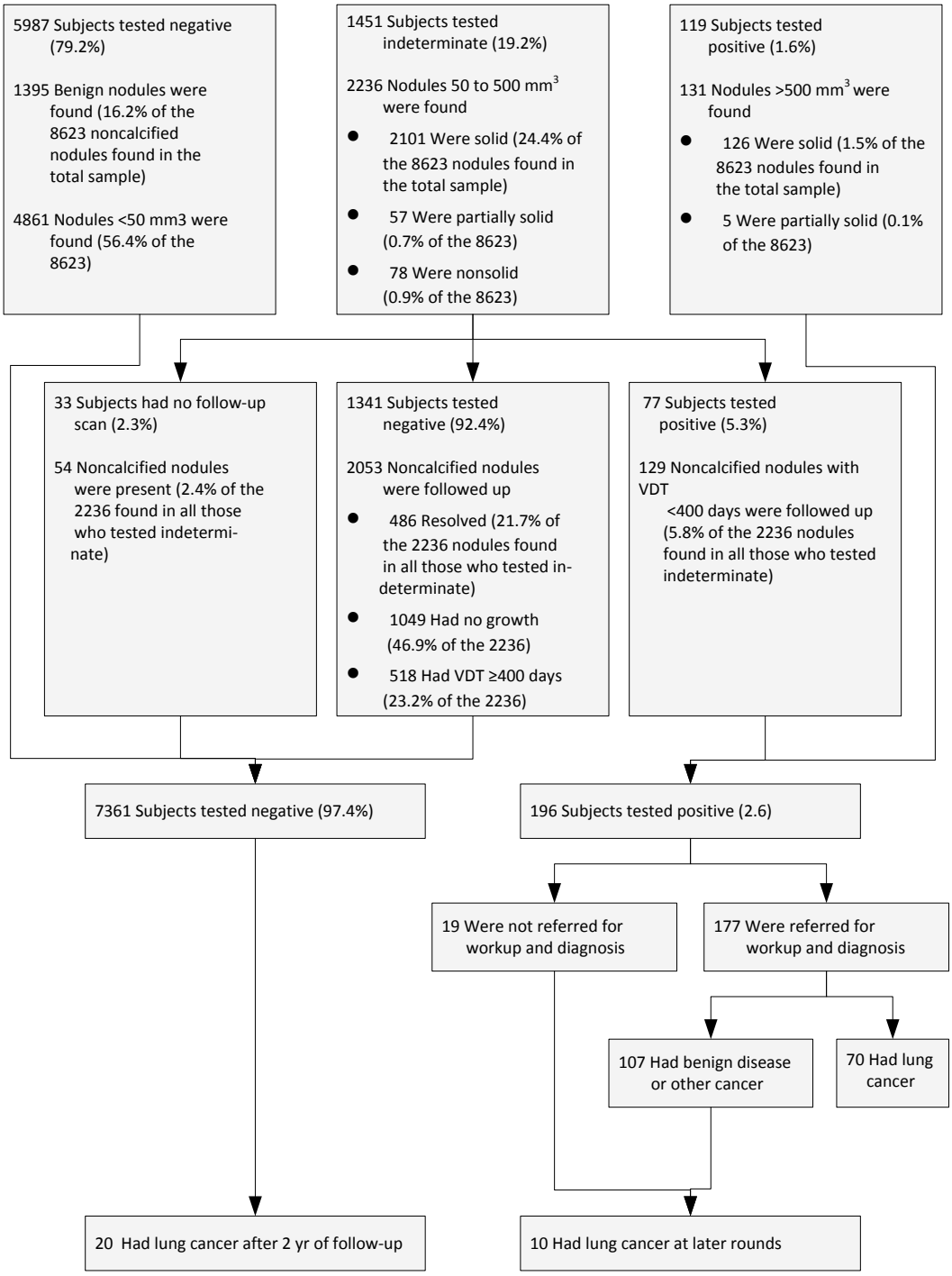


Figure 3. *Results of the First Round Screening. Some participants had more than one nodule. VDT denotes volume doubling time.*

Automated volumetric data were manually adjusted in the case of 6.3% of the nodules. The screening results were determined to be negative in 5987 participants (79.2%), indeterminate in 1451 (19.2%), and positive in 119 (1.6%) (Figure 3). A total of 1536 follow-up scans were obtained 100±19 days, on average, after the baseline scan in participants with an indeterminate result. Including the outcome of these follow- up scans, the results from round one of the screening were negative in 7361 participants (97.4%) and positive in 196 (2.6%). Of the 196 participants with a positive scan, 177 were referred for workup; 19 were not referred (9 because of a decision by the tumor board, 3 because of an administrative error, and 7 because they were already receiving treatment from another specialist). Lung cancer was diagnosed in 70 of the 177 participants who had a positive scan (39.5%); the diagnosis was made mainly by means of an invasive procedure (85.7%). These 70 participants had 72 lung cancers, of which 46 (63.9%) were classified as pathological stage I. In three subjects, no tissue for a histologic diagnosis could be obtained. These subjects received high-dose radiotherapy because the lesions were growing and were assessed as positive on a positron-emission tomographic (PET) scan. Of the remaining 107 subjects with a positive scan, 100 had benign disease and 7 had metastases from another cancer. In round one, the proportion of invasive procedures that revealed benign disease was 27.2%. The lung-cancer detection rate in round one was 0.9% (70 of 7557 subjects). There were four interval cancers, all of which were stage IV adenocarcinomas; three of these were new noncalcified nodules, and one, which had been seen in the first round, had a volume-doubling time of more than 600 days at the 3-month follow-up. The sensitivity of round-one screening was 94.6% (95% confidence interval [CI], 86.5 to 98.0), the specificity 98.3% (95% CI, 98.0 to 98.6), the positive predictive value 35.7% (95% CI, 29.3 to 42.7), and the negative predictive value 99.9% (95% CI, 99.9 to 100.0). Thus, in a subject with a positive CT screening test, the probability that the lesion would be malignant was 36%; with a negative screening test, the probability that a participant would not have lung cancer was 99.9%. Among the 7361 negative CT scans in round one, 20 lung cancers were detected during the 2 years of follow-up: 3 were round-one interval cancers, and 17 were detected in the round-two screening. On the basis of this information, the negative predictive value was 99.7% (95% CI, 99.6 to 99.8). All 126 participants with a positive screening result at round one but with a negative workup returned to the screening program. After a mean follow-up of 785±263 days, 10 of these 126 subjects received the diagnosis of pulmonary adenocarcinoma, which appeared to have originated from a suspicious nodule that was detected in round one (Table 1).

Table 1. *Subjects with a positive 1st round test result and a false negative workup in whom lung cancer was diagnosed in the suspicious 1st round nodule at later screening rounds.*

	1st round screening						Final lung cancer diagnosis			
	Moment of first detection	Consistency	Size at first detection	VDT (Days)	Highest level procedure	Diagnosis	Interval (Months)	VDT (Days)	Diagnosis	pTNM
Case 1	3-months FU	Partial-solid	50-500mm^3	< 400	FBR with washing	No malignancy	23	< 400	Adenocarcinoma	T1N0M0
Case 2	3-months FU	Non-Solid	50-500mm^3	< 400	FBR with washing	Inconclusive	36	< 400	Adenocarcinoma	T1N0M0
Case 3	Baseline	Solid	> 500mm^3	NA	FNA	Fibrosis	27	< 400	Adenocarcinoma	T1N0M0
Case 4	3-months FU	Solid	50-500mm^3	< 400	Computer Tomography	Rest of pneumonia	20	< 400	Adenocarcinoma	T1N0M0
Case 5	3-months FU	Solid	50-500mm^3	400-600	FBR with washing	No malignancy	11	< 400	Adenocarcinoma	T1N1M0
Case 6	Baseline	Solid	> 500mm^3	NA	FBR with washing	No malignancy	26	> 600	Adenocarcinoma	T1N2M0
Case 7	Baseline	Solid	> 500mm^3	NA	No work-up*	NA	14	400-600	Adenocarcinoma	T1N0M0
Case 8	3-months FU	Solid	50-500mm^3	< 400	FBR with washing	No malignancy	24	< 400	Adenocarcinoma	T1N0M0
Lung cancer detected during 3rd round										
Case 9	3-months FU	Solid	25 mm	NA	FBR with washing	No malignancy	37	NA	Adenocarcinoma	T2N0M0
Case 10	3-months FU	Solid	> 500mm^3	NA	FBR with washing	Fibrosis	32	> 600	Adenocarcinoma	T2N0M0

Definition of abbreviations: VDT:volume doubling time; FU:follow-up; FBR:Flexible bronchoscopy; FNA:fine needle aspirate; NA:not applicable; *protocol violation.

Second Round

In accordance with the trial's protocol, all the participants in the first round of screening, except those in whom lung cancer had been diagnosed, were invited to undergo screening in the second round,[12] which was conducted from April 2005 through April 2008. A total of 7289 participants underwent screening 384±59 days after the round one screening (Figure 1). In 1588 (21.8%) of these participants, a total of 2320 new nodules were detected, 29.2% of which had a volume of less than 15 mm^3 or had been missed in round one. Automated volumetric data were manually adjusted in the case of 5.4% of the new nodules and 1.9% of previously existing nodules. The second-round screening result was negative in 6719 participants (92.2%), indeterminate in 480 (6.6%), and positive in 90 (1.2%) (Figure. 4).

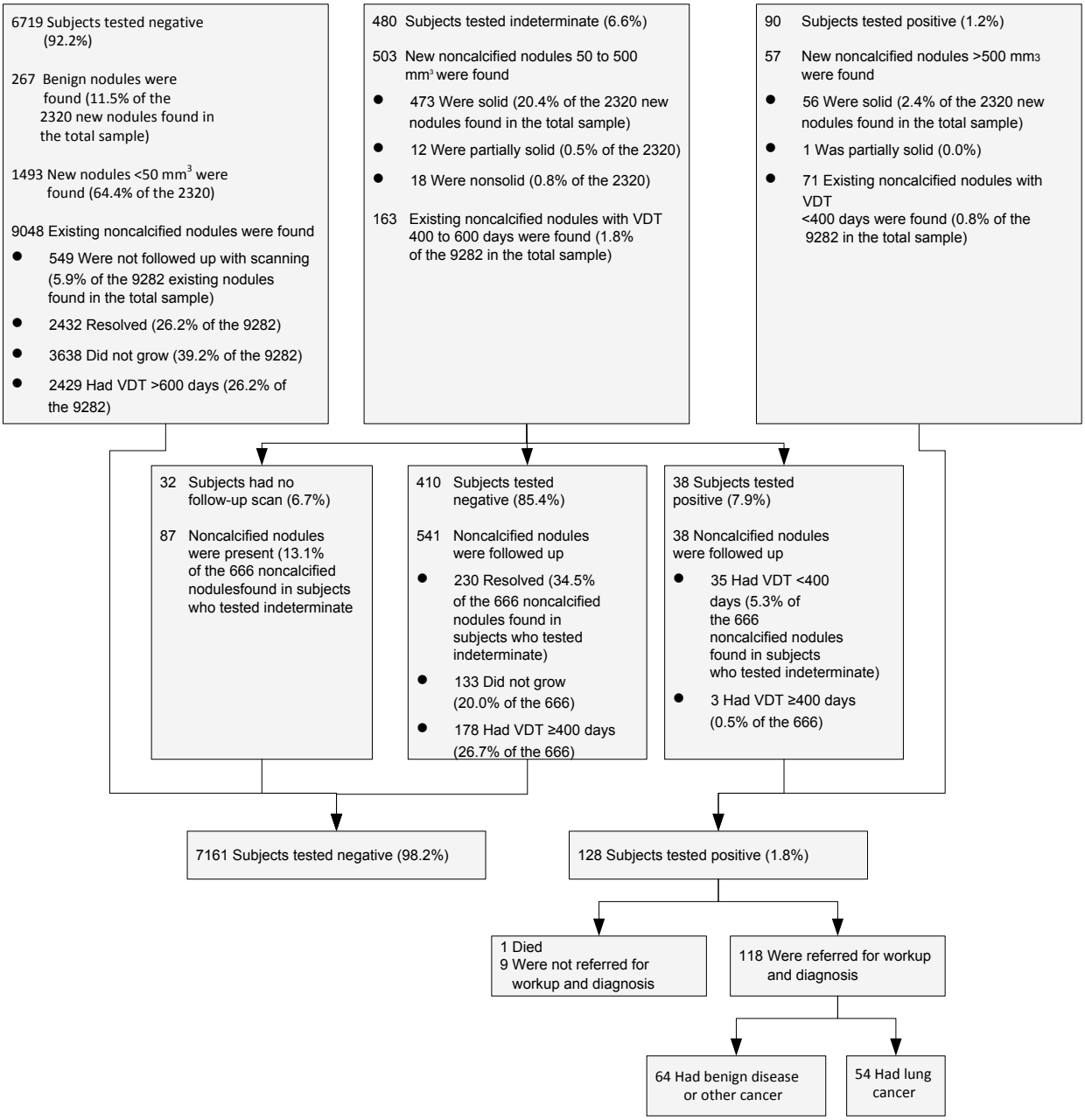


Figure 4. Results of the Second Round Screening. Some participants had more than one nodule. VDT denotes volume doubling time.

Table 2. *Additional diagnostic evaluations in participants with an indeterminate or positive test result following first and second round screening of the NELSON trial in comparison with the literature.*

	NELSON[10]			PluSS[24]	Cosmos[21-23]	Toronto[20]	LSS[†18, 19]		
Variable	**All**	**No Lung Cancer No. (%)**	**Lung cancer No. (%)**	**All No. (%)**	**All No. (%)**	**All No. (%)**	**All No. (%)**	**No Lung Cancer No. (%)**	**Lung cancer No. (%)**
Round one screening	**7,557 (100)**	**7,487 (100)**	**70 (100)**	**3,642 (100)**	**5,203 (100)**	**3,352 (100)**	**1,586 (100)**	**1,556 (100)**	**30 (100)**
Clinical evaluation	181 (2)	111 (2)	70 (100)	1,477 (41)	NA	NA	244 (15)	217 (14)	27 (90)
Recall chest CT scan	1,438 (19)	1,419 (19)	19 (27)	821 (23)[$]	482 (9)	628 (19)	325 (21)	305 (20)	20 (67)
Recall chest CT scans/subject	1.1	1.1	1.2	1.4	NA	NA	1	1	1
Chest X-ray	55 (1)	27 (0)	28 (40)	NA	NA	NA	92 (6)	80 (5)	12 (40)
PET or PET/CT	0 (0)	0 (0)	0 (0)	NA	160 (3)	NA	NA	NA	NA
MRI	5 (0)	2 (0)	3 (0)	NA	NA	NA	NA	NA	NA
Lung function test	147 (2)	78 (1)	69 (99)	NA	NA	NA	73 (5)	55 (4)	18 (60)
Bronchoscopy	149 (2)	84 (1)	65 (93)	NA	NA	NA	29 (2)	16 (1)	13 (43)
FNA	13 (0)	5 (0)	8 (11)	NA	4 (0)	57 (2)	46 (3)	18 (1)	28 (93)
Invasive procedure*	92 (1)	32 (0)	60 (86)	90 (3)	106 (2)	48 (1)	53 (3)	23 (2)	30 (100)
Round two screening	**7,289 (100)**	**7,235 (100)**	**54 (100)**	**3,423 (100)**	**4,867 (100)**	**2,686 (100)**	**1,398 (100)**	**1,390 (100)**	**8 (100)**
Clinical evaluation	125 (2)	71 (1)	54 (100)	1,450 (42)	NA	NA	NA	NA	NA
Recall chest CT scan	275 (4)	267 (4)	8 (15)	1,386 (41)[$]	142 (3)	NA	NA	NA	NA
Recall chest CT scans/subject	1.1	1.1	1.4	1.1	NA	NA	NA	NA	NA
Chest X-ray	35 (0)	17	18 (33)	NA	NA	NA	64 (4)	NA	NA
PET or PET/CT	0 (0)	0 (0)	0 (0)	NA	66 (1)	NA	NA	NA	NA
MRI	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA	NA	NA
Lung function test	103 (1)	55 (1)	48 (89)	NA	NA	NA	70 (4)	NA	NA
Bronchoscopy	98 (1)	46 (1)	46 (85)	NA	NA	NA	14 (1)	NA	NA
FNA	3 (0)	3 (0)	0 (0)	NA	NA	16 (1)	18 (1)	NA	NA
Invasive procedure*	61 (1)	13 (0)	48 (89)	NA	NA	NA	NA	NA	NA

Definition of abbreviations: FNA:Fine needle aspirate; PET:Postron emission tomography; CT: computer tomography; MRI:Magnetic resonance imaging; NA: not available; †Diagnostic follow-up available for 316/325 and 351/360 participants with a positive test result at 1st and 2nd round screening, respectively; *includes: lung biopsy or wedge resection, video -assisted thoracotomy, thoracotomy, mediastinoscopy and mediastinotomy; $: included PET and PET/CT.

Among participants with an indeterminate result, 276 had a follow-up scan 77±36 days after the second-round screening and 231 had a follow-up scan 364±36 days after the second-round screening. The follow-up scans were positive in 38 subjects, and when the results of these positive follow-up scans were added to the results of the 90 positive screening scans, there were 128 subjects (1.8%) with positive second-round scans. Of these 128 participants, 1 patient died as a result of a metastatic colon carcinoma and 118 were referred for workup; 54 of the 118 who were referred for workup (45.8%) received the diagnosis of lung cancer, mainly after undergoing an invasive procedure (88.9%). The nine participants who were not referred for workup (four because of a decision by the tumor board, four because of an administrative error, and one because the patient was already receiving treatment from another specialist) were invited to participate in the third round of screening 2 years later. In one of these nine, lung cancer was found 23 months after the first detection of the nodule in a nodule that had not been seen previously. Of the remaining 64 subjects with a positive scan, 62 had benign disease and 2 had another cancer (1 a thymoma and 1 lymphoma). There were two subjects with suspicious lesions from whom no tissue could be obtained for histologic diagnosis. These subjects were treated with high-dose radiotherapy because the lesions were new and growing and were positive on a PET scan. The 54 participants with lung cancer had 57 cancerous nodules, 42 of which (73.7%) were classified as pathological stage I, including 3 that were synchronous double tumors. The lung-cancer detection rate was 0.5% (40 of 7289) during the first year after the second-round screening and 0.8% (57 of 7289) for the entire 2-year period after the second and third rounds of screening. One stage IV small-cell and one stage IV large-cell interval carcinoma, both of which were present in nodules that had been absent at the time of the second-round screening, were diagnosed during the first year after the second-round screening. The sensitivity of the second-round screening was 96.4% (95% CI, 86.8 to 99.1), the specificity was 99.0% (95% CI, 98.7 to 99.2), the positive predictive value was 42.2% (95% CI, 33.9 to 50.9), and the negative predictive value was 99.9% (95% CI, 99.9 to 100.0).

Additional Diagnostic Investigations

The recall rates for CT scans among participants with indeterminate test results were 19.0% and 3.8% in rounds one and two, respectively (Table 2 in the Supplementary Appendix). No diagnostic PET or PET–CT scanning was performed in participants with positive test results, and fine-needle biopsy procedures were performed in less than 1% of the subjects. The rate of invasive diagnostic procedures was 1.2% in round one and 0.8% in round two.

Discussion

In a population that was at an increased risk for lung cancer, our strategy of screening for lung cancer with the use of volume CT diminished the need for follow-up evaluation in participants with an indeterminate test result. This strategy was especially useful during the second-round screening. It reduced the number of follow-up examinations in participants with a positive test result without reducing the overall sensitivity of the technique, as compared with that reported in the literature.[4-8, 21, 24-28] This report concerns itself only with how to deal with an abnormality that has been detected on a CT scan in this population; it does not address the usefulness of screening for lung cancer with the use of CT scanning. The rate of interval cancers that were found in participants in our trial was similar to that found in participants in other trials.[27] The proportion of early (stage I) lung cancers detected in round one (63.9%) was similar to that found in other randomized trials,[25, 26, 28] but lower

than that found in nonrandomized trials (e.g., the proportion in the International Early Lung Cancer Action Program [I-ELCAP] was 86%, and the proportion in a trial performed at the Mayo Clinic was 75%).[6, 7, 27] The lung-cancer detection rate in round one in I-ELCAP was higher than that in NELSON (1.3% vs. 0.9%),[7] despite similar median ages of the participants and a higher number of pack-years smoked by participants in NELSON. The discrepancy was probably due to the fact that the proportion of women, who tend to have slow-growing cancers,[29, 30] was higher in I-ELCAP than in NELSON. Moreover, in I-ELCAP surgeons removed any nonsolid nodule that was larger than 8 mm, instead of waiting for the nodule to grow before removing it, as was done in NELSON. In our trial of subjects who had an increased risk of lung cancer, we found that the chances of finding lung cancer on a CT scan at 3 months, 1 year, and 2 years after a negative first-round test were 0, 1 in 1000, and 3 in 1000, respectively. In round one, the proportion of invasive procedures that revealed benign disease was 27.2%, which is similar to that found in other trials.[5, 6, 18-24, 26] The advantages of volumetric measurements become fully apparent when a volumetric comparison can be made with a previous indeterminate CT scan. Because there were no comparative CT scans available at round one, the first-round recall rate was almost as high as that in other trials (Table 2). The LungCare software version that we used is not proprietary and can be used with any CT data set, regardless of the CT system, for evaluation of solid nodules and the solid component of partially solid noncalcified nodules smaller than 500 mm^3. With manual correction, the mean relative deviation from the true lesion volume was only −0.3±6.5% for these types of lesions.[13] As an absolute standard for negative test results, we used the absence of lung cancer after 2 years of follow-up, a period that is considered to be sufficient for concluding that a nodule is benign. The 400-day threshold for volume-doubling time that we used was based on current opinion that lung cancers with a volume-doubling time of 400 days or more are overdiagnosed cases.[29, 31] A volume-doubling time of 500 days is regarded as the upper limit for lung cancer, even though some tumors may grow more slowly[32-34]; our upper limit was set at 600 days. If a lower upper limit had been used, the rate of false negatives would have increased, but the rate of false positives would have decreased. Therefore, the ranges for volume-doubling time that we used are not definite and could be improved. Finally, before we can make clinically directive recommendations, our strategy requires validation in an independent study.

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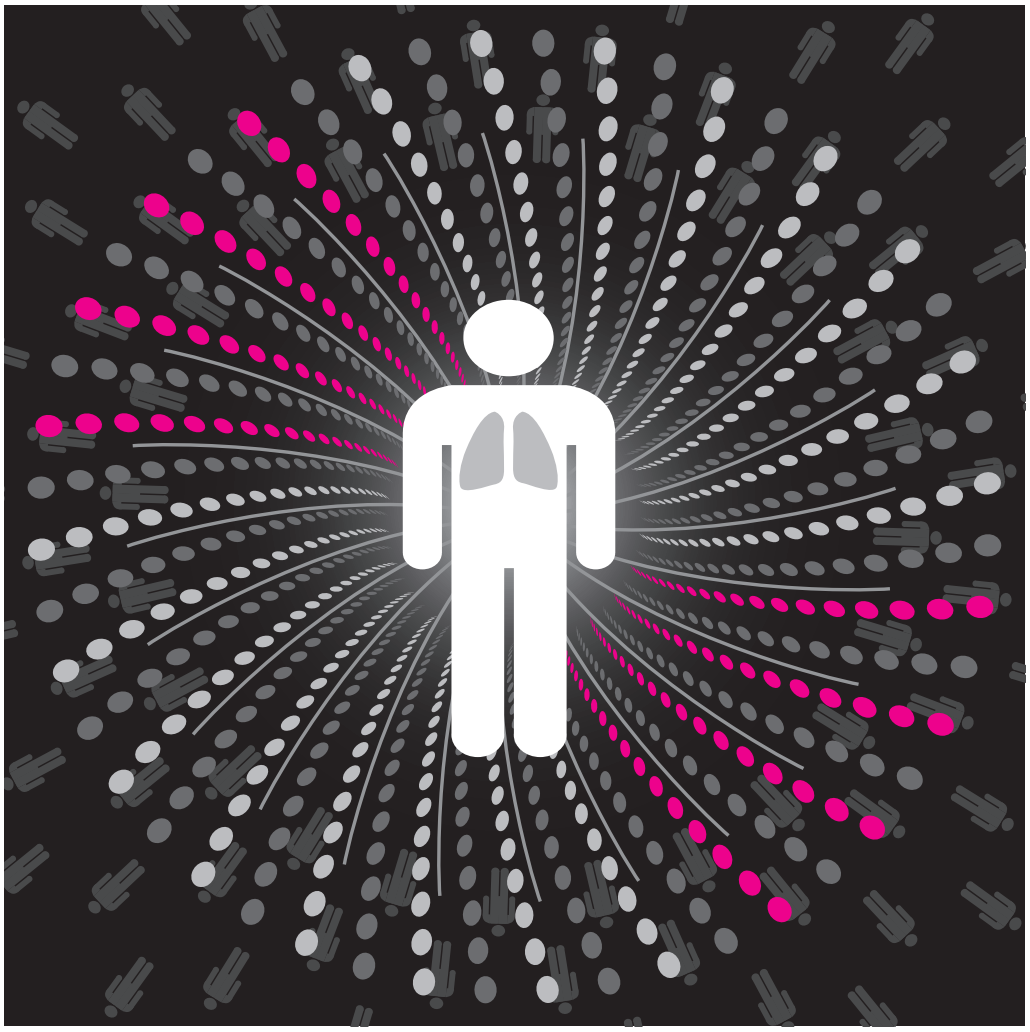
Part II

Management of suspicious pulmonary nodules: imaging studies and bronchoscopy

Chapter 4



How to deal with incidentally detected pulmonary nodules less than 10mm in size on CT in a healthy person

Susan C. van't Westeinde, Harry J. de Koning, Dong-Ming Xu, Henk C. Hoogsteden, and Rob J. van Klaveren

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ABSTRACT

The high frequency of non-calcified pulmonary nodules (NCN) <10mm incidentally detected on a multi-detector CT (MDCT) of the chest raises the question of how clinicians and radiologists should deal with these nodules. Management algorithms for solitary pulmonary nodules >10mm do not carry across to sub-centimeter lesions. Purpose of this review is to provide a 10-step approach for routinely detected sub-centimeter NCN on a MDCT in healthy persons in order to be able to make an optimal discrimination between benign and malignant NCNs. Recommendations are primarily based on individual cancer risk, the presence or absence of calcifications and nodule size. In nodules >4—5mm nodule consistency, margin and shape should be taken into account. Next steps in the nodule evaluation are the assessment of localization, nodule number, presence or absence of growth and volume doubling time. Growth is defined as a volume doubling time of 400 days or less, based on volumetry. For nodules <4mm, a follow-up CT at 12 months is recommended in high risk persons, whilst for low-risk persons no follow-up is needed. If no growth is observed at 12 months, no further follow-up is required. For solid, smooth or attached indeterminate NCN between 5 and 10mm we recommend an annual repeat scan, whilst for purely intra-parenchymal nodules a 3-month repeat scan should be made to assess growth. Growing lesions with a volume doubling time <400 days require further work-up and diagnosis, otherwise an annual repeat scan to assess growth is recommended.

Introduction

The high frequency of small pulmonary nodules incidentally detected on a multi-detector CT (MDCT) of the chest made for purposes other than lung cancer screening, raises the question of how clinicians and radiologists should deal with these nodules. In the pre-CT scan era pulmonary nodules detected on a routine chest X-ray were usually solitary, i.e. solitary pulmonary nodules (SPN). They are defined as being <30mm in size, usually >10mm, completely surrounded by pulmonary parenchyma and not associated with lymphadenopathy, atelectasis, or pneumonia.[1] There is a significant amount of literature available on the predictive factors for malignancy in SPNs. Correct discrimination between benign and malignant is important to avoid unnecessary invasive procedures, morbidity and costs.[2-5] By entering SPN characteristics (size, edge, location, type of calcifications) and patient risk factors (age, prior history of cancer, smoking history) in the web-based questionnaire, which can be found at http://www.chestxray.com/SNP/SNProb.html, the probability that an SPN is malignant can be provided on-line.[6] Despite this decision algorithm futile invasive surgical procedures for benign lesions by video-assisted thoracoscopic surgery (VATS) or thoracotomy occur in approximately 50% (range 9—68%) of the SPNs detected.[2-4, 7, 8] With the advances in radiological techniques and the introduction of MDCTs with small collimations in our routine medical practice more and also smaller, sub-centimeter nodules are being detected (Fig. 1). More than 50% of the SPN on chest X-ray appear to be multiple on CT[5, 9, 10] and prevalence rates of small pulmonary nodules detected on MDCT range between 17 and 51% in various screening programs.[9, 11-13] Sub-centimeter nodules are very common, accounting for about 80% of all non-calcified nodules (NCN) detected[14, 15] and malignancy rates between 1 and 18% have been reported.[11, 15, 16] The most challenging category is formed by the 5—10mm NCN, so called indeterminate nodules, representing 23—53% of all pulmonary NCN detected at baseline screening in a high risk population.[10-12, 17] Due to their small size they are less amenable than larger nodules to characterization by means of 18F-labeld-2-deoxy-D-glucose positron-emission tomography (FDG-PET); CT contrast enhancement or percutaneous biopsy and the accuracy of CT-guided biopsies is significantly lower.[18] NCNs <5mm, arbitrary called ‘‘ditzels’’, comprise up to 50% of all NCNs detected at baseline screening[14] and are essentially not seen on a chest X-ray unless calcified. The advances in knowledge derived from the low-dose multi-detector screening programs for lung cancer in high risk persons, especially experience on how to deal with nodules detected at baseline screening without information from previous CT scans, can be applied to individual high risk healthy subjects with incidentally detected pulmonary nodules on a standard dose MDCT. The purpose of this review is to provide an up-to-date approach to routinely detected sub-centimeter NCNs on MDCT in healthy persons in order to be able to make an optimal discrimination between benign and malignant NCNs. Although this review will especially focus on sub-centimeter lesions, comparisons with larger SPNs will be made. Reviews on the further work-up and treatment of potential malignant nodules can be found elsewhere.[6, 19-25]

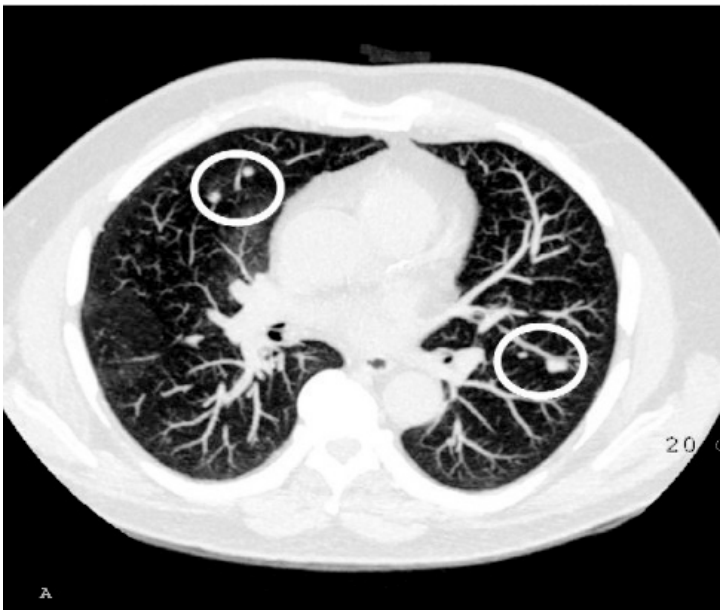

Figure 1. *Example of a patient with multiple small non-calcified pulmonary nodules, which often poses clinicians and radiologists for a diagnostic dilemma (transverse thin-section image, Sensation-16, Siemens Medical Solutions, Forchheim, Germany).*

Patient characteristics

The first step in the evaluation of a NCN detected on a routine MDCT is, as for the larger SPN, to assess a person's individual lung cancer risk. The following factors are widely accepted as independent risk factors for lung cancer: tobacco consumption, advanced age, the presence of chronic obstructive pulmonary disease (COPD), a previous history of cancer and lung fibrosis (Table 1).[26-28] In patients with a history of cancer, the probability that a pulmonary nodule is malignant increases when there is a history of extrathoracic cancer.[29] Patients with a known malignancy are more likely to have either a metastasis or to develop a second primary lung cancer.[30, 31] Patients with a history of lung or head and neck cancer in particular are at high risk with a cumulative increase in lung cancer risk of 2—3% per year for the development of a second primary lung cancer.[32, 33] High risk smokers can be defined as those with a smoking history of at least 30 years and an average consumption of at least 20 cigarettes a day, and ex-smokers who quit <10 years ago.[34] There is strong evidence that smoking duration is much more important than the number of cigarettes smoked per day.[35] The relationship between lung cancer risk and duration of smoking cessation is uncertain.[36] Halpern et al.[37] found smoking cessation beneficial at any age, with much greater benefits for those quitting at a younger age. Others state however that the difference between quitters and current smokers appears to be explained almost entirely by differences in duration of smoking by the two groups.[36] Age is a major independent risk factor; cancer is rare in patients younger than 35 years of age.[38] The likelihood of malignancy in SPN has been found to increase more than twofold for every 10-year increase in age[39], with peak incidence in the eighth decade of life.[29]

Table 1. *Individual assessment of lung cancer risk*

Variable	Risk of lung cancer		
	Low	Intermediate	High
Age	<45 years	45—60 years	>60 years
Smoking	Never	Current and former <20 cigarettes/day <30 years of smoking Quit >10 years	Current and former >20 cigarettes/day >30 years of smoking Quit <10 years
(Previous) malignancy	None	>5 years	<5 years

Nodule calcification

After assessing the individual cancer risk, the next step in the evaluation of pulmonary nodules is to determine whether a nodule is calcified or not, and if so, what the calcification pattern is (Table 2). For sub-centimeter nodules a high resolution CT scan with a collimation <2.5mm is needed in order to be able to determine the pattern of calcification, if present. A solitary pulmonary nodule without calcifications is called a non-calcified nodule. A nodule <5mm is defined as non-calcified if it appears uniformly less dense than the ribs (on bone and lung windows).[40] A nodule 5—20mm is defined as non-calcified if less than 50% of its surface is ''calcified'', calcification does not correspond to a classical benign pattern (complete, central, lamellated, popcorn), and/or the edge is spiculated.[40] In benign SPNs benign calcification patterns can be central, laminated, popcorn or diffuse, based on which the diagnosis of benignity can reliably be made.[41, 42] However, a pattern of benign calcification is only present in a minority of benign SPN. Diederich et al.[10] observed homogeneously calcified nodules in only 7% of individuals with SPN. Additionally, malignant lesions can also be calcified, with an amorph pattern in up to 14%.[42]

Nodule size

The most important determinant for malignancy is nodule size (Table 2). Many investigators have established the positive correlation between nodule diameter and cancer risk.[10-12, 14, 17, 23, 43] A pleural plaque is not a nodule and therefore needs no follow-up. Cancer risk in <5mm ditzels is low, but not absent. In the Early Lung Cancer Action Project (ELCAP) study, 1 malignant lesion was detected among 99 participants with nodules measuring 2—5mm (1%).[11] Gohagan et al.[12] identified lung cancer in 4% of all ditzels. Therefore, ditzels cannot routinely be neglected as negative findings because a very low proportion may harbor lung cancer.[11, 15] The most important factor for determining the probability of malignancy in ditzels is the presence of growth, as surface characteristics are unreliable due to their small size.[44] According to the Fleischner Society recommendations[23] no repeat scan should be made for low risk persons, while high risk persons should receive a repeat scan at one year. If unchanged at that interval, no further follow-up is required. Xu et al. retrospectively investigated the role of size, shape, margin and CT density in the differentiation between benign and malignant NCNs in 469 nodules (indeterminate nodules measuring 5—10mm and potential malignant nodules >10mm) detected at baseline screening of the Dutch—Belgian lung cancer screening trial (NELSON).[13] Although univariate analysis showed that lobulated, spiculated, irregular and larger nodules above 10mm had an increased likelihood

for lung cancer compared to smooth, round or polygonal and indeterminate nodules between 5 and 10mm, respectively, the 95% confidence intervals were wide, except for tumor size. In multivariate analysis only tumor size (volume) remained highly significantly associated with the presence of lung cancer with small 95% confidence intervals.[13]

Nodule consistency

Apart from size, nodule consistency is also important for the assessment of cancer risk (Table 2). A non-solid nodule, previously also called ground-glass opacity (GGO), is a density through which aerated lung parenchyma is visible. A part-solid nodule contains a solid component that partly obliterates the aerated part. The solid part represents the collapse of alveoli and may contain fibrosis and possible tumor cells. Among all NCN detected, solid nodules are most common (56%), followed by non-solid nodules (12%) and part-solid nodules (7%).[45] The malignancy rate is highest for partly solid nodules (63%) followed by nonsolid (18%) and solid nodules (7%)[45] (Table 2). Scars with GGO areas around it may mimic part-solid nodules, but they are not associated with an increased cancer risk, whereas true part-solid nodules are. The malignancies detected in pure GGOs are usually bronchioalveolar carcinomas (BACs).[46, 47] Many authors have established the minimal invasive behavior and excellent prognosis of BAC[48], but more research is needed to obtain information about the relation between the proportion of GGO and clinical outcome. Until then, frequent follow-up is warranted for part-solid and non-solid lesions. In the NELSON trial, part-solid nodules with a solid component >500mm^3 (>10mm in diameter) are referred for immediate work-up and diagnosis. For part-solid lesions with a solid component between 50 and 500mm^3 (5—10mm in diameter) and for non-solid nodules >8mm in diameter a 3-months follow-up CT is recommended.[49] Asamura et al. even recommends follow-up CTs every 4 months for GGO lesions <10mm.[47]

Nodule margin and shape

Scalloped borders and lobulation are associated with intermediate risk of cancer, irregular margins with high cancer risk[25, 46], whilst smooth borders are more suggestive of a benign diagnosis (Table 2). Lobulation is defined as an abrupt bulging of the contour of the lesion and spiculation as the presence of thicker strands extending from the nodule margin into the lung parenchyma without reaching the pleural surface.[29, 47] A typical feature of benign hamartomas is their smooth or lobulated border. This explains why scalloped or lobulated borders are only associated with an intermediate cancer risk (Table 2). Gurney[29] calculated likelihood ratios for SPNs ranging between 14 and 47mm in size based on several patient and nodule characteristics including nodule margin. The question is, however, whether these features to predict malignancy can be carried across to sub-centimeter nodules. Swensen et al.[6] also included smaller SPN in their prediction model (range 4—30mm, mean 12.3mm) and identified a spiculated margin as one of the independent risk factor for malignancy. Xu et al.[13] retrospectively analyzed the internal and external features of indeterminate and potential malignant NCNs 5—10mm in size detected within the context of the NELSON trial. They found an increased likelihood of malignancy in lobulated and spiculated versus smooth nodules and irregular versus round and polygonal nodules although these differences narrowly reached significance. The reasons for this weaker correlation with malignancy compared to SPNs is probably due to the fact that with increases in size nodules become more lobulated, spiculated and irregular in shape. This is supported by serial CT scan data from Lindell et al.[46] based on 48 tumors detected within

the Mayo Clinic lung cancer-screening program. In 20 of them, the margin in 80% became more spiculated and irregular over time. On the other hand, Xu et al. found no change in morphology, shape and margin over time in 372 indeterminate pulmonary nodules between 5 and 10mm.[48] Xu et al.[49] also found that non-spherical nodules, defined as a maximal diameter larger than twice the minimal diameter of the nodule, had an 8.5-times higher risk for malignancy than typical spherical nodules (Table 2). For BAC, an equal distribution of smooth, irregular and spiculated margins has been found.[31] For nodules with cavitation it has been shown that a wall thickness >16mm is associated with malignancy and a wall thickness <4mm with benign lesions.[50] For subcentimeter nodules however, cavitations and wall thickness are of limited value, given their small dimensions.

Table 2. *10-step approach to estimate cancer risk in incidentally detected sub-centimeter pulmonary nodules detected on multi-detector CT in high-risk healthy persons.*

	Step	Lung cancer risk
1	Assess individual cancer risk [29,38,39]	See Table 1
2	Is the nodule calcified? [18,40]	Benign pattern: low No: potentially malignant Malignant pattern: high
3	Estimate the largest nodule diameter [6,14]	<5mm: low 5—10mm: intermediate >10mm: high
4	Determine the nodule consistency [45,47,49]	Solid: low Non-solid: intermediate Part-solid: high
5	Define the nodule margin [29]	Smooth: low Lobulated or scalloped: intermediate Spiculated: high
6	Define the nodule shape	Spherical: low Non-spherical: high
7	Where is the nodule situated? [29,54]	Lower lobes: low (Right) upper lobe(s): high Attached to vessel/pleura/fissure: low Purely intra-parenchymal: high
8	Does the nodule density increase over time [52]	No: no increase in cancer risk Yes: increased cancer risk
9	Is the nodule growing? [49]	No, PVC <25%: low Yes, PVC ≥25%: high
10	What is the VDT of growing nodules? [64,65]	VDT >600 days: low VDT 400—600 days: intermediate VDT <400 days: high

VDT: volume doubling time; PVC: percentage volume change.

Nodule location

Intra-pulmonary location appears to be a useful discriminator between benign and malignant indeterminate NCNs. Xu et al.[49] found that of the solid indeterminate nodules between 50 and 500mm^3 (5—10mm in diameter) 54% were attached to either a vessel or a fissure or were pleuralbased and, 73% were smooth. At one year of follow-up, none of these attached or smooth nodules had evolved towards cancer. Therefore, in attached and smooth indeterminate nodules an annual repeat scan suffices.[49] In addition Takashima et al. found a high association between benignity for lesions with concave margins and polygonal

shape which were demarcated on CT by interlobular septa (80% of 30 lesions) or intra-lobular bronchioles or arteries (20%).[47] Localization in upper lobes, especially in the right upper lobe, has also been established as a risk factor for cancer, not only for SPNs but also for sub-centimeter lesions[46, 51-55] (Table 2).

The number of nodules

The number of pulmonary nodules detected has increased with the introduction of thin-slice MDCT scanners. In high-risk persons, each nodule detected should be regarded as potentially malignant, irrespective of the total number of nodules detected. This is illustrated by Crow et al.[31] Their study found that the metastases in patients who died of cancer had a predominant sub-pleural and peripheral distribution and were usually between 2 and 10mm in size. The numbers of lesions found in this study was not helpful in distinguishing benign from metastatic disease. Other investigators did not find an association between cancer risk and the number of nodules detected.[10, 11, 15]

Nodule growth

Nodule growth and the assessment of the volume doubling time (VDT) are valuable tools to discriminate between benign and malignant nodules, particularly for sub-centimeter NCN, which are less amenable to invasive diagnostic procedures, contract enhancement studies and PET imaging. Growth is highly associated with malignancy, whilst regression or disappearance of lesions establishes the benign nature of the nodule. In the NELSON trial growth has been defined as a 25% increase in volume after at least a 3-months follow-up period, corresponding with a volume doubling time of <400 days.[56] Accurate growth can even be detected in lung cancers as small as 5mm when CT imaging is repeated within a 30-day interval.[57] Serial measurement of volumes, rather than diameters, and computer calculated VDTs are suggested to be accurate enough for the assessment of growth [61—63].[58-60] However, with the current available volumetry software, growth can only be reliably assessed in solid nodules and not in part-solid or non-solid nodules or nodules attached to the pleura, vessels or fissures. For most malignant nodules the VDT ranges between 30 and 400 days (Table 2)[61, 62], while the probability that a nodule with a VDT >600 days is malignant is very low.[63] In the NELSON trial we therefore classified growing nodules into three groups; VDT <400 days, 400—600 days and >600 days, with, respectively, high, intermediate and low cancer risk[56] (Table 2). In the NELSON trial, we found for indeterminate nodules with a VDT <400 days that the positive predictive value of growth for malignancy was only 63%.[49] Therefore, the real value of the growth criterion has to be prospectively investigated based on data of ongoing screening trials. For nodules with growth at 3-months follow-up immediate referral and work-up for diagnosis is generally recommended.[18] It is generally accepted that in the absence of visible growth over a 2-year period a nodule can be regarded as benign.[64] However, BAC and typical carcinoids occasionally appear to be stable for 2 or more years.[25] Cancers may also show sigmoid shaped growth patterns, i.e. without obvious growth over a prolonged period followed by a sudden acceleration in growth. [65] Yankelevitz and Henschke[66] reviewed three surgical series with lesions measuring 10—14mm detected on chest radiography and found that the predictive value for benign disease based on these studies was 65% for 2-year stability.[66, 67] Despite this uncertainty, it seems reasonable, based on current available knowledge, to regard a nodule stable in size for at least 2 years as benign.

CT density and contrast enhancement

Increase in nodule density has been found to be associated with an increased cancer risk in indeterminate solid pulmonary nodules between 5 and 10mm in size during 1 year of follow-up[48] (Table 2). Contrast enhancement CT can be used to differentiate between benign and malignant SPN >7—10mm because the perfusion of malignant pulmonary nodules is both quantitatively and qualitatively different from that of benign lesions.[68] Although excellent high negative predictive values for contrast enhancement have been described for indeterminate nodules >7mm[69], this technique is usually not applicable for nodules <10mm. The intensity of the contrast enhancement is directly related to the vasculature of the nodule, which is increased in malignant nodules.[70] Typically, contrast enhancement <15 Hounsfield Units (HU) is strongly predictive of a benign lesion, whereas enhancement of >20 HU is indicative of malignancy with a sensitivity of 98%, specificity of 58% and an accuracy of 77%.[71] The low false-negative rate of CT-enhancement is potentially valuable in decision-making. Yamashita et al.[72] reported similar results. Earlier studies focused on the early phase of dynamic CT, but more recent studies were able to increase the specificity by adding the delayed nodule washout phase to HDCT studies. With a wash-in of >25 HU and a wash-out between 5 and 13 HU the sensitivity, specificity, and accuracy for detecting a malignancy were between 81 and 94%, 90 and 93%, and 85 and 92%, respectively.[69, 73, 74]

Positron-emission tomography (PET)

A standard uptake ratio of 18F-labeled-2-deoxy-D-glucose (FDG-PET) >2.5 is generally considered to be indicative of malignancy. Sensitivities, specificities and accuracies for malignancy vary between 88 and 96%, 70 and 90% and 83 and 93%, respectively.[21, 75] Although there is a place for FDG-PET in the evaluation of NCNs >10mm[76], there is consensus that there is no role for PET in the discrimination between benign and malignant NCNs in high risk subjects because of the high pre-test probability that a nodule of this size is malignant.[77] In addition, false-negative results can be observed in carcinoids, BACs, adenocarcinoma with BAC features and lesions <10mm.[78, 79] Even in NCNs >10mm the performance of PET within a screening program might be less than expected. In a series of 25 lesions only 39% of the malignant non-BAC lesions (mean size 19mm) and 43% of the benign lesions were PET positive.[80] Published data with a high sensitivity, specificity and accuracy mostly pertain to nodules that are both solid and 10mm or greater in diameter.[76] In 17 studies reviewed for the diagnostic accuracy of PET, PET was found to characterize pulmonary nodules with fairly high sensitivity (80—100%) and a lower and more variable specificity (40—100%). Using a summary receiver operating curve (ROC) method, point estimates for pooled sensitivity and specificity were 87% and 83%, respectively.[77, 81] In a meta-analysis by Gould et al.[82] of 40 studies that examined FDG-PET, a summary ROC was established and, for current practice a sensitivity of 96.8% and corresponding specificity of 77.8% was found. In small subcentimeter nodules the PET scan is not sensitive enough to detect malignant pulmonary nodules.[83] Therefore, its use in such nodules should not be recommended. It is probable that a nodule volume and respiration adjusted standard uptake value (SUV) could help in solving the size and respiratory motion problem particularly for nodules located close to the diaphragm.

Recommendations for follow-up

We should realize, that the recommendations for SPNs do not carry across to sub-centimeter lesions. Based on the experience from lung cancer screening trials, several guidelines for the follow-up of MDCT detected nodules have been developed [18, 24, 76, 77, 84], but it is a rapidly evolving field, and with the increasing knowledge derived from ongoing screening trials, it is very likely that these recommendations will change in the upcoming years and a multivariate cancer risk model for NCN <10mm will become available that is comparable to the one available for SPNs. Based on these new data, it might be expected that the number of repeat scans recommended today for the follow up of these nodules will also decrease. Currently, recommendations are primarily based on the individual cancer risk (Table 1) the additional nodule characteristics should also be taken into account (Table 2). In Table 1, we define low, intermediate and high-risk people, but most follow-up recommendations only recognize low and high-risk subjects. The 10-step approach and risk stratification in Table 2 is based on data from CT screening trials for lung cancer in high-risk subjects. For nodules <4mm, a follow-up CT at 12 months is recommended for high risk persons, whilst for low-risk persons a follow-up scan is not a standard recommendation.[14, 77, 84] If no growth is detected at 12 months, the Fleischner Society[23] recommends no further follow-up, but Winer-Muram[18] recommends another repeat scan at 24 months for intermediate and high-risk population. The ELCAP protocol[84] recommends a follow-up CT at 12 and 24 months for NCN <5mm. Arriving at a management strategy for indeterminate nodules (5—10mm in diameter) is challenging. The ACCP guidelines recommend frequent follow-up for high-risk individuals with nodules measuring 6—8mm (6, 12 and 24 months). Winer-Muram recommends an additional intensive follow-up regimen (3, 6, 12 and 24 months, or direct biopsy) for intermediate and high-risk population. Based on results from our NELSON trial we demonstrated that for a large subgroup of indeterminate nodules a repeat scan at 3 or 6 months is not needed. Of all solid indeterminate nodules between 50 and 500mm^3 (5—10mm in diameter) 55% was attached to either a vessel, a fissure or was pleural based and 73% was smooth. At 1 year of follow-up, none of the attached or smooth nodules had evaluated towards cancer. Therefore, in attached and smooth indeterminate nodules an annual repeat scan suffices, while only for a small subgroup of purely intra-parenchymal indeterminate nodules a 3-month repeat scan is recommended.[49] In case of growth at 3-months follow-up, a histological diagnosis should be obtained. If no growth is present, we advice a repeat CT scan 9—12 months later, in concordance with the I-ELCAP protocol[84] but in contrast to several other guidelines in which a more frequent follow-up is recommended.[18, 77] For the more slowly growing non-solid nodules a follow-up scan after 3 months is also not required and instead a repeat scan after 6—12 months is recommended. Follow-up recommendations for SPN >10mm are outside the scope of this review and can be found elsewhere.[21, 23, 24, 77, 84]

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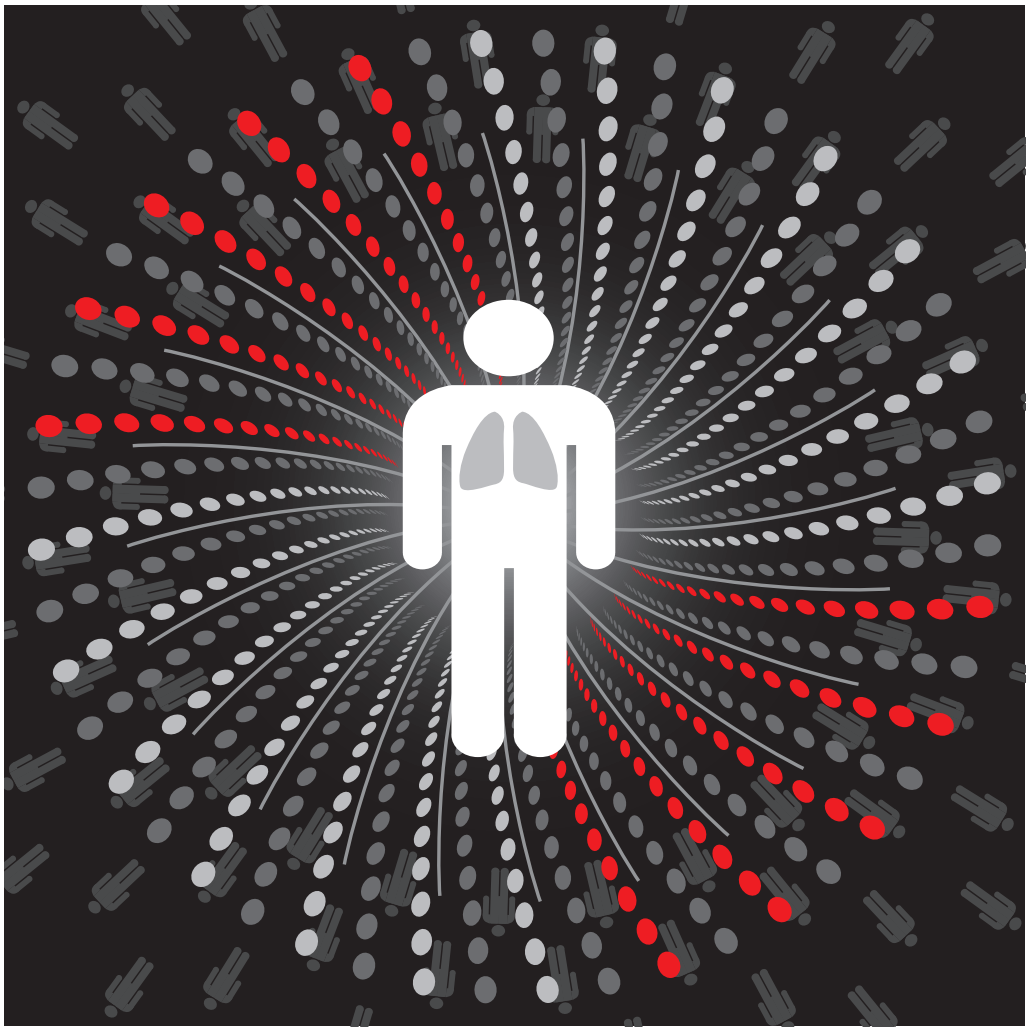
Chapter 5



Stem Cells and the Natural History of Lung Cancer: Implications for Lung Cancer Screening

Rob J. van Klaveren, Susan C. van't Westeinde, Bart-Jan de Hoop, Henk C. Hoogsteden

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ABSTRACT

Lung cancer is not simply a single disease, but a collection of several phenotypically very diverse and regionally distinct neoplasias. Its natural history is complex and not yet fully understood. Stem cells and the complex interaction with the microenvironment of the tumor and the immune system play an important role in tumor progression and metastasizing capacity. This finding explains why lung cancer does not always follow the multistep carcinogenetic and exponential growth model and why small lesions do not always equate to early-stage disease. Despite the fact that volume doubling times are increasingly used as surrogate markers for the natural history of lung cancer and as estimates for the proportion of overdiagnosed cases, it is only a momentary impression. At baseline screening especially, screen-detected lung cancer cases are preferably detected when they are in the indolent phase of their growth curve (length-biased sampling), from which it can by no means be concluded that they may not progress or metastasize at a later stage. Because the natural history of lung cancer is only partly elucidated, conclusions on the impact of over diagnosis in lung cancer screening are premature.

The Current Paradigm of Lung Cancer Development

Lung cancer is a collection of several phenotypically diverse and regionally distinct neoplasias. In the absence of screening, lung cancer patients present only when they become symptomatic. At that time, the disease is usually incurable due to its advanced stage with local or distant metastases. Although chest X-ray screening trials in the 1970s were negative, recent advances in technology have lead to new observational and randomized trials with low-dose, multidetector CT techniques.[1-4] These trials try to answer the question of whether it might be possible to detect smaller and therefore more curable lesions by CT and to reduce lung cancer mortality. Based on West's universal law of growth in living organisms, it has been demonstrated that tumor size correlates with clinical outcome.[5] Guiot and colleagues showed that tumors follow a universal exponential growth curve under unrestricted dietary conditions.[6] Adjustments to these growth dynamics have been made due to the effect of lack of nutrient supply, increases in mechanical stress, growth promotor/inhibitor interaction, and the impact of interactions with the microenvironment.[7] Based on many experimental and clinical observations, it has now been accepted that tumors initially grow rapidly (exponentially or superexponentially), but, according to the Gompertzian growth curve model, increasingly slow their growth as they become larger so that the tumor size trends to a constant level as time increases.[8, 9] According to this model, metastatic dissemination, tumor cell invasion, and angiogenesis will start once a tumor reaches a ''critical'' volume, due to the rising mechanical stress exerted by the microenvironment.[6] This threshold has been investigated for breast cancer and lung cancer in which a strong relationship between, respectively, tumor size and axillary and mediastinal lymph node involvement and survival has been observed.[2, 10-12] A consequence of the current paradigm of lung cancer development is that there is a threshold before which treatment (surgical resection) can be curative, whereas, later, it can only be locally effective. The question remains as to whether this multistep carcinogenetic model always reflects the observed natural history of lung cancer. The validity of predictions on survival time based on the exponential growth model, including the assumption that death occurs, on average, after 40 to 41 tumor doublings, has been questioned because the estimated survival times based upon these models are much longer than those observed in reality.[13] So far, there is no evidence that size always correlates with biologic behavior and that small lesions are always equivalent to early-stage disease (Fig. 1).[14] In patients with lung cancer who undergo surgical resection for early Stage I or II disease, only 60% to 70% will be cured, whereas the other patients, despite having early-stage disease and complete surgical resections, have recurrence of their disease and ultimately die. Another consequence of adherence to the current growth paradigm is that malignant nodules will continue to develop and grow unless they are surgically removed. Yet it may be the case that some will stabilize, shrink, or grow so slowly that even if left in situ they will not all develop into lethal lesions.[15] Finally, multistep carcinogenesis may not be able to account for dramatic cases of lung cancer that develop in very short intervals (Fig. 2). The low interval cancer rate observed in lung cancer screening trials might argue against the frequent occurrence of this type of rapidly evolving cancers, but, given the lack of long-term follow-up on negative screens in the published series so far and the lack of individual nodule history tracking, current available data should be interpreted with caution. This evidence suggests that although the current paradigm is well supported and might be applicable for a certain subset of cancer cases, it does not explain all lung cancer biology.

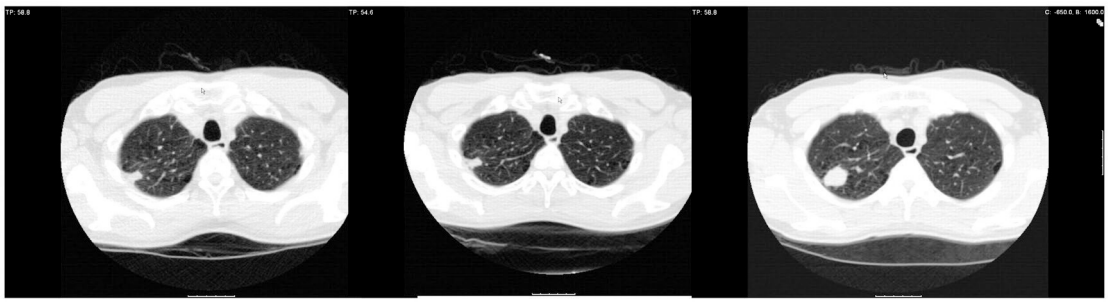

Figure 1. *A 52-year-old man with a 14-mm nodule in the right upper lobe (left). A 3-month repeat scan showed no growth (middle), but an evaluation 1 year later showed significant growth and the detection of an adenocarcinoma of the lung with mediastinal lymph node involvement (pT2N2Mx) (right).*

Volume Doubling Time and the Natural History of Lung Cancer

Based on the observation that tumor size at the time of detection is not always consistent with the biological behavior of a tumor, it has been proposed that the volume doubling time (VDT) could serve as a surrogate maker for lung cancer biology. With the conduct of CT lung cancer screening trials and the use of computerized volumetric software, new information on the natural history of screen-detected lung cancer is rapidly accumulating. It has been found that CT screen-detected lung cancer has markedly longer VDTs, and that a substantial portion has substantially longer VDTs (> 400 days) compared to those detected in routine medical care.[13] Based on this observation, it has been hypothesized that screen-detected lung cancer might represent a disease entity of its own and not be the precursor of advanced-stage disease.[16] Hence, advanced-stage lung cancer may not have had detectable and curable disease in the past. Based on this hypothesis, two different types of lung cancer have been proposed: screen-detected and advanced-stage disease lung cancer.[16] Evidence for this view has been derived from the comparison of the pooled data of three observational CT screening trials with the Bach's lung cancer risk model.[17] In this comparison, lung cancer screening led to the detection of more early-stage disease than expected, without a reduction in the proportion of advanced-stage disease. However, the use of the VDT as a surrogate marker for lung cancer biology has several limitations. Due to the fact that the VDT data are so far largely based on 2D manual measurements, VDT assessments are subject to measurement errors. In addition, the VDT is not a reflection of the total growth curve of the tumor, but merely a momentary impression. Nodule growth may be absent for a certain period of time, and tumors may even shrink or show very slow growth (VDT > 400 days) with a sudden acceleration in growth and metastasizing behavior. In addition, indolent or even absent tumor growth may be associated with the development of distant metastasis. Therefore, we believe that it is inappropriate to assume that lung cancer cases with a VDT > 400 days are, per definition, overdiagnosed cases based on the argument that it would take more than 30 years to grow from a 1 cm lesion to a size that is usually lethal, because it is based on the simplified assumption that cancers double at a constant rate, which is, without doubt, inaccurate. Recent advances in knowledge regarding

the potential role of cancer stem cells in the natural history of lung cancer and its interaction with the microenvironment and the immune system may provide alternative explanations for the observed biological behavior of lung cancer that does not always fit into the multistep carcinogenetic model.

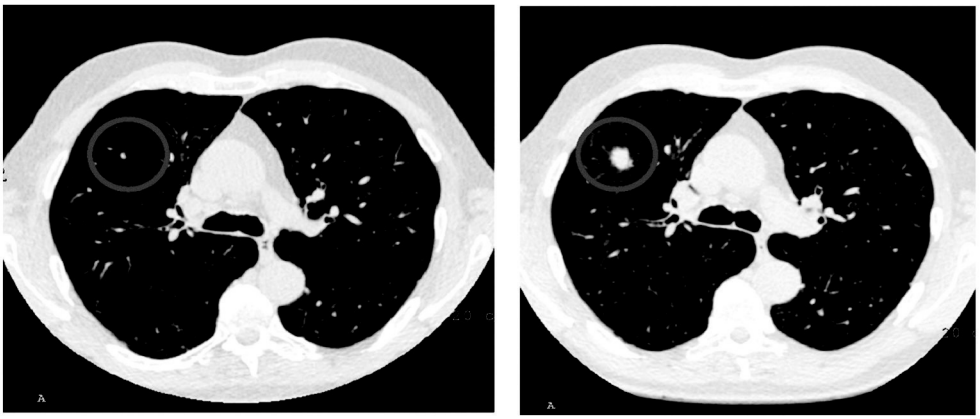

Figure 2. *A 63-year-old man with a small pulmonary nodule <5 mm in the right upper lobe. At the 1-year follow-up, the nodule had significantly grown and upon work-up appeared to be a stage IV adenocarcinoma of the lung with brain metastases.*

Cancer Stem Cells and Lung Cancer Development

Cigarette smoke results in epithelial damage and signaling events that elicit wound repair and a proinflammatory state. The presence of proinflammatory cytokines and chemokines released from healing wounds may be responsible for the recruitment of differentiated cells such as neutrophils and macrophages, and it may also lead to organ-specific stem cell proliferation and the recruitment and proliferation of bone marrow- derived stem cells.[18, 19] Respiratory stem cells and bone-marrow-derived stem cells have the function to repair injured or destroyed tissues within the lung by their capability to self-renew and differentiate into mature cells.[20, 21] Most adult tissues harbor stem cells, and, in lung cancer tissue, a rare population of cancer stem-like cells has been identified.[22-24] There is mounting recent evidence that there are two different processes of (lung) cancer development: a localized and a systemic one.[22] The prevailing view is that lung cancer development starts as a localized process in which the disease originates from the transformation of lung epithelial cells or lung cancer progenitor cells by carcinogens. The metastatic potential in progenitor cells could be acquired by accumulating genetic and/or epigenetic alterations occurring during cancer progression (multistep carcinogenesis). Alternatively, they may also arise from transformed stem cells through genetic mutation or from epithelial cells, which acquire stem-cell physiology through activation of distinct gene expression profiles[22, 25, 26], although validation of this cancer stem cell concept in solid tumors is still lacking (Fig. 3). Kim and colleagues have been the first to identify a rare population of bronchioalveolar cancer stem cells (BASCs) in lung cancer mouse models, and they hypothesized that BASCs might be the putative precursor cells of lung adenocarcinomas, although without definitive evidence so far.[27] Stem cells appear to be protumorigenic and must first receive at least one permanent genetic mutation to destabilize their growth prior to cancer initiation. Once mutated, cancer

stem cells have limitless proliferative capacity and give rise to daughter progenitor cancer cells that have limited proliferative capacity.[22, 25, 26] In the systemic route of lung cancer development, stem cells have the ability to circulate and home to different organs without acquiring their metastatic potential. A stem-cell-derived lung cancer might thus, from the very beginning, be a systemic disease and be incurable with local resection. There is indeed evidence that the presence of cancer stem cells in human tumors, including lung cancer, correlates with clinical outcome.[28] The functional properties of cancer stem cells may also be influenced through external signals mediated by further differentiated cancer cells and host stroma cells, including activated fibroblasts and infiltrating immune cells such as macrophages and endothelial cells, and cancer stem cells may remain dormant, without metastasizing capacity, for a certain period of time. So far, the metastatic phenotype has been regarded as a cell-autonomous alteration specified by the genome of the cell. However, there is also evidence that cancer cells acquire their metastatic phenotype due to exposure of epithelial cancer cells to paracrine signals that they receive from mesenchymal cell types within the tumor-associated stroma.[29] Recent reports propose that bone-marrow-derived mesenchymal stem cells are recruited in large numbers to the stroma of developing tumors through the release of various endocrine and paracrine signals. Upon interaction with the cancer cells, the metastatic potential is largely increased, but it may revert to a lower metastatic state once they are no longer in contact with these stem cells.[30] These data illustrate that the tumor microenvironment facilitates metastatic spread by eliciting reversible changes in the phenotype of cancer cells and highlights the recently discovered critical role of chemokine networks in malignant progression. Certain tumors recruit, at a certain moment, bone-marrow-derived endothelial progenitor cells, which appear to be pivotal for the progression of avascular, dormant or micrometastatic tumors to lethal macrometastatic ones. They do so by producing distinct pro-angiogenetic chemokines, which interact with these endothelial progenitor cells to initiate and possibly maintain nascent vessels within specific primary and metastatic lesions. These data suggest that bone-marrow-derived hematopoietic progenitor cells initiate metastatic colonization, the so-called angiogenetic switch.[31, 32] When these events occur in the natural history of cancer development is yet unknown, but this process might be independent of tumor size.

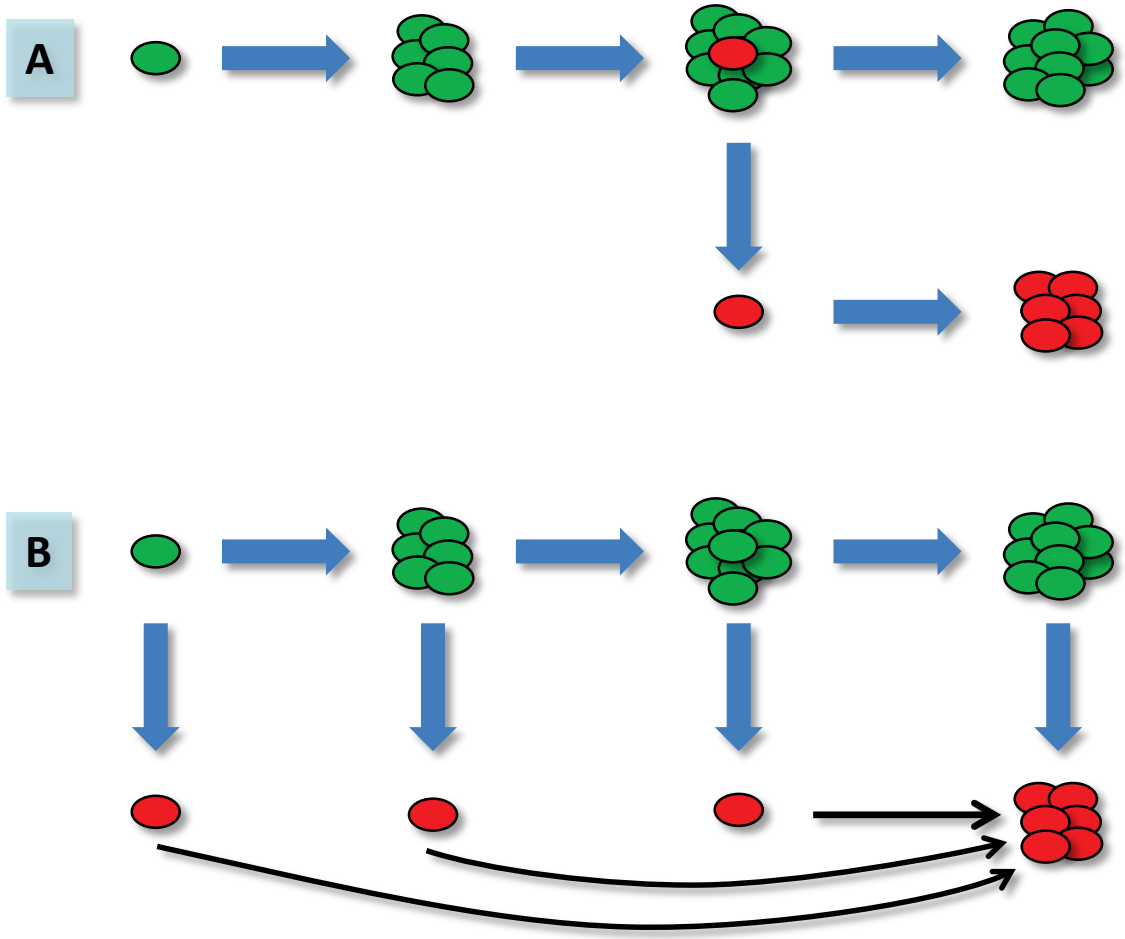

Figure 3. *Schematic representation of lung cancer development. A, the localized, multistep carcinogenetic model and B, the hypothesized systemic, bone marrow-derived stem cell model. Screening for lung cancer could potentially be effective in model A when the disease is detected before it has metastasized, but not in B.*

Conclusion

The natural history of lung cancer is complex, diverse, and not yet fully understood. So far, lung cancer evolution has been interpreted according to the exponential growth model, but there is increasing evidence that the natural history of lung cancer does not always fit this model. Bone-marrow-derived stem cells and the complex interaction with the microenvironment of the tumor and immune system may play an important role in tumor progression and the achievement of metastasizing capacity. There is, in our opinion, no biological rationale why CT-detected early-stage lung cancer should be regarded as a distinct group of cancer. The only appropriate conclusion is that screen-detected lung cancer cases are preferably detected when they are in the indolent phase of their growth curve (length-biased sampling), from which it can by no means be concluded that they may not progress or metastasize at a later stage. As the natural history of lung cancer is only partly elucidated, conclusions on the impact of overdiagnosis in lung cancer screening are premature.

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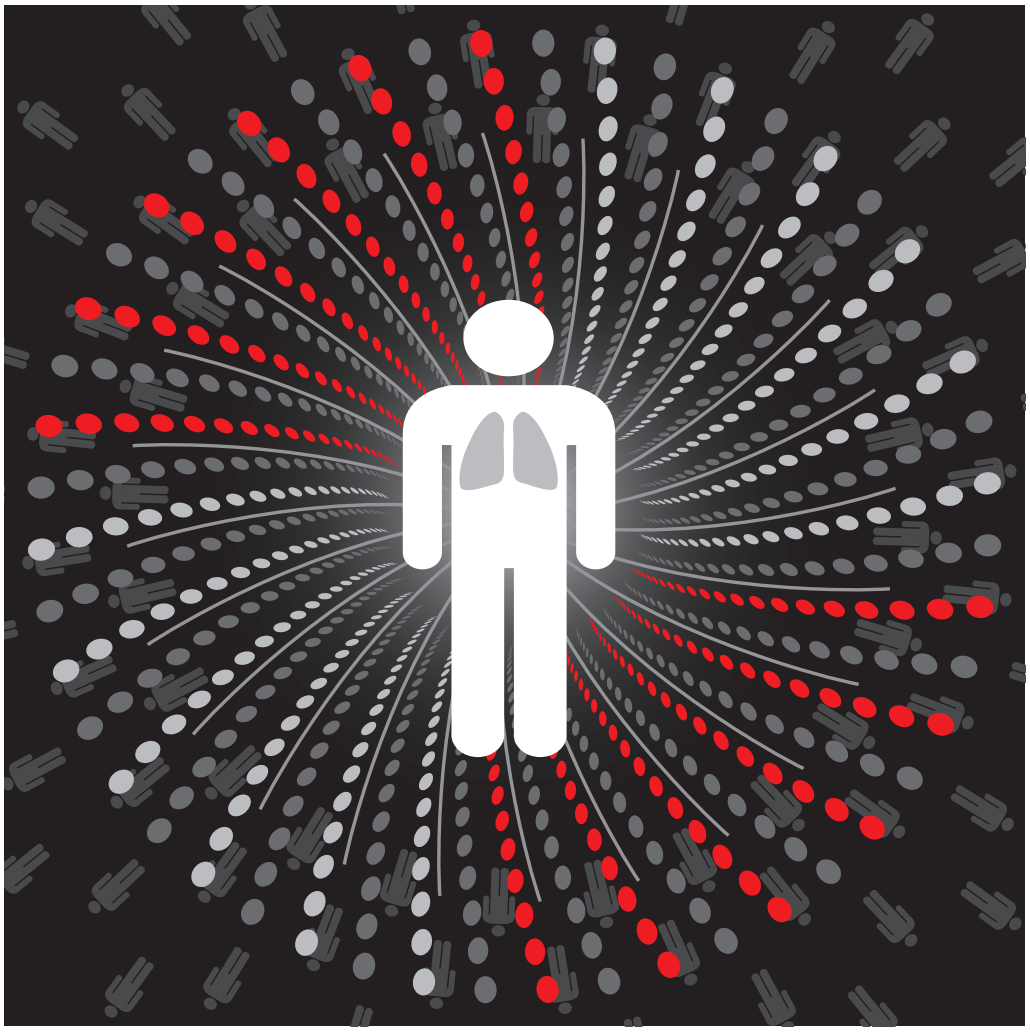
Chapter 6



The role of standard-dose CT-scans with intravenous contrast for the evaluation of suspicious nodules in screen positives in the NELSON lung cancer screening trial

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To Be Submitted

Abstract

Purpose: To retrospectively determine the role of standard-dose CT scans with contrast during the analysis of suspicious, screen-detected nodules.

Materials and methods: The current study is a sub study of the NELSON randomized controlled lung cancer screening trial; informed consent was obtained from all subjects. In the NELSON trial 7,557 subjects underwent a low-dose CT scan at baseline screening. Following baseline, a second round screening (one year after baseline) and a third round screening (two years after the second round), a total of 415 subjects had a positive test result. In the current study, we report on 332 subjects who underwent a standard dose CT scan of chest and upper abdomen with contrast as part of the workup by the pulmonologist. The gold standard was a histological diagnosis of malignant disease or a two-year period of follow-up at a minimum without evidence of cancer.

Results: The median age of the subjects was 61 (range 50–75), the median number of pack-years was 43 (range 21–160) and 57% of the subjects were female. CT scans made during analysis by the pulmonologist were classified as “suspicion of cancer”, “indeterminate” or “normal, no suspicion of cancer” by the radiologists in the participating centers. In the large majority of subjects, the CT scan had an indeterminate result. When the indeterminate results were included with the “suspicion of cancer” results, the diagnostic value of CT for detecting lung cancer showed a sensitivity, specificity, positive predictive value and negative predictive value of 92.2% (95% Confidence Interval (CI): 86.8–95.6), 41% (95% CI: 33.1–48.5), 61% (95% CI: 54.8–67.1) and, 84% (95% CI: 73.5–90.7), respectively. In almost 50% of subjects, no histology was obtained and the workup was concluded using imaging studies. In about 1/3 (113/332) of subjects, a follow-up CT scan was made during analysis. After a follow-up scan, 22% (25/113) were diagnosed with lung cancer, which was in stage I in 84%. In subjects who underwent a follow-up scan, the diagnostic value was as follows: 94.4% (95% CI: 80–99), 70% (95% CI: 58.5–79.8), 59.6% (95% CI: 45.8–72.1) and, 96.4% (95% CI: 86.6–99.4), respectively. In subjects with a benign diagnosis after analysis and who had undergone a follow-up scan, surgery for a benign form of the disease was performed less often: 13% compared with 23% in those who did not receive a follow-up scan.

Conclusion: In subjects referred following a positive screening result with an inconclusive non-invasive workup, follow-up CT plays an important role and may help reduce resections for the benign disease; after follow-up CT scans, 22% were diagnosed with lung cancer. The ideal interval for follow-up CT remains to be established; our data suggest that a follow-up scan during analysis by the pulmonologist should be made within an interval of three months at a maximum. There is consequently an important role for CT to play in monitoring nodule growth. We therefore recommend that volumetric measurements according to the NELSON protocol should be made during analysis by the pulmonologist.

Introduction

In Europe, lung cancer is the most common cause of death from cancer (20%), followed by colorectal cancer (12%), breast cancer (8%), and stomach cancer (7%).[1] Recently, the largest randomized controlled lung cancer screening study in the world showed a reduced lung cancer mortality of 20% in the arm with CT screening.[2] The mortality results of the NELSON lung cancer screening trial, the largest European randomized lung cancer screening trial, are yet to be released. Following baseline CT screening in other lung cancer screening studies, 23–27% of subjects have a positive test result and are referred to the pulmonologist, representing between 233–7,191 subjects who undergo further (invasive) investigations.[2,3] Despite the fact that only high-risk subjects were screened, as defined by age and smoking history, the prevalence of lung cancer was low, approximately 2.7–3.8%. In the NELSON trial, because of the use of volume doubling time (VDT) in the screening algorithm, the number of test-positives was remarkably lower at 2.6%, and lung cancer was detected in 36% of test-positives.[4] In lung cancer screening studies, large numbers of subjects are referred for analysis; it is a challenge to diagnose suspicious nodules, as 83% are smaller than 1 cm in diameter.[3] In test-positives of lung cancer screening studies, the diagnostic evaluations most often concern further imaging studies and invasive procedures are performed infrequently.[2,5,6] In the CT arm of the National Lung Cancer Screening Trial (NLST), 18,146 subjects were referred and a total of 8,807 chest CTs were made. Despite the importance of imaging studies during analysis by the pulmonologist, the large numbers of CT scans and repeat CT scans made, literature on the sensitivity, specificity and predictive value of screen-detected nodules is sparse.[2,7] We retrospectively analyzed the role of standard-dose CTs made after referral to the pulmonologist.

Methods

NELSON trial participants were current and former smokers at high risk for lung cancer. Detailed information on the inclusion and exclusion criteria have already been reported.[8] Current and former smokers aged 50–75 with a smoking history of >15 cigarettes a day during >25 years or >10 cigarettes a day during >30 years (quit ≤10 years ago) were invited. Subjects with moderate or poor self-assessed health unable to climb two flights of stairs and persons with a body weight ≥140 kg were excluded, as well as those with a history of other types of cancer. The prospective screening study was approved by the Ministry of Health and by the medical ethical boards of each of the four participating hospitals. Written informed consent was obtained from all participants. In the NELSON trial, 7,557 subjects underwent a CT scan at baseline; the second screening round was performed one year after baseline and the third screening round two years after the second round.[4] Subjects with a positive test result were referred for workup to a pulmonologist and, depending on the result of imaging studies, resection of the suspicious lesion was performed. The standard non-invasive workup included a physical exam, pulmonary function test, bronchoscopy, FDG-PET scan and standard-dose CT scans with intravenous contrast of the chest and upper abdomen.

CT data acquisition and image reading

Low-dose screening CT

Data acquisition and image reading were as has been described previously.[9] In brief, all four participating screening sites used 16-detector CT scanners (Sensation 16 with Mx8000 IDT from Siemens Medical Solutions, Forchheim, Germany, or Brilliance 16P from Philips Medical Systems, Cleveland, Ohio, USA). Scan data were obtained in a spiral mode, with 16 x 0.75 mm collimation and 1.5 pitch. No contrast was administered. Data acquisition and scanning conditions were standardized and equal for baseline and repeat screening. Digital workstations (Leonardo® from Siemens Medical Solutions, Erlangen, Germany) were used in all screening sites with commercially available software for semi-automated volume measurements (LungCare® from Siemens Medical Solutions, version Somaris/5: VA70C-W).

Diagnostic CT with intravenous contrast

The same scanners as mentioned above were used. Scan data were obtained in a spiral mode, with 16 x 0.75 mm collimation and 1.5 pitch. In Utrecht, Groningen and Leuven, 60–150 mL of intravenous contrast medium containing 550–652 mg of iodine per milliliter (Visipaque™, GE Healthcare) was administered with an injection-scanning delay of 30–50 seconds and administered at a rate of 2–2.5 ml per second. In Haarlem, an intravenous contrast medium containing 350 mg of iodine per milliliter was used (Omnipaque, GE Healthcare). For all diagnostic CTs, the chest and the upper abdomen were scanned.

The radiologists of the four centers issued reports of the chest CT scans without using pre-specified reporting criteria; this is in contrast to the NELSON scans which were interpreted by radiologists in Groningen only according to the NELSON nodule management protocol.[9] The reporting by radiologists of the local centers in the same way as for non-screening purposes reflects daily practice. The reporting of the screening CTs on the other hand was highly protocolized.

The diagnostic scan report was composed of two sections: a descriptive section and a conclusive section. The diagnostic CT result was prospectively scored by the radiologist in terms of “suspicion of cancer,” “normal” or “indeterminate,” without the use of specified criteria. When the radiologist classified the scan as suspicion of lung cancer, staging studies for lung cancer were performed. When the conclusion of the scan was benign, the analysis was terminated and the subject continued screening in the NELSON study. Results of other studies, such as FDG-PET, as well as the bronchoscopy result were also taken into account. In the event of an indeterminate result, the pulmonologist continued the analysis, which most often consisted of (follow-up) imaging studies outside the NELSON protocol. The conclusions of the radiology report were entered into the NELSON database. As no criteria were specified for classifying the conclusion as “normal,” “indeterminate” or “suspicion of cancer,” we retrospectively reviewed the report and scored all nodule characteristics and other abnormalities described in the report. The form of this evaluation is given in Supplementary Table 1. Lymphadenopathy was defined as the occurrence of lymph nodes with a diameter >1 cm.

In the event of an indeterminate result in the NELSON trial, a repeat scan was recommended. During analysis by the pulmonologist, in addition repeat scans were made; we refer to this type of scan as follow-up CT scans.

Statistics

The reference standard (gold standard) was surgery or a histological biopsy of the suspicious nodule. If no surgery was performed during workup and a subsequent follow-up period of at least two years produced no evidence of cancer, the result was considered benign. Data were analyzed using SPSS (version 17.0, SPSS Inc, Chicago, IL, USA). A two-tailed Mann-Whitney U test was used to analyze continuous data in the absence of a normal distribution. The Chi-squared (χ^2) test was used for binomial or categorical data and Fisher's exact test was used for small groups. Statistical significance was defined as a *p*-value <0.05.

Results

A total of 415 subjects had a positive test result following CT screening between April 2004 and December 2008 and in 80% (332/415) a diagnostic CT chest with contrast was made (Figure 1). In 12 subjects a CT scan without contrast was made; the reason for this was unclear in nine subjects, while two subjects had a relative contra-indication and in one subject the vessel in the arm was not palpable. In 50 subjects (12%) no CT scan was made for reasons that are unclear. In addition, twenty-one (5%) of subjects had not been referred to the pulmonologist for further analysis. Significantly faster growing nodules and cases of lung cancer were seen in the group who underwent a CT of the chest when compared to the subjects who were excluded from analysis (Table 1).

Table 1. *Comparison of participant and nodule characteristics of included and excluded subjects.*

Characteristics	CT with contrast N=332 (%)	No CT with contrast N=83 (%)	p-value
Participant			
Sex (female)	57 (17)	11 (13)	0.39
Age, median (range)	61 (50–75)	62 (50–73)	0.73
Pack years, median (range)	43.2 (20.7–159.5)	39.2 (21.5–110.2)	0.56
Nodule characteristics low-dose screening CT			
Diameter, mean (SD) in mm	18.0 (±12.8)	20.2 (±11.7)	0.59
VDT <400, days	145 (44)	25 (30)	**0.025**
Central localization	39 (12)	7 (8)	0.39
Upper Lobe	172 (52)	38 (46)	0.33
Part solid	26 (8)	3 (4)	0.18
Non-solid	6 (2)	1 (1)	0.58
Solid	296 (89)	73 (88)	0.75
Screen round			
First round	144 (43)	48 (58)	**0.018**
Second round	97 (29)	22 (27)	0.63
Third round	91 (27)	13 (16)	**0.027**
Scan type			
Regular screening	213 (64)	60 (72)	0.16
Repeat scan	119 (36)	23 (28)	0.20
Outcome after workup			
Benign	176 (53)	54 (65)	0.072
Other cancer	12 (4)	6 (7)	0.13
Lung cancer	144 (43)	23 (28)	**0.006**
Total	332 (100)	83 (100)	
Clarification of abbreviations: CT: Computed Tomography; VDT: volume doubling time			

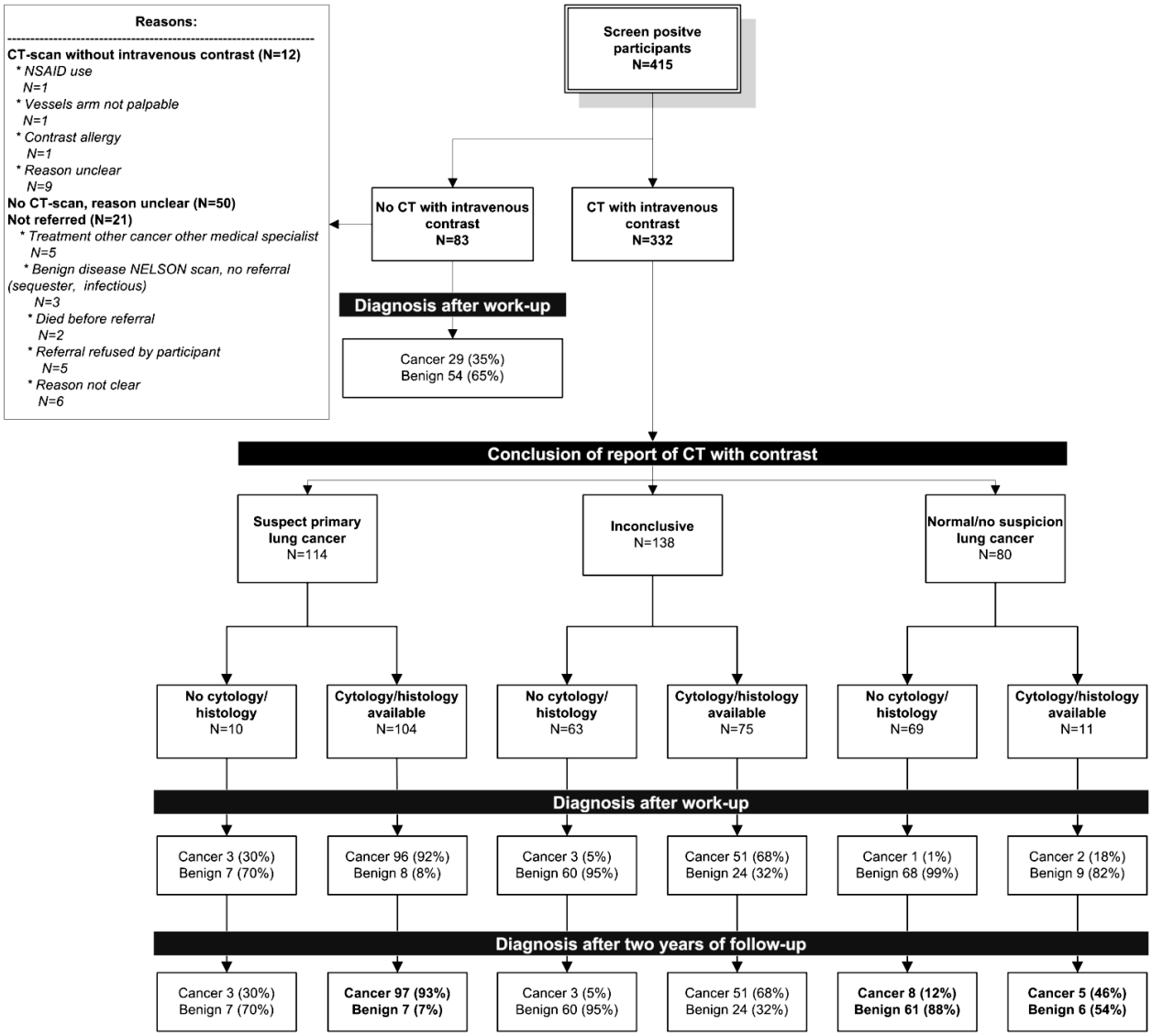

Figure 1. *Outcome of the CT scans with intravenous contrast made for the evaluation of 332 test positives of the NELSON randomized lung cancer screening trial. At the bottom of the figure the final diagnosis at a minimum of 2 years of follow-up after the initial analysis was provided; changes are indicated in bold type.*

Diagnostic value of standard-dose CT with contrast

Suspicious nodule characteristics and other abnormalities mentioned in the radiological report on the standard-dose CT were scored on the form provided in Supplementary Table 1. The malignant and benign characteristics described in the report are provided with regard to the conclusion of the diagnostic CT (Table 2). It can be noted that the conclusion of the diagnostic CT in the majority (42% (138/332)) of cases was indeterminate and that the conclusion was benign in only 24% (80/332). Furthermore, there is some overlap between the conclusion and the characteristics described. The CT results (indeterminate, suspicion of cancer, or normal) were used to calculate the diagnostic values (Table 3). When the indeterminate results were added to the suspicion of cancer results, the diagnostic value of CT for detecting lung cancer showed a sensitivity, specificity, positive predictive and negative predictive value of 92.2% (95% CI: 86.8–95.6), 41% (95% CI: 33.1–48,5), 61% (95% CI: 54.8–67.1) and 84% (95% CI: 73.5–90.7) respectively. In subjects who underwent a

follow-up scan, the diagnostic value was as follows: 94.4 (95% CI: 80–99%), 70% (95% CI: 58.5–79.8), 59.6% (95% CI: 45.8–72.1) and 96.4% (95% CI: 86.6–99.4) respectively.

Table 2. *Summary of the retrospective evaluation of the radiological report on the diagnostic CT with regard to nodule characteristics, presence of lymphadenopathy and other signs suggestive of malignancy on the diagnostic CT made in test-positives of the NELSON lung cancer screening trial after a positive screening result. The form of the retrospective evaluation of the radiological report is provided in Supplementary Table 1.*

Summary of characteristics described in report on diagnostic CT with contrast	**Conclusion of diagnostic CT with contrast**		
	Suspicion of cancer N=114 (100)	**Indeterminate N=138 (100)**	**Normal, no suspicion of lung cancer N=80 (100)**
Nodule size			
Larger	30 (26)	12 (9)	0
Smaller/disappeared	0	11 (8)	29 (36)
Nodule characteristics(border, aspect)			
*Suspicious characteristics**			
1 Suspicious characteristic	52 (46)	28 (20)	7 (9)
2 Suspicious characteristics	21 (18)	14 (10)	2 (3)
3 Suspicious characteristics	6 (5)	2 (1)	0
4 Suspicious characteristics	3 (3)	0	0
Any suspicious characteristics	82 (72)	44 (32)	9 (12)
Benign characteristics†			
1 Benign characteristic	2 (2)	29 (21)	23 (29)
2 Benign characteristic	1 (1)	1 (1)	0
3 Benign characteristic	0	0	1 (1)
Any benign characteristics	3 (3)	30 (22)	24 (30)
Lymphadenopathy	34 (30)	13 (9)	4 (5)
Other signs suggestive of malignancy‡	8 (7)	0	0

Clarification of abbreviations and symbols: CT: Computed Tomograpy.
*Suspicious border characteristics: lobulated, spiculated, ill-defined, cavitation, irregular border, pleural tags, growth in other structures and eccentric calcification.
†Benign border characteristics: smooth, attached nodule (fissure, vessel)
‡Renal cell carcinoma (1), metastasis colon cancer (2), bone metastases (1), liver metastases (1), multiple lung metastasis (3).

Table 3. *Diagnostic result of diagnostic CT made in test-positives referred to the pulmonologist for analysis. The results of all follow-up scans made during workup, both low dose and with contrast, have been included in calculation II, and the results after the last follow-up scans with contrast only is provided in section III. In both instances the result of the last scan is taken into account.*

Conclusion diagnostic CT with contrast	Cancer	Benign	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI
I Results after workup (all subjects, n=332)										
Cancer or indeterminate	153	99	98.1	94–99.5	44	36.4–51.4	61	54.4–66.7	96	88.7–99
Normal	3	77								
Cancer	99	15	63.5	55.3–70.9	92	86.1–95	87	78.9–92.2	74	67.4–79.4
Normal or indeterminate	57	161								
Result after two years of follow–up (all subjects, n=332)										
Cancer or indeterminate	154	98	92.2	86.8–95.6	41	33.1–48.5	61	54.8–67.1	84	73.5–90.7
Normal	13	67								
Cancer	100	14	59.9	52–67.3	92	85.9–95.1	88	79.9–92.9	69	62.6–75.2
Normal or indeterminate	67	151								
II Results after follow–up CT (both low–dose and CT iv contrast, n=113)										
Cancer or indeterminate	30	27	100	89–100	67	57–77	53	39–66	100	92–100
Normal	0	56								
Cancer	21	3	70	52–83	96.1	88.2–98.9	87.5	66.5–96.7	90	81–95
Normal or indeterminate	9	80								
III Results after follow-up CT and two years of follow-up (both low-dose and CT iv contrast, n=113)										
Cancer or indeterminate	34	23	94.4	80–99	70	58.5–79.8	59.6	45.8–72.1	96.4	86.6–99.4
Normal	2	54								
Cancer	21	3	58.3	40.9–74	96.1	88.2–98.9	87.5	66.5–96.7	83.1	73.4–89.9
Normal or indeterminate	15	74								

Follow-up CT

During analysis by the pulmonologist, one or more follow-up scans were made in about one third (109/332) of subjects before proceeding to invasive diagnostic procedures. The large majority, 82% (192/235), of follow-up scans were standard-dose CT scans with contrast. Subjects with a benign result after workup and who underwent a follow-up scan were less often operated for benign lesions: 23% compared with 13% (Figure 2). A total of 276 follow-up CTs were made, of which 42 CTs were low-dose CTs without contrast (Table 4). A second scan was made 3–4 months later (median 99 days; range 2–374 days) on average (time interval between first scan made during analysis and final follow-up scan), following which 16 subjects were diagnosed with stage IA/B lung cancer, one with stage IIA and one with stage IIIA (Table 4). Two subjects were diagnosed with pulmonary metastases of a colon carcinoma, one subject with prostate cancer, one subject with Grawitz tumour (1) and one subject with a pulmonary lymphoma. Following the second or third follow-up scans, 25 subjects were diagnosed with lung cancer in stage I: 84% (21/25). The median follow-up range in stage I lung cancer cases was 88 days (range 6–490). After follow-up CT-scans, three subjects were diagnosed with stage IIIA NSCLC (median follow-up time: 197 days (range: 17–374).

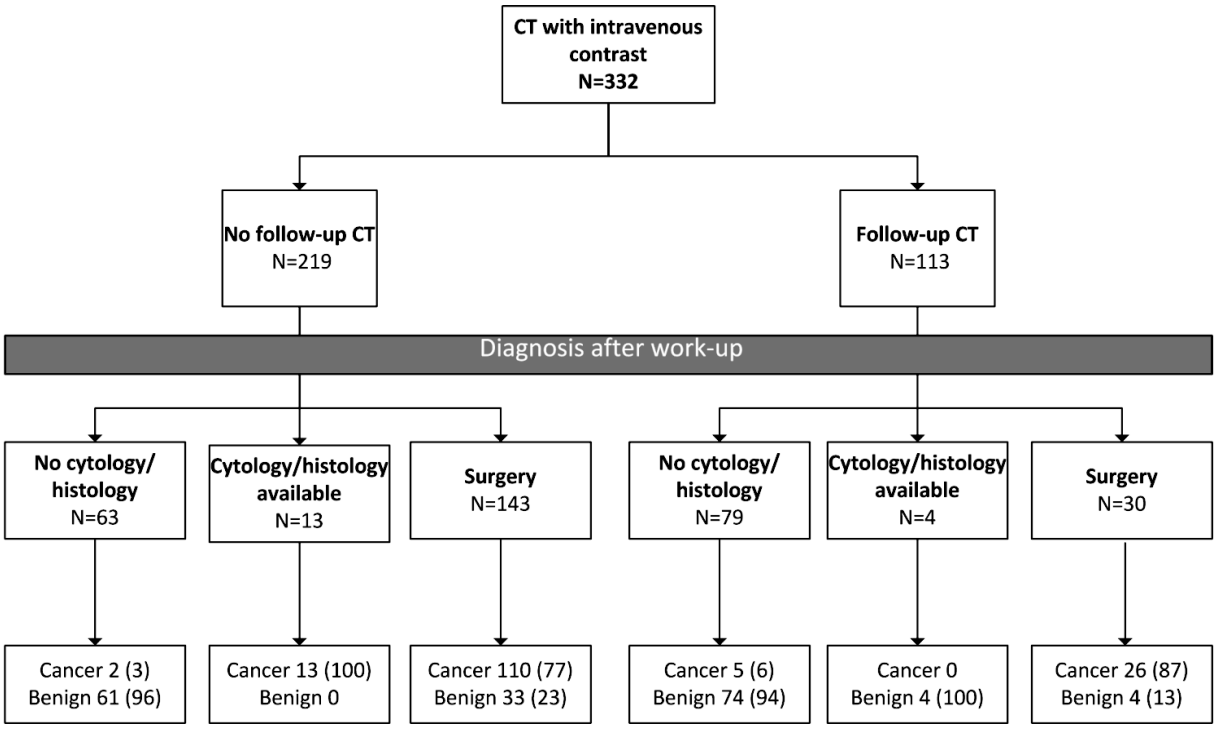

Figure 2. *Frequency of follow-up scans made after referral to the pulmonologist and outcome of workup. A follow-up scan was made more often of subjects with a benign conclusion of the workup based on imaging studies. In the subjects who did not undergo a follow-up scan, a higher rate of resections for benign disease was noted. Follow-up scans were made less often in subjects diagnosed with cancer.*

Table 4. *Cancer diagnosis after a follow-up scan during analysis by the pulmonologist: lung cancer stage, number of scans and time interval. In 113 subjects, about 1/3 of referred subjects, more than one CT-scan was made during analysis. Of 276 follow-up scans, 42 (15%) were low-dose scans without contrast. The time interval was measured (in days) between the first CT scan of workup and the subsequent follow-up scan. After a follow-up scan, 25 subjects were diagnosed with lung cancer, which was stage I in 84% (21/25).*

Follow-up scan, number	Conclusion of CT-scan			Number of scans	Number of scans without contrast	Time interval (median days, range)	Cancer diagnosis (n)	Cancer diagnosis after follow-up scan and lung cancer stage N=30
	Cancer	Indeter-minate	Benign					
1st scan	14 (12)	71 (63)	28(25)	113 (100)	0	NA	NA	NA
2nd scan	20 (17)	42 (37)	51 (45)	113 (100)	14	99 (2–374)	20	13 stage IA, 3 stage IB, 1 stage IIA,1 stage IIIA, 2 other cancer
3rd scan	0	35 (92)	3 (8)	38 (100)	5	228 (17–547)	8	5 Stage IA, 2 Stage IIIA, 1 other cancer
4th scan	1 (11)	5 (56)	3 (33)	9 (100)	3	414 (86–831)	2	2 other cancer
5th scan	0	2 (67)	1 (33)	3 (100)	2	710 (453–930)	0	NA
Last scan	24 (21)	33 (29)	56 (50)	113 (100)	18	118 (6–930)	30	
Total				276	42	NA	30	

Cancer diagnosis after a follow-up scan (N=30)							
Lung cancer stage* Other cancer	Number of subjects	Median diameter (range, mm)†	Median follow-up during analysis (d)	Volume doubling time <400 days	Volume larger than 500 mm^3	Calculation VDT not possible	
						New nodule	Baseline nodule
Stage IA	18	10.8 (6–27.8)	105 (23–490)	14	5	3	1
Stage IB	3	33.9 (25.1–5.4)	13 (6–57)	1	3	0	2
Stage IIA	1	48.5	76	NA	1	1	0
Stage IIIA	3	14.6 (12.5–8.1)	197 (17–374)	1	3	1	1
Other cancer‡	5	12.8 (7.6–20.8)	121 (67–444)	2	3	0	3

Clarification of abbreviations and symbols: CT: computed tomography; VDT: volume doubling time.
*According to the 6th edition of the TNM stage classification for lung cancer.
†Median maximal diameter on NELSON low-dose screening CT.
‡Lung metastasis colon carcinoma (2 subjects), lung metastases prostate cancer (1 subject), lung metastasis Grawitz tumor (1 subject), pulmonary lymphoma (1 subject).

Overview of diagnostic investigations and outcome

Only 15% (47/324) of nodules measured <8 mm in maximum diameter. In this group, a relatively large number of fast-growing nodules was noticed (Table 5), as a result of the NELSON nodule management protocol. In addition, twice as many surgical procedures had been performed for the benign form of the disease as compared to the largest nodule group: 19% (9/47) compared to 8% (16/190). In the smallest nodule group, 38% was diagnosed with cancer as opposed to 50% in the largest nodule group. On average, follow-up scans were made in 38% of cases. The nodule size of stage IA lung cancers (median size 10.8 mm, range 6–27.8 mm) was smaller than stage III lung cancers (14.6 mm, range: 12.5–18.1 mm). Therefore, the small nodule group is an important group for detecting early-stage lung cancers, although the percentage of detected lung cancers is lower.

Table 5. *The result of imaging studies with regard to nodule size on the positive NELSON screening CT in 324 subjects with suspicious pulmonary nodules. Eight subjects were not included because of non-nodular abnormalities.*

Imaging studies	Nodules <500 mm3				Nodules >500 mm^3	
	Nodules <8 mm		Nodules >8 mm			
	N (%)	Cancer cases/N (%)	N (%)	Cancer cases/N (%)	N (%)	Cancer cases/N (%)
Mean nodule diameter (range)	6.5 (4.7–7.8)	NA	9.3 (8.0–16.7)	NA	19.4 (9.7–67.9)	NA
FDG-PET scan result for suspicious nodule						
FDG-positive	5 (14)	5/5 (100)	24 (34)	20/24 (83)	83 (52)	73/83 (88)
FDG-indeterminate	2 (6)	0	4 (6)	2/4 (50)	24 (15)	9/24 (38)
FDG-negative	28 (80)	11/28 (39)	42 (60)	12/42 (29)	52 (33)	9/52 (17)
Total PET scans	35 (100)	16/35 (46)	70 (100)	34/70 (49)	159 (100)	91/159 (57)
NELSON low-dose CT						
VDT<400 days	41(87)	17/41 (42)	64 (74)	27/64 (42)	38 (20)	25/38 (66)
Diagnostic CT chest						
Repeat diagnostic CT	18 (38)	7/18 (39)	32 (37)	6/32 (19)	59 (37)	14/59 (24)
Any suspicious border **	4 (9)	4/4 (100)	26 (30)	18/26 (69)	69 (36)	47/69 (68)
Total subjects	47 (100)	18/47 (38)	87 (100)	38/87 (44)	190 (100)	95/190 (50)
Outcome after workup	N (%)		N (%)		N (%)	
Benign diagnosis						
Benign, no cytology/histology	19 (40)		38 (44)		77 (41)	
Benign, cytology/histology	1 (2)		1 (1)		2 (1)	
Benign, surgery	9 (19)		10 (11)		16 (8)	
Benign, total	29 (62)		49 (56)		95 (50)	
Cancer diagnosis						
Cancer, no cytology/histology	3 (6)		0		4 (2)	
Cancer, cytology/histology	1 (2)		3 (3)		9 (5)	
Cancer, surgery	14 (30)		35 (40)		82 (43)	
Stage I disease /lung cancer (%)	13/15 (87)		30/34 (88)		55/86 (64)	
Cancer, total	18 (38)		38 (44)		95 (50)	
Total	47 (100)		87 (100)		190 (100)	

Clarification of abbreviations and symbols: NA: not applicable; FDG-PET: Fluorodeoxyglucose postron emission tomography; CT: Computed tomography; VDT: Volume doubling time; SD: Standard deviation

* Suspicious border characteristics: lobulated, spiculated, ill-defined, cavitation, irregular border, pleural tags, growth in other structures, and eccentric calcification.

None of the nodules was <4 mm in size; 5 nodules were smaller than 6 mm in diameter, two of them were diagnosed with lung cancer.

Lymphadenopathy

Of nodules <8 mm in diameter, nodal involvement was established in only 4% (2/47) on diagnostic CT; in nodules of intermediate size (volume <500 mm^3, diameter <8 mm) this was 4.6% (4/87) and in the largest nodules (volume >500 mm^3) 16% (30/190) (Table 6). In six subjects diagnosed with lung cancer in nodules <500 mm^3 with lymph node metastasis, the pulmonary nodules were PET-positive; in addition, the mediastinum was PET-positive in four of these subjects. In two subjects (2/6) the mediastinal lymphadenopathy was also visible on

low-dose CT, which was made with a median time-interval of 33 days (range: 1–343 days) earlier.

Table 6. *Lymphadenopathy on CT and nodal involvement after analysis: in 39 (27%) subjects diagnosed with lung cancer, the mediastinal or hilar lymph nodes were involved. In larger nodules, nodal involvement was noted more often. The median time interval between the NELSON low-dose screening CT and the (first) diagnostic CT scan was 33 days (range: 1–343 days). In five subjects, the time interval was >150 days; this was due to an administrative error for one subject and a tumor board decision for the remainder.*

	Outcome after workup							
	Benign	Other Cancer	Lung cancer	Lung cancer and nodal involvement				
				N0	N1	N2	N3	Nx*
Nodule size category								
Nodule volume <500 mm^3	78 (44)	5 (42)	51 (35)	45 (43)	1 (9)	4 (19)	1 (20)	0
Nodule diameter <8 mm	29 (16)	1 (8)	17 (12)	15 (14)	0	1 (5)	1 (20)	0
Nodule diameter >8 mm	49 (28)	4 (33)	34 (24)	30 (29)	1 (9)	3 (14)	0	0
Nodule volume >500 mm^3	93 (53)	5 (42)	92 (64)	60 (57)	10 (91)	16 (76)	4 (80)	2 (100)
NELSON SCAN								
Lymphadenopathy NELSON scan	0	0	7 (5)	1 (1)	1 (9)	4 (19)	1 (20)	0
Diagnostic CT-scan								
Any lymphadenopathy	14 (8)	2 (17)	35 (24)	10 (10)	4 (36)	15 (71)	5 (100)	1 (50)
Unexpected nodal involvement during thoracotomy	0	0	10 (7)	0	5 (45)	5 (24)	0	0
Total subjects	176 (100)	12 (100)	144 (100)	105 (100)	11 (100)	21 (100)	5 (100)	2 (100)
Clarification of symbol: * Two subjects with stage IV cancer in whom no further evaluation of mediastinal lymph nodes was done.								

Discussion

Diagnostic value of CT

In the current study we investigated the role of CT chest and upper abdomen with intravenous contrast and the role of repeat CT. We demonstrated a moderate diagnostic value of CT. When the indeterminate results were included with the "suspicion of cancer" results, the diagnostic value of CT for detecting lung cancer showed a sensitivity, specificity, positive predictive value and negative predictive value of 92.2% (95% Confidence Interval (CI): 86.8–95.6), 41% (95% CI: 33.1–48.5), 61% (95% CI: 54.8–67.1) and 84% (95% CI: 73.5–90.7), respectively. This can be explained by the fact that the majority of standard-dose CT scan results were classified as indeterminate. In subjects who underwent a follow-up scan, the diagnostic value was as follows: 94.4 (95% CI: 80–99%), 70% (95% CI: 58.5–79.8), 59.6% (95% CI: 45.8–72.1) and 96.4% (95% CI: 86.6–99.4), respectively. Previously it was reported that the inter-observer agreement on the interpretation of pulmonary findings at low-dose CT screening is moderate to substantial.[10] Seeman et al.[11] compared the performance of

spiral CT and HRCT based on morphological characteristics. For the identification of malignant solitary pulmonary nodules, spiral CT (without contrast) had a sensitivity of 89% and a specificity of 61%; in the case of HRCT, this was 91% and 57%, respectively. Sato et al.[12] investigated the diagnostic value of a pre-operative CT scan in a non-lung cancer screening setting for suspected lung cancer. In this group, a lung cancer diagnosis was confirmed in 98% (1717/1755) following surgery. This study showed that subjects with suspected lung cancer in reality have a much higher a priori probability of lung cancer, in contrast to screen-positives of lung cancer screening studies.
However, with the use of hemodynamic characteristics the specificity is better: a specificity of 90%–93% and sensitivity of 81%–94% have been reported.[13,14] Swensen and colleagues found a lower specificity of 58% and a sensitivity of 98%.[15] The intensity of the contrast enhancement is directly related to the vasculature of the nodules, which is higher in malignant nodules.[16] However, Zhang et al. found that peak enhancement levels were elevated in both malignant (41 HU) and inflammatory benign nodules (44 HU), as opposed to non-inflammatory nodules (13 HU). [17] After treatment (3–4 months later), inflammatory nodules showed significantly reduced enhancement rates that made discrimination possible. The technique is generally not used in small pulmonary nodules (<10 mm),[18]; in additon, intratumoral necrosis and low cardiac output may contribute to low peak enhancement and a false negative result.[17]

Border characteristics

Gurney et al.[19] found that spiculation, thickness of the cavity wall, and diameter were the most important radiographic characteristics for malignant nodules. In this study, however, nodules were evaluated on chest radiography or CT scans obtained with older CT techniques. In a recent study by Harders et al.[20], calcification patterns and pleural retraction on high-resolution spiral CT were associated with malignancy. In a retrospective analysis of screen-detected lung cancers, the most frequently observed type of margin was spiculated (41%) and smooth (40%) while 20% had lobulated margins.[21] We previously showed the limited value of border characteristics and shape for predicting lung cancer.[22] The reporting of margin characteristics may be subject to inter-observer variation. To overcome this difficulty, computer-aided diagnosis (CAD) can be helpful. With this method, morphological nodule features within the volume of interest (density, sphericity, irregularity of surface, volume, and maximal diameter) can be quantified. In the United States, seven academic centers work together in order to support CAD development and validation.[23] They collaborate in the Lung Image Database Consortium (LIDC) as well as in Image Database Resource Initiative (IDRI) which contains data on well over 7000 nodules. This initiative may lead to an improvement in the classification and grading of suspicious nodule characteristics.

Follow-up scan

We have demonstrated that a lower rate of resection for the benign disease was observed in subjects who had undergone a follow-up CT, regardless of nodule size. Because of the lower prevalence of cancer in the nodules <500 mm^3 group (38–44% as opposed to 50%), it seems justified to consider a repeat scan before proceeding to more invasive type of investigations in the case of indeterminate imaging results. It has been previously reported that tumor boards of lung cancer screening studies are in general more likely to employ

radiological follow-up instead of surgery.[24] However, a risk of making follow-up CTs during analysis is that of tumor progression, as even small nodules can potentially metastasize.[25] We showed that 12% (6/51) of subject with nodules <500 mm^3 exhibited lymph node metastases (Table 6). Following a repeat scan, 22% (25/113) of subjects were diagnosed with lung cancer, which was stage I in 84% (21/25). We think this is a very acceptable percentage. For stage I lung cancer cases following a repeat scan, the median follow-up time was approximately 100 days. Although the ideal interval for follow-up CTs during analysis remains to be established, our data suggest that the interval until the first follow-up CT should be no longer than approximately three months.

It has been previously reported that the advent of CT and lung cancer screening studies, combined with a high number of repeat standard-dose CTs made during analysis by the pulmonologist, has led to additional exposure to radiation.[7,26] Therefore, if a decision for a follow-up CT is made, this should preferably be a low-dose CT scan, using the same software as the screening CT to establish volume doubling time in order to reduce the radiation exposure and to avoid the problem of a possible difference in volume measurement between different CT protocols. Lindell et al. studied 18 subjects with lung cancer of whom >4 CT scans had been made. These lung cancers were relatively smaller (median size 1 cm) and showed steep growth curves.[27] In addition they found that previous nodule growth may not always be predictive of malignancy. However, their study included a relatively low number of cancer cases. Modeling studies of previous nodule growth and subsequent lung cancer risk in larger populations with a significant number of lung cancer cases still need to be done. Subjects with a low or indeterminate risk of lung cancer during analysis by the pulmonologist should preferably undergo follow-up with imaging studies in order to reduce invasive procedures for benign nodules. Ideally, risk stratification should be based on a validated decision model, which takes into account volume doubling time, nodule size, FDG-PET result, patient-related risk factors, the setting of the CT scan (during analysis by the pulmonologist or a lung cancer screening setting), and standardized reported margin characteristics. Such a decision model may provide clinical guidance during analysis to decide between proceeding with invasive procedures or follow-up with imaging studies. If it is decided to perform another CT scan during workup, this should preferably be a low-dose CT using the same software as the screening protocol to establish a volume doubling time. More research is needed to establish the ideal interval for follow-up. However, our data suggest that a repeat scan should be made with a maximum interval of three months.

Lymphadenopathy

Standard-dose CT with contrast and 18FDG-PET are the golden standard for non-invasive staging of the mediastinum.[28] Therefore, all participants in lung cancer screening trials should undergo these investigations prior to surgery to exclude metastases. The question is whether all test-positives should undergo a standard-dose CT scan with contrast. A lower rate of lymph node metastasis was noted in lung cancer cases with nodules <500 mm^3 as opposed to nodules >500 mm^3 (4.5% versus 16%). In an Italian lung cancer screening study which included PET-CT as part of the screening tool, standard-dose CT was employed for nodules >8 mm in diameter.[5] In order to reduce radiation exposure, we suggest considering a low-dose (PET-)CT for nodules <500 mm^3, because 60% of them will be benign nodules. In the case of PET-positivity or other suspicious findings, a standard-dose CT of the chest and upper abdomen with contrast should be made. Because standard-dose CTs involve more

than twice as much radiation exposure, 14–18 mSv as opposed to 5–7 mSv[29], this seems reasonable.

Limitations

A limitation of our study was that there was no protocol for diagnostic CT for classifying the suspiciousness of pulmonary nodules. On the other hand, the reports were drawn up in the same way as for subjects outside the screening program and thus reflect daily practice. Retrospectively, we tried to establish how the conclusions of CT reports were made. However, we have provided insight into suspicious nodule characteristics and other abnormalities described in this report and on which the conclusions below are based. The strength of our study is that we either had histological confirmation of the screening result or a two-year follow-up period at a minimum.

Conclusions

In the current study we have showed the limited value of a single diagnostic CT with contrast for diagnosing nodules after a positive screen result. This is due to the high rate of indeterminate nodules and the presence of inter-observer agreement on the interpretation of pulmonary findings. Nevertheless, we have showed the importance of follow-up CT: in about 1/3 of subjects a follow-up CT scan was made which was associated with a lower rate of resection for benign disease. In subjects with an inconclusive non-invasive workup who underwent repeat scans, 22% was diagnosed with lung cancer after a follow-up scan. If it is decided to make another CT during workup, this should preferably be a low-dose CT using the same software as the screening protocol to establish a volume doubling time. Although more research is necessary to establish the ideal interval for follow-up, our data suggest that a repeat scan should be made within an interval of three months at a maximum.

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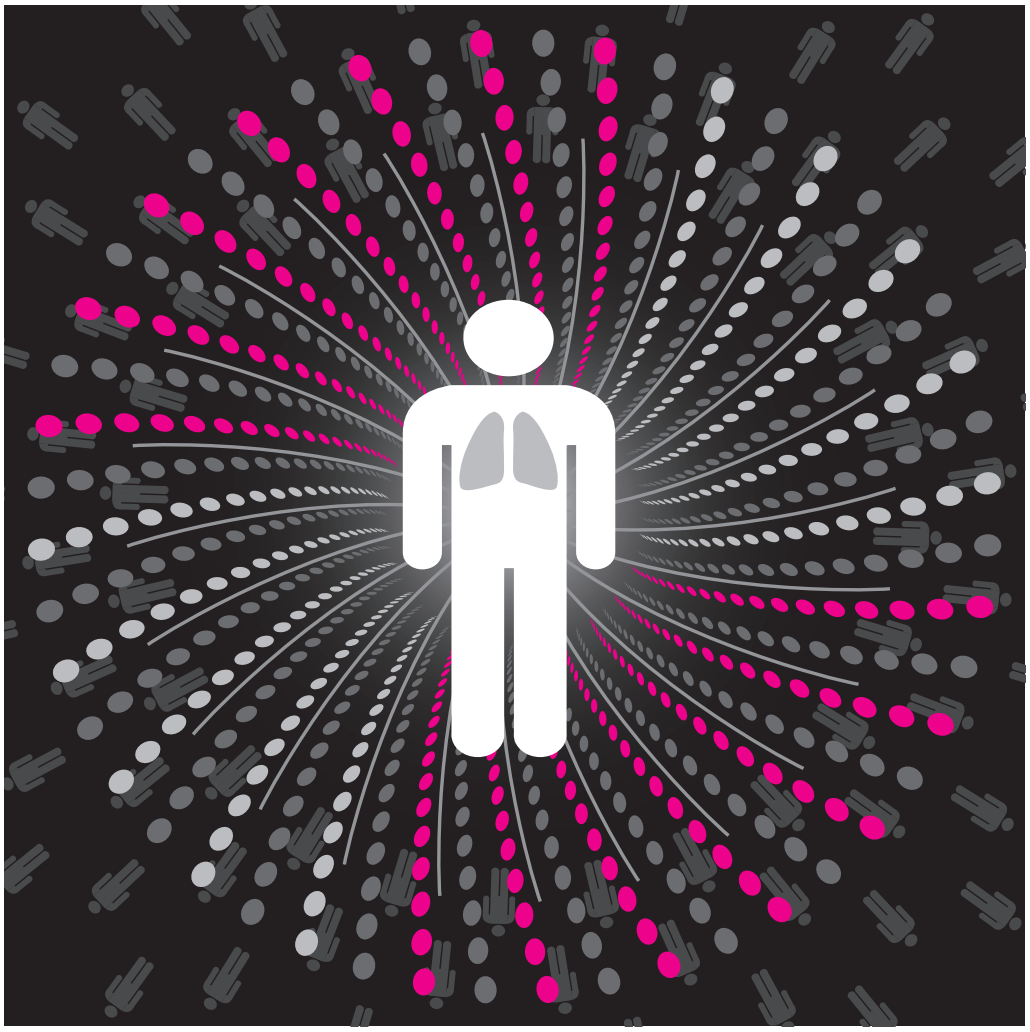
***Supplementary Table 1**. Form for the retrospective evaluation of pulmonary nodules on CT during evaluation after referral because of a positive screening result. The result of the diagnostic CT was prospectively scored by the radiologist as "suspect," "normal" or "indeterminate" without the use of specified criteria. During this study all radiological reports were retrospectively reviewed and evaluated for the description of nodule characteristics.*

Form for the retrospective evaluation of the radiological report on diagnostic CT after a positive screening result	
Conclusion of the report on diagnostic CT during workup for suspected lung cancer as entered in the NELSON database	
o Suspect for malignancy	
o Normal, no suspicion for lung cancer	
o Indeterminate/too aspecific for diagnosis	
Retrospective evaluation of the radiological report	
Type of CT	Signs suggestive benignity
o Low dose, no contrast	o None
o Diagnostic CT, contrast	o Hamartoma
Aspect suspicious lesion	o Benign calcification
o Nodule	o Interstitial Lung Disease
o Other, non-nodular lesion	o Attached (vessel, fissure)
Nodule size, compared with NELSON scan	o Smooth
o Disappeared	
o Smaller	
o Stable	Nodule suspect for malignancy
o Larger	o None
o Not specified	o Scalloped border
Suspicious non-nodular lesion	o Calcification, eccentric or punctate
o None	o Pleural tags
o Pleuritic effusion	o Cavitation or pseudocavitation
o Atelectasis	o Spiculated border
o Infiltrate	o Irregular border
o Lymfadenopathy, hilar	o Poorly defined margins
o Lymfadenopathy, mediastinum	o Bronchial obstruction or compression
o Mediastinal mass	o Growth in other structures
o Mass	
o Other	

Chapter 7



The Role of the (18)F-Fluorodeoxyglucose-Positron Emission Tomography Scan in the Nederlands Leuvens Longkanker Screenings Onderzoek Lung Cancer Screening Trial

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ABSTRACT

Background: In computed tomography lung cancer screening programs, up to 30% of all resections are futile.

Objective: To investigate whether a preoperative positron emission tomography (PET) after a conclusive or inconclusive nonsurgical workup will reduce the resection rate for benign disease in test positive participants of a lung cancer screening program.

Methods: (18)F-Fluorodeoxyglucose-PET scans were made in 220 test positives. Nodules were classified as positive, indeterminate, or negative based on visual comparison with background activity. Gold standard for a positive PET was the presence of cancer in the resection specimen or the detection of cancer during more than 2 years follow-up. Sensitivity, specificity, positive predictive value, and negative predictive value (NPV) were calculated at participant level and 95% confidence intervals (CIs) constructed.

Results: The sensitivity of PET to detect cancer was 84.2% (95% CI: 77.6 – 90.7%), the specificity 75.2% (95% CI: 67.1 – 83.3), the positive predictive value 78.9% (95% CI: 71.8 – 86.0), and the NPV 81.2% (95% CI: 73.6 – 88.8). The resection rate for benign disease was 23%, but 26% of them had a diagnosis with clinical consequences. A preoperative PET after an inconclusive nonsurgical workup reduced the resection rate for benign lesions by 11 to 15%, at the expense of missing 12 to 18% lung cancer cases. A preoperative PET after a conclusive nonsurgical workup reduced the resection rate by 78% at the expense of missing 3% lung cancer cases.

Conclusion: A preoperative PET scan in participants with an inconclusive nonsurgical workup is not recommended because of the very low NPV, but after a conclusive nonsurgical workup, the resection rate for benign disease can be decreased by 72%.

INTRODUCTION

The utility of low-dose multidetector low-dose computed tomography (CT) screening is being investigated in several nonrandomized[1-5] and randomized trials.[6-9] Two large randomized screening trials investigate whether CT screening leads to a reduction in lung cancer mortality. The largest one, the National Lung Screening Trial has randomized 53,476 smokers between annual CT screening or chest x-ray for three annual screening rounds.[6] The "Nederlands Leuvens Longkanker Screenings Onderzoek" (NELSON) is the second largest randomized lung cancer screening trial in which CT screening in year 1, 2, 4, and 6.5 is compared with a control population without screening. The nodule management strategy used in the NELSON trial is based on the volume of new noncalcified nodules and the volume doubling time (VDT) of previously existing ones, without the need for additional evaluations by fine needle aspirate, positron emission tomography (PET), or radiological evaluation after antibiotics.[10] As a result of this management strategy, 27% and 19% of the surgical resections performed at baseline and second round screening, respectively, have been performed for benign disease.[7] Question is, whether a PET scan could be used to reduce the resection rate for benign disease in a lung cancer screening setting. The purpose of this study was to investigate whether a preoperative PET after either an inconclusive or a conclusive nonsurgical workup, which included a physical examination, standard CT with contrast, and a bronchoscopy, will reduce the resection rate for benign disease.

METHODS AND MATERIALS

Study Population

NELSON trial participants were current and former smokers at high risk for lung cancer. Detailed information on the inclusion and exclusion criteria has been reported before.[11] The prospective screening study was approved by the Dutch Minister of Health and by the Medical Ethical Boards of each of the four participating hospitals. Written informed consent was obtained from all participants, which included the ability to use data for future research, including the current prospective side study. In this study, participants have been included with a positive baseline or second round test result between April 2004 and October 2008.

CT Data Acquisition and Image Reading

Data acquisition and image reading were as described before.[10] In brief, all four participating screening sites used 16-detector CT scanners (Sensation-16, Siemens Medical Solutions, Forchheim, Germany Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH). Scan data were obtained in a spiral mode, with 16 X 0.75 mm collimation and 1.5 pitch. No contrast was administered. Data acquisition and scanning conditions were standardized and equal for baseline and repeat screening. Digital workstations (Leonardo, Siemens Medical Solutions, Erlangen, Germany) were used in all screening sites with commercially available software for semiautomated volume measurements (LungCare, Siemens Medical Solutions, version Somaris/5: VA70C-W).[12, 13]

Nodule Management and Diagnostic Workup

At baseline, a scan was considered positive if any noncalcified nodule had a solid component more than 500 mm^3 (> 9.8 mm in diameter) or indeterminate if the volume of the largest solid nodule or the solid component of a partially solid nodule was 50 to 500 mm^3 (4.6 – 9.8 mm in diameter) or more than 8 mm in diameter for nonsolid nodules.[10] Subjects with an indeterminate result had a follow-up scan 3 months later to assess growth. Significant growth was defined as a change in volume between the first and second scan of ≥25%. Subjects with positive screening tests were referred to a chest physician for workup and diagnosis.[7] If lung cancer was diagnosed, the participant was treated for the disease and went off screening; if no lung cancer was found, the regular second round CT scan was scheduled 12 months after the baseline scan. For participants with one or more new nodules on the second round scan, the result (positive or negative) was based on size of the nodule, as for round one; in case of an indeterminate result, a follow-up scan was performed 6 weeks later.[10] For participants with previously detected nodules, the second round result was based on the VDT. If there was no growth or if the VDT was more than 600 days, the screen was declared negative.[7] If the VDT was less than 400 days or if a new solid component had emerged in a previously nonsolid nodule, the scan was considered to be positive. When the VDT was 400 to 600 days, the test was indeterminate, and a follow-up scan was done 1 year after the second round. With a VDT less than 400 days, the final result was considered to be positive, otherwise negative. If both new and existing nodules were present, the nodule with the largest volume or fastest growth determined the result. All participants with a negative second round result were invited to undergo the third screening round 2 years after the second round. Workup and staging were standardized for all screening sites according to (inter-) national guidelines and included a physical examination, a standard CT scan with contrast of the chest and upper abdomen, a bronchoscopy, and (18)F – fluorodeoxyglucose - PET (FDG-PET).[10, 14, 15] After a negative nonsurgical workup, subjects were referred for surgery to obtain histology of the suspicious nodule. Bronchoscopies were done for the evaluation of the central airways and (if possible) to diagnose lung cancer or benign disease. PET scans were made for preoperative staging purposes in cases the nodule turned out to be malignant during surgery. Pulmonologists were not blinded to the PET result. Therefore, PET results may have influenced the decision to resect nodules, although the NELSON protocol asked for resection irrespective of the outcome of the PET scan. National and international pathology review panels evaluated all cytological and histological specimens. A procedure was classified as surgical if it was a mediastinoscopy, video-assisted thoracoscopy (VATS), or thoracotomy. Resections for benign disease were in this study limited to thoracotomies or VATS procedures for benign lung lesions.[16, 17] A clinical relevant benign diagnosis was defined as a new benign diagnosis that influenced subsequent patient management, including medication and/or treatment changes.

(18)F-Fluorodeoxyglucose-PET

Data acquisition.

FDG-PET scans were performed by Siemens ECAT ACCEL PET (Haarlem), Siemens ECAT EXACT PET 962 (Groningen), Siemens Biograph 2-slice PET/CT (Haarlem, Leuven), and Philips Allegro PET scanner (Utrecht). Each of the four centers used different FDG-PET protocols. All

patients were asked to fast for at least 6 hours before the PET/CT scan. After administering 300 to 400 MBq radiotracer, the images were obtained. The uptake time after injection of FDG was standard for each center (90 minutes for Groningen and 60–75 minutes in the other centers). The PET data were acquired in three-dimensional mode (Leuven, Haarlem) and 2D mode (Groningen, Utrecht). PET-acquisition time was 4 to 5 minutes per table position, with a complete scan time of approximately 30 minutes. The whole body (CT) PET extended from the head to the upper tights. PET images were reconstructed by the ordered subset expectation maximization algorithm, with attenuation correction in all centers, with the exception of Utrecht where Row Action Maximum Likelihood Algorithm was used. No respiratory gating was used.

Data processing.

Standard uptake values (SUV) have not been used because different PET cameras were used, and no standard reference values were available.[18] At each institution, the nuclear physicians used always the same work stations (Dicom or Siemens work station) at standard settings. FDG-PET scans were classified as positive, indeterminate, or negative based on visual comparison with the background activity after single reading at each of the four centers. The FDG-PET results were matched with the suspicious nodule on CT or, in case no nodules were present, a pulmonary mass (> 3 cm in diameter), a (postobstructive) infiltrate, or an atelectatic area.

Data Analysis

For this retrospective analysis, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FDG-PET was calculated for four different groups; all participants with a positive baseline or second round test result; participants with a negative noninvasive workup; participants with a positive test result and a suspicious nodule more than 500 mm^3; and participants with a positive test result and a suspicious nodule with a VDT less than 400 days. In the first analysis, PET positive and indeterminate test results were taken together and considered PET positive, in the second analysis PET indeterminate and negative results were taken together and considered PET negative. Gold standard for the outcome of FDG-PET was the pathological diagnosis of the suspicious lesion or if no surgical resection was performed, the presence or absence of cancer during at least 2 years of follow-up. If a subject was diagnosed with lung cancer after an initial benign diagnosis and the interval between the first PET scan and the second workup was more than 200 days, this new cancer was not included in the calculation of the diagnostic value of PET because of the long time interval; 95% confidence intervals (CIs) were constructed by SPSS software package version 15.0. In the absence of normal distribution, data were presented as medians with a range.

RESULTS

Participant and Nodule Characteristics

In total, 324 subjects had a positive test result after baseline and second round screening. Their median age was 62 years (range: 50–75 years), the median number of pack-years smoked was 43 (range: 21–160 pack-years), and 20% were women. The characteristics of

the suspicious nodules detected in these test-positive participants are listed in Table 1. In 95 test-positive participants, no PET scan was made: 29 were not referred for workup, and in 66 participants (55 + 11), this was a tumor board decision (Figure 1). Nodule size was significant larger in the group who underwent a PET scan, but there were no significant differences in VDT or nodule consistency between the two groups. The mean nodule size of the 293 solid nodules was 648 mm^3 (28–5486 mm^3), of the 16 nodules with mixed attenuation 526 mm^3 (169–4610 mm^3), and of the four pure ground-glass nodules 452 mm^3 (135–638 mm^3).

Table 1.*Characteristics of the suspicious nodules in 324 test-positive participants of the NELSON lung cancer screening trial.*

	FDG-PET (%) N=229	No FDG-PET (%) N=95	p-value[a]
Nodule size			
< 50 mm^3 (< 4.6 mm)	3 (1)	2 (2)	
50-500 mm^3 (4.6-9.8 mm)	64 (28)	37 (39)	
> 500 mm^3 (>9.8 mm)	159 (70)	48 (50)	**<0.001**
NA[b]	3 (1)[b]	9 (9)[c]	
Volume doubling time (VDT)			
VDT > 600 d	7 (3)	7 (7)	
VDT 400-600 d	4 (2)	3 (3)	
VDT < 400 d	96 (42)	31 (32)	0.53
NA[d]	122 (53)	55 (57)	
Nodule consistency			
Solid	212 (93)	81 (84)	
Part-solid	13 (6)	3 (3)	
Ground glass	1 (0)	3 (3)	0.23
Not specified	3 (1)	9 (10)	

[a] Fisher's exact test.
[b] No nodules (*n* = 3): multiple metastasis (1 subject), atelectasis (1), and consolidation (1).
[c] No nodules (*n* = 9): Langerhans histiocytosis (1 subject), atelectasis (3), consolidation (3), pleural fluid (1), and mediastinal mass (1).
[d] Calculation VDT not possible (*n* = 177): baseline nodules (116), new nodules (55), and no nodules (6).
NA, not available; FDG-PET, (18)F-fluorodeoxyglucose-positron emission tomography.

Nonsurgical Workup

In total, 240 test-positive participants were referred to a chest physician for nonsurgical workup, which included a bronchoscopy and a standard dose CT with contrast. The diagnostic procedures performed during bronchoscopy were washings (65%), brushings (25%), endobronchial biopsies (7%), transbronchial biopsies (3%), and transbronchial punctions (1%) but no lavages. The role of bronchoscopy and CT scan with intravenous contrast made during evaluation by the pulmonologist will be described separately. In 93 participants, nonsurgical workup was conclusive and in 147 inconclusive. In case of regression or disappearance of a nodule on CT with intravenous contrast, the workup was terminated and considered as benign. All 147 subjects with an inconclusive nonsurgical workup were referred for surgery (Figure 1).

Surgical Workup

In 11 of 147 participants with an inconclusive nonsurgical workup, no PET scan was made (tumor board decision). In 46% (5/11), these resections were done for benign disease; in one of them (1/5), the diagnosis had clinical consequences (Langerhans cell histiocytosis) (Figure 1). The remaining 136 patients underwent a PET scan and were subsequently operated upon. Twenty-three percent (31/136) of these resections were done on benign nodules (Figure 1). In these 31 patients, five VATS procedures and 26 thoracotomies (15 wedge resections, seven lobectomies, and four histological true-cut biopsies) have been performed. Twenty-six percent (8/31) of the resections for benign disease had clinical consequences with respect to follow-up or initiation of treatment and included latent tuberculosis (2), active tuberculosis (1), aspergilloma (2), tumorlet (2), and atypical adenomatous hyperplasia (1). Nine subjects were diagnosed with malignancies other than lung cancer after surgery: pulmonary metastasis from colon (3), prostate (2), oral cavity (1), esophagus (1), a thymoma, and maltoma of the lung (Figure 1).

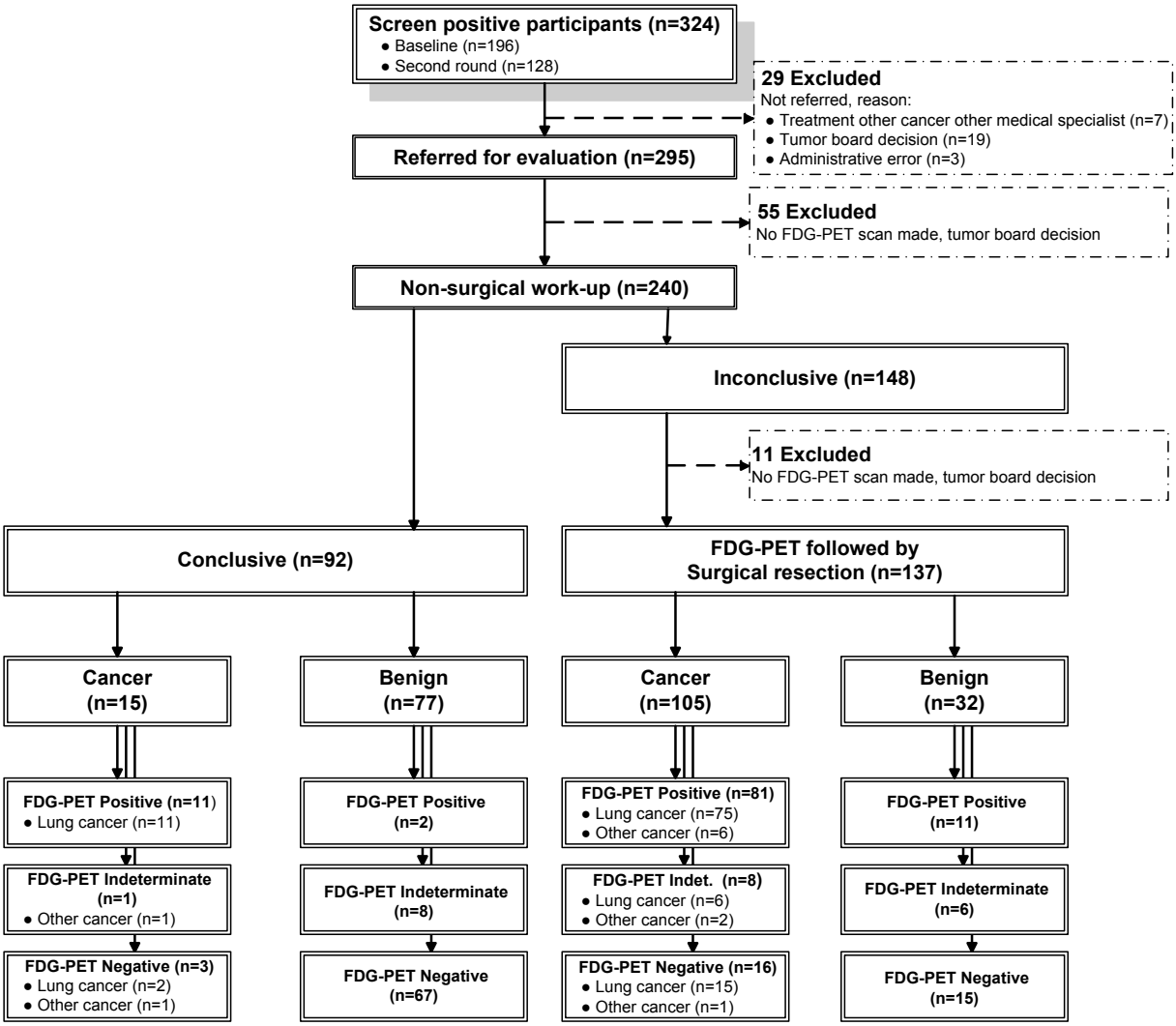

Figure 1. *Overview of subjects with a positive screening result after baseline and second round screening with respect to type of workup and outcome of (18)F-fluorodeoxyglucose-positron emission tomography (FDG-PET).*

FDG-PET Performance

The median time between PET and surgery was 28 days (range: 5–203 days). In Tables 2 and 3, the lung cancer diagnoses and nodule characteristics are presented. Of the 109 lung cancers detected, 17% was PET negative, 79% positive, and 4% indeterminate (Table 3). Of the PET positive, negative, and indeterminate lung cancers, 20%, 53%, and 17%, respectively, was less than 500 mm^3. The one pure ground-glass nodule was PET negative and the four partial solid lesions PET positive, except for the carcinoid, which was PET negative. For all test-positive subjects (*n* = 229), the sensitivity, specificity, PPV, and NPV of PET was 84%, 75%, 79%, and 81%, respectively, when the indeterminate test results were considered PET positive. In 25% (27/109), PET was false positive (Table 4). When the indeterminate test results were considered PET negative, the sensitivity, specificity, PPV, and NPV were 77%, 88%, 88%, and 77%, respectively. In 12% (13/109), PET was false positive (Table 4). During follow-up, eight subjects were diagnosed with lung cancer after an initial negative workup during baseline or second round screening (Table 5). The median time interval between the first and second workup was 716 days (259–974 days). Based on this retrospective information, the sensitivity, specificity, PPV, and NPV of the initial PET were 80%, 75%, 80%, and 75%, respectively, when the indeterminate test results were considered PET positive. When the most recent PET was taken, these values were 84%, 75%, 81%, and 78%, respectively. The role of PET was also investigated for all testpositive subjects in whom the suspicious nodule was larger than 500 mm^3 (> 9.6 mm in diameter) (*n* = 156); these data are presented in Table 4. Finally, we investigated the role of a preoperative PET in 137 patients who underwent surgical resection of the suspicious nodule after an inconclusive nonsurgical workup. The sensitivity, specificity, PPV, and NPV were 85%, 47%, 84%, and 48%, respectively, when the indeterminate test results were considered PET positive (Table 4). When the indeterminate test results were considered PET negative, the sensitivity, specificity, PPV and NPV were 77%, 66%, 88%, and 47%, respectively (Table 4).

Table 2. *Histological diagnoses, FDG-PET result, and nodule characteristics of the 32 subjects who underwent surgery for benign disease during baseline and 2nd round screening of the NELSON lung cancer screening trial.*

No.	Histological Diagnosis	PET	Maximum Diameter (mm)	Consistency	Volume Doubling Time (d)
Benign / normal tissue					
1	Lymph node	Negative	6	Solid	< 400
2	Lymph node	Negative	8	Solid	< 400
3	Lymph node	Negative	6	Solid	< 400
4	Lymph node with sinus histiocytosis	Indeterminate	16	Solid	< 400
5	Lymph node	Positive	15	Solid	< 400
6	Lymph node	Negative	12	Solid	< 400
7	Lymph node	Negative	6	Solid	< 400
8	Hamartoma	Negative	11	Solid	New nodule
9	Hamartoma	Negative	12	Solid	New nodule
10	Hamartoma	Negative	7	Solid	< 400
11	Hamartoma	Indeterminate	16	Solid	New nodule
12	Infarction	Indeterminate	8	Solid	400-600
13	Infarction	Negative	15	Solid	New nodule
14	Infarction	Indeterminate	33	Solid	New nodule
15	Infarction	Positive	17	Solid	New nodule
16	Fibrosis	Positive	29	Solid	New nodule
17	Focal organizing pneumonia	Indeterminate	13	Solid	New nodule
18	Pulmonary apical cap	Positive	15	Solid	< 400
19	Mixed papilloma	Negative	10	Solid	< 400
Infectious / inflammatory nodules					
20	Granuloma and necrosis	Positive	13	Solid	New nodule
21	Granuloma and necrosis	Positive	12	Solid	New nodule
22	Granuloma and necrosis	Negative	8	Solid	< 400
23	Granuloma	Negative	10	Solid	< 400
24	Granuloma	Negative	9	Solid	< 400
25	Organizing pneumonia	Positive	17	Solid	New nodule
26	Organizing pneumonia	Positive	11	Solid	< 400
27	Aspergilloma	Positive	14	Solid	< 400
28	Aspergilloma	Negative	17	Solid	New nodule
29	Lymphoid hyperplasia	Indeterminate	14	Solid	New nodule
Preinvasive lesions					
30	Tumourlet	Positive	21	Solid	< 400
31	Tumourlet	Negative	9	Solid	< 400
32	Atypical adenomatous hyperplasia	Positive	34	partial-solid	New nodule

[a] *No histology obtained of suspicious nodule, mediastinoscopy only, and the 2 yr follow-up period was eventless. FDG-PET, (18)F-fluorodeoxyglucose-positron emission tomography.*

Table 3. *Histological diagnoses, FDG-PET result and nodule characteristics of 109 subjects diagnosed with lung cancer during baseline and 2nd round screening of the NELSON lung cancer screening trial.*

No.	Histological Diagnosis	PET (%)		Median Diameter (mm, Range)	Consistency (%)		Volume Doubling Time (d)[a]	
58	Adenocarcinoma	Positive	46 (79)	14 (5-68)	Solid	53 (95)[b]	VDT > 600	3 (11)
		Indeterminate	4 (7)		Part solid	3 (5)	VDT 400-600	3 (11)
		Negative	8 (14)		Ground glass	0	VDT <400	22 (78)
20	Large cell carcinoma	Positive	17 (85)	18 (6-45)	Solid	20 (100)	VDT > 600	0
		Indeterminate	1 (5)		Part solid	0	VDT 400-600	0
		Negative	2 (10.0)		Ground glass	0	VDT <400	7 (100)
16	Squamous cell carcinoma	Positive	14 (88)	19 (7-47)	Solid	15 (94)	VDT > 600	0
		Indeterminate	1 (6)		Part solid	1 (6)	VDT 400-600	0
		Negative	1 (6)		Ground glass	0	VDT <400	8 (100)
6	Broncho alveolair cell carcinoma or adenocarcinoma with BAC features.	Positive	2 (33)	13 (9-22)	Solid	5 (83)	VDT > 600	1 (20)
		Indeterminate	0 (0)		Part solid	0 (17)	VDT 400-600	0
		Negative	4 (67)		Ground glass	1 (17)	VDT <400	4 (80)
3	Carcinoid	Positive	1 (33)	17 (13-20)	Solid	2 (67)	VDT > 600	0
		Indeterminate	0 (0)		Part solid	1 (33)	VDT 400-600	0
		Negative	2 (67)		Ground glass	0	VDT <400	1 (100)
2	Small cell lung cancer	Positive	2 (100)	15 (15-15)	Solid	2 (100)	VDT > 600	0
		Indeterminate	0		Part solid	0	VDT 400-600	0
		Negative	0		Ground glass	0	VDT <400	1 (100)
4	Diagnosis lung cancer, no cytology/histology	Positive	4 (100)	20 (12-21)	Solid	4 (100)	VDT > 600	1 (100)
		Indeterminate	0		Part solid	0	VDT 400-600	0
		Negative	0		Ground glass	0	VDT <400	0

[a]Numbers do not add up because for baseline and new nodules no VDT can be calculated
[b]Numbers do not add up to 58 because one subject had a postobstruction infiltrate and no nodules on CT.
FDG-PET, (18)F-fluorodeoxyglucose-positron emission tomography; VDT, volume doubling time; CT, computer tomography.

Table 4.*Diagnostic performance of FDG-PET during baseline and 2nd round screening of the NELSON randomized controlled lung cancer screening trial.*

PET result	Cancer	Benign	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
All subjects (*n* = 229)						
Positive or indeterminate	101	27	84.2 (77.6-90.7)	75.2 (67.1-83.3)	78.9 (71.8-86.0)	81.2 (73.6-88.8)
Negative	19	82				
Subjects with nodules ≥ 500mm³ (> 9.8 mm) (n=159)						
Positive or indeterminate	80	24	90.9 (84.9-96.9)	66.2 (55.2-77.2)	76.9 (68.8-85.0)	85.5 (76.1-94.8)
Negative	8	47				
In-conclusive non-surgical work-up (n=137)						
Positive or indeterminate	89	17	84.8 (77.9-91.6)	46.9 (29.6-64.2)	84.0 (77.-0-91.0)	48.4 (30.8-66.0)
Negative	16	15				
Conclusive non-surgical work-up (n= 92)						
Positive or indeterminate	12	10	80.0 (59.8-100)	87.0 (79.5-94.5)	54.5 (33.7-75.4)	95.7 (91.0-100)
Negative	3	67				
All subjects (*n* = 229)						
Positive	92	13	76.7 (69.1-84.2)	88.1 (82.0-94.2)	87.6 (81.3-93.9)	77.4 (70.1-84.8)
Negative or indeterminate	28	96				
Subjects with nodules ≥ 500mm³ (> 9.8 mm) (*n* = 159)						
Positive	73	11	83.0 (75.1-90.8)	84.5 (76.1-92.9)	86.9 (79.7-94.1)	80.0 (71.0-89.1)
Negative or indeterminate	15	60				
In-conclusive non-surgical work-up (*n* = 137)						
Positive	81	11	77.1 (69.1-85.2)	65.6 (49.2-82.1)	88.0 (81.4-94.7)	46.7 (32.1-61.4)
Negative or indeterminate	24	21				
Conclusive non-surgical work-up (*n* = 92)						
Positive	11	2	73.3 (51.0-95.7)	97.4 (93.8-100)	84.6 (65.0-100)	94.9 (90.1-99.8)
Negative or indeterminate	4	75				

PPV, positive predictive value; NPV, negative predictive value; CI, Confidence interval; FDG-PET, (18)F-Fluorodeoxyglucose-positron emission tomography

DISCUSSION

In this study, we evaluated the role of PET in 229 subjects with a positive baseline or second round test result. The prevalence of cancer in this population was 52%. The sensitivity of PET to detect cancer 84.2% (95% CI: 77.6 – 90.7%), the specificity 75.2% (95% CI: 67.1 – 83.3), the PPV 78.9% (95% CI: 71.8–86.0), and the NPV 81.2% (95% CI:73.6 – 88.8). For subjects with nodules larger than 500 mm^3, the sensitivity was 90.9% (95% CI: 84.9 – 96.6%), the specificity 66.2% (95% CI: 55.2 – 77.2%), the PPV 76.9% (68.8 – 85.0%), and the NPV 85.5% (95% CI: 76.1 – 94.8%). The resection rate for benign lesions was 23%; a preoperative PET after an inconclusive nonsurgical workup reduced the futile resection rate with 11 to 15%, at the expense of missing 12 to 18% lung cancer cases. A preoperative PET after a conclusive nonsurgical workup reduced the futile resection rate by 78% at the expense of missing 3% lung cancer cases.

Several investigators evaluated the role of PET in a lung cancer screening setting. FDG-PET was part of their CT screening protocol for nodules ≥7 mm,[4] more than 8 mm, and growing nodules less than 8 mm[19] or nodules ≥10 mm and growing nodules more than 7 mm.[20] Pastorino et al.[4] reported on the results of 42 PET scans, Bastarrika et al.[20] on 25, and Veronesi et al.[19] on 157 PET scans. Sensitivities and specificities of PET in these settings ranged between 69 to 90% and 81 to 93%, respectively.[4, 19, 20] They concluded that a combination of CT and PET effectively detects lung cancer and may help to reduce unnecessary surgeries for benign lesions[4, 19, 20] Veronesi et al.[19] reported an overall specificity of 93% for PET but with a wide range between 68% and 100%. For nodules ≥10 mm, the sensitivity was 91% at a specificity of 68%. The other two authors did not report on the value of PET in larger nodules only. Also, Lindell et al.[21] investigated the role of PET. They found that 32% of the lung cancers were PET negative. This might be due to the fact that they are usually smaller (mean size 10 mm) and/or low-grade lung cancers.[21] Our false-negative lung cancers rate was with 16% lower, probably because the median nodule size of all cancers detected was above 14 mm (Table 3). The overall sensitivity in our study was comparable with the aforementioned studies,[4, 19, 20] but the specificity was lower. For nodules ≥9.8 mm, however, our results are comparable with those reported by Veronesi et al. for nodules ≥10 mm.

Question is whether the sensitivities and specificities of PET found in lung cancer screening setting differ from nonscreening series. Wahidi et al.[22] reviewed 17 studies on PET for the evaluation of solitary pulmonary nodules. The median specificity in these studies was 82.6% (range: 40– 100%), with a corresponding sensitivity of 87% (range: 80–100%). In a meta-analysis of 40 studies on pulmonary nodules and mass lesions, a sensitivity of 97% at a specificity of 83.3% was found.[23] The sensitivities and specificities in a lung cancer screening setting are thus slightly lower than in a nonscreening setting, most likely because of smaller tumor sizes, differences in the a priori lung cancer probability, and distribution in tumor histology in lung cancer screening. When the use of PET was limited in our study to subjects with suspicious nodules ≥500 mm^3 (≥9.8 mm), the specificity remained very low with only a slight increase in sensitivity. This can be explained by the fact that many of the new and growing nodules ≥500 mm^3 and with a VDT less than 400 days were false PET positive and represent enlarged lymph nodes, hyperplastic lymphoid tissue, or granulomas.

In a multidetector CT lung cancer screening setting, the resection rate for benign lesions at baseline varied between 0% and 43% with a median value of 19%.[3-5, 8, 9, 20, 24-30] This demonstrates that by using the NELSON nodule management strategy, in which the number

of recall CT scans was strictly limited to only 1 per screening round and in which volumetric software evaluation replaced FNA, PET, or evaluations after antibiotics, similar resection rates for benign disease were found in comparison with the literature.[10] Although there is no consensus what an acceptable resection rate for benign lesions is, a rate between 10% and 20% can be regarded as acceptable. This means that the resection rate for benign disease in the NELSON lung cancer screening trials was too high but after adjustment for clinical relevant disease (17%), within the acceptable range.

Question was, whether a preoperative PET scan could help to reduce the resection rate for benign lesions after a negative nonsurgical workup. In the scenario that PET negative and indeterminate test results are regarded as PET negative (Table 4) instead of 137 subjects, only 92 participants would have been operated with a reduction in the resection rate for benign disease from 23% (31/137) to 8% (11/137). If PET positive and PET indeterminates are taken together (Table 4), the resection rate for benign disease would have been 12% (17/137). Thus, a preoperative PET can help to reduce the resection rate for benign disease but at the expense of missing, respectively, 24 and 16 lung cancer cases, which is unacceptable due to the low NPV of PET in this setting, and should not be recommended. Also, other investigators demonstrated that lung cancer can show faint FDG uptake, which should not be neglected.[31] In small malignant pulmonary nodules less than 20 mm and less than 10 mm, 19% and 20% was PET negative, respectively.[32, 33]

In contrast, the role of PET after a conclusive nonsurgical workup was evident; the resection rate for benign disease in this group decreased from 84% (78/93) to 12% (11/93) at the expense of only 3% (3/92) additional missed cancers because of the very high NPV of 96% (Table 4). Thus, after a conclusive nonsurgical workup, the resection rate for benign disease can be decreased by 72%.

Limitation of our study was that there was no standardized FDG-PET protocol, which could have been a potential source of bias, although it reflects our daily practice of evaluating pulmonary nodules. Differences in FDG-uptake and imaging time may have led to differences in FDG-uptake in tumor to background ratio and, thus, may have influenced the PET results. No second reading was done, which may have led diminished the reproducibility. Another limitation of our study is that, we were not able to calculate SUVs because there were no national standards available for comparison between the institutes at the time of the study.[15] Nevertheless, several authors recommended qualitative analysis over quantitative analysis[31, 34, 35] because no improvement in accuracy was observed by semiquantitative approaches over visual analysis of pulmonary nodules 10 to 30 mm [31] or ≥7 mm.[35] The same was found for nodules with a SUV less than 2.5.[34] The classical threshold of SUV 2.5 may be inappropriate for diagnosing malignancies with low FDG-uptake[36, 37] and a lower cutoff of 1.5 to 2 might be more appropriate.[4, 19] Another important limitation of the study is that, although the PET was made for staging purposes in case the nodule turned out to be malignant at surgery, the investigators were not blinded to the outcome of the PET result with respect to the uptake by the suspicious nodule. Therefore, outcome of the nonsurgical workup (conclusive or inconclusive) may have been influenced by the outcome of the PET result. Our nodule management strategy was based on VDT and nodule size only and did not include the use of transthoracic needle biopsies.[7] This should not be regarded as limitation of this study but rather the result of our NELSON nodule management strategy based on which the workup of nodules was performed. In conclusion, a preoperative PET scan in participants with an inconclusive nonsurgical workup is not recommended because

of the very low NPV, but after a conclusive nonsurgical workup, the resection rate for benign lesions can be decreased by 72%.

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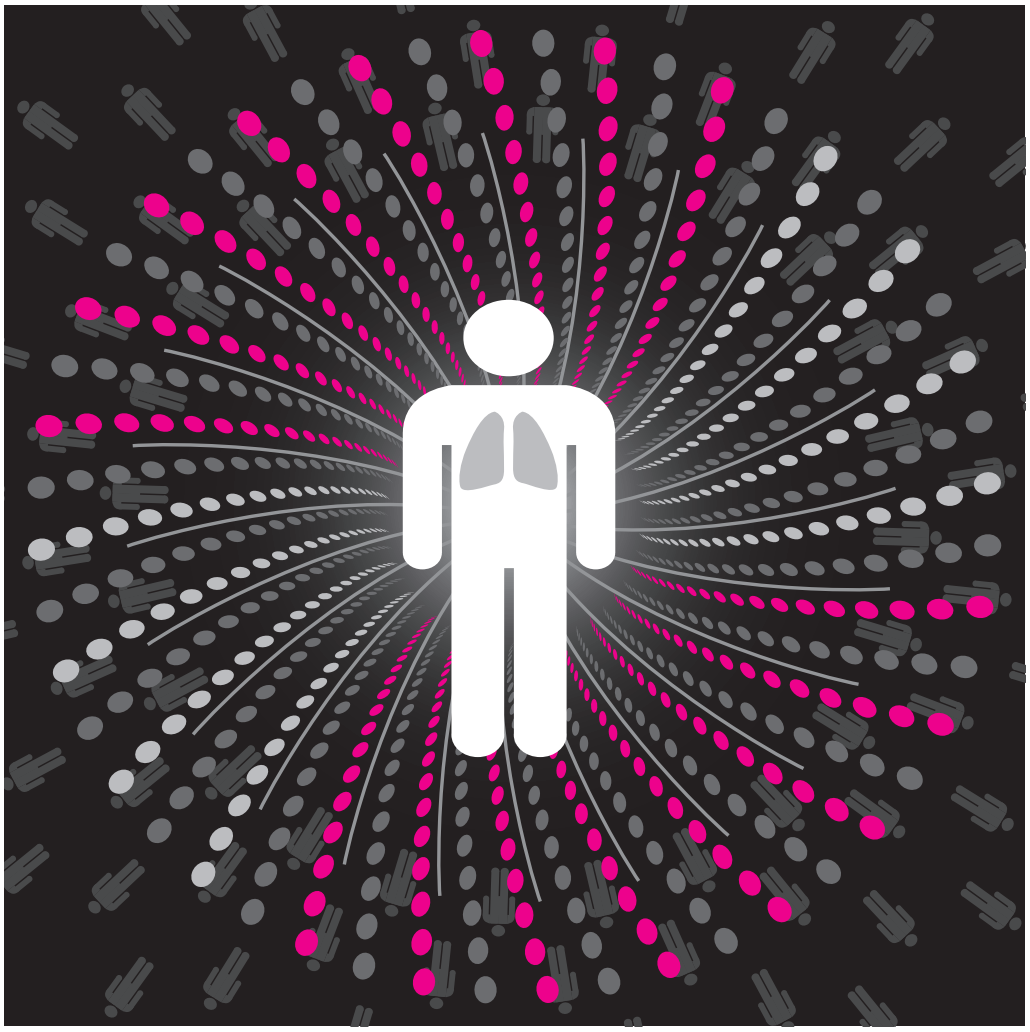
Chapter 8



The role of conventional bronchoscopy in the work-up of suspicious CT screen detected pulmonary nodules

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Abstract

Background: Up to 50% of the participants in computer tomography (CT) lung cancer screening trials have at least one pulmonary nodule. The role of a conventional bronchoscopy in the work-up of suspicious screen-detected pulmonary nodules to date is unknown. If a bronchoscopic evaluation could be eliminated, the cost-effectiveness of a screening program could be enhanced and the potential harms of bronchoscopy avoided.

Methods: All consecutive participants showing a positive test result between April 2004 and December 2008 were enrolled. The diagnostic sensitivity and negative predictive value (NPV) were calculated at the level of the suspicious nodules. In 95% of the nodules the gold standard for the outcome of the bronchoscopy was based on surgical resection specimens.

Results: A total of 318 suspicious lesions were evaluated by bronchoscopy in 308 subjects. The diameter of the nodules averaged 14.6 mm (SD: 8.7) while only 2.8% of nodules were >30 mm in diameter. The sensitivity of bronchoscopy was 13.5% (95% confidence interval (CI): 9.0%-19.6%), the specificity 100%, the PPV 100% and the NPV 47.6% (95% CI: 41.8%-53.5%) Of all cancers detected, 1% was detected by bronchoscopy only and retrospectively invisible on both low-dose CT and CT with intravenous contrast.

Conclusion: Conventional white-light bronchoscopy should not be routinely recommended for test-positive participants in a lung cancer screening program.

Trial registration number: ISRCTN63545820; Nelson longkanker screenings onderzoek.

Introduction

Depending on the geographic region, 26-51% of participants in multi-detector computer tomography (CT) lung cancer screening trials showed at least one non-calcified pulmonary nodule on their CT scan.[1-4] The likelihood of these nodules being malignant is size dependent.[1, 5] The Fleischner Society guideline recommends a recall CT, positron-emission tomography (PET) and/or a biopsy for nodules >8 mm detected on CT,[5] but no bronchoscopy. The American College of Chest Physicians (ACCP) guideline recommends only evaluation by bronchoscopy under the condition that an air-bronchogram is present on CT, or in centers with expertise in newer techniques.[6, 7] Literature on the role of newer techniques, such as ultrathin bronchoscopy, autofluorescence bronchoscopy and CT-guided bronchoscopy in lung cancer screening settings is sparse; to our knowing McWilliams et al.[8] it the only who reports on the role of autofluorescence bronchoscopy in a lung cancer screening trial. The diagnostic yield of bronchoscopy to evaluate solitary pulmonary nodules outside CT screening programs varies from 51-76%[9-14] and is highly dependent on the size and location of the nodule.[9, 10, 13-15]

The nodule management strategy of the Dutch-Belgian randomized lung cancer screening trial (NELSON) is only based on the size and the volume-doubling time (VDT) of nodules detected by CT without the use of fine-needle aspirate (FNA), PET or evaluation after antibiotics.[1] Test positives were referred for the work-up of suspicious nodules which included a physical exam, a standard CT scan with contrast and bronchoscopy.[5, 6, 16, 17] Recently a large randomized lung cancer screening trial showed a 20% mortality reduction with low-dose CT screening.[18] In the low-dose CT-arm 320 subjects (1.8% of test positives) underwent bronchoscopy with neither a biopsy nor cytological testing while 391 subjects (2.2% of test positives) underwent bronchoscopy with a biopsy or cytological testing.[18] They do not report on the diagnostic performance of bronchoscopy in their study. In the study performed by McWilliams e*t al*,[19] all participants were offered an autofluorescence bronchoscopy to detect central airway lesions and 67% (378/561) of participants underwent bronchoscopy. Ideally, all subjects should have undergone bronchoscopy for this purpose. Four subjects (18% (4/22) were diagnosed with radiologically occult[19] lung cancer following bronchoscopy. In the NLST the purpose of bronchoscopy appears to be inspection of the central airways in about 45% (320/711) of cases, while in the other cases cytology or histology specimens were obtained. It is unclear to what extent the ACCP guidelines were followed. In both studies no nodule criteria were specified in the decision to perform bronchoscopy. So far, lung cancer screening trials do not carry specific recommendations with respect to the role of bronchoscopy in the work-up of suspicious nodules after a positive test result, and[2, 20-22] a significant numbers of bronchoscopies have been performed.[18] Screening detects more early-stage lung cancers whereas advanced-stage lung cancers that are present as interval cancers amenable to bronchoscopy are excluded from the analysis.[1] Our hypothesis was that the diagnostic value of bronchoscopy in this work-up process might be low because suspicious nodules are usually small and often peripherally located.[1, 20, 21] If this is true, bronchoscopic evaluation could be eliminated from the standard work-up of suspicious CT-detected nodules, which would enhance the cost-effectiveness of a lung cancer screening program and avoid the harms of bronchoscopy. Therefore, our objective was to investigate prospectively the diagnostic value of bronchoscopy in the NELSON lung cancer screening trial and to evaluate the diagnostic yield of the various diagnostic techniques used during bronchoscopy.

Materials and Methods

Study Population

The nodule management strategy of the NELSON trial has been described earlier.[16, 23] In short, 15,822 individuals with a high risk of lung cancer participated in a randomized trial with a low-dose CT scan (n = 7,915) during baseline screening (first round), one year later (second round) and three years later (third round, two years after the second round) or no screening (n = 7,907). All consecutive subjects showing a positive test result during baseline screening, and the second and third screening rounds between April 2004 and the end of December 2008 were included in this study. The participants showed a positive test result when a pulmonary nodule larger than 500 mm^3 (> 9.8 mm in diameter) was detected or when the nodule was growing with a VDT of <400 days.[1, 16, 19] If the solid component of the nodule was 50-500 mm^3 the test result was undetermined and a repeat scan was made to assess the VDT. When the VDT was < 400 days on the repeat scan, the test was considered positive, otherwise it was negative.[1, 16] The NELSON trial was approved by the Ethics Committees of all participating centers and all participants provided written informed consent.

Bronchoscopy

Conventional bronchoscopies were performed by experienced pulmonologists working at the four screening sites.[16] During white-light bronchoscopy, bronchial washings were performed for cytology and culture, while bronchial brushings and biopsies were taken (52C-1 forceps) in the case of central lesions. In less than 1% of cases biopsies were performed under fluoroscopic guidance. The bronchoscopists did not use CT fluoroscopic guidance or ultrathin bronchoscopes. Flexible Pentax video-bronchoscopes were used in Utrecht while Groningen and Haarlem used Olympus flexible video-bronchoscopes with Leuven using both. Endobronchial abnormalities were classified as “visible tumor” or “constriction or compression of the airways”. Nodules within the inner third, middle and outer third of the hilar-costal distance on CT were classified as central, intermediate or peripheral. If bronchoscopy revealed cancer, the outcome of the bronchoscopy was considered positive, otherwise it was negative. The gold standard for, and the final diagnosis of the outcome of the bronchoscopy were based on the pathology result of the surgical resection specimen of the suspicious lesion, or if no surgical resection was performed, the presence or absence of cancer during at least two years of follow-up after the first and second screening rounds and at least one year of follow-up after the third round. Nodules with a VDT of > 400 days at follow-up were considered benign.[1]

Data Analysis

Statistical analyses were performed using SPSS version 17.0 (SPSS inc, Chicago, IL, USA). The sensitivity was defined as the ratio between the number of positive bronchoscopies and the number of positives according to our gold standard. The diagnostic sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated at the level of the suspicious nodules. Suspicious nodules that were not approached during bronchoscopy were excluded from the analysis. The Mann-Whitney U test was used for continuous variables, and the χ^2-test for binomial and categorical data. Binary logistic regression was used to determine the effect of the individual nodule characteristics on the

diagnostic yield of bronchoscopy. In the multivariate analysis the characteristics with a p-value of ≤ 0.10 were included for a stepwise-forward procedure. P-values <0.05 were considered significant.

Results

Of the 415 test-positive participants, 74.2% (308/415) underwent bronchoscopy to evaluate 318 suspicious lesions; 25.8% (107/415) did not undergo bronchoscopy for several reasons (Fig. 1). In 2.4% (10/415) of cases referral was based on non-nodular lesions on CT. Six bronchoscopies were performed (Fig.1) on these participants. No significant differences were found in the participant and the nodules characteristics of those who did and those who did not undergo bronchoscopy (Table 1), except for a gender difference and a cancer detection rate of 22.4% (24/107) in the group without bronchoscopy as compared to 57.8% (178/308) in the bronchoscopy group (p < 0.0001, Fig. 1).

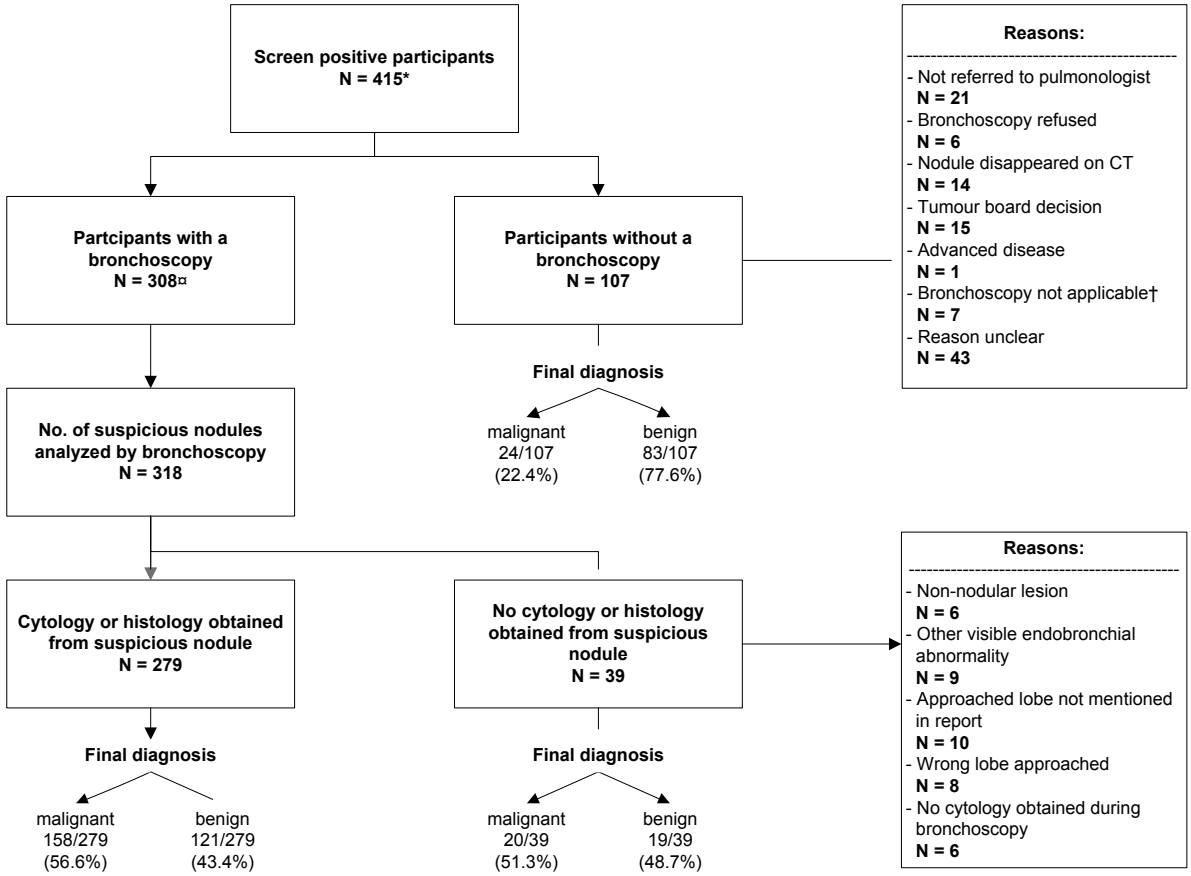

Figure 1. *Outcome of the bronchoscopies performed for the evaluation of 308 screen positives of the NELSON randomized lung cancer screening trial.Definition of abbreviations.* Including 10 participants referred for non-nodular lesions detected on screening CT (interstitial lung disease, pneumonia, lobar atelectasis, pleural effusion, pleural thickening or mediastinal mass) † Lesion could not be approached by bronchoscopy (non-nodular lesion or pleural-attached nodule)*

Table 1. *Comparison of participant and nodule characteristics between those who did and did not undergo a bronchoscopy*

Characteristics		Bronchoscopy	No bronchoscopy	p
Participant	N(%)	308 (74.2)	107(25.8)	
Gender	Female N (%)	60/308 (19.5)	8/107 (7.5)	<0.0001
Age	Mean (range)	62 (50-75)	62 (51-74)	0.44
Pack Years	Mean (range)	47 (21-160)	43 (22-108)	0.12
Nodule				
Diameter	Mean (SD) in mm	14.6 (8.7)	14.6 (9.1)	0.78
VDT	< 400 days N (%)	132/146 (90.4)	39/46 (84.8)	0.29
Localisation*	Central N (%)	38/296 (12.8)	9/98 (9.2)	0.33
Lobe	Upper lobe N (%)	152/298 (51.0)	48/100 (48.0)	0.60
Screen round				
First round	N (%)	144/308 (46.8)	44/107 (41.4)	0.31
Second round	N (%)	91/308 (24.5)	29/107 (27.1)	0.63
Third round	N (%)	73/308 (23.7)	34/107 (31.8)	0.10
Scan type				
Regular screening round	N (%)	202/308 (65.6)	67/107 (62.6)	0.58
Repeat scan	N (%)	106/308 (34.4)	40/107 (37.4)	0.58

Definition of abbreviations: VDT = Volume Doubling Time
Statistical analysis: Mann-Whitney U and χ^2 test
* Central = inner 1/3 rd of the costal-hilar diameter on CT

The average maximum diameter of the suspicious nodules was 14.6 mm, with the maximum diameter varying from 5-68 mm (SD: 8.7 mm), and 2.8% being > 30 mm. Cancer was diagnosed on the basis of bronchoscopy in only 24 of the 318 suspicious lesions. Suspicious nodules identified as cancer by bronchoscopy were significantly larger (Odds Ratio (OR) = 1.07, p <0.0001, 95% confidence interval (CI): 1.02-1.13) and were more often visible during bronchoscopy (OR = 87.6, p<0.0001, CI:4.9-564.9) as compared to the cancer cases missed by bronchoscopy (Table 2).

Table 2. *Uni- and multivariate analysis of the diagnostic bronchoscopies in subjects diagnosed with cancer in the nelson trial.*

Characteristics	Cancer diagnosed by bronchoscopy N = 24	Final diagnosis cancer N = 178	Univariate		Multivariate	
			OR (95%CI)	p	OR (95%CI)	p
Nodule*						
Diameter (mm)	26.0 (SD:3.6)	17.7 (SD: 0.7)	1.08 (1.04 - 1.13)	<0.0001	1.07 (1.02 - 1.13)	<0.0001
VDT > 400 days	0/5 (0%)	8/86 (9.3%)	1			
< 400 days	5/5 (100%)	78/86 (90.7%)	-	-		
Localization*						
Peripheral	11/22 (50.0%)	146/176 (83.0%)	1		1	
Central†	11/22 (50.0%)	30/176 (17.0%)	7.11 (2.71 - 18.63)	<0.0001	0.44 (0.04 - 5.16)	0.52
Middle and lower lobe	5/21 (23.8%)	64/175 (36.6%)	1			
Upper lobe	16/21 (76.2%)	111/175 (63.4%)	1.99 (0.69 - 5.71)	0.20		
Screen round						
First round	12/24 (50.0%)	74/178 (41.6%)	1			
Second round	6/24 (25.0%)	51/178 (28.7%)	0.69 (0.24 - 1.97)	0.49		
Third round	6/24 (25.0%)	53/178 (29.8%)	0.66 (0.23 - 1.89)	0.44		
Scan type						
Regular screening round	17/24 (70.8%)	123/178 (69.1%)	1			
Repeat scan	7/24 (29.2%)	55/178 (30.9%)	0.91 (0.35 - 2.34)	0.84		
Bronchoscopy						
Normal	11/24 (45.8%)	155/178 (87.1%)	1		1	
Bronchial compression	4/24 (16.7%)	12/178 (6.7%)	6.54 (1.70 - 25.19)	<0.0001	4.06 (0.56 - 29.21)	0.16
Visible tumour	9/24 (37.5%)	11/178 (6.2%)	58.91 (11.31 - 306.83)	<0.0001	87.61 (4.90 - 564.88)	<0.0001

Definition of abbreviations: CI = confidence interval; OR = Odds Ratio; VDT = Volume Doubling Time.
Statistical analysis: logistic binary regression.
† Central = inner 1/3 rd of the costal-hilar diameter on CT.
* The denominator is not always equal to 24 or 178 because it was not possible to classify all nodules.

Based on our gold standard, in total 178 cancer cases were detected among these 318 lesions, including 167 lung cancer cases. In 77% (137/178) of cases the gold standard was based on surgical resection specimens, in 18.5% (33/178) of cases it was based on surgical biopsies (mediastinoscopy, true-cut biopsies performed during surgery) and in 4.5% (8/178) of cases it was based on the combination of a new and growing PET-positive lesion on CT. Based on this, the sensitivity of bronchoscopy to detect cancer was 13.5% (24/178) (CI: 9.0%-19.6%) and the NPV 47.6% (140/294) (95% CI: 41.8%-53.5%). Because no false positive diagnoses were made by bronchoscopy, the specificity and PPV were 100%. However, 48.4% (154/318) of bronchoscopic diagnoses were false negatives (Table 3).

Table 3. *Overview of the false negative diagnoses made by bronchoscopy in subjects with cancer in the nelson trial*

Cytological or histological diagnoses		N (%)
No abnormality		101 (65.6)
Infectious		
	Aspergillus	1 (0.6)
	Aspecific inflammation	42 (27.3)
Pre-invasive lesion		
	Atypia	1 (0.6)
Benign, other		
	Fibrosis	2 (1.3)
	Resolving haemorrhage	1 (0.6)
	Metaplasia	6 (3.9)
False negative bronchoscopic diagnoses / total no. of bronchoscopic diagnoses		154/318 (48.4)

In 7.5% (23/308) of all bronchoscopies, an endobronchial abnormality was found, and in 47.8% (11/23) of cases the tumor was endobronchially visible. When an endobronchial tumor was visible the sensitivity of bronchoscopy to detect cancer was 81.8% (9/11) (95% CI: 47.8%-96.8%). In 2.6% of the 308 bronchoscopies an endobronchial tumor was detected which was not visible on CT, also in retrospect. This accounts for 4.5% (8/178) of all cancer cases detected by CT screening in this period. Of these eight additional cancer cases, only 3 (1.7%, 3/178) were stage I, the remaining five were stage III or IV. When the diagnostic performance of bronchoscopy was limited to the suspicious nodules visible on CT, the sensitivity to detect cancer was 8.3% (14/168) (95% CI: 4.8%-13.9%) and the NPV 47.6% (140/294) (95% CI: 41.8%-53.5%).The sensitivities of the various diagnostic techniques used during bronchoscopy ranged from 7.9% for brushes to 45.8% for endobronchial biopsies (Table 4). During the bronchoscopies, minor complications (nose bleeding and mild bleeding after the biopsy) occurred in only 0.6% (2/308) of cases. There were no major complications.

Table 4. *Diagnostic value of the different diagnostic procedures performed during bronchoscopy in 308 screen positives of the Nelson trial.*

Diagnostic technique	Malignancy		Diagnostic values			
	Bronchoscopy	Final diagnosis	Sensitivity (%)	95% CI	NPV (%)	95% CI
Wash	17/322 (5.3%)	182/322 (56.5%)	9.3	(5.7 - 14.8)	45.9	(40.2 - 51.7)
Brush	6/125 (4.8%)	76/125 (60.8%)	7.9	(3.3 - 17.0)	41.2	(32.4 - 50.6)
TBNA	2/6 (33.3%)	6/6 (100.0%)	33.3	(6.0 - 75.9)	0	(0 - 6.0)
TBB	1/12 (8.3%)	8/12 (66.7%)	16.7	(0.9 - 63.5)	44.4	(15.3 - 77.3)
EBB	11/40 (27.5%)	24/40 (60.0%)	45.8	(26.2 - 66.8)	55.2	(36.0 - 73.0)
Overall	37/505 (7.3%)	296/505 (58.6%)	12.5	(9.1 - 16.4)	44.7	(40.1 - 49.3)

Definition of abbreviations: CI = confidence interval; EBB = endobronchial biopsy; NPV = negative predictive value transbronchial biopsy; TBNA = transbronchial needle aspiration.
There were no false-positive diagnoses made by bronchoscopy, therefore all specificities and positive predictive va were %

Discussion

In this study we prospectively evaluated the diagnostic value of conventional white-light bronchoscopy in the NELSON lung cancer screening trial. The overall sensitivity was 13.5% and the NPV 47.6%. The sensitivity was only 8.3% when limited to CT-detected suspicious nodules. Of all cancers detected within the time frame of this study, 4.5% were identified by bronchoscopy only and were invisible on CT.

In non-screening studies, the sensitivity of conventional bronchoscopy varies from 51 to 76%, [9-14] which is much higher than the 13.5% in the NELSON trial. This can be explained by the fact that in our study only 2.8% of the nodules were larger than 30 mm while this ranged from 48-72 mm in non-screening studies.[9, 10, 13, 14] We also found fewer endobronchial abnormalities (7.3% versus 8-64%).[10-12] Both nodule size and endobronchial visibility turned out to be independent predictors for a high diagnostic yield in our study.

As far as we know, only Kanemoto *et al*. retrospectively evaluated the diagnostic value of bronchoscopy in a selected study population in which 108 suspicious pulmonary nodules had been detected by mass screening (Chest X-ray or CT).[24] All nodules were ≤ 20 mm and 42% were malignant based on the diagnosis obtained by fluoroscopy-guided bronchoscopy or lung biopsy. The drawback of that study is the selection bias of the study population and the absence of a gold standard for the outcome of the bronchoscopy. As a result, the investigators were unable to provide data on the diagnostic performance of bronchoscopy in this screening program.

According to current guidelines, bronchoscopy is only recommended for the evaluation of nodules with an air-bronchogram[6, 25, 26] without a standard position in the routine work-up of suspicious pulmonary nodules. Although we did not evaluate whether the presence of an air-bronchogram increased the diagnostic yield of bronchoscopy, our results clearly demonstrate that because of its very low sensitivity and negative predictive value, bronchoscopy is not justified for the evaluation of CT screen detected suspicious pulmonary nodules. Although the use of more advanced bronchoscopic techniques is not yet recommended by the ACCP,[6] we believe that electromagnetic-navigated, or peripheral endobronchial ultrasound-guided bronchoscopy might play a role in the near future for the evaluation of this type of smaller nodule because of their higher sensitivity for peripherally located lesions, ranging from 59 to 74% [27-30] and from 49 to 80% ,[27, 31-34] respectively. In addition, ultrathin bronchoscopy might play a future role in the diagnostic evaluation of peripheral pulmonary nodules.[35, 36]

Because of the poor diagnostic performance of conventional bronchoscopy, we do not recommend a routine conventional bronchoscopy for test-positive screenees, even though bronchoscopy did lead to the detection of 4.5% more cancers which were radio-occult on CT. Only one third of these were early stage and suitable for treatment with a curative intent. It is arguable what percentage of missed lung cancers is acceptable. We believe this depends on the setting, lung cancer screening or daily practice. In lung cancer screening trials very large numbers of subjects, even if they only involve test positives, are exposed to an invasive investigation with the accompanying costs, morbidity and patient anxiety. The benefit of bronchoscopy as a complement to CT screening with an additional 4.5% lung cancer diagnosis is too small, also because only 38% of these radio-occult cancers were stage I. The reason that these eight bronchoscopically-detected cancers were invisible on CT is only partly due to the use of low-dose scan techniques because in one out of these eight cancers the lesion was visible in retrospect on the standard-dose CT scans performed in the

work-up of these test-positive participants. Other investigators reported that only between 1[37]- 5%[6] of CT-occult tumors were detected with white light bronchoscopy while 18% were detected using autofluorescence bronchoscopy.[19] Additional diagnostic techniques, such as brushings and biopsies, should only be applied to evaluate visible endobronchial tumors. In our study we recorded a sensitivity of more than 80% for brushing and biopsies.
The strength of our study lies in the fact that it was prospectively conducted and that for the majority of the suspicious nodules histological conformation was obtained by either surgical resection or biopsy. So far, the diagnostic value of a conventional bronchoscopy has not previously been properly evaluated in a CT screening population consisting of asymptomatic high-risk participants from the general population. In addition, we were able to evaluate the diagnostic value of bronchoscopy based on the individual nodule level. Despite this, our study also has its limitations. First of all, the proportion of females and the cancer detection rate in the group that did not undergo bronchoscopy was lower than in those who underwent bronchoscopy. Because gender was not associated with a higher diagnostic yield in our study, this did not introduce selection bias. The cancer detection rate in the group without bronchoscopy was lower because 20% (21/107) of cases were referred for non-nodular lesions or because the suspicious nodule had disappeared on the diagnostic CT with contrast. If all test-positive screenees had undergone bronchoscopy, the sensitivity would even have been lower, which further strengthens our conclusions. In our work-up protocol, bronchoscopy was only performed on test-positive participants. To date, it is unknown what the diagnostic value of conventional bronchoscopy would be if all screenees were to undergo bronchoscopy. This is currently under investigation in the Pan-Canadian lung cancer screening trial.[38]
In conclusion, conventional bronchoscopy should not be routinely recommended for test positives in a lung cancer screening program.

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The role of all authors:

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Rob van Klaveren*: Conception, design, data interpretation, critically revising the draft texts of the article and providing final approval.

Rene Vernhout: acquisition of data, data management, critically revising the draft texts of the article and providing final approval.
Harry Groen, Jan-Willem Lammers, Carla Weenink, Kristiaan Nackaerts, Matthijs Oudkerk, Willem Mali, Frederik Thunnissen, Harry de Koning: conception, design, acquisition of the data, critically revising the draft texts of the article and providing final approval.

* Guarantors of the paper

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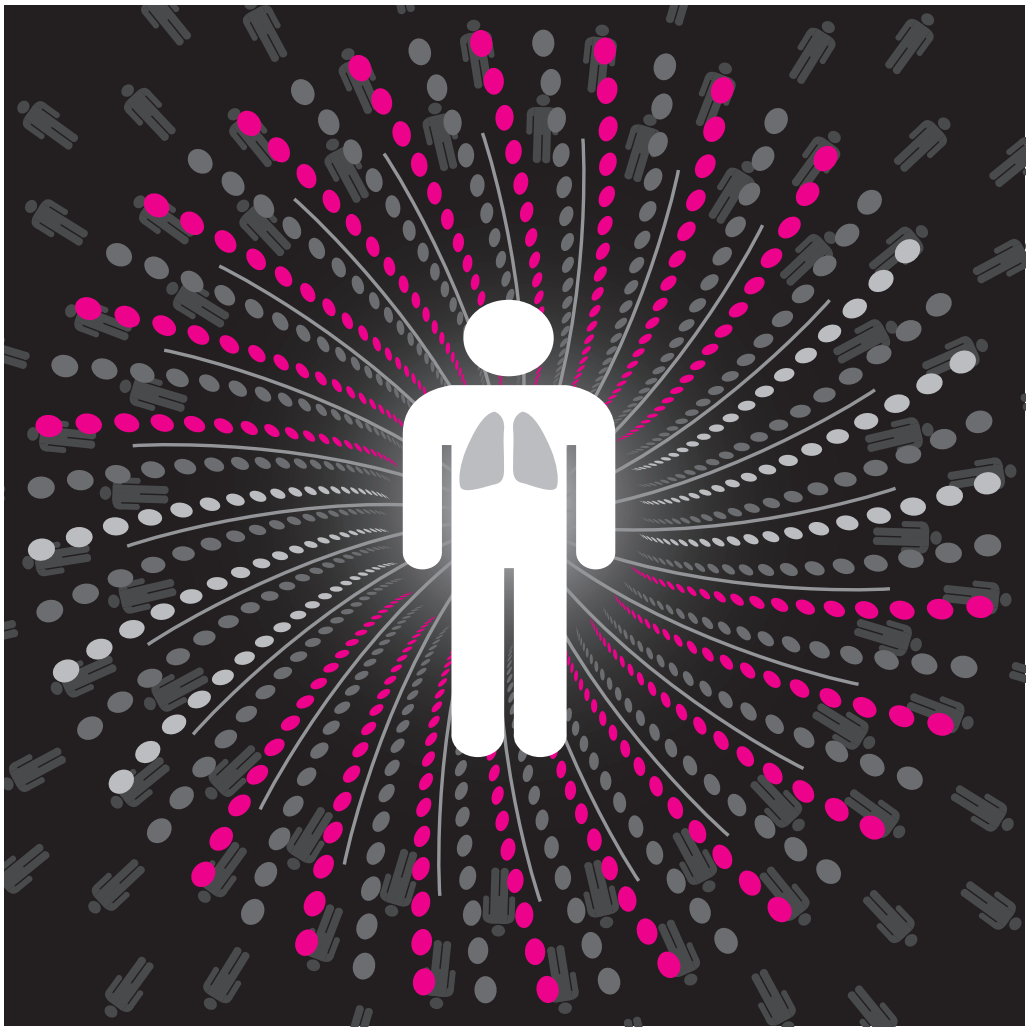
Part III

Management of suspicious pulmonary nodules: surgical procedures

Chapter 9



Complications following lung surgery in the Dutch-Belgian randomised lung cancer screening trial

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Abstract

Objective: To assess the complication rate in participants of the screen arm of the NELSON lung cancer screening trial who underwent surgical resection and to investigate, based on a literature review, whether the complication rate, length of hospital stay, re-thoracotomy and mortality rates after a surgical procedure were different from non-screening series, taking co-morbidity into account.

Methods: Between April 2004 and December 2008, 198 subjects underwent thoracic surgery. Co-morbid conditions were retrieved from the medical records. Postoperative complications were classified as minor and major.

Results: In total, 182 thoracotomies, 5 thoracotomies after Video-Assisted Thoracoscopic Surgery (VATS) and 11 VATS procedures were performed. In these patients, 36% had chronic obstructive lung disease, 16% coronary artery disease, 14% diabetes mellitus and 11% peripheral vascular disease. Following thoracotomy, 47% (88/187) had ≥ 1 minor (7-57% in literature) and 10% (18/187) ≥ 1 major complication (2-26% in literature); following VATS, 38% (6/16) had ≥ 1 minor complication, but no major complications. Seventeen percent (3/18) of major complications and 21% (20/96) of minor complications were seen in subjects operated for benign disease. The re-thoracotomy rate was 3% and there was no 30-day mortality after thoracotomy or VATS (0-8.3% in literature). The mortality rate of 0% after surgical procedures is low when compared to non-screening series (0-8.3%); the rate of complications (53%) is within the range as compared to non-screening series (8.5-58%).

Conclusion: In conclusion, mortality rates after surgical procedures are lower in the NELSON lung cancer screening trial than in non-screening series. The rate of complications is within the same range as in non-screening series.

Introduction

It has been shown that lung cancer screening by low-dose multi-detector computer tomography (CT) can detect lung cancer in a high proportion at an early stage.[1] Before considering implementation of CT screening, a reduction in lung cancer mortality has to be demonstrated by randomised clinical trials and the balance between the benefits and harms of screening have to be evaluated thoroughly. Important aspects to take into account are the effect of CT screening on health-related quality of life, and the occurrence of complications associated with the work-up and treatment of participants with a positive test result. Patient-related factors such as a poor general health status, age and co-morbidity contribute to the risk of postoperative pulmonary complications.[2] Screening populations usually consist of heavy current and former smokers at an advanced age and at high risk for co-morbid disease. In several studies it has been shown that co-morbidity can predict morbidity and mortality of surgical procedures.[3] In order to be able to make a fair comparison with the mortality and complication data reported in non-lung cancer screening series, the co-morbidity of the screen population has to be assessed. Our objective was to assess the complication rate in participants in the screen arm of the Dutch-Belgian lung cancer screening trial (NELSON) who underwent a surgical resection and to investigate, based on a literature review, whether the complication rate, length of stay and re-thoracotomy and mortality rates after a surgical procedure were different from non-screening series.

Patients and methods

Inclusion criteria and work-up

NELSON trial participants were current and former smokers at high risk for lung cancer. Detailed information on the in- and exclusion criteria have been reported before.[4] Current and former smokers aged 50-75 with a smoking history of > 15 cigarettes/day during > 25 years or > 10 cigarettes/day during > 30 years (quit ≤ 10 years ago) were invited. Subjects with a moderate or bad self-reported health unable to climb two flights of stairs and persons with a body weight of ≥ 140 kg were excluded, as were those with a history of other cancers. The prospective screening study was approved by the Ministry of Health and by the Medical Ethical Boards of each of the four participating hospitals. Written informed consent was obtained from all participants. In the NELSON trial, 7,557 subjects underwent a CT scan at baseline, the second screening round (one year after baseline) and the 3rd screening round (two years after the second round).[1] Subjects with a positive test result were referred for work-up to a pulmonologist and, depending on the outcome of this work-up, a resection of the suspicious lesion was performed. The standard non-invasive work-up included a physical exam, pulmonary function test, bronchoscopy, FDG-PET-scan and a standard-dose CT scan with intravenous contrast of the chest and upper abdomen.

CT data acquisition and image reading

Data acquisition and image reading were as described before.[5] In brief, all four participating screening sites used 16-detector CT scanners (Sensation-16, Siemens Medical Solutions,

Forchheim, Germany Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH, USA). Scan data were obtained in a spiral mode, with 16 x 0.75 mm collimation and 1.5 pitch. No contrast was administered. Data acquisition and scanning conditions were standardised and equal for baseline and repeat screening. Digital workstations (Leonardo®, Siemens Medical Solutions, Erlangen, Germany) were used in all screening sites with commercially available software for semi-automated volume measurements (LungCare®, Siemens Medical Solutions, version Somaris/5: VA70C-W).

Nodule management and diagnostic work-up

At baseline, a scan was considered positive if any non-calcified nodule had a solid component > 500 mm^3 (>9.8 mm in diameter) and indeterminate if the volume of the largest solid nodule or the solid component of a partially solid nodule was 50-500 mm^3 (4.6-9.8 mm in diameter) or > 8 mm in diameter for non-solid nodules.[5] Subjects with an indeterminate result had a follow-up scan three months later to assess growth. Significant growth was defined as a change in volume between the first and second scan of ≥ 25%. Subjects with positive screening tests were referred to a chest physician for work-up and diagnosis.[1] If lung cancer was diagnosed, the participant was treated for the disease and went off screening; if no lung cancer was found the regular second round CT scan was scheduled 12 months after the baseline scan. For participants with one or more new nodules on the second-round scan, the result (positive or negative) was based on size of the nodule, as for round one; in the case of an indeterminate result, a follow-up scan was performed six weeks later.[5] For participants with previously existing nodules, the second-round result was based on the volume doubling time (VDT). If there was no growth, or if the VDT was > 600 days, the scan was declared negative.[1] If the VDT was < 400 days, or if a new solid component had emerged in a previously non-solid nodule, the scan was considered to be positive. When the VDT was 400-600 days, the test was indeterminate and a follow-up scan was done one year after the second round. With a VDT of < 400 days, the final result was considered to be positive. If both new and existing nodules were present, the nodule with the largest volume or fastest growth determined the result. All participants with a negative second-round result were invited to undergo the third screening round two years after the second round. Work-up and staging were standardised for all screening sites according to national and international guidelines and included a physical exam, a standard CT scan with contrast of the chest and upper abdomen, FDG-PET scan and a bronchoscopy.[5] Subjects with a negative non-surgical work-up were referred for surgery to obtain histology of the suspicious nodule. Bronchoscopies were done in accordance with Dutch national guidelines in order to evaluate the central airways and (if possible) to diagnose lung cancer or benign disease. Pulmonologists and thoracic surgeons were not blinded to the PET result. All subjects with suspected lung cancer were discussed in multidisciplinary tumour boards, which included a thoracic surgeon, before progressing to surgery; all imaging studies were available during these meetings. National and international pathology review panels evaluated all cytological and histological specimens.

Operative details

All resections were performed at one of the four screening centres, of which three were academic institutions and one a peripheral hospital. In Groningen three experienced thoracic surgeons were involved, in Haarlem two, in Leuven three and in Utrecht eleven.

Participants with a benign diagnosis after non-surgical work-up were scheduled for the next screening round. In the remaining test-positive subjects, the suspicious nodules were removed either by VATS or thoracotomy with wedge resection and frozen section. A pre-operative tissue biopsy was not routine. Lobectomies were performed only for central nodules that could not be approached by wedge resection, meaning limited resections were performed for benign lesions. If lung cancer was diagnosed by VATS, the procedure was converted to an open thoracotomy with sampling of the lobar, interlobar, hilar and mediastinal lymph nodes; this is because VATS resection for lung cancer was not yet fully implemented in daily practice in the Netherlands at the time of the present study. A mediastinoscopy was performed before proceeding to VATS or thoracotomy in subjects with mediastinal lymph nodes larger than 10 mm in the short axis and/or FDG-PET positive mediastinal lymph nodes. No specific strategies were employed to prevent prolonged air leak, such as reinforced staple lines. The chest tube was removed if there was no air leak and the fluid production was 200 ml or less per 24 hours.

Data collection and co-morbidity scoring

The date, nature, number and outcome of all adverse events related to all diagnostic and treatment procedures between April 2004 and 31 December 2008 were entered into an electronic web-based database - the NELSON Management System - by investigators at the four screening sites after completion of the diagnostic work-up and therapeutic procedures. In addition, a hard copy of the medical records of all subjects referred for work-up and treatment was centrally stored at the data centre of Erasmus MC Rotterdam in order to review for complications. Co-morbid conditions were retrieved from the medical records based on the medical history at the time of referral because of a positive test result. Subjects were defined as having chronic obstructive pulmonary disease (COPD) when the forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) ratio was < 0.70 and/or the medical history mentioned COPD and the participant used inhaled steroids and/or bronchodilators. Coronary artery disease included a history of myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty or angina pectoris. Peripheral vascular disease included a history of intermittent claudication, abdominal aneurysm, percutaneous transluminal angioplasty or bypass grafting of the peripheral arteries.

Literature search

A review of the literature was performed using a Pubmed search up to February 2011. The search string consisted of a combination of medical subject headings [MeSH] and keywords including ‘Lung Neoplasms’, ‘Postoperative Complications’, ‘Co-morbidity’, ‘Mortality’, ‘Thoracotomy’, ‘Thoracic Surgery, Video-Assisted’ and related synonyms. We summarised the main results of the literature study and the current study with regard to co-morbidity and adverse events following thoracotomy in forest plots. This was not done for VATS procedures in view of the low number of VATS procedures in the current study. Lack or incomplete reporting of co-morbidity was not used as an exclusion criterion. Studies in which all participants had previously received chemotherapy and/or radiotherapy were excluded. For studies without classification of complications, complications were scored according to our definitions of minor and major complications, provided that a complete overview of all complications was reported. In addition, in the case of studies that graded

complications based on the Common Terminology Criteria for Adverse Events, grade 4-5 events were considered major complications.

Definitions of complications

Postoperative mortality was defined as death within 30 days after the operation or within the same hospital admission. According to EuroSCORE[6] and Birim et al.[7], major complications included bleeding requiring re-operation, empyema, pneumonia (Center for Disease Control and Prevention definition of nosocomial pneumonia[2]) myocardial infarction, renal failure requiring temporary or permanent dialysis, postoperative stroke, critical arrhythmia (ventricular fibrillation, ventricular tachycardia) and pulmonary embolism. Additional major complications included respiratory failure requiring ventilator support for > 48 hours[8] and postoperative heart failure with pulmonary oedema.[9] We classified a chylothorax, hemothorax and gastro-intestinal complications requiring operative re-intervention (re-thoracotomy) or laparotomy as major complications. Non-life threatening complications were classified as minor complications. All minor and major complications were scored for each VATS and thoracotomy procedure.

Statistical analysis

Data were analyzed using SPSS (version 17.0, SPSS Inc., Chicago, IL, USA). A two-tailed Mann-Whitney U test was used to analyze continuous data in the absence of normal distribution. The Chi-squared (χ^2) test was used for binomial or categorical data and the Fisher's exact test for small groups. Statistical significance was defined as a p-value < 0.05. Asymmetric confidence intervals (CI) were calculated for the literature study data presented in Figures 2-3 using log-linear regression, where we estimated the observation as the log of a β; a weighted standard error (S.E.) was calculated for this β and subsequently the CI was obtained.

Results

Background and treatment characteristics

A total of 415 subjects had a positive test result following CT screening between April 2004 and December 2008. The role of FDG-PET in the work-up of these test-positive participants has been described elsewhere. In 17 of the participants surgical procedures consisted of a mediastinoscopy only; 15 were subsequently diagnosed with lung cancer, which was at an early stage in 2, who were inoperable because of co-morbidity (Figure 1). In 178 participants the final benign diagnosis was based on FDG-PET, CT with intravenous contrast, or biopsies. Transthoracic biopsies were only performed in 5% (22/415) of test-positive participants. In 22 participants the diagnosis was cancer; subjects did not undergo resection because of advanced stage disease (13 subjects) or co-morbidity (9 subjects), the latter were treated with stereotactic radiotherapy. In these 22 subjects the diagnosis was based on biopsies in 15 cases and on imaging studies in 7 cases. In 198 participants, non-surgical work-up showed lung cancer or was inconclusive. These subjects underwent a resection either by thoracotomy (n=182), VATS converted to thoracotomy (n=5) or wedge resection by VATS (n=11) (Figure 1). The characteristics of the subjects who underwent a resection are

presented in Table 1 and Table 2. The most frequent co-morbid conditions were COPD (36%), coronary artery disease (16%) diabetes mellitus (14%) and peripheral vascular disease (11%) (Table 2).

Table 1. *Characteristics of the participants of the NELSON lung cancer screening trial who underwent a thoracotomy and/or Video-Assisted Thoracoscopic Surgery (VATS) after a positive screening test.*

Characteristics	Lung surgery (N=198)
Age (range)	61 (50-74)
Female (%)	35 (18)
Pack years (range)	46 (21-133)
COPD (%)	71 (36)
GOLD I FEV1 ≥ 80%	38 (19)
GOLD II 50% ≤ FEV1 < 80%	20 (10)
GOLD III 30% ≤ FEV1 < 50%	6 (3)
Stage unknown (%)	7 (4)
Type of resection (%)	
Lobectomy or bilobectomy	137 (70)
True cut biopsy, segment- or wedge resection	56 (26)
Pneumonectomy	4 (2)
Sternotomy	1 (0.5)
Lung cancer (%)	139 (70)
Benign disease (%)	47 (24)
Other cancer (%)	12 (6)
Clinical Lung cancer stage* (%)	
I	117 (84)
II	18 (13)
III (3 T4N0M)	3 (2)
IV (1 T1N0M0)	1 (1)
Pathological Lung cancer stage (%)	
I	112 (81)
II	11 (8)
III (4 T1N2M0; 2 T2N2M0; 2 T4N1M0; 1 T4N0M0; 2 T3N2M0)	11 (8)
IV	5 (4)
Definitions of abbreviations and symbols: COPD=Chronic Obstructive Pulmonary Disease; GOLD=Global Initiative for Chronic Obstructive Lung Disease. * Sixth edition of TNM lung cancer classification	

Table 1 shows the clinical and pathological lung cancer stages. Three subjects with clinical stage III (T4N0M0) were operated and a microscopic complete resection could be achieved. Five subjects had pathological stage IV lung cancer after surgery. Two of them had an indeterminate pre-operative FDG-PET result which in retrospect appeared to be metastatic lesions. In two patients the pre-operative FDG-PET was false-negative for distant metastasis. In one subject no pre-operative FDG-PET was made due to an administrative error; the postoperative FDG-PET scan showed distant metastasis. Of eight patients with pathological stage III disease this was due to unforeseen N2 disease in seven patients and in one to a bronchoalveolar carcinoma in the middle lobe which was resected; a second suspicious upper lobe nodule could not be found during surgery. The clinical stage at that time was cT1N0M1. One month later the upper lobe nodule showed rapid growth and mediastinal

lymphadenopathy was noted (clinical stage T1N2M0); a mediastinoscopy showed metastasis of a large cell carcinoma.

Table 2. *Co-morbidity in NELSON participants who underwent a thoracotomy and/or Video-Assisted Thoracoscopic Surgery (VATS).*

Co-morbidity	Lung surgery (n=198) (%)
Chronic obstructive pulmonary disease	71 (36)
Coronary artery disease	31 (16)
Diabetes Mellitus	28 (14)
Peripheral vascular disease	22 (11)
Peptic ulcer disease	7 (4)
Cerebrovascular disease	5 (3)
Congestive heart failure	5 (3)
Connective tissue disease	4 (2)
Any prior tumor	16 (8)
Chronic kidney disease	2 (1)

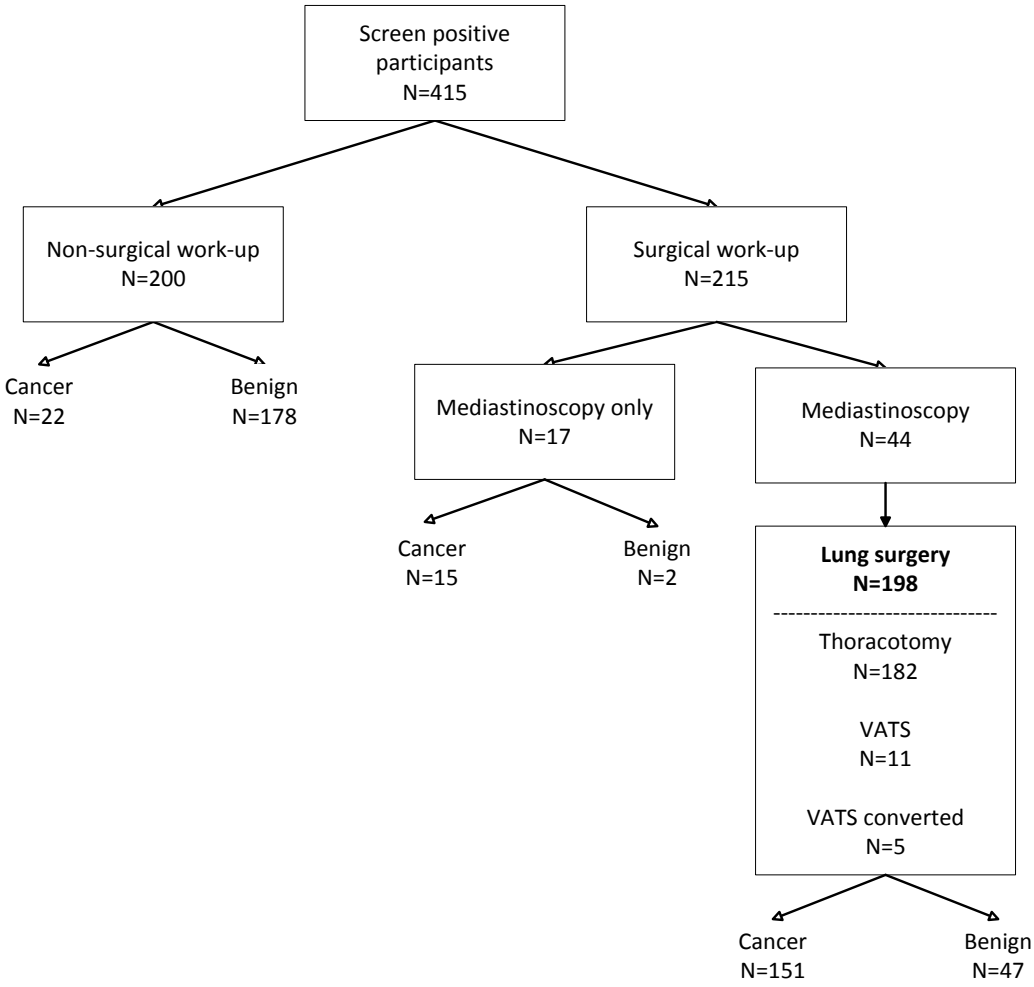

Figure 1. Surgical procedures and outcome in 415 screen positives of the NELSON randomised lung cancer screening trial.

Complications after surgery

Tables 3 and 4 present all the complications observed. Following thoracotomy, 47% (88/187) had at least one minor and 10% (18/187) at least one major complication. Thirty-eight percent (6/16) of the VATS procedures was complicated by at least one minor complication, but no major complications have been observed. As 5% had both minor and major complications, the proportion of participants with any complication was 53%. Seventeen percent (3/18) of major complications and 21% (20/96) of minor complications were seen in subjects operated for benign disease. The overall median length of hospital stay was 13 days (2-51 days) after thoracotomy and 8 days (4-12 days) after VATS. In subjects with minor complications this was 15 days (6-51 days) and 9 days (7-12 days), respectively. In the case of major complications following thoracotomy, the median length of stay was 21 days (range 8-51 days). The re-thoracotomy rate was 3% after thoracotomy and 0% after VATS. Re-admissions occurred in 5% of those who underwent a thoracotomy (eight after minor complications and one after a major complication), but were absent after VATS. There was no 30-day mortality after the thoracotomies or VATS procedures in NELSON.

Table 3. *Overview of all minor complications following 187 thoracotomies and 16 Video-Assisted Thoracoscopic Surgery (VATS) procedures performed in the NELSON trial.*

Minor complication	Thoracotomy (%)	VATS (%)
Air-leakage more than > 5 days	42 (23)	5 (31)
Supraventricular tachycardia	17 (9)	0
Infection	16 (9)	1 (6)
Diaphragm paralysis	10 (5)	0
Chest tube more than > 5 days due to persistent pleural fluid	8 (4)	0
Atelectasis	8 (4)	1 (6)
Drop hand	3 (2)	0
Wound infection	3 (2)	0
Delirium	3 (2)	0
Chest pain	3 (2)	0
COPD exacerbation	2 (2)	2 (13)
Blood transfusion	2 (2)	0
Urinary retention	2 (2)	0
Hemoptysis	2 (2)	0
Persistant ptosis	1 (1)	0
Paralysis serratus anterior muscle	1 (1)	0
Deep venous thrombosis	1 (1)	0
Ileus	1 (1)	0
Pleuritic effusion	1 (1)	0
Dyspnea	1 (1)	0
Definition of abbreviations: COPD=Chronic Obstructive Pulmonary Disease; VATS=Video-Assisted Thoracoscopic Surgery.		

Table 4. *Overview of the major complications following thoracotomy in 187 participants of the NELSON trial.*

Major complications	N (%)
Pneumonia	10 (5)
Empyema	2 (1)
Bleeding, re-operation	1 (1)
Chylothorax, re-operation	1 (1)
Pulmonary embolism	1 (1)
Respiratory failure	1 (1)
Myocardial infarction	1 (1)
Congestive heart failure	1 (1)
Ventricular tachycardia	1 (1)
Bowel perforation	1 (1)

Table 5 shows that a higher rate of minor complications was seen in the case of more extensive resections. Limited resections (true-cut biopsies, wedge and segment resections) were associated with a lower rate of minor complications (OR 0.51, 95% confidence interval 0.26-1.03, p-value 0.06) as compared to bilobectomy/lobectomy and pneumonectomy. No significant correlation could be established for type of resection and risk of major complications. Five subjects were re-admitted because of minor complications: in three subjects with chest pain and one with dyspnea a pulmonary embolism could be excluded; in one subject with pleuritic effusion an empyema was excluded; no repeat chest tube placement or thoracentesis was necessary (Table 3). Atelectasis was diagnosed by chest X-ray in nine subjects, on five of whom a bronchoscopy was performed.

Table 5. *Complications according to type of* resection.

Surgical Procedures		Minor complications following thoracotomy					Major complications following thoracotomy				Surgical procedure	Minor complications following VATS				
Type of surgery	N (%)	1	2	3	Any (%)*	Total	1	2	Any (%)*	Total	N (%)	1	2	3	Any (%)*	Total
True-cut biopsy	6 (3)	2	0	0	2 (33)	2	0	0	0	0						
Wedge resection	35 (19)	8	3	0	11 (31)	14	3	0	3 (9)	3	16 (100)	4	1	1	6 (38)	9
Segmentectomy	4 (2)	1	0	0	1 (25)	1	1	0	1 (25)	1						
Lobectomy	131 (70)	40	26	3	69 (53)	101	11	2	13 (10)	15						
Bilobectomy	5 (3)	1	2	1	4 (80)	8	1	0	1 (20)	1						
Sleeve resection	1 (1)	0	0	0	0	0	0	0	0	0						
Pneumonectomy right	1 (1)	1	0	0	1 (100)	1	0	0	0	0						
Pneumonectomy left	3 (2)	0	0	0	0	0	0	0	0	0						
Sternotomy	1 (1)	0	0	0	0	0	0	0	0	0						
Total	187 (100)	53	31	4	88 (47)	127	16	2	18 (10)	20	16 (100)	4	1	1	6 (38)	9
Clarification of symbol: * Percentage of type of surgery																

Data from the literature review

Our literature search revealed 16 studies on thoracotomy and 12 studies on both thoracotomy and VATS which met our selection criteria (supplementary Table 1). The prevalence of co-morbidity in the literature on thoracotomy ranged between 43% and 80% (Bach 2001, Birim, Zuydendorp 2003, supplementary Table 1A). Figure 2 shows the prevalence of co-morbidities in subjects who underwent a thoracotomy in non-lung cancer screening studies. The most frequently reported co-morbid conditions were COPD (10-52%), coronary artery disease (10-52%), diabetes mellitus (7-19%) and peripheral vascular disease (6-26%). The number of lobectomies performed during thoracotomy procedures varied between 40% and 100% (Cattaneo 2008, Suemitsu 2009), while pneumonectomies were done in 0-27% (Pagni 1998, Memtsoudis 2006, Yang 2009). The median percentage of stage I disease in the thoracotomy group was 69.0% (range: 31-100%).[10, 11] The mortality rates reported after a thoracotomy varied between 0% and 8% (Figure 3). The National Emphysema Treatment Trial (NETT) found a 90-day mortality of 5% following lung volume reduction surgery in subjects with severe emphysema (mean FEV1 0.7 L (26% of predicted)).[12] Figure 3 shows that major and minor complications after thoracotomy varied in the ranges of 4-26% and 7-57%, respectively. The median length of stay after a thoracotomy reported in the literature was 5-22 days (Sugiura 1999, Boffa 2008). The reported re-thoracotomy rates after a thoracotomy varied between 0% and 9% (Sugiura 1999, Birim, Maat 2003).

In the majority of the studies on VATS, lobectomies were performed. Complications after VATS were reported in 9-51% (Kim 2010, Petersen 2010) and major complications in only 0-12% (Infante 2011, Jaklitsch 1996, Petersen 2010). The median length of stay after a VATS reported in the literature was 4-23 days (Sugiura 1999, Villamizar 2009). The reported re-operation rate after a VATS varied between 1% and 5% (Sugiura 1999, Paul 2010), with a mortality rate of 0-4% (Belgers 2010, Handy 2009).

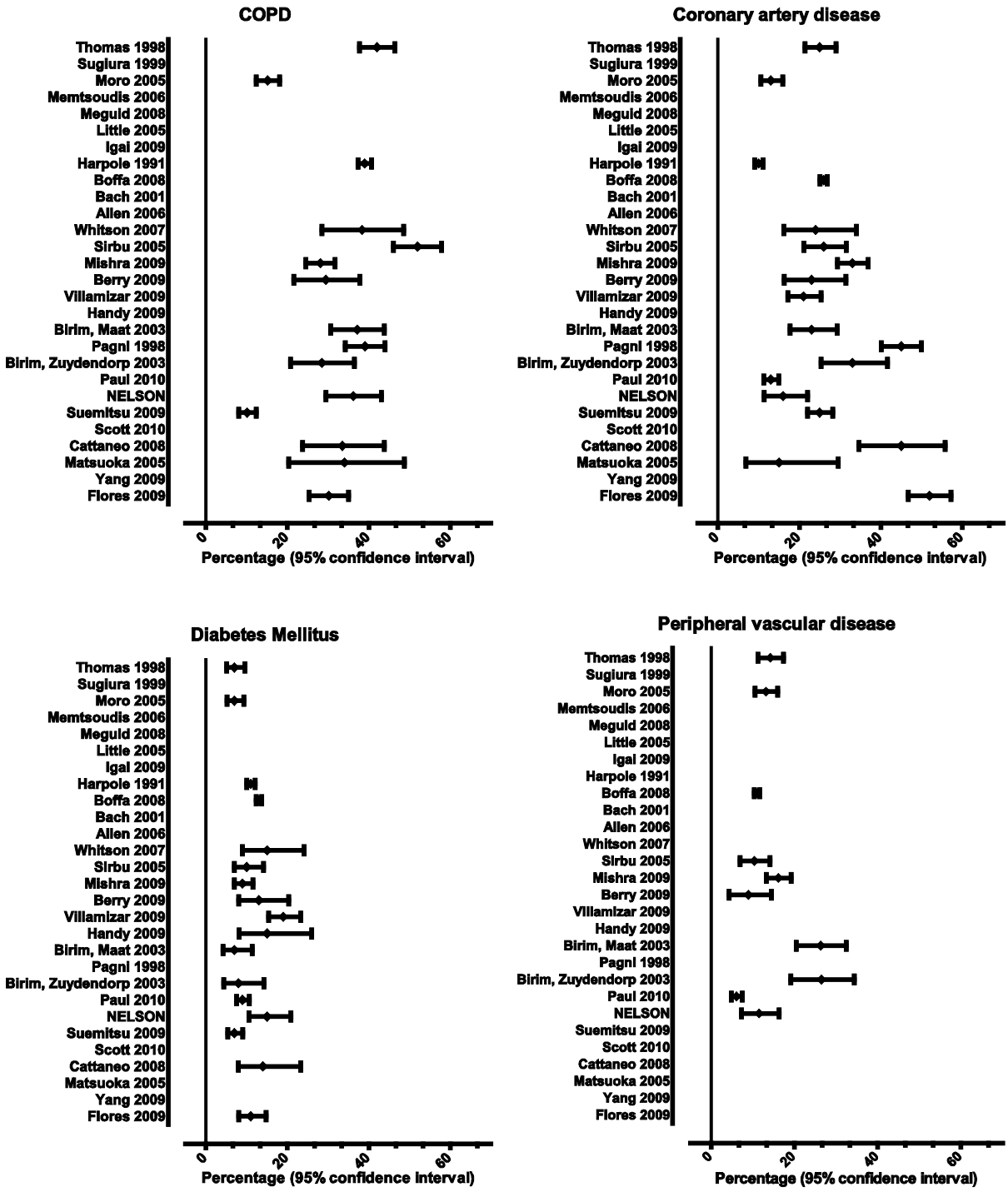

Figure 2. *Prevalence of chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus and peripheral vascular disease in NELSON lung cancer screening participants who underwent a thoracotomy in comparison with non-screening series from the literature.*

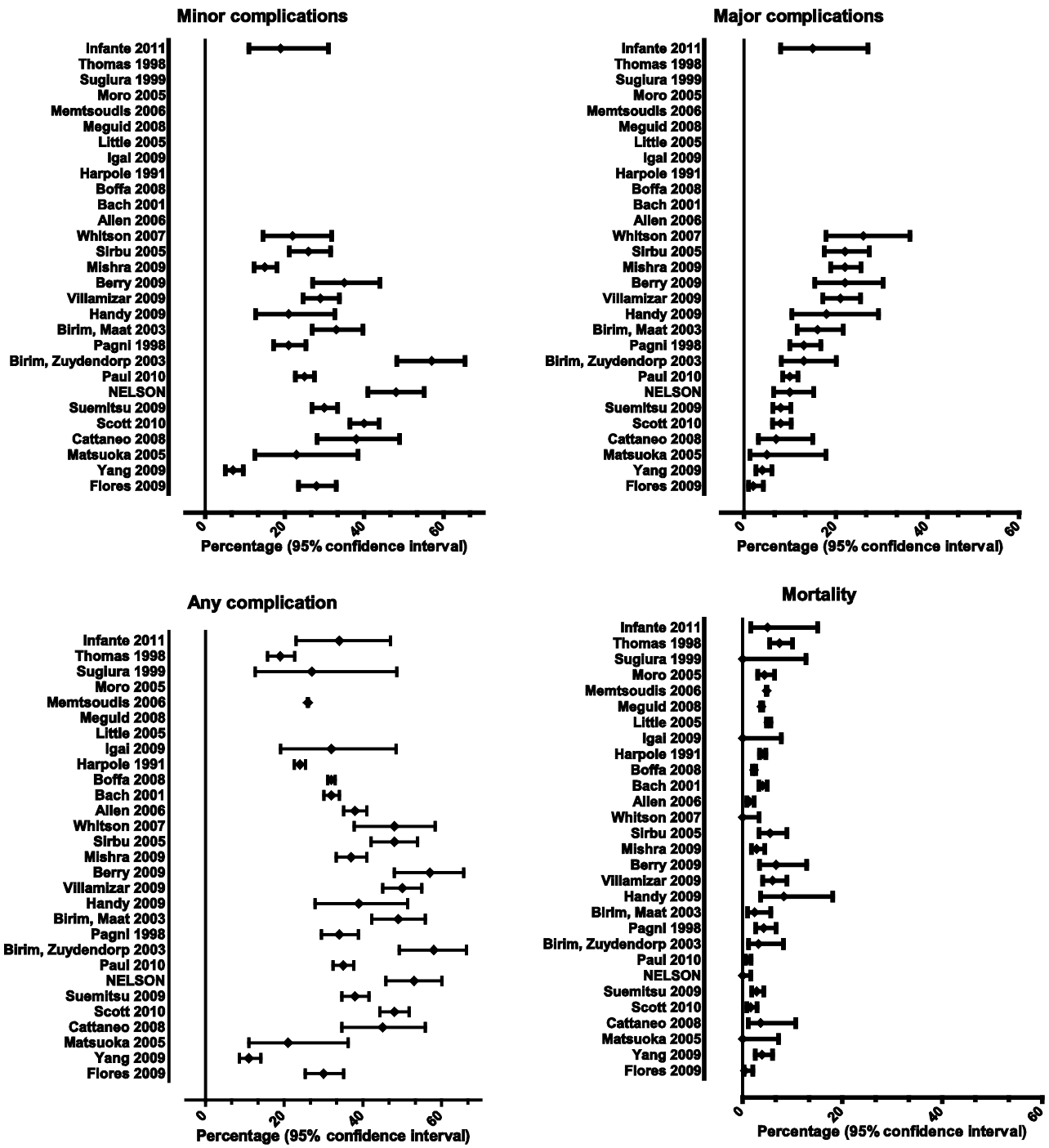

Figure 3. *Complication and mortality rates after thoracotomy in the NELSON lung cancer screening trial in comparison with non-screening series from the literature.*

Discussion

Our study compared the complications rates, length of hospital stay, re-thoracotomy and mortality rates of participants in the NELSON trial who underwent thoracic surgery with data from non-screening series. The comparison with non-screening series could be made because we demonstrated that the age range and co-morbidity level of the NELSON trial participants who underwent a surgical resection was the same as in non-screening series.

Literature review and complications

The studies included in our literature review displayed a large heterogeneity with respect to the definition, classification and way in which data on complications have been collected so far. For example, prolonged air leak has been defined as > 5 days[7] and > 7 days.[13] In addition, chest-tube management with regard to output differs in studies or is not defined. Few authors make a distinction between minor and major complications, and complication data are collected by reviewing individual patient charts, based on ICD-9 codes[14] or on claims in Medicare files.[3] The latter methods may lead to underreporting of complications, especially for minor complications. Probably because we screened all individual patient files, our minor complication rates are in the higher range of what has been reported before. The most important observation was the relatively low rate of major complications and the absence of postoperative mortality after the thoracotomy and VATS procedures performed in the screen arm of the NELSON trial. This could probably be explained by the fact that screening participants are normally asymptomatic individuals, that screen-detected tumours are usually smaller[15, 16] and that a pneumonectomy was required less often in the NELSON compared with the literature, where more complex resections with a higher expected complication rate were performed. Nevertheless, the proportion of stage I disease was in the same range of what has been reported in our literature review of non-screening series.

Lung cancer screening studies and complications

In a recent study, Infante et al.[17] reported on the outcome of surgical procedures in the DANTE trial. A total of 59 subjects underwent a thoracotomy procedure. Three died following the thoracotomy and a total of 20 complications was noted, which were major complications in nine subjects. No major complications or postoperative deaths were seen in subjects diagnosed with benign disease. Fifteen subjects underwent a VATS procedure; no postoperative deaths or major complications were noted in this subset of patients. The postoperative mortality rate in the DANTE study was higher than expected; all subjects had central tumours of stage IIA or higher, two had co-morbid conditions and two had undergone a pneumonectomy. Veronesi et al.[18] reported that 25% of subjects developed complications following thoracotomy and VATS procedures, which were serious in 6% and required re-operation in 2%. No postoperative complications or mortality were noted in the subjects with benign disease. While only two subjects underwent a pneumonectomy in their study[18], pneumonectomies were performed on four subjects in our study. Infante et al.[17] performed a relatively high number of pneumonectomies, in seven subjects in total, which may explain the higher mortality rate. The rate of major complications in lung cancer screening studies is at the lower limit when compared to the literature. Mortality rates are also at the lower limit[18]; however, with more extensive resections the rate may be the same

as in the literature.[17] An important observation to make is that no major complications and no deaths were seen in subjects operated for benign disease.[17, 18] In our study however, 17% (3/18) of major complications and 21% (20/96) of minor complications were seen in subjects operated for benign disease.

Length of stay after VATS and thoracotomy

Despite these observations, the LOS after thoracotomy and VATS procedures was not shorter for NELSON participants than the average. This can be explained by the fact that patients in the Netherlands and Belgium usually stay in the surgery or pulmonary medicine department and do not routinely go to a short-stay facility after surgery. It has been shown that LOS decreases when the use of skilled nursing facilities increases.[19] Another possible explanation may be that in the Netherlands and Belgium it is socially much less accepted to discharge patients home after three or four days. None of the participants in the NELSON study went to a long-term nursing facility. Prolonged air leak has been described as the most important factor for prolonged hospital stay[20]; this was not the case the current study, presumably because of less severe emphysema.

Type of resection

In the NELSON trial, VATS procedures were only performed for wedge resections, whereas in the majority of studies VATS was used to perform lobectomies, which is a major difference. This is due to the fact that VATS lobectomy had only recently been introduced in the Netherlands at the time of the study.[21] The proportion of lobectomies in the thoracotomy group was comparable to the literature. Therefore, and because of the low number of VATS procedures in the current study, the comparison we made between the VATS results in the NELSON screening trial and the non-screening series from the literature should be interpreted with caution. There is general consensus in the literature that morbidity and mortality rates after VATS are lower than after thoracotomy, and that patients have a better postoperative physical functioning and a shorter postoperative length of stay.[22] In addition, the oncological validity of VATS resections for lung cancer has been proven as five-year survival rates are similar as after thoracotomy.[23] We therefore believe that lung cancer screening sites should be equipped to perform VATS procedures, especially in view of the substantial risk of false-positive test results and resections for benign disease.[1]

Summary

In the NELSON lung cancer screening trial, the rate of minor complications after thoracotomy and VATS was in the upper range of what has been reported for non-screening series, while the rate of major complications was in the lower range. The postoperative length of stay was not shorter than in the literature. The re-thoracotomy rate for complications such as a hemothorax requiring re-intervention was in the same range in NELSON as that reported in the literature, but no re-thoracotomies were performed after VATS. No postoperative deaths were observed after the thoracotomy and VATS procedures. To our knowledge, this is the first report on the prevalence of co-morbidity and of complications in a lung cancer screening population. Veronesi et al.[18] presented data on

complications in abstract form in their lung cancer screening study, but without information on co-morbidity. Their results support our encouraging data, which demonstrate that participants are at low risk of major complications or postoperative death following thoracotomy or VATS lung cancer screening. However, the high rate of resection for benign disease and associated morbidity continues to be a concern. Seventeen percent of the major complications and 21% of the minor complications were seen in subjects operated for benign disease. The use of FDG-PET[24] and combination of FDG-pet and volume doubling time[25] may help to reduce the number of resections for benign disease. In conclusion, mortality rates after surgical procedures were lower in the NELSON lung cancer screening trial than in non-screening series. The rate of minor and major complication is within same the range as in non-screening series.

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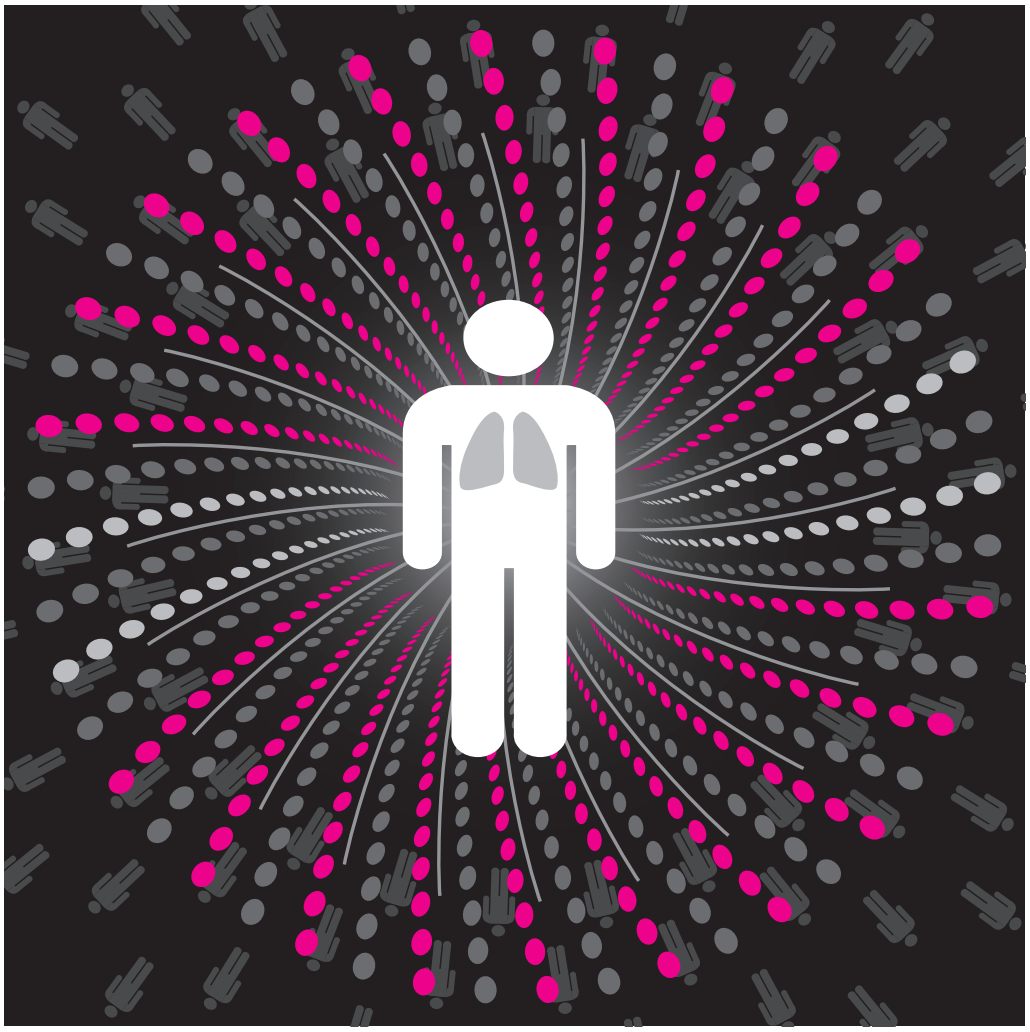
Chapter 10



Difficulties encountered during surgical procedures for suspicious pulmonary nodules in the Dutch-Belgian Lung Cancer Screening Trial.
When is benign really benign?

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ABSTRACT

Background: With the NELSON nodule management strategy, based on nodule volume and, volume-doubling time only early stage lung cancer is detected in a high proportion. The surgical management and diagnosis of screen detected nodules remains challenging. This study reports on the outcome of subjects who were diagnosed with benign lesions after surgical procedures.

Objective: We evaluated the reliability of the histology in subjects who had undergone surgery with a benign result at baseline or 2nd round screening in the NELSON lung cancer screening trial.

Methods: Test positives were referred to a chest physician for work-up and diagnosis. For all subjects operated for benign lesions the pathological reports of the resected specimen and, the surgical reports were reviewed for information on localization of the nodule that had been removed. The location (segment), size and information on additional nodules on the low-dose screening CT were in addition available. We correlated radiological findings with the clinical findings and determined whether histology of a given suspicious nodule had been obtained. No pre-operative localization techniques had been used in this subset of subjects.

Results: A total of 37 subjects underwent surgical procedures for benign disease after a positive screening result. We describe 10 subjects in whom one or more suspicious nodules were not removed during a surgical procedure. Three of them (8%) were diagnosed with lung cancer in previously existing nodules with follow-up. We discuss these three cases in detail. In 27% (10/37) of subjects with a benign result following surgery in one or more suspicious nodules no histology had been obtained.

Conclusions: For subcentimeter pulmonary nodules localized >5mm from the pleural surface pre-operative localization should be considered.[1] Following resection of the nodule, correlation of the surgical report, histology and CT features is important to ensure that the suspicious nodule has been removed. In case of doubt CT scan of the resected specimen before fixation by the pathologist can be considered, to ensure that the suspicious lesion is included in the resected specimen.

INTRODUCTION

With lung cancer screening, early stage lung cancers are detected in a high proportion.[2-4] The National Lung Screening Trial (NLST) randomised 53,476 smokers between annual low-dose CT (LDCT) screening or chest X-ray for 3 annual screening rounds; recently they demonstrated a 20% mortality reduction from lung cancer in the LDCT-arm.[2] The Nederlands Leuvens Longkanker Screenings Onderzoek (NELSON) is the second largest randomized lung cancer screening trial in which CT screening in year 1, 2 and 4 is compared with a control population without screening.[4] Following baseline screening in other lung cancer screening studies, between 23-27% of subjects had a positive result, resembling about 233-7,191 subjects who undergo further (invasive) investigations.[2, 5] Despite the fact that only high-risk subjects are screened, as defined by age and smoking history, the prevalence of lung cancer is relatively low, 2.7-3.8% at baseline screening. [2, 5] In the NELSON lung cancer screening trial the number of test-positives were remarkably lower with 2.6%; lung cancer was detected in 36% of test-positives.[4] Diagnostic evaluation most often consists of further imaging studies and, in only about 5% of test-positives surgical procedures were performed.[2] In the NELSON study the rate of benign histology at resection was 27% at baseline;[4] in literature between 0-17% of resections for benign lesions has been described.[3, 5, 6]

In this paper we describe difficulties encountered during surgical procedures for suspicious pulmonary nodules with a benign result after analysis and, the rate of false-negative results following resection at baseline and 2nd round screening.

METHODS

Study population

NELSON trial participants are current and former smokers at high risk for lung cancer. Detailed information on the in- and exclusion criteria have been reported before.[7] The prospective screening study was approved by the Ministry of Health and by the Medical Ethical Boards of each of the four participating hospitals. Written informed consent was obtained from all participants.

CT data acquisition and image reading

Data acquisition and image reading was as described before.[8] In brief, all four participating screening sites used 16-detector CT scanners (Sensation-16, Siemens Medical Solutions, Forchheim, Germany Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Cleveland, OH, USA). Scan data were obtained in a spiral mode, with 16 x 0.75 mm collimation and 1.5 pitch. No contrast was administered. Data acquisition and scanning conditions were standardized and equal for baseline and repeat screening. Digital workstations (Leonardo®, Siemens Medical Solutions, Erlangen, Germany) were used in all screening sites with commercially available software for semi-automated volume measurements (LungCare®, Siemens Medical Solutions, version Somaris/5: VA70C-W).

Nodule management and diagnostic work-up

The nodule management strategy was as described before.[8] Subjects with a positive test result were referred to a chest physician for work-up and diagnosis. Work-up and staging was standardized for all screening sites according to (inter-) national guidelines.[9, 10] The standard non-invasive work-up included a physical exam, a bronchoscopy and a standard dose CT scan with intravenous contrast of the chest and upper abdomen. Subjects with an inconclusive outcome of the non-invasive work-up were referred for invasive work-up which included either a mediastinoscopy, video-assisted thoracoscopy (VATS) or thoracotomy. The national and international pathology review panels evaluated all cytological and histological specimens in order to reach consensus. The NELSON nodule management system is unique because of individual nodule tracking; all nodule characteristics were entered on the individual nodule level. The conclusions of the histological or cytological evaluation and the localization were available. The radiological data of a given nodule and, the histological or, cytological result of this nodule were coupled in the data-base. Each pathological result had a dropdown list which included every nodule (showing unique nodule number, localization and, size) of the last NELSON low-dose CT which was made before the given investigation was done. When the histological specimen was a reliable biopsy of a given (suspicious) nodule, this nodule was selected on the drop-down list.

Operative details

All resections were performed at one of the four screening centres, of which three were academic institutions and one a peripheral hospital. In Groningen three experienced thoracic surgeons were involved, in Haarlem two, in Leuven three and in Utrecht eleven. Participants with a benign diagnosis after non-surgical work-up were scheduled for the next screening round. In the remaining test-positive subjects, the suspicious nodules were removed either by VATS or thoracotomy with wedge resection and frozen section. A pre-operative tissue biopsy was not routine. Lobectomies were performed only for central nodules that could not be approached by wedge resection, meaning limited resections were performed for benign lesions. If lung cancer was diagnosed by VATS, the procedure was converted to an open thoracotomy with sampling of the lobar, interlobar, hilar and mediastinal lymph nodes; this is because VATS resection for lung cancer was not yet fully implemented in daily practice in the Netherlands at the time of the present study. A mediastinoscopy was performed before proceeding to VATS or thoracotomy in subjects with mediastinal lymph nodes larger than 10 mm in the short axis and/or FDG-PET positive mediastinal lymph nodes. No specific strategies were employed to prevent prolonged air leak, such as reinforced staple lines. The chest tube was removed if there was no air leak and the fluid production was 200 ml or less per 24 hours. Preoperative localizing procedures had been used in less than 5% and, had not been used in subjects diagnosed with benign disease following surgery.

RESULTS

Participants

Following baseline and 2nd round screening, 324 subjects had a positive test-result and, 295 subjects underwent further analysis by the pulmonologist. Twenty-nine subjects had not

been referred because of treatment of other cancer by other specialist (7 subjects), tumour board decision (19 subjects) or, an administrative error (3 subjects).
During analysis by the pulmonologist 52% (154/295) underwent surgical procedures; 70% (108/154) was diagnosed with lung cancer, 6% (9/154) with other cancer and, 24% (37/154) with benign lesions. The median age of 37 subjects who had undergone surgery for benign disease was 61 years (range 52-72 years), the median number of pack-years smoked was 41 (range 21–105 pack-years) and 15% was female. The nodule characteristics of the participants referred for further analysis are provided in Table 1.

Table 1. *Characteristics of the suspicious nodules in 324 test-positive participants of the NELSON lung cancer screening trial.*

	Total Number (%)	Nodules not approached during surgery Number (%)
Nodule consistency		
Ground glass	4 (1)	0
Part solid	16 (5)	2 (20)
Solid	292 (90)	8 (80)
Not specified	12 (4)	0
Number of suspicous nodules		
1	272 (84)	5 (56)
2	26 (8)	2 (22)
3	6 (2)	0
4	4 (1)	2 (22)
5	1 (0)	0
6	3 (1)	0
No nodules*	12 (4)	0
Nodule size		
<50 mm^3	5 (2)	1 (10)
50-500 mm^3	101 (31)	4 (40)
> 500 mm^3	206 (64)	5 (50)
Not specified	12 (4)	0
Volume doubling time (VDT)		
VDT >600 d	14 (4)	1 (10)
VDT 400-600 d	7 (2)	1 (10)
VDT < 400 d	126 (39)	5 (50)
Not specified	177 (55)	3 (30)
Nodule localization		
Central	34 (11)	1 (10)
Total	324 (100)	10 (100)

In case of ≥1 suspicious nodule, the characteristics of the largest nodule is provided.
Clarification of symbol: *: No nodules: multiple metastasis (1 subject), atelectasis (4) and sonsolidation (4), pleural fluid (1), mediastinal mass (1), Langerhans histiocytosis.

Surgical procedures

Of the 37 subjects who underwent surgery for benign disease, 76% (28/37) underwent thoracotomy, 19% (7/37) VATS and, in 5% (2/37) mediastinoscopy was done. During VATS and thoracotomy in 57% (20/35) wedge resection was done, in 20% (7/35) lobectomy, in 9%

(3/35) true-cut biopsy only and, in 3% (1/35) segmentectomy. Subject one had a lesion of the left lower lobe, on the CT this lesion had the aspect of an infiltrate (Table 2).

Table 2. *Outcome of 10 of the 37 subjects who underwent an invasive diagnostic procedure with a benign histological result, but in whom one or more of the suspicious nodule(s) remained in situ during baseline and 2nd round screening of the NELSON trial.*

Subject No.	Suspicious nodule(s)			Surgical intervention	Reason not resected	Histological diagnosis	Outcome at 3rd screening round
	Lobe	Volume ($mm^{3)}$	VDT				
Baseline screening							
1	LLL	2279	NA	Wedge LLL		Lymphoma**	Negative
	LUL	639	NA	No	Not palpable	NA	
2	RLL	47	<400	Biopsy RLL†		Lymph node, infarction, normal lung tissue	Negative
	LLL	85	<400	No	Not approached	NA	
	LLL	50	<400	No	Not approached	NA	
	RUL	34	<400	No	Not palpable	NA	
3	LLL	69	<400	No	Not approached	NA	Negative
	RLL	24	new	Wedge RLL		Lymph node	
	ML	15	new	Wedge RML		Lymph node	
4	LUL	134	<400	No	Not approached	NA	Negative
	LLL	69	<400	No	Not approached	NA	
	RLL	121	<400	Wedge RLL		Hyalin collagenous nodule	
	RLL	39	<400				
5	ML	252	<400	No	Not approached	NA	Lung cancer LUL T1aN0M0
	LUL	707	>600	No	Not approached	NA	
	NA			Mediastinoscopy		Sarcoidosis	
6	ML	310	<400	No	Not palpable	NA	Death*
	RUL	204	new	Wedge RUL		Lymphocytic inflammation	
7	RUL	126	400-600	Wedge RUL (VATS)		Fibrosis	Lung cancer RUL T1aN0M0
8	LLL	4610, ps	<400	No	Not approached	NA	Negative
	LUL	No nodule on screening CT		True-cut biopsy LUL Thoracotomy		Atypical Adenomatous hyperplasia	
2nd round screening							
9	RLL	936	new	No	Not approached	NA	Negative
	LUL	2089	new	No	Not approached	NA	
	NA			Biopsy Lymph node 7		Normal lymph node	
10	RLL	876	new	Wedge RLL (thoracotomy)		Infarction	Lung cancer RLL T2aN2M0

Clarification of abbreviations and symbols: NA: not applicable, calculation VDT not possible (ie: new nodule or baseline nodule); VDT: volume-doubling time. LLL: left lower lobe; LUL: left upper lobe; RLL: right lower lobe; ML: middle lobe; RUL: right upper lobe; AAH: atypical adenomatous hyperplasia.
* Centraal Bureau Statistiek (Statistics Netherlands) cause of death: conduction disorder (Heartblock NOS).
**With further evaluation in this subject no other localizations of lymphoma were found. Therefore this subject continued to participate in the NELSON lung cancer screening trial.

The left upper lobe nodule was deemed suspicious because of the size and, spiculation. During surgery however, the left lower lobe lesion appeared palpable and, the surgeon performed a wedge resection of the left lower lobe (LLL) nodule following which a diagnosis of a MALT lymphoma was made. The other nodule was not palpable during surgery and could not be removed. Follow-up at 3rd round screening did not show any nodule growth and, the LLL lesion was not visible, for it had been removed during previous surgery. In 10 subjects at least one of the suspicious nodules could not be approached or was not palpable during the surgical procedure and could, therefore, not be removed (Table 2). During follow-up however three subjects (subject number 5, 7 and, 10), were diagnosed with lung cancer.

Subject no. 5.

Subject no. 5. is male and 64 years old at the time of the baseline scan. This scan showed lymphadenopathy and, two pulmonary nodules of which one >500 mm^3; the subject was not referred but instead a standard dose repeat-scan at 3 months was made during evaluation by the pulmonologist. The small middle lobe nodule showed significant growth (VDT <400 days) and, the subject was referred for further analysis (Figure 1). During workup a bronchoscopy and a mediastinoscopy were performed. The cytology of the bronchoscopy showed no signs of malignancy, the histology of the mediastinal lymph nodes showed granuloma. No further investigations were done to obtain histology or cytology of the suspicious nodules. Instead, 2 standard dose repeat CT's with contrast had been made; the interval between the last standard dose CT and the positive screen result was 7 months; the nodules did not show any growth. The result at 2nd round screening was indeterminate; one month later a repeat scan was made which did not show any growth.

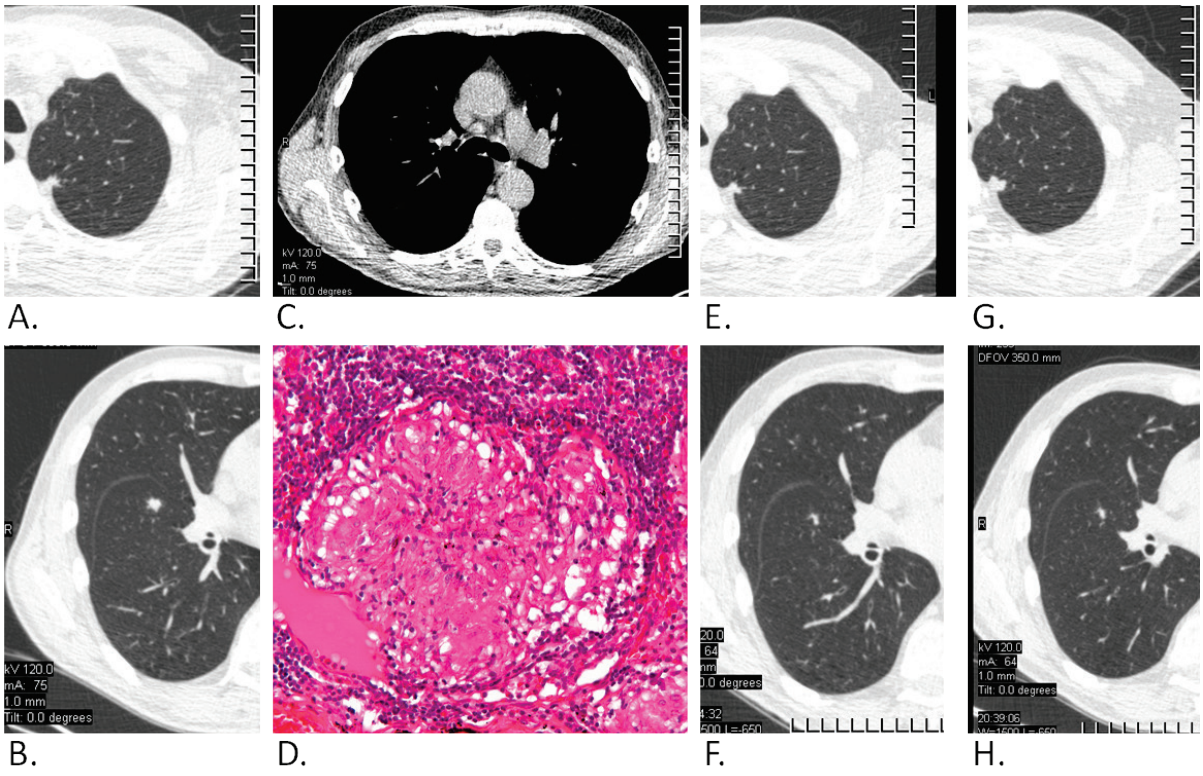

Figure 1. *MDCT-scan showing a left-upper lobe nodule (A) and middle lobe nodule with a VDT <400 days before surgery ((B, C) Subject no. 5). The histology of the mediastinal lymph node showed granuloma (Figure D, medium power, paraffin embedded tissue, H&E staining). Figures E. and F. show the MDCT scan which was made 1.5 years later and, Figure G. and H.*

show the evolution of the nodules 2 years and 8 months after the mediastinoscopy. Figure G. shows that the border of the left upper lobe nodule has changed, without significant nodule growth. A transthoracic biopsy of the left upper lobe nodule was performed and the subject was diagnosed with NSCLC.

At the 3rd screening, round the left upper lobe nodule did not show significant growth but the aspect had changed; at baseline this nodule was smooth, now spiculation was seen. The patient used aspirin and clopidogrel because of a recent coronary stent placement. The tumor board decided to perform no further analysis of the mediastinum, considering the risks of a re-mediastinoscopy and the fact that the lymphadenopathy was unchanged. On a FDG-PET scan the mediastinum showed indeterminate uptake with qualitative evaluation; there was no evidence for distant metastasis and the left upper lobe nodule was FDG-negative. A transthoracic true-cut biopsy of the left upper lobe showed an adenocarcinoma; a diagnosis of cT1aN0M0 lung cancer was made and the subject underwent stereotactic radiotherapy.

Subject no. 7.

This 72-year old male had an indeterminate baseline result because of an 89 mm^3 right upper lobe nodule. A follow-up scan which was made 3 months later showed fast nodule growth (VDT <400 days). Because the nodule did not show any suspicious characteristics another repeat CT was made 3 months later; again a VDT of less than 400 days was noted and the nodule now measured 158 mm^3 (Figure 2A). The subject was referred to the pulmonologist. An FDG-PET scan was made and indeterminate uptake of the right upper lobe nodule was noted. VATS (wedge resection) was performed and the histology was consistent with fibrosis (Figure 2B). An MDCT-scan made 5 months after the VATS showed postoperative changes with a nodule that was not clearly demarcated and not pleural attached; it was therefore classified as a new nodule by the NELSON radiologist (Figure 2C). On an MDCT scan which was made more than two years later the nodule showed growth and the patient was referred for workup. Doubt existed as to whether a new nodule had developed, or the nodule had not been removed during previous surgery. This subject underwent a lobectomy and was diagnosed with pT1N0M0 NSCLC.

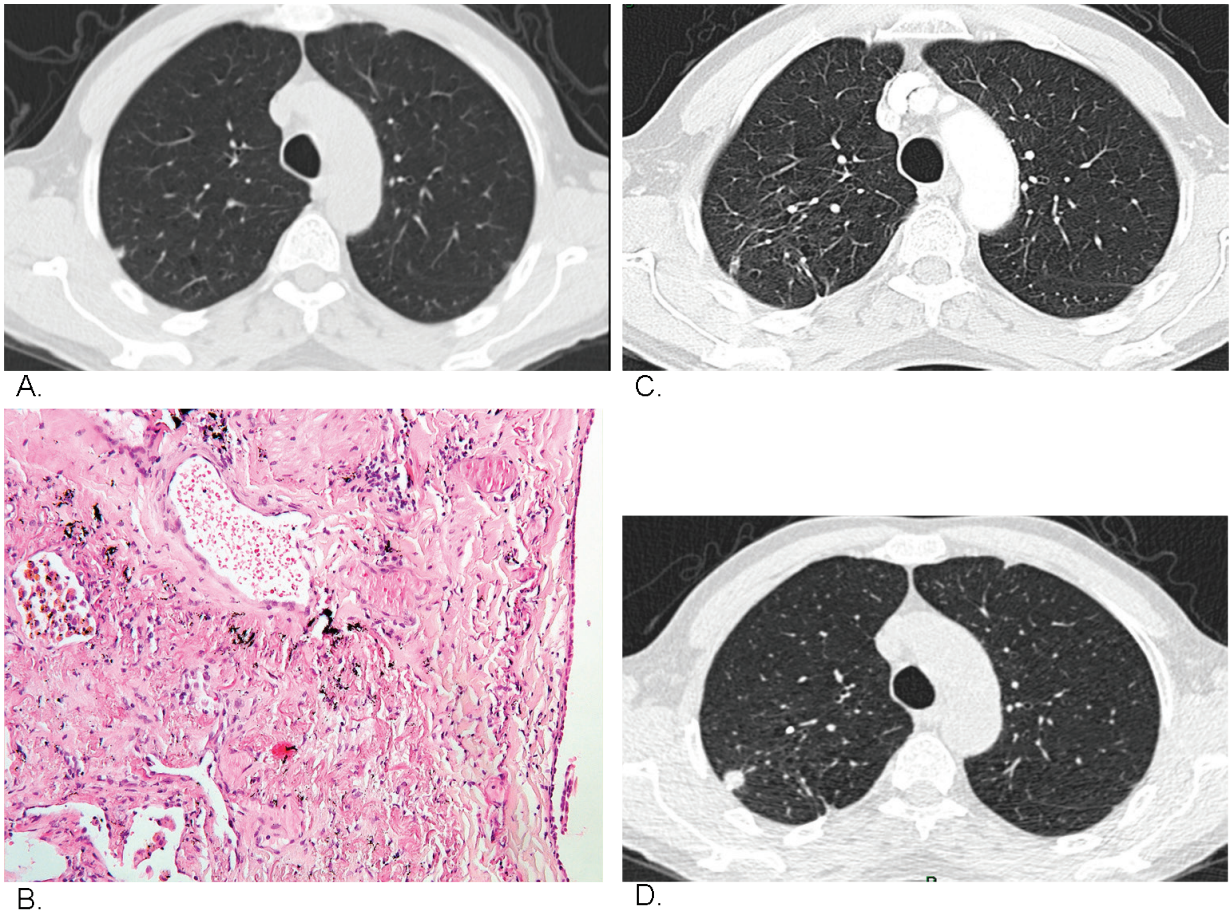

Figure 2. *MDCT-scan of right upper lobe nodule (126 mm³) before operation in subject No. 7. (Figure 2A). Wedge resection of the right upper lobe, obtained by means of a VATS procedure: a medium power view showing subpleural fibrosis (Paraffin embedded tissue, H&E staining) (B). An MDCT-scan made 5 months after the VATS shows postoperative changes and a nodule that is not clearly demarcated and not pleural attached; it was therefore classified as a new nodule by the NELSON radiologist (C). On a MDCT scan made more than two years later (D) the nodule showed growth and the patient was referred for work-up; the subject underwent a lobectomy and was diagnosed with T1N0M0 lung cancer.*

Subject no. 10.

This 62 year old male was diagnosed with a "new" right lower lobe nodule, measuring 876 mm^3 with cavitation at 2nd round screening (Figure 3A). In retrospect, this nodule was also visible on the baseline scan. The subject was referred to the pulmonologist. An FDG-PET scan showed uptake of the RLL nodule and, no further uptake was noted. During a thoracotomy a wedge resection was performed, histology showed a subpleural granuloma with necrosis (Figure 3B and 3D). An MDCT scan, which was made 5 months after the wedge resection, showed that the lesion had grown and had not been removed during surgery. This subject was diagnosed with cT2aN2M0 squamous cell carcinoma after a mediastinoscopy and treated with chemotherapy and radiotherapy.

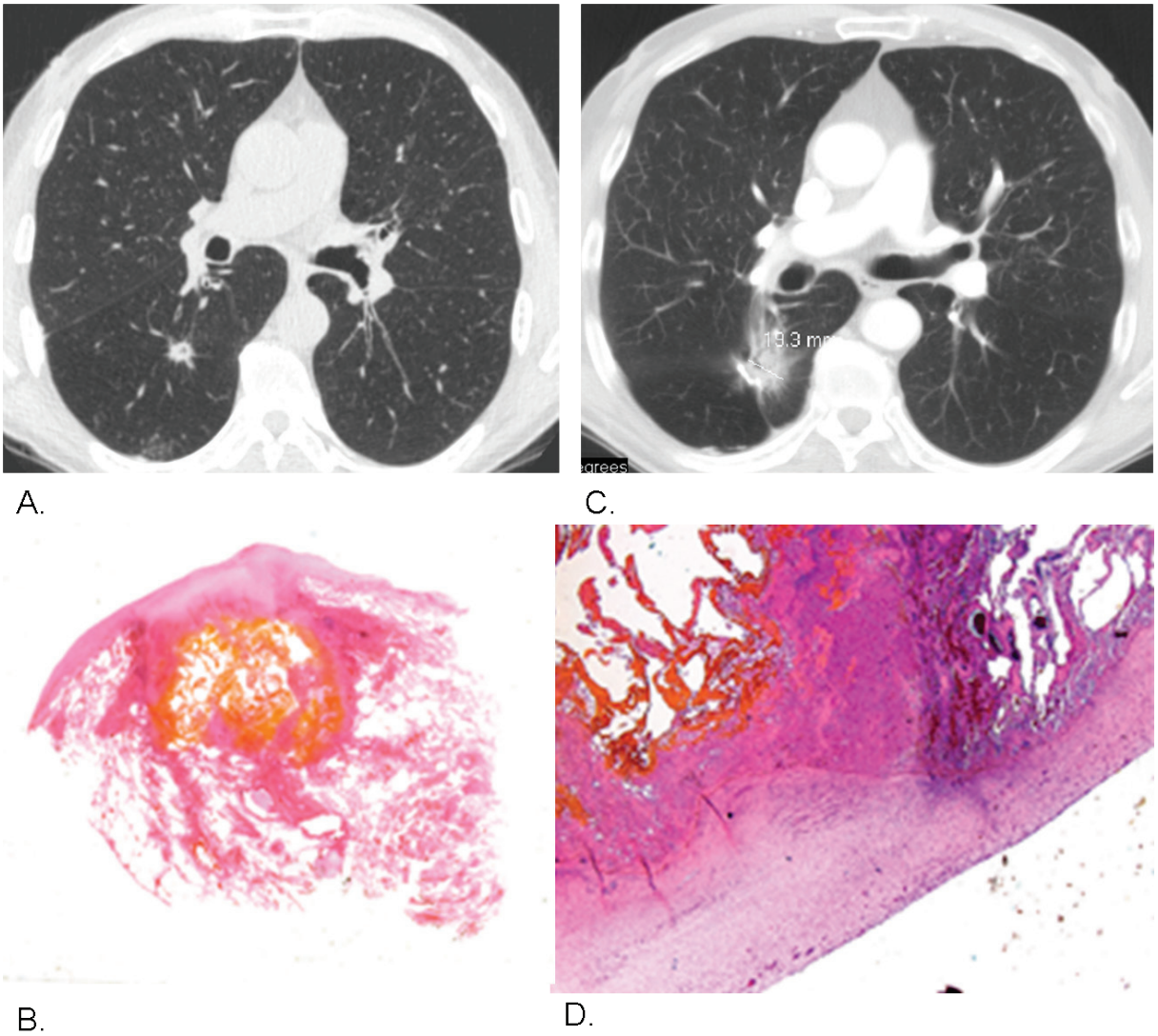

Figure 3. *MDCT image of a new right lower lobe nodule (volume 876 mm³) in subject No. 10 (A). A wedge resection of right lower lobe was performed during a thoracotomy. Histology showed a granuloma with an area of necrosis and a subpleural localization (low-power overview, Figure 3B), on the left panel a detail is shown (Figure 3D, medium power). A MDCT scan which was made 5 months after the wedge resection, showed that the lesion had grown and had not been removed during surgery (C). This subject was diagnosed with T2N2M0 lung carcinoma.*

Discussion

By using the NELSON nodule management strategy the proportion of surgical procedures for benign disease during baseline and 2nd round screening was 24% (37/154); in 6.5% (10/154) of subjects who underwent surgery one or more suspicious nodules had not been removed during surgery. We showed how complex the diagnostic evaluation of suspicious nodules can be; especially in subjects with multiple nodules, centrally located nodules and, nodules which cannot be palpated because of their weak consistency or very small size. When it becomes clear during analysis of a suspicious nodule that surgery is indicated, video-assisted thoracoscopic surgery (VATS) is the optimal choice. In comparison with open lobectomy,

VATS lobectomy is associated with a lower morbidity and, less postoperative pain.[11-13] Current literature suggests that VATS and open lobectomy are oncologically equivalent.[14] At the time of baseline screening and 2nd round screening, VATS procedures were not yet fully implemented in daily practice in the Netherlands and Belgium.[15]

Localizing suspicious pulmonary nodules

In lung cancer screening studies, over 50% of suspicious pulmonary nodules are less than a centimeter in size.[5] The small size of the nodules poses a challenge for the thoracic surgeon.[5] The difficulty of VATS is to detect subpleural nodules, which are frequently not visible or palpable.[16] The difficulty in resecting small nodules also has been addressed by Suzuki et al, who reported that 63% of the nodules ≤10 mm in size and >5 mm distance from the pleural surface could not be detected by VATS.[1] Even with pre-operative localizing techniques such as hook wire localization 3-10% of the nodules could not be resected by VATS;[17-19] the most common reason being impossibility to localize the pulmonary nodule. Following hookwire localization, a pneumothorax was seen in 8%-24% and, hookwire dislodgement in 5-8%; the pneumothorax cases did not require any intervention.[16, 17] Mayo et al,[18] who used microcoils instead of hookwires reported 3% (2/75) dislodgments and, 97% of the 75 nodules could be successfully removed at fluoroscopy-guided VATS excision. A pneumothorax requiring chest tube placement occurred in two (3%) and, an asymptomatic hemothorax occurred in one patient. The most commonly used localizing technique is hookwire localization; it is accurate in localizing the lesion, simple to operate, and, there are generally no serious complications. The presence of the wire hook makes it possible to exert light traction, and thus facilitating the positioning of the endostapler.[16] It has been recommended to perform preoperative markings for subcentimeter pulmonary nodules localized >5mm from the pleural surface;[1] others suggested >15 mm from the pleural surface.[17] Apical and diaphragmatic localization are limitations to the procedure.
Non-solid nodules can be difficult to palpate during surgery. In case of doubt a CT scan of the resected specimen before fixation by the pathologist can be considered, to ensure that the suspicious lesion is included in the resected specimen (Figure 4).

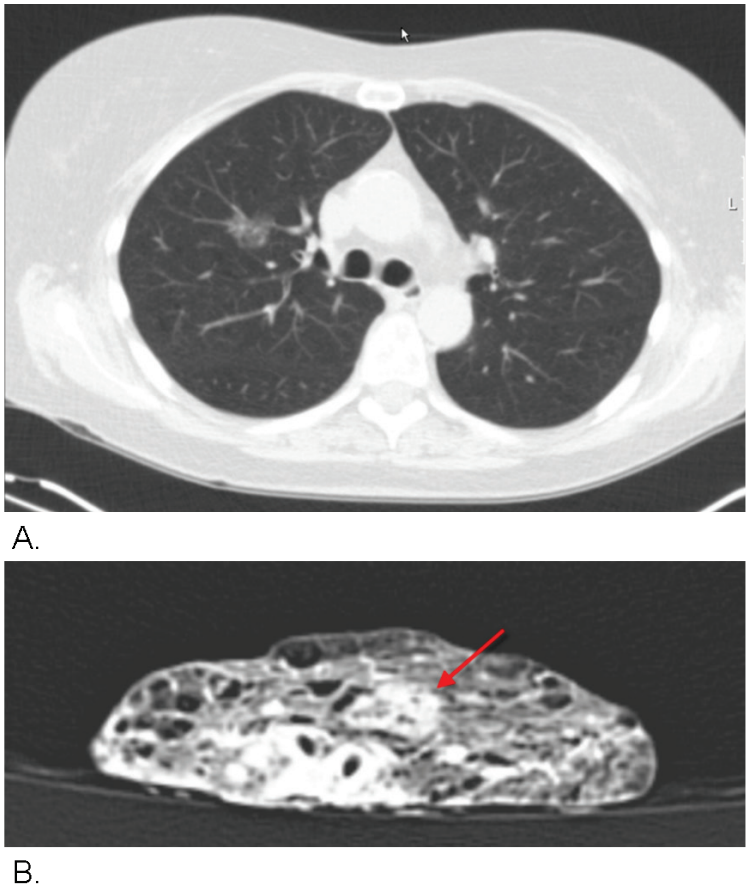

Figure 4.*Multidetector CT-scan of a ground glass lesion of the right upper lobe in a 57-year-old woman (Mx8000 IDT, Philips Medical Systems, Cleveland, OH, USA) (A). Lobectomy specimen of lesion right upper lobe of the same participant. The suspicious lesion (red arrow) was in the resection specimen and histology showed a bronchiolo-alveolar cell carcinoma (B).*

Additional pulmonary nodules, correlation of histology and CT features

It has been previously reported that the presence of additional pulmonary nodules in case of a primary lung cancer may pose the physician for a dilemma.[20] We showed that the same is true in subjects who have undergone surgical procedures, with a non-lung cancer result. This is especially the case when both lungs harbor suspicious nodules. After surgery with a benign result in one lung, the chest physician will more likely perform repeat imaging studies, to follow-up on nodule growth, rather than performing another surgical procedure on the contralateral lung. We showed that in subjects in whom one or more suspicious nodules had not been approached during surgery, this approach was successful in 70% (7/10). However, in one subject no histology of the suspicious nodules was obtained, instead mediastinoscopy was performed (subject no. 5). This case illustrates how a fast-growing middle lobe nodule, suspicious at first, shows decrease in size over time and, how the aspect of another small nodule changed and appeared to be malignant. In the other two cases (no. 7 and 10) diagnosed with lung cancer after follow-up, careful examination of post-operative CT chest and, pathological correlation might have prevented the delayed diagnosis of lung cancer. In subject no. 7 correlation of histological landmarks (subpleural

localization) would have indicated that in subject no.7 instead of the centrally localized suspicious nodule, a subpleural lesion had been removed.
In the cases of subject no. 5 and 7 it is disputable whether lung cancer was already present at the time of the first surgical work-up, or had developed during follow-up. We think however that in case no. 10 lung cancer was present at the time of the first surgery because of the nodule size, FDG-PET positivity and, presence of cavitation and spiculation. This leads to at least one false negative result of thoracic surgery. To our knowledge, this is the first to report on false negative results after thoracic surgery. Thoracic surgery is in general considered as the gold standard for a cancer diagnosis. However, with the aid of individual nodule tracking and systematic correlation of clinical results more cases may become evident.
In conclusion, in 27% (10/37) of subjects with a benign result following surgery of one or more suspicious nodules no histology had been obtained. Three subjects (8%) were diagnosed with lung cancer in previously existing nodules during follow-up.
For subcentimeter pulmonary nodules localized >5mm from the pleural surface pre-operative localization should be considered.[1] Following resection of the suspicious nodule, correlation of the surgical report, histology and CT features is important to ensure that the suspicious nodule has been totally removed. In case of doubt a CT scan of the resected specimen before fixation by the pathologist can be considered, to ensure that the suspicious lesion is included in the resection specimen.

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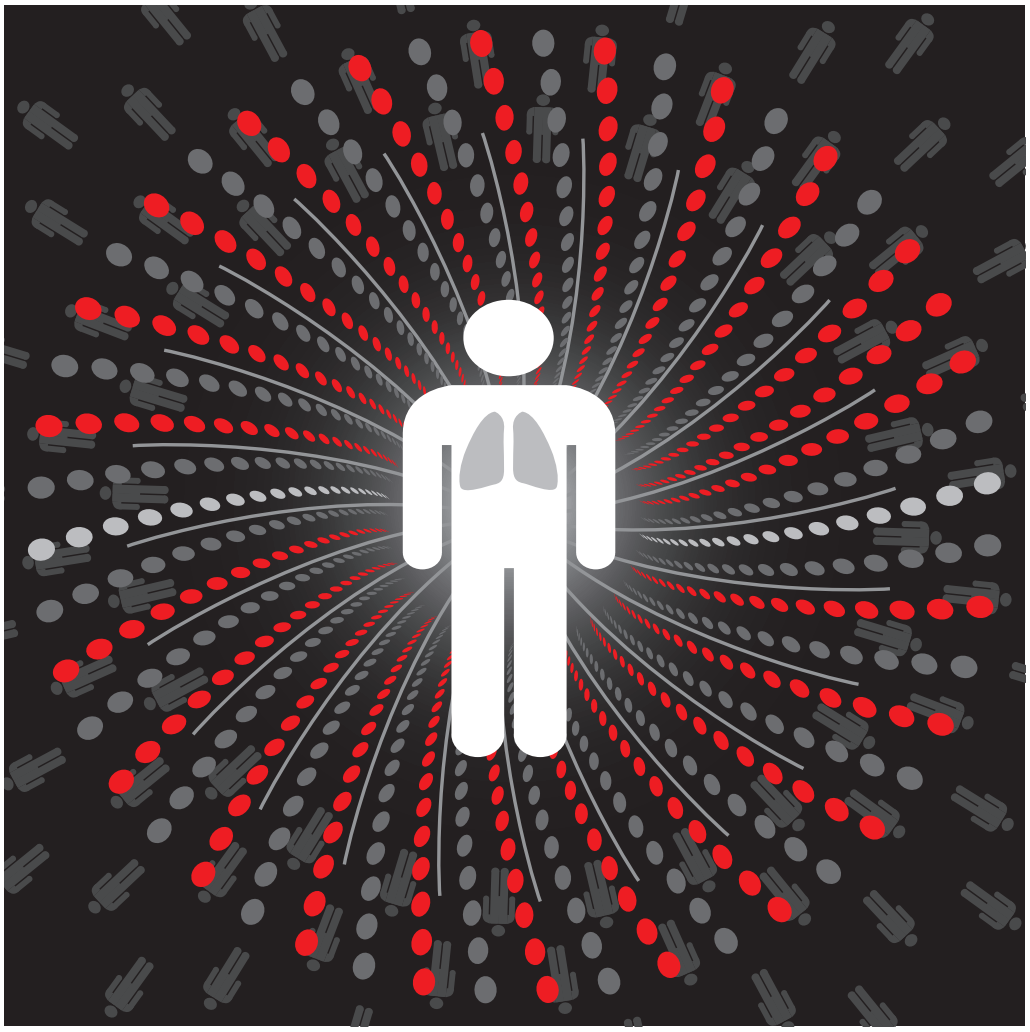
Part IV

General discussion and Summary

Chapter 11



Discussion & Summary

Discussion & Summary

To appreciate the findings of the studies presented in this thesis, several issues need to be discussed. First, we discuss the strengths and limitations of the presented research. Subsequently, we elaborate on confounding and other causes of bias in the context of diagnostic evaluation of screen detected pulmonary nodules. Concluding, we discuss the relevance of the research findings and suggestions for clinical management and future research.

Strengths

Studies with small numbers of patients suffer from significant random error and chance findings. Strength of our study was that we were able to include large numbers of individuals with a high risk of lung cancer in a multi-centre trial. To give insight into possible sources of bias we provided nodule and participant characteristics of subjects who did and, who did not undergo a certain investigation. In all studies the flow of patients included in the study was presented according the STARD principle.[1] Another asset of our study was that we collected detailed information on all nodules on the individual nodule level in a highly protocolized way according to the NELSON nodule management system. This enabled us to follow-up on all nodules and, study the growth as defined by volume doubling time, nodule consistency and, nodule border. Furthermore, this enabled us to study the evolvement of nodule growth in subjects with benign nodules and, subjects who were diagnosed with cancer during follow-up. Because the large majority of cancer cases were biopsy proven and, in case of benign nodules we had a follow-up of a minimum of two years we had a very reliable golden standard. Moreover, because the histology of all screen detected cancers was reviewed by an international tumor board (chapter 3) and, the histology of benign resected specimens were reviewed by Dr. Thunnissen (chapter 10). In order to avoid the underestimation of complications we reviewed all individual patient charts in subjects who had undergone invasive procedures (chapter 9). The data on outcome of all diagnostic investigations were prospectively scored and entered in a web-based database. The data were checked for completeness by the coordinating clinical data management centre in Rotterdam. In this centre all clinical data on referred subjects were stored and, a hardcopy of all medical files was available. Multiple queries were sent to the participating centers for missing or unclear data. Therefore, there were relatively few missing values in our studies.

Limitations

A volume and volume doubling time (VDT) based screening algorithm is a new approach in lung cancer screening studies. We showed that with VDT the rate of positive screen results was much lower. As a result a lower number of participants were referred for further diagnostic evaluations, reducing the cost, patient anxiety and, attendant morbidity. We showed that with this approach an excellent sensitivity and specificity was obtained. The results with regard to overall mortality and, lung cancer specific mortality, determine whether lung cancer screening is effective for reducing lung cancer mortality. A limitation is the absence of a central protocol for the diagnostic procedures performed during work-up after referral. As multiple specialists in each centre (pulmonologists, radiologists, nuclear medicine specialists, and surgeons) contributed to the work-up and treatment of the

participants we think that the differences between the centers, caused by interobserver bias, are neglectable. All centers worked according to national and international guidelines for the analysis of (suspected) lung cancer. The diagnostic value of the investigations may therefore reflect daily practice, which can also be seen as a positive aspect. The indications for the investigations were not protocolized. Therefore, there may be selection of subjects who were most likely to benefit from a certain investigation. This may lead to an overestimation of the diagnostic value of a given investigation. For example, subjects with small nodules are less likely to benefit from an FDG-PET because of the detection limit; and therefore may have undergone less often an FDG-PET. However, a substantial number of subjects with small suspicious nodules did undergo a FDG-PET investigation, not for diagnosing the nodules, but for pre-operative staging purposes. We think this source of bias is limited as shown by STARD diagrams and subject/nodule characteristics of subjects who did and, who did not undergo a certain investigation.

Relevance of research findings

Introduction (Chapter 1).

Chapter 1 provides a general introduction. Lung cancer epidemiology, pulmonary nodules, lung cancer screening, the NELSON study, lung cancer staging and, initial treatment of lung cancer are discussed.

Part I: Lung cancer screening and the NELSON trial

Screening and early detection of lung cancer (Chapter 2).

Many biomarkers have been reported to distinguish lung cancer patients from individuals without cancer. However, few biomarkers are in clinical use. Although studies report high specificities and/or sensitivities, most of them lack reproducibility and none of them have been validated in independent large-scale clinical trials.

Although smoking is the main cause of lung cancer, only 10%-20% of smokers develop the disease.[2]

Current lung cancer screening trials include high-risk subjects as defined by age and smoking history. However, the implementation of a biomarker profile may help to identify which subjects are at highest risk for developing lung cancer and are most likely to benefit from screening with CT. This would lead to an increased cost-effectiveness of a low-dose CT screening program.[3]

In lung cancer screening studies up to 70% will have an indeterminate nodule.[4] Following baseline screening between 10-20% of participants had a positive test result and, subsequently in 1-2% of participants a lung cancer diagnosis was made.[5] The implementation of biomarkers may reduce the rate of unnecessary (invasive) procedures, unnecessary follow-up with sequential imaging and, prevent diagnostic delay of lung cancer diagnosis. Recently, Bigbee et al[6] developed a panel of 10 serum biomarkers for the detection of stage I/II lung cancer. Using this 10-biomarker panel a sensitivity of 73.3% and specificity of 93.3% was found in a verification set compromising 30 randomly selected clinical lung cancer cases and 30 cancer free participants of the Pittsburgh Lung Screening Study. In their study the biomarker panel served as an adjunct to CT imaging. Currently, the

accuracy of biomarkers seems too low to serve as a stand-alone test and more research is necessary to determine its optimal role.

Another role of biomarkers is to predict tumor behavior and prognosis. Currently, the prognosis and therapy of lung cancer largely depend on stage at presentation. In subjects diagnosed with stage I lung cancer the 5-year survival is between 60-85%.[7, 8] Thus, subjects diagnosed with early stage disease have high rates of relapse, even after potentially curative treatment. Circulating tumor cells (CTC) are cells that disseminate from the primary tumor through the circulatory system and may have the capability of forming distant metastases. In subjects who underwent surgery for lung cancer an elevated CTC count was associated with a poorer prognosis.[9, 10] Kratz et al[11] developed a 14-gene expression assay on tissue samples to predict survival in resected non-squamous, NSCLC. Based on the assay result the subjects were stratified in three risk-categories; low, intermediate and high, associated with a 5-year overall survival of 71%, 58% and 49%, respectively. Thus, the use of biomarkers may help to establish the prognosis and, identify subjects who may benefit from adjuvant chemotherapy or need closer follow-up with CT.[11]

Finally, the role of biomarkers in chemoprevention of lung cancer remains to be elucidated. The identification of oncogenic pathways is of importance, agents targeting these pathways could provide therapeutic and chemopreventive opportunities at the premalignant stage of lung cancer.[12] Recently, Male et al[13] found that Ra1A, an important effector of Ras, is activated in NSCLC cell lines. More research is necessary to reveal therapeutic, preventive and diagnostic value. Gustafson et al[12] studied the poshpatidylinositol 3-kinase (PI3K) oncogenic pathway in cytologically normal proximal airway epithelial cells of smokers at risk for lung cancer. They showed that the in vitro inhibition of the PI3K oncogenic pathway was successful. Although these studies seem promising, one has to be aware of unexpected results of chemoprevention studies. The largest chemo-prevention trial showed no reduction in the incidence of lung cancer and, raised the possibility that the dietary supplementation may actually have led to an increase in mortality.[14]

In conclusion, biomarkers can be useful in determining high-risk patients, distinguishing benign from malignant nodules, predictive of lung cancer prognosis, help to elucidate oncogenic pathways and explore options for chemoprevention. More research is necessary to investigate the optimal biomarker panel for different purposes. Because currently the diagnostic value of lung cancer biomarkers as a stand-alone test is too low, more research is necessary to investigate the implementation of biomarkers in clinical decision models combined with results of CT images (VDT, nodule features) and, patient characteristics. In the NELSON lung cancer screening trial research effort related to blood biomarkers and the prediction of lung cancer is underway.

Management of lung nodules detected by volume CT scanning (Chapter 3).

In chapter 3 we described the novel nodule management strategy and the results following baseline and second round screening. In other lung cancer screening studies following baseline CT-screening between 23-27% of subjects had a positive test result and were referred to the pulmonologist, resembling between 233-7,191 subjects, who undergo further (invasive) investigations.[15, 16] Despite the fact that only high-risk subjects are screened, as defined by age and smoking history, the prevalence of lung cancer is low, approximately 2.7-3.8%. In the NELSON trial, because of the use of VDT in the screening algorithm, the number of test-positives was remarkably lower with 2.6% and, lung cancer

was detected in 36% of test-positives.[17] Stage I lung cancer was detected in 64% in round one.

Two other lung cancer screening trials in addition employ a nodule management protocol based on volumetric analysis: the Danish randomized lung cancer screening trial[18] and the UK Lung Screen (UKLS) randomized trial.[18] The main purpose of VDT in these lung cancer screening studies is to predict benign versus malignant pulmonary nodules. The results of the UKLS trial have to be awaited; in the DLCST in addition a relatively low number of test-positives (8.7%) was noted after baseline screening.[18]

Several lung cancer screening trials who did not employ volumetric assessments and VDT as part of their screen regiment retrospectively investigated the previous nodule growth of screen detected lung cancers.[19-22] For BAC[19], adenocarcinoma/BAC[23] and ground-glass nodules[21, 22] the median VDT varied between 251 and 813 days. The majority of lung cancers with a VDT longer than 400 days were detected in women, 85% (11/13).[19] Prevalent adenocarcinomas more often were slow growing as 75% had a VDT >365 days as opposed to 11% in the nonprevalent adenocarcinomas.[23] Based on their results Wilson et al[23] suggested a more cautious follow-up in subjects with new nodules. In the NELSON study at 2nd round screening for newly the detected nodules the interpretation (positive or negative result) was based on the size of the nodule, as it had been in round one.

Based on the results of volumetric assessments in the afore mentioned lung cancer screening trials, it has been suggested that lung cancers with a VDT of > 400-days may represent overdiagnosis.[19, 21-23] There is however one study that did not show a significant difference between VDT and histological type of lung cancer detected in daily practice.[24] They studied 149 lung cancer cases, the median VDT was 207 day and 15% (21/149) did not increase in volume between examinations, when corrected for interval between the CT's in 6% of cancer cases no nodule growth was seen. We therefore think that lung cancers with a VDT >400 days are not per definition overdiagnosed cases. The ranges for VDT that we used are not definite and could be improved. Furthermore, our nodule management strategy requires validation in an independent study.

The mortality results of the NELSON trial will be published in the near future. Several other randomized lung cancer screening trials recently published these results. The Danish lung cancer screening trial (DLCST) presented results after 5 annual screening round (median follow-up 4.81 years).[25] In the screening group the rate of stage I lung cancers was six times higher compared with the control group. This did not translate in a reduction of lung cancer mortality; 15 (0.73%) died in the screening group, while 11 (0.54%) died in the control group (p-value: 0.42). They found no significant difference in the absolute number of late stage cancers in both groups. The Italian DANTE trial in addition could not establish a mortality reduction with lung cancer screening.[26] Three times as many stage I disease patients were found in the low-dose CT (LDCT) arm as opposed to the control-arm. However, after three year follow-up no significant mortality reduction was found in the LDCT-arm and the number of advanced lung cancer cases was the same as in the control arm. The largest lung cancer screening study in the world, the National Lung Screening Trial (NLST) randomized 26,722 participants in the low-dose CT group and 26,732 subjects in the chest radiography group. After a median follow-up period of 6.5 years the mortality results were established: in the low-dose CT arm the lung cancer a relative reduction in lung cancer mortality of 20% was found and, an all-cause mortality reduction of 6.7%. In the DANTE lung cancer screening trial (LDCT, 1,276; control, 1,196) and the Danish trial (LDCT, 2,052; control, 2052) a lower

number of subjects were enrolled and the median follow-up at the time of calculation of mortality results was shorter as compared to the NLST.
The question is how the larger number of early stage lung cancers in the DANTE Trial and DLCST should be interpreted. These cases might represent overdiagnosis, indolent lung cancers that would not have led to the death of the participant. On the other hand, the lead time until clinical diagnosis of lung cancer is not known. Therefore, these cases also might represent earlier diagnosis of lung cancer and a true stage shift. It has been hypothesized that the lead time may vary between 1-5 years;[25] this would mean that with longer follow-up time their results may be approximately the same as in NLST. Besides the duration of follow-up the number of enrolled subjects might explain why the DANTE and DLCST did not show a mortality reduction as opposed to the NLST. We showed previously that in order to detect a 20-25% mortality reduction 10 years after randomization, 17,300-27,900 subjects are needed.[27] Considering these numbers, the DANTE trial and the DLCST are underpowered. Therefore, no firm conclusions can be drawn from these studies.
Following the results of the NLST showing a 20% lung cancer mortality reduction, the National Comprehensive Cancer Network launched a guideline for lung cancer screening, taking nodule consistency into account.[28] However, there is a large variation in screen regiments and the ideal screening regiment remains to be established. Participants of lung cancer screening trials have different risk-profiles because of different inclusion criteria with regard to age and pack-years. In some studies subjects undergo an annual CT scan,[18] whereas in other studies CT's are made at longer intervals.[17] Several studies in addition used volume doubling time[17, 18] and FDG-PET as part of their screening regiment.[29, 30] Results of different trials may therefore be difficult to interpret and compare. Large numbers of indeterminate and suspicious nodules are found, leading to secondary work-up studies associated with costs, patient anxiety and risk of complications. It is therefore important to establish an optimal screening strategy in order to develop an effective and, cost-efficient screening strategy.
Two European Lung cancer screening trials may have lacked power to establish a mortality reduction.[25, 26] Therefore, it would be very interesting to pool data from European randomized trials to improve our knowledge on potential harms and benefits of lung cancer screening with low-dose CT. This is may be a challenging project due to the differences in study design. The ideal nodule management strategy with regard to nodule volume and VDT remains to be established; modeling studies of previous nodule growth of lung cancers detected in the NELSON study are currently underway.

Part II: Management of suspicious pulmonary nodules: imaging studies and bronchoscopy

How to deal with incidentally detected pulmonary nodules less than 10 mm in size on CT in a healthy person (Chapter 4).

In this chapter we provided a 10-step approach for the management of incidentally detected pulmonary nodules. A large body of literature exists for the management of incidentally detected pulmonary nodules.[31-33] Recent literature showed that the compliance with Fleischner Society guideline for management of small lung nodules varied between 35-61%; a better compliance would have reduced the number of unnecessary follow-up CT examinations.[32, 34] In a recent review Ost and Gould discuss decision making in patients with pulmonary nodules.[35] They recommend that firstly the probability of lung cancer, based on

clinical risk-factors and CT characteristics should be determined.[35] Secondly, the pro en cons of surgery should be discussed with the patient, taking into account surgical risk and, risk of surgery for a benign lesion. Based on surgical risk and clinical probability of cancer different management strategies are provided. The National Comprehensive Cancer Network (NCCN) guideline for lung cancer screening states that the possible risks and benefits of lung cancer screening should be discussed with the patient.[28] The nodule management algorithms are based on nodule growth, diameter and nodule consistency. The NCCN definition of growth is based on assessment of mean diameter of the nodule (mean of longest diameter and its perpendicular diameter); volume assessments are not taking into account.

Stem cells and the natural history of lung cancer: implications for lung cancer screening (Chapter 5).

In chapter 5 we discussed two hypothesizes of lung cancer development and the possible consequences for lung cancer screening. The classical model is localized multi-step carcinogenesis; metastatic dissemination, tumor cell invasion and angiogenesis are thought to start when the tumor reaches a 'critical' volume. The second hypothesis, the cancer stem cell model, is based on the recent finding of circulating carcinogenic stem cells and, considered as a systemic bone-marrow derived disease from the start. Stem cells are suspected to rely on signals from their stromal environment, such as growth factors.[36] For successful metastatic colonization stromal niche signals are crucial.

Kim et al. was the first to discover bronchioalveolar stem cells (BASC), and hypothesized that BASC's might be the precursor lesions of lung adenocarcinomas.[37] Xu et al[38] tried to identify the cells of origin of lung cancer in mice with K-Ras induced lung adenocarcinoma. After K-Ras activation, proliferation in type II pneumocytes and BASC's was noted. However, only type II cells appeared to progress to adenocarcinoma. Therefore, non-stem cells may also serve as precursor lesions of lung cancer development.

Epithelial-to-mesenchymal transition (EMT) was defined as a process occurring during early embryonic development whereby cells lose their epithelial characteristics and obtain mesenchymal phenotypes. Mesenchymal cells lack the architectural structure of epithelial cells and are more motile and invasive. However, recently EMT has been associated with local invasion and distant metastases.[39, 40] The induction of EMT in mammary epithelial cells lead to the development of mesenchymal traits and the expression of stem cell markers.[41] The authors found that EMT led to a great increase in the number of self-renewing cells. During the process of tumor metastasis, often enabled by EMT, disseminated cancer cells would require self-renewal capability, similar to that exhibited by stem cells.[41]

For cancer cell proliferation metabolic enzymes in addition are crucial; cancer stem cells metabolic oncogenes are required for tumorigenesis. Recently, several metabolic enzymes have been linked to cancer genesis.[42, 43] These findings support the status of metabolic reprogramming as a new hallmark of cancer.[44] It has been shown that tobacco smoke may induce EMT in an early stage, which appeared to lead to the acquisition of stem cell like properties.[45] More research is necessary to establish the role of stem cells and EMT in lung cancer development. The detection of EMT or, tobacco induced epigenetic changes associated with EMT, may help to indentify subjects who are at risk for lung cancer and may benefit from lung cancer screening.

CT-scan with contrast (Chapter 6).

In Chapter 6 we demonstrate the limited value of a single diagnostic CT with contrast for diagnosing pulmonary nodules after a positive screen result. When the indeterminate results were included with the "suspicion of cancer" results, the diagnostic value of CT for detecting lung cancer showed a sensitivity, specificity, positive predictive value and negative predictive value of 92.2% (95% Confidence Interval (CI): 86.8–95.6), 41% (95% CI: 33.1–48.5), 61% (95% CI: 54.8–67.1) and 84% (95% CI: 73.5–90.7), respectively. This can be explained by the fact that the majority of standard-dose CT scan results were classified as indeterminate. Previously it was reported that the inter-observer agreement on the interpretation of pulmonary findings at low-dose CT screening is moderate to substantial.[46]

In test-positives of lung cancer screening studies, the diagnostic evaluations most often concern further imaging studies and invasive procedures are performed infrequently.[15, 47] In the CT arm of the National Lung Cancer Screening Trial (NLST), 18,146 subjects were referred and a total of 8,807 chest CTs were made.[15] We have demonstrated that a lower rate of resection for the benign disease was observed in subjects who had undergone a follow-up CT, regardless of nodule size. Because of the lower prevalence of cancer in nodules <500 mm^3 (38–44%) as opposed to nodules >500 mm^3 (50%), it seems justified to consider a repeat scan before proceeding to more invasive type of investigations in the case of indeterminate imaging results. It has been previously reported that tumor boards of lung cancer screening studies are in general more likely to employ radiological follow-up instead of surgery.[48] However, a risk of making follow-up CTs during analysis is that of tumor progression, as even small nodules can potentially metastasize.[49] Following a repeat scan, 22% (25/113) of subjects were diagnosed with lung cancer, which was stage I in 84% (21/25). We think this is a very acceptable percentage.

The advent of CT and lung cancer screening studies, combined with a high number of repeat standard-dose CTs made during analysis by the pulmonologist, has led to additional exposure to radiation.[50, 51] Therefore, when it is decided to make a 2nd CT during work-up, this should preferably be a low-dose CT scan, using the same software as the screening CT to establish volume doubling time in order to reduce the radiation exposure and to avoid the problem of a possible difference in volume measurement between different CT protocols.

FDG-PET (Chapter 7).

In this chapter the role of FDG-PET in 229 subjects with a positive baseline or second round test result was discussed. The sensitivity of PET to detect cancer 84.2% (95% CI: 77.6 – 90.7%), the specificity 75.2% (95% CI: 67.1 – 83.3), the PPV 78.9% (95% CI: 71.8–86.0), and the NPV 81.2% (95% CI:73.6 – 88.8). The resection rate for benign lesions was 23%; a preoperative PET after an inconclusive nonsurgical workup reduced the futile resection rate with 11 to 15%, at the expense of missing 12 to 18% lung cancer cases. A preoperative PET after a conclusive nonsurgical workup reduced the futile resection rate by 78% at the expense of missing 3% lung cancer cases.

The role of FDG-PET has been investigated in several other lung cancer screening studies; it was concluded that a combination of CT and PET effectively detects lung cancer and may help to reduce unnecessary surgeries for benign lesions.[29, 30, 52, 53]

The role of FDG-PET for diagnosing pulmonary nodules detected in daily practice has been investigated by several authors. Gould et al. demonstrated a sensitivity of 96.8% and a specificity of 77.8% for the detection of cancer pulmonary nodules and mass lesions.[54] FDG-

PET was an accurate noninvasive imaging test, although few data exist for nodules smaller than 1 cm in diameter.[54]
According to the ACCP guidelines FDG-PET is recommended for nodules with a low-to-moderate pretest probablity of malignancy (5-60%) and indeterminate solitary pulmonary nodules (SPN) that measuring at least 8-10 mm in diameter. In patients with an SPN that has a high pretest probability of malignancy (> 60%) or patients with a subcentimeter nodule that measures < 8 to 10 mm in diameter, FDG-PET is not recommended to characterize the nodule.[31] In the Danish lung cancer screening trial the FDG-PET result and VDT were independently predictive of lung cancer; the combined use of FDG-PET result and VDT resulted in a sensitivity of 90% and specificity of 82%.[55]
In a recent study 1.7% (25/1500) subjects who underwent a FDG-PET scan incidental abdominal findings were found; in 36% % (9/25) a diagnosis of malignancy was made.[56]
Thus, the use of FDG-PET scans made in participants of lung cancer screening trials may lead to additional relevant findings, but may also incur additional examinations for benign lesions. Recently, it was shown that FDG-PET/CT compared to CT alone improved the characterization of pulmonary nodules measuring <1 cm in diameter and, therefore may help to reduce unnecesary surgeries.[57]
In conclusion, the value of a preoperative PET-scan in participants with an inconclusive nonsurgical workup to diagnose pulmonary nodules was limited, but after a conclusive nonsurgical workup, the resection rate for benign lesions can be decreased by 72%.

Bronchoscopy (Chapter 8).
In this chapter we evaluated the diagnostic value of conventional white-light bronchoscopy in the NELSON lung cancer screening trial. The overall sensitivity was 13.5% and the negative predictive value (NPV) 47.6%. The sensitivity was only 8.3% when limited to CT-detected suspicious nodules. Of all cancers detected within the time frame of this study, 4.5% were identified by bronchoscopy only and were invisible on CT.
Auto-fluorescence bronchoscopy (AFB) was developed to detect preinvasive lesions, based on the observation that moderate to severe dysplasia and carcinoma in situ show less fluoresence than normal tissue when excited by blue light.[58] Although there is a high variability in reported prevalence of preinvasive lesions, AFB is efficient for the detection and localization of neoplastic and pre-neoplastic lesions.[59, 60] A European randomised trial comparing AFB with white light bronchoscopy (WLB) only with WLB and AFB in addition showed that AFB was superior for the detection of preneoplastic lesions.[58] They found a relatively low prevalence of pre-invasive lesions of 3.9%. This raises the question whether AFB is suitable screening tool for mass screening for lung cancer; moreover because there have been concerns about the high rate of false positive results of AFB.[61]
Electromagnetic-navigated, or peripheral endobronchial ultrasound-guided bronchoscopy might play a role in the near future for the evaluation of this type of smaller nodule because of their higher sensitivity for peripherally located lesions, ranging from 59 to 74%[62-65] and from 49 to 80%,[62, 66-69] respectively. Recently, Santonico et al described a novel technique of bronchoscopic air-sampling.[70] This technique makes it possible to zoom-in close on the cancerous lesion; different subtypes of cancer were correctly classified in 75%.
Because of the limited diagnostic performance of conventional bronchoscopy, we do not recommend a routine conventional bronchoscopy for test-positive screenees. However, we recommend that subjects who undergo surgery should undergo a bronchoscopy for staging purposes.

Part III: Management of suspicious pulmonary nodules: surgical procedures

Complications following lung surgery in the Dutch-Belgian randomised lung cancer screening trial (Chapter 9).

In chapter 9 we compared the complications rates, length of hospital stay, re-thoracotomy and mortality rates of participants in the NELSON trial who underwent thoracic surgery with data from non-screening series. The rate of minor complications after thoracotomy and VATS was in the upper range of what has been reported for non-screening series, while the rate of major complications was in the lower range. The postoperative length of stay was not shorter than in the literature. The re-thoracotomy rate for complications such as a hemothorax requiring re-intervention was in the same range in NELSON as that reported in the literature, but no re-thoracotomies were performed after VATS. No postoperative deaths were observed after the thoracotomy and VATS procedures. In conclusion, mortality rates after surgical procedures were lower in the NELSON lung cancer screening trial than in non-screening series. The rate of minor and major complication is within same the range as in non-screening series.

Difficulties encountered during surgical procedures for suspicious pulmonary nodules in the Dutch-Belgian lung cancer screening trial (Chapter 10).

In this chapter we describe subjects with a benign result following surgery in whom in one or more suspicious nodules no histology had been obtained during surgery. In 27% (10/37) one or more suspicious nodules were not approached during surgery. Three subjects (8%) were diagnosed with lung cancer in previously existing nodules during follow-up. For subcentimeter pulmonary nodules localized >5mm from the pleural surface pre-operative localization should be considered.[71] Following resection of the suspicious nodule, correlation of the surgical report, histology and CT features is important to ensure that the suspicious nodule has been totally removed. In case of doubt a CT scan of the resected specimen before fixation by the pathologist can be considered, to ensure that the suspicious lesion is included in the resection specimen.

Recommendations for future research

Risk-models

The use of risk models may help to identify subjects who may benefit the most from participating in a lung cancer screening trial. It is interesting to implement a patient-related risk-model in a lung cancer screening setting; this will be investigated by the Liverpool Lung Project (LLP). The Liverpool Lung Project (LLP) will take the following factors into account: pack-years, family history of lung cancer, exposure to asbestos, pneumonia, or prior malignant tumor.[72] Subjects are included when they have sufficient risk of developing lung cancer according to the Liverpool Lung Project risk model. Recently a new risk-model was published, in contrast to the Bach model which is based on subjects who smoked 10-60 cigarettes per day for 25-55 years, this model was based on former all former smokers and current cigarette smokers. The predictive accuracy was superior to the Bach model applied to the same data.[73] This model in addition may help to identify subjects who are at greatest risk of lung cancer and select subjects for a lung cancer screening trial.

The analysis of suspicious pulmonary nodules is challenging. Therefore, a clinical decision model to aid clinical decision making for the work-up of screen detected suspicious pulmonary nodules would be helpful. Such a model should ideally consist of radiological parameters, FDG-PET result and, patient-related risk factors. The radiologic parameters should contain nodule border characteristics, consistency, suspicious lymphadenopathy and volume doubling time. Patient-related risk-factors for lung cancer have been used in several different risk-models. The Bach model is based on: age, sex, prior history of asbestos exposure, duration of smoking, average amount smoked per day while smoking, and duration of abstinence from smoking for former smokers.[74] Previous medical history of obstructive lung disease, type of asbestos exposed to, or findings on CT-chest were not included because they were not easily available in their study. The Spitz model used the following risk factors: pack years, family history of any cancer or smoking related cancers, exposures to asbestos and wood dusts, emphysema and, hay fever.[75] The external validation of the discriminatory power, as established by D'Amelio was similar: 0.66; 0.69 and, 0.69.[76] More research is necessary to determine the role of risk-models in a lung cancer screening program. Possible roles of risk models are the selection of subjects to participate in a lung cancer screening program and guiding of management of indeterminate CT-screening results. In addition, more research is necessary to evaluate the role of biomarker panels in such risk-models.

Nodule evaluation after a positive test-result

The work-up of suspicious pulmonary nodules is challenging. In the current studies no protocols for the work-up of suspicious pulmonary nodules were specified in advance. For research purposes it is recommendable that the results of investigations are reported in a highly standardized way. Furthermore, as the management of pulmonary nodules often is discussed in multidisciplinary teams, the outcome of tumor board decisions should be available in the database of clinical trials.

Smoking cessation

Participants of a screening regiment who are current smokers should undergo counseling to quit smoking. For smoking cessation several approaches exist varying from time intensive methods such as motivational interviewing to a standard self-help brochure or, computer tailored smoking cessation intervention. For as far as we know, the former has not been studied in a lung cancer screening setting; the latter two strategies were employed in the NELSON trial and, showed quit rates of 16% and, 13% respectively.[77] Motivational interviewing (MI) has shown quit rates varying between 3 and 35% and, it has been suggested that MI was effective when delivered by primary care physicians or counselors.[78] Furthermore, CT-images can be shown to the patient and, this may influence smoking behavior. As primary prevention is at least equally important as secondary prevention, more effort should be done to implement effective smoking cessations programs in a lung cancer screening study. The participation in a lung cancer screening trial should be no means act as a "license to smoke", because of the potential reassuring of screening.

Design of a lung cancer screening program

Lung cancer screening can be done by means of organized mass screening or, ad hoc screening. For screening for cervical cancer it has been shown that mass-screening is the best strategy to achieve a substantial decrease in the incidence and, mortality due to cervical cancer.[79] Mass screening for lung cancer should only be offered to the general public when results of other randomized lung cancer screening trials confirm the results of the NLST. A target population should be defined in terms of age, pack-years of smoking and, other risk-factors. Question is whether different criteria should be applied for men and women with regard to pack-years. It was reported that women with lung cancer had smoked fewer pack years as compared to men.[80] Furthermore, fewer women with lung cancer were smokers. About 25% of all lung cancers worldwide are not attributable to smoking.[81] This raises the question whether never-smokers should be able to undergo lung cancer screening. With web-based pre-screening, high-risk subjects can be identified. A website can in addition be helpful to organize a lung cancer screening program: making appointments for a CT-scan, web-based smoking cessation programs and, questionnaires to follow-up on smoking behavior. Participants can access the result of their CT on the website by using their personal account after logging in.

Currently, subjects with incidentally detected nodules, or subjects with increased risk may undergo screening for lung cancer; provided they are well informed about the benefits and potential risks of lung cancer screening. Mass screening for lung cancer should be offered to the general public in the Netherlands when results of the NELSON trial confirm the results of the NLST. Whether or not lung cancer screening will be introduced to the general public, lung cancer screening has delivered a large body of knowledge that will be beneficial for other smoking related diseases and may contribute to a better understanding of lung cancer biology. Furthermore, algorithms to deal with incidentally detected pulmonary nodules, on CT-chest made for other purposes have been designed based on this experience.

General conclusions

- There is lack of evidence for the implementation of biomarkers in a lung cancer screening trial as none of them have been validated in independent large-scale clinical trials. In the near future however biomarkers may lead to an increased cost-effectiveness of a low-dose CT screening program by indentifying subjects at high risk of lung cancer and reducing the rate of false-negative results.
- The novel nodule management strategy based on volume and volume doubling time resulted in a relatively low number of test positives of a lung cancer screening trial and lung cancer was detected with a high sensitivity and excellent negative predictive value.
- A large body of literature exists for the management of incidentally detected pulmonary nodules. However, the optimal (follow-up) strategy based on nodule volume, volume doubling time and nodule consistency remains to be established.
- In test-positives of lung cancer screening studies, the diagnostic evaluations most often concern further imaging studies. Although we showed a poor specificity of CT-scan with contrast to diagnose pulmonary nodules, an important role was to follow-up on nodule growth. Therefore, repeat-scans made during work-up should preferentially be a low-dose CT scan, using the same software as the screening CT to establish volume doubling time in order to reduce the radiation exposure and to avoid the problem of a possible difference in volume measurement between different CT protocols.
- The value of a preoperative PET-scan in participants with an inconclusive nonsurgical workup to diagnose pulmonary nodules was limited, but after a conclusive nonsurgical workup, the resection rate for benign lesions can be decreased by 72%.
- Because of the limited diagnostic performance of conventional bronchoscopy, we do not recommend a routine conventional bronchoscopy for test-positive screenees.
- In the NELSON trial after lung surgery lower mortality rates were found as compared to non-screening series. The rate of minor and major complication is within same the range as in non-screening series.
- Surgery of (small) pulmonary nodules can be challenging. We recommend the use of pre-operative localization techniques for subcentimeter pulmonary nodules localized >5mm from the pleural surface. A post-operative CT scan can be made to ensure that the suspicious lesion was included in the resection specimen.

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Nederlandse samenvatting

(Summary in Dutch)

Longkanker

Longkanker is een van de meest voorkomende vormen van kanker en de belangrijkste doodsoorzaak van overlijden door kanker. In de 19e eeuw was longkanker een extreem zeldzame ziekte, in 1878 betrof slechts 1% van alle kankers vastgesteld bij autopsie in het Instituut van Pathologie in Dresden kwaadaardige longtumoren. In heb begin van de 20e eeuw nam het aantal gevallen van longkanker gestaag toe; evenals de sigaretten consumptie. In de 1e helft van de 20e eeuw werden de gevaren van roken onvoldoende onderkend, pas in de vroege jaren vijftig werden de eerste artikelen gepubliceerd over de gevaren van roken. Slechts een minderheid van de patiënten, ongeveer 15%, presenteert zich met longkanker in een vroeg stadium en komt in aanmerking voor chirurgie. In een vroeg stadium is er over het algemeen geen sprake van symptomen; symptomen die bij longkanker kunnen optreden zijn klachten van moeheid, kortademigheid, pijnklachten of het ophoesten van bloed.

Screenen voor longkanker

Primaire preventie, maatregelen om het stoppen met roken te bevorderen en om te voorkomen dat mensen beginnen met roken, is van groot belang. Het doel van longkanker screening (secundaire preventie) is om longkanker in een vroeg stadium te diagnosticeren wanneer de kans op curatie groter is om zo een daling van de mortaliteit door longkanker te bewerkstelligen. In de jaren ‘80 werden verschillende longkanker screening studies verricht. Rokers ondergingen tijdens deze studie meerdere malen een longfoto (X-thorax). Er werd echter geen overlevingsvoordeel aangetoond. Een CT-scan (Computed Tomography) van de thorax kan gedetailleerd de borst in beeld brengen en is gevoeliger voor het detecteren van afwijkingen in de longen dan een standaard longfoto. CT-screenen wordt gedaan met lage dosis CT-scans. Dit geeft een effectieve stralingsdosis van circa 0,65 mSv, in tegenstelling tot 3,5-7 mSv voor een standaard dosis CT-scan. Recent toonde een Amerikaanse studie aan dat door longkanker screenen met lage dosis CT-thorax een reductie van de longkanker mortaliteit van 20% werd bereikt. De NELSON studie (Nederlands Leuvens Longkanker Screenings Onderzoek) is de op 1 na grootste gerandomiseerde longkanker screening studie ter wereld. Wanneer er een verdachte afwijking gezien wordt op de CT wordt de deelnemer doorverwezen naar de longarts voor nader onderzoek. Verder onderzoek kan bestaan uit een bronchoscopie, een FDG-PET scan (Fluorodeoxy Glucose Positron Emision Tomography), een CT-thorax met intraveneus contrast of, een punctie van de afwijking. Wanneer deze onderzoeken de verdenking op longkanker ondersteunen of bevestigen, en de afwijking resectabel is, komt de patiënt in aanmerking voor chirurgie. In ongeveer 60% van de gevallen van longkanker gediagnosticeerd door longkanker screening studies betreft dit een vroeg stadium van longkanker, en komen patiënten in aanmerking voor operatie, mits de algehele conditie en longfunctie dit toelaat.

Er kleven potentiële nadelen aan het screenen voor longkanker. Zo worden er in een groot aantal deelnemers pulmonale nodules (vlekjes op de long <3 centimeter) gezien, waarvan het merendeel goedaardig is. In een deel van de gevallen blijkt dat er onderzoeken, of zelfs chirurgische ingrepen worden verricht voor een, retrospectief, goedaardige afwijking.

Dergelijke vals positieve bevindingen leiden tot stress bij de patiënt en het verder oplopen van kosten voor de gezondheidszorg.
Er zijn verschillende vormen van bias (vertekening) die mogelijk op kunnen treden tijdens longkanker screening studies. Lead time bias is een vorm van bias die optreed wanneer de ziekte in een vroeger stadium, wanneer er nog geen symptomen zijn, gediagnosticeerd wordt, zonder dat de prognose hierdoor verbeterd. Hierdoor is de waargenomen overlevingsduur toegenomen, zonder dat het natuurlijk beloop van het ziektebeeld werd beïnvloed.
Length time bias is een vorm van selectie bias die optreed wanneer er door de gekozen screenings intervallen vooral ziekte processen met een langdurig ziektebeloop worden gedetecteerd. Wanneer er door screenen meer langzaam groeiende longkankers worden gedetecteerd kan dit de indruk geven dat longkanker screenen het leven heeft verlengd. Door middel van een gerandomiseerde opzet kunnen deze vormen van bias worden voorkomen.

De NELSON studie
De NELSON studie is een gerandomiseerde longkanker screening studie die screenen met CT-thorax vergelijkt met een controle groep die geen screening ondergaat. Uniek van de NELSON studie is het gebruik van een nieuwe nodule management strategie. Dit is een strategie die gebaseerd is op volumemetrische bepalingen van afwijkingen op de CT-thorax. Wanneer er op de CT-thorax een vlekje (nodule) op de long wordt gezien wordt dit zeer nauwkeurig opgemeten met behulp van een speciaal hiervoor ontwikkeld software programma. Het volume van de nodule wordt berekend en, indien er een voorgaande scan beschikbaar is wordt het verschil in volume bepaald en kan de volume verdubbelingtijd worden berekend (Volume doubling time, VDT). Op grond van het volume van de nodule en, indien beschikbaar, de volume verdubbelingtijd wordt het testresultaat van de scan bepaald. Bij een positieve uitslag wordt de deelnemer doorverwezen naar de longarts voor verdere analyse, bij een onbepaalde uitslag wordt een herhaal CT scan ingepland om de VDT vast te stellen. Bij een negatieve uitslag kan de deelnemer volgens het gebruikelijke schema het longkanker screening programma doorlopen.

Beschrijving van het onderzoek

Het doel van het onderzoek beschreven in dit proefschrift was het bepalen van de rol van de verschillende onderzoeken die werden verricht tijdens de analyse die deelnemers van de NELSON longkanker screening studie ondergingen na doorverwijzing naar de longarts vanwege een positief screening resultaat. Het uiteindelijke doel is om de effectiviteit en efficiëntie van longkanker screening studies te verbeteren.

Het proefschrift is ingedeeld in vier delen. Het eerste deel beschrijft longkanker screenen en de NELSON studie. Het tweede deel onderzoeken die werden verricht tijdens de analyse door de longarts en het derde deel chirurgie van voor longkanker verdachte afwijkingen. In het 4^{e} deel is de discussie en samenvatting opgenomen.

Part I: longkanker screenen en de NELSON trial

Hoofdstuk 1, de algemene inleiding worden pulmonale nodules (vlekjes op de long), longkanker screenen, de NELSON studie, en de stadiering en initiële behandeling van longkanker besproken.
In **hoofdstuk 2** wordt vroeg detectie van longkanker besproken. Er wordt een overzicht gegeven van negen gerandomiseerde longkanker screening studies. Verder wordt de rol van biomarkers in bloed, sputum, broncho-alveolaire lavage vloeistof en uitgeademde lucht besproken. Ondanks het feit dat sommige studies een goede sensitiviteit en/of specificiteit rapporteren, zijn de resultaten over het algemeen niet goed reproduceerbaar. Er is meer onderzoek nodig om de resultaten te valideren in trials met grotere aantallen deelnemers. In hoofdstuk 3 wordt de nieuwe nodule management strategie van de NELSON studie besproken. In andere longkankerscreening studies hebben tussen de 23 en 27% van de deelnemers een positief testresultaat, terwijl slechts 2.7-3.8% van de deelnemers gediagnosticeerd wordt met longkanker. In de NELSON studie werd door het gebruik van volume bepaling en VDT een veel lager aantal testpositieven gevonden van 2.6% en na baseline screenen werd in 0.9% van de deelnemers de diagnose longkanker gesteld. Het merendeel van de longkanker casussen betrof longkanker in een vroeg stadium, na baseline screenen was 64% stadium I en, na de 2^{e} ronde screenen was dit 78%. Na de 1^{e} screenings ronde werd longkanker gedetecteerd met een sensitiviteit van 94.6% en de negatief voorspellende waarde was 99.9%.

Part II: Management van suspecte pulmonale nodules: beeldvormende studies en bronchoscopie.

In **hoofdstuk 4** wordt een 10-stappen benadering voor het management van pulmonale nodules kleiner dan 1 cm beschreven. **Hoofdstuk 5** gaat over de rol van stamcellen bij de ontwikkeling van longkanker en de consequenties van de veelvormigheid van longkanker voor longkanker screenen wordt besproken. Na doorverwijzing naar de longarts voor analyse van een verdachte nodule werd een standaard dosis CT met contrast (diagnostische CT) van de thorax en bovenbuik gemaakt. De waarde van een diagnostische CT om nodules te diagnosticeren is beperkt; dit komt doordat het grootste deel van de nodules aspecifiek zijn. We lieten zien dat in ongeveer 1/3 van de deelnemers die werd doorverwezen voor verder onderzoek een herhaal CT scan werd verricht. In de groep van deelnemers die een herhaal CT scan onderging was het aantal chirurgische ingrepen voor goedaardige afwijkingen lager. Een belangrijke reden om een vervolg scan te maken is het vervolgen van eventuele groei van de nodule. Er wordt daarom geadviseerd om tijdens de diagnostische CT die na doorverwijzing wordt gemaakt ook volume bepalingen te verrichten om eventuele groei betrouwbaar te kunnen vaststellen (**Hoofdstuk 6**).
Huidige richtlijnen raden aan om geen PET-scan te verrichten in het geval van nodules met een lage tot matige kans op maligniteit en in het geval van kleine nodules (8-10 mm). In **hoofdstuk 7** bespreken we de rol van FDG-PET tijdens de analyse van suspecte nodules door de longarts. In deelnemers met een conclusieve work-up die geen chirurgie ondergingen vanwege het vermoeden op een benigne nodule, had FDG-PET een negatief voorspellende waarde van 96%. In deelnemers die chirurgie ondergaan was de PET-scan van belang als stadiërings onderzoek.

Een bronchoscopie wordt niet standaard aangeraden vanwege de lage opbrengst: van alle gedecteerde longkankers was 4,5% CT-occult en alleen door bronchoscopie vastgesteld. Om wordt die reden zouden deelnemers van een longkanker screening studie niet standaard een bronchoscopie moeten ondergaan (**Hoofdstuk 8**).

Part III: Management van suspecte pulmonale nodules: chirurgische procedures

In **hoofdstuk 9** wordt ingegaan op complicaties die werden gezien na longchirurgie in de NELSON trial in deelnemers die geopereerd werden na analyse door de longarts. We toonden aan de complicaties procentueel gezien vergelijkbaar zijn met de getallen die worden gerapporteerd in artikelen over longchirurgie in niet-longkanker screening studies. Het kan een uitdaging zijn voor de chirurg om suspecte nodules te opereren, vooral wanneer deze klein van afmeting en/of diep in de long gelegen zijn. Aanbevelingen worden gedaan om ervan verzekerd te zijn dat de verdachte nodule adequaat wordt geresecteerd (**Hoofdstuk 10**).

De resultaten van een Amerikaanse studie lieten zien dat longkanker screenen een veelbelovende modaliteit is om een longkanker mortaliteit reductie te bewerkstelligen. Alvorens longkanker screenen ingevoerd kan worden in Nederland dienen de mortaliteit resultaten van de NELSON afgewacht te worden. Tijdens een analyse door de longarts zijn beeldvormende studies in de vorm van CT-thorax en FDG-PET in het bijzonder van belang om een eerste schifting te maken tussen deelnemers met meest waarschijnlijk een benigne nodule, en deelnemers die mogelijk chirurgie moeten ondergaan. Tijdens een diagnostische CT-thorax na doorverwijzing dienen volume metingen volgens het screenings protocol gemaakt te worden om eventuele nodule groei vast te kunnen stellen. Een bronchoscopie wordt niet standaard aanbevolen. Voor kleine nodules of dieper gelegen nodules wordt pre-operative markering aangeraden. In geval van twijfel na de OK kan een CT vervaardigt worden van de deelnemer of van het resectie preparaat, om er zeker van te zijn dat de nodule is verwijderd. Een belangrijk probleem van longkanker screenen blijft het relatief grote aantal onderzoeken voor, retrospectief gezien, benigne aandoeningen. Toekomstig onderzoek moet uitwijzen of het gebruikt van biomarkers kan leiden tot een lager aantal ingrepen voor goedaardige afwijkingen.
Er blijven nog veel vragen onbeantwoord. Er moet een doelpopulatie voor screenen worden gedefinieerd; vooralsnog is deze gedefinieerd op basis van rook historie en leeftijd. Er zijn verschillende criteria voor leeftijd en minimaal aantal pack-years. Het is de vraag of er verschillende criteria voor pack-years voor mannen en vrouwen moeten gelden. Nader onderzoek is nodig om te bepalen wat het ideale screenings interval is, gebaseerd op nodule volume en volume verdubbelingtijd. Momenteel worden er binnen de NELSON modellering studies verricht om de voorpellende waarde van nodule groei en afmeting voor de ontwikkeling van longkanker te bepalen. Voorts wordt er onderzoek verricht naar de rol van biomarkers bepaald uit bloed van deelnemers van de NELSON studie. Een gevalideerd beslismodel dat uitslagen van beeldvormende onderzoeken en patiëntgebonden risicofactoren implementeert zou de analyse van verdachte nodules door de longarts kunnen vergemakkelijken.

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About the author

The author was born on February 20th, 1979 in Middelburg, the Netherlands. She completed secondary school (VWO) in 2007 at "Sint Willibrord College" in Goes and subsequently started with medical school at the University of Utrecht. During her medical studies she did several internships abroad: Gynaecology in 's Lands Hospital, Paramaribo, Suriname (2002) and, Ear Nose & Throat (ENT) in the Massachusetts Eye and Ear Infirmary, Boston, USA (2003). In 2003 she obtained her medical degree and started as a resident internal medicine in the Groene Hart Hospital, Gouda. In 2004 she worked as a surgical resident in the Gelderse Vallei Hospital, Ede. In 2005 she started as a resident internal medicine as part of her clinical training in pulmonology in the Groene Hart Hospital, Gouda. In 2007 she started the PhD project which resulted in this thesis at the Erasmus MC, under supervision of Dr. R.J. van Klaveren, Prof. dr. H.C. Hoogsteden and, Prof. dr. H.J. de Koning. This research was combined with clinical training in pulmonology at Erasmus MC. During her residency, she completed a rotation tuberculosis at the pulmonary department at Groote Schuur Hospital in Cape Town, South Africa. In January 2010 she paused her clinical training for one year and worked full-time as a researcher. In December 2011 she finalized her specialization in pulmonology and, in January 2012 she started working as a pulmonologist in the Maasstad Hospital in Rotterdam.

De auteur van dit proefschrift is geboren op 20 februari 1979 te Middelburg in Nederland. Na het doorlopen van het VWO op het sint Willibrord College in Goes begon zij aan de studie geneeskunde aan de Universiteit van Utrecht. Het co-schap gynaecologie werd in 's Lands Hospitaal, Paramaribo, Suriname gelopen (2002) en het co-schap Keel- Neus- en Oorheelkunde (KNO) in Massachusetts Eye and Ear Infirmary, Boston, USA (2003). In 2003 behaalde zij haar artsenbul en begon als arts assistent niet in opleiding (ANIOS) interne geneeskunde in het Groene Hart Ziekenhuis in Gouda. In 2004 werkte zij als ANIOS chirurgie in Ziekenhuis de Gelderse Vallei te Ede. In 2005 begon ze als arts-assistent in opleiding (AIOS) aan de vooropleiding interne geneeskunde in het Groene Hart Ziekenhuis. In 2007 begon zij met promotie onderzoek, wat tot dit proefschrift geleid heeft, onder begeleiding van Dr. R.J. van Klaveren, Prof. dr. H.C. Hoogsteden en Prof. dr. H.J. de Koning. Dit onderzoek werd gecombineerd met de opleiding tot longarts. Tijdens haar opleiding volgde ze een stage tuberculose bij de afdeling longziekten in het Groote Schuur Ziekenhuis in Kaapstad, Zuid-Afrika. In 2010 onderbrak zij haar opleiding om een jaar voltijds onderzoek te doen. In december 2011 rondde zij haar opleiding tot longarts af en sinds januari 2012 is zij werkzaam als longarts in het Maasstad Ziekenhuis te Rotterdam.

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Van ‘t Westeinde SC, Sanders CJ, van Weelden H. Photodynamic therapy in a patient with Darier's disease. J Eur Acad Dermatol Venereol. 2006 Aug;20(7):870-2

PhD Portfolio

Summary of PhD training		
Name of PhD student:	Susan van 't Westeinde	
Erasmus MC Department:	Pulmonology/Public Health	
PhD period:	2007-2012	
Promotors:	Prof. dr. H.C. Hoogsteden	
	Prof. dr. H.J. de Koning	
Courses	**Year**	**Workload (hours)**
Cursus Stralingshygiëne voor medisch specialisten 4A/M	2007	16 hours
Intensive Tropical Medical Course Blantyre, Malawi	2007	20 hours
1st UCT-UCLA Symposium Exercise Testing, Methods and Interpretation Cape Town, South Africa	2008	16 hours
Winter ILD School Davos, Switzerland	2009	17 hours
Presentations		
World Conference on Lung Cancer *Invasive procedures and the role of FDG-PET in the NELSON trial* Poster San Francisco, United States	2009	20 hours
NELSON Symposium *The role of FDG-PET scan in the NELSON lung cancer screening trial* Oral presentation Utrecht, the Netherlands	2009	40 hours
International Conference on CT Screening for Lung Cancer *Complications following surgical procedures in the NELSON lung cancer screening trial* Oral presentation Copenhagen, Denmark	2010	40 hours
American Thoracic Society International Conference *Complications following lung surgery in the NELSON lung cancer screening trial* Poster New Orleans, United States	2010	20 hours
(Inter)national conferences		
World Conference on Lung Cancer San Francisco, United States	2009	32 hours
Critical Care and Thoracic Society Conference	2008	16 hours

Cape Town, South Africa		
International Conference on CT Screening for Lung Cancer Copenhagen, Denmark	2010	16 hours
NELSON Symposium Utrecht, the Netherlands	2009	8 hours
American Thoracic Society International Conference New Orleans, United States	2010	32 hours
World Conference on Lung Cancer Amsterdam, the Netherlands	2011	32 hours
Membership		
European Respiratory Society		
Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose		
The International Association for the Study of Lung cancer