CT-morphological characteristics of screen-detected lung cancer: predictors for histopathological diagnosis?

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Summary
This study, part of the Dutch-Belgian lung cancer screening trial (NELSON), aimed to identify CT-morphological features capable of discriminating between histopathological subtypes of lung cancer.
To achieve this, a retrospective analysis of 197 solid lung cancers detected by low-dose CT screening in 192 NELSON participants was performed. Morphological CT features studied were nodule shape, margin, location and vessel attachment. Tumors were divided into four groups based on histopathology: adenocarcinoma, squamous cell carcinoma, large cell carcinoma and neuro-endocrine cancers.
The majority of all types of cancer had a spherical shape. Margins were most often lobulated (39.3-45.9%) and spiculated (22.2-35.7%) without significant difference between histopathology groups. Most nodules (63.5%) were located in the upper lobes, adenocarcinoma significantly more often (71%) than other cancers.
The results of this study suggest that location in the upper versus lower lobes is the only morphological feature potentially useful for differentiating between types of lung cancer in malignant nodules detected in CT lung cancer screening.

Samenvatting
Dit onderzoek, dat deel uitmaakt van het Nederlands-Leuvens Longkanker Screenings onderzoek (NELSON), had als doel het identificeren van CT-morphologische kenmerken van longkankers, die gebruikt kunnen worden om kankers op basis van CT beeld van elkaar te onderscheiden.
Om dit te bereiken is een retrospectieve analyse uitgevoerd van 197 solide longkankers die door middel van low-dose CT screening in 192 NELSON-deelnemers zijn gevonden. De morfologische kenmerken die zijn bestudeerd zijn vorm, randen, locatie en hechting aan vaten. De kankers werden voor dit onderzoek onderverdeeld in vier groepen: Adenocarcinoom, plaveiselcelcarcinoom, grootcellig carcinoom en neuro-endocriene kankers.
Het merendeel van alle groepen kanker was rond van vorm. De meeste kankers hadden gelobde (39.3-45.9%) of sprietverige (22.2-35.7%) randen, zonder significant verschil in frequentie tussen de typen kankers. De meeste nodules (63.5%) werden in de bovenste longkwabben gevonden, adenocarcinoom met 71% significant vaker dan de andere typen kanker.
De resultaten van het onderzoek suggereren dat de longkwab waar in een nodule zich bevindt het enige morfologische kenmerk is dat mogelijk bruikbaar zou zijn om onderscheid te maken tussen verschillende types longkanker op basis van CT-beelden.
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I: Introduction

Lung cancer and smoking

Lung cancer is the leading cause of cancer-related death in males, and the second in females. In 2008, 1.6 million new lung cancer cases were detected worldwide, and 1.4 million people died from lung cancer (1). In 2012, the average 5-year survival rate of lung cancer patients in the Netherlands was 13% (2).

As is well-known, smoking plays a major role in the development of lung cancer. About 85-90% of lung cancer patients are either smokers or former smokers. Especially small-cell lung carcinoma is closely related to smoking habits; its incidence follows the smoking trends in the population with a 20-year delay (3). In the Netherlands, at present, 26.2% of men smoke, compared to 20.5% of women (4). Although these percentages have decreased in the past 10 years (in 2003 the percentages were 32% and 25%, respectively), they are still high. Compared to the rest of the world, especially the percentage of female smokers is high (5).

Undeniably, the best way to lower the incidence of lung cancer is primary prevention in the form of discouraging smoking and stimulating smoking cessation. Anti-smoking measures and several methods to stimulate and assist smoking cessation have proven to be somewhat successful. However, even with these measures, the number of smoking-related deaths remains high. Ex-smokers, as well as current smokers, are still at an increased risk of developing lung cancer (6). In fact, approximately half of the patients diagnosed with lung cancer are former smokers. Primary prevention alone is apparently not effective enough to oust lung cancer as the leading cause of cancer-related death. To decrease the lung cancer mortality rate, it is essential to detect lung cancer at an earlier stage, when curative measures are still an option.

Presently only 20% of lung cancer cases is considered operable at the time of diagnosis (7). In small cell lung carcinoma, 80% of the cases are not only inoperable but altogether incurable at the time of diagnosis (3). This is mainly caused by the fact that lung cancer is often asymptomatic during the earlier stages of disease. In as many as 40-50% of the cases where lung cancer is diagnosed in an early stage (I or II) the patient is asymptomatic (8,9). By the time symptoms emerge, the lung cancer is often at an advanced stage, and is quite likely to have either invaded local tissues or metastasized to distant locations. Regional or distant metastatic spread is found in 70-80% of lung cancer cases at initial diagnosis (10), making curative treatment impossible. As stated earlier, the overall 5-year survival rate for lung cancer is 13%, whereas the 5-year survival for stage I lung cancer in non-screening setting – if treated - is 45-65% (2). Stage I lung cancers detected through CT-screening have even shown 10-year survival rates of up to 92% in case of surgical treatment (11).

Screening modalities

Secondary prevention in the form of lung cancer screening has not been universally implemented yet, as - until recent years - screening trials did not seem to improve the patient’s outcome. Some early screening studies using chest X-ray and sputum cytology showed improved survival in the screened groups. However, no improvement in terms of reduced overall lung cancer mortality was found (12-14). Lung cancer screening by using multidetector low-dose computer tomography (MDCT) seems more promising. This type of screening focuses on the detection of solitary pulmonary nodules. A solitary pulmonary nodule is defined as an approximately round or oval parenchymal lesion
smaller than three centimeter, not associated with lymphadenopathy, atelectasis, pneumonia or pleural effusion (15-18).

In lung cancer screening, sensitive lung nodule detection is of great importance. To improve the accuracy of nodule detection, several methods have been tried. A previously used method was double reading, in which two radiologists read a scan independently. This is not a widely used practice, as it is time-consuming and the benefits of a second reader are limited (19,20). A recent development is computer-aided detection (CAD) which utilizes software to increases the rate of nodule detection. Initially, the use of CAD caused a dramatic increase in false-positives compared to double reading. However, using CAD as assistant reader in addition to visual detection by a radiologist as well as using a nodule volume cut-off point (nodules < 50mm³ are ignored) reduces the amount of false-positives to the point where CAD is more effective than double reading (19,20).

**Screening trials**

In 2011, the world’s largest randomized CT screening trial, the National Lung Screening Trial (NLST), presented its results. This study showed a 20% lung cancer specific mortality reduction in patients screened with MDCT compared to patients screened with chest X-ray, as well as a 7% overall mortality reduction after three annual screening rounds and six years of follow-up (21). Aside from the mortality reduction, 61% of the tumors detected by screening were diagnosed as stage I tumors. To accomplish this, 26,722 high-risk subjects underwent annual MDCT screening for 3 years. Positive screening results were defined as any non-calcified pulmonary nodule measuring at least 4 mm in its maximal transversal diameter. In the three screening rounds, 39.1% of the individuals had at least one positive result.

Critics of lung cancer screening have a different opinion on the increased amount of lung cancers found at an early stage in screening, as compared to the general population. Their hypothesis is that these early stage tumors are not potentially aggressive tumors caught early, but rather a case of overdiagnosis bias (22,23). They pose that these tumors may very well be indolent; tumors which will not progress to cause symptoms or kill the patient during normal anticipated life-span, thus making the chance of discovery under normal circumstances highly unlikely. Since these cancers would, in theory, not progress, treatment wouldn’t prevent illness or death. Instead, the patient would be subjected to the risks (and costs) of diagnostic and therapeutic interventions.

These skeptical studies mention overdiagnosis rates of 25-30% (22,23). This view is widely disputed (24). For example, if left untreated, the majority - if not all - of patients with screen-detected stage I lung cancer will die within five years (11,25,26). A recent study, which used a comparative model with data from five recent CT-screening studies to extrapolate the most efficient screening method, showed that with proper guidelines and patient adherence, overdiagnosis would range somewhere between 1.4% and 8.3% (24,27).

A number of European randomized lung cancer CT screening trials are currently ongoing. The collective goal of these trials is to confirm the 20% reduction in lung cancer mortality found in the NLST trial, within a reasonable period of time. These European trials, collectively known as EUCT (28), include the Danish Lung Cancer Screening Trial (DLCST) (29), Multi-centric Italian Lung Detection Trial (MILD) (30), Italian Lung Cancer Computer Tomography Screening Trial (ITALUNG) (31), the Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Assays.
(DANTE) (32), the German Lung Cancer Screening Intervention Study (LUSI) (10), the United Kingdom Lung Cancer Screening Trial (UKLS) (33) and finally the Dutch–Belgian lung cancer screening trial (NELSON) (34,35).

All EUCT trials feature a CT-screening arm (in which low-dose MDCT is used) and a non-screening arm, between which participants are randomized. All participants are heavy smokers, either current or former (defined as ≤ 10 years of abstinence), with an average number of pack years ranging from 36 to 47. The trials differ in number and frequency of screening rounds (Table 1).

Although all of these trials use LD-MDCT, the trials differ in methods of image analysis. NELSON, LUSI and UKLS are the only trials that use volumetric analysis for classification of initial appearance and growth of nodules. The other EUCT trials measure the nodule diameter, but volumetric analysis is not performed.

Some of the EUCT trials have concluded their data collection, but are awaiting long term results in terms of the aforementioned mortality reduction. The DANTE and LUSI trial continually collect mortality data. The first mortality data from the NELSON trial will become available in 2015, whereas the data from UKLS will not be available until at least 2018.

Table 1: EUCT trial data

<table>
<thead>
<tr>
<th></th>
<th>NELSON (34,35)</th>
<th>DLCST (29)</th>
<th>LUSI (10)</th>
<th>DANTE (32)</th>
<th>ITALUNG (31)</th>
<th>MILD (30)</th>
<th>UKLS (33)</th>
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<tr>
<td>Screen rounds</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>10 or 5</td>
<td>1</td>
</tr>
<tr>
<td>Screen interval</td>
<td>1.2 and 2.5 yrs</td>
<td>1 year</td>
<td>1 year</td>
<td>1 year</td>
<td>1 year</td>
<td>Randomized 1 or 2</td>
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<tr>
<td>Screen arm(n)</td>
<td>7915</td>
<td>2052</td>
<td>2029</td>
<td>1276</td>
<td>1613</td>
<td>1190/1186 b</td>
<td>4000 c</td>
</tr>
<tr>
<td>Control arm (n)</td>
<td>7907</td>
<td>2052</td>
<td>2023</td>
<td>1196</td>
<td>1593</td>
<td>1723</td>
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<tr>
<td>Age at inclusion(yrs)</td>
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<td>50-70</td>
<td>50-69</td>
<td>60-74</td>
<td>55-69</td>
<td>&gt; 49</td>
<td>50-75</td>
</tr>
<tr>
<td>Mean age at randomization (yrs ± SD)</td>
<td>59 (6)</td>
<td>57 (5)</td>
<td>58 (5)</td>
<td>65 (5)</td>
<td>61 (4)</td>
<td>59 (6)</td>
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<td>Min. pack years</td>
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<td>20</td>
<td>25/30 a</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<td>Mean pack years (±SD)</td>
<td>42 (19)</td>
<td>36 (13)</td>
<td>36 (18)</td>
<td>47 (25)</td>
<td>43 (18)</td>
<td>43 (15)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

a To be included as a current or former smoker, participant had to have smoked more than 15 cigarettes a day for over 25 years, or 10 cigarettes a day for 30 years.

b The MILD trial randomized 1186 participants to the biennial CT group and 1190 to the annual group.

c The UKLS trial is currently in a pilot phase with 4000 participants. If the pilot design proves feasible, another 28000 participants will be added to the screen arm, making a total of 32000 participants.

NELSON Trial

The NELSON trial is a multicenter Dutch-Belgian trial and is – to this day - the largest population-based randomized lung cancer CT-screening trial in Europe and the second largest in the world. It differs from the NLST trial by screening interval, a more stringent referral policy for nodules, and a control arm wherein individuals receive no screening, as opposed to NLST’s X-ray arm. According to the NELSON nodule management protocol, nodules were analyzed using volumetry software, whereas NLST used the largest measured diameter in 2D as size criterion.
Participants
Participants of the NELSON study were current or former smokers with a smoking history of >15 cigarettes/day for >25 years or >10 cigarettes/day for >30 years. At the time of recruitment they were between 50 and 75 years of age. Recruitment took place through mail via population registries. Excluded were applicants with moderate or bad self-reported health who were unable to climb two flights of stairs. Applicants with a body weight >140 kg were excluded as well, because participants were required to have enough cardiopulmonary reserve to undergo surgery if necessary. Applicants that already underwent pneumonectomy and applicants with a history of breast cancer, melanoma or renal cancer were excluded as well, to avoid diagnostic problems (such as distinguishing between primary and metastatic disease). Applicants with a history of other cancers were eligible only if curatively treated at least five years ago, without signs of recurrence at the time of inclusion (34).

Referral and work-up
The 15,822 participants included in the NELSON trial were randomized 1:1 to screening (n=7,915) and no screening (n=7,907). The screening arm of the trial received MDCT screening at baseline (first round), one year later (second round), three years later (third round) and 5.5 years later (fourth round). At the time of the baseline scan, the screening test result could be either negative (invitation for the next screening round), indeterminate (invitation for a repeat scan) or positive (referral), based on the potential nodule’s volume. Any nodule with a volume greater than 500 mm$^3$ lacking a benign pattern of calcification was instantly screened positive and the participant was referred to a pulmonologist for diagnostic work-up (35). In case of consecutive CT scans, nodules were matched to nodules detected on previous scans in order to determine whether the nodule was new or previously detected. In case of a previously detected nodule, this matching made it possible to detect changes in volume and estimate the volume doubling time (VDT). The volume doubling time is the time in days it takes a nodule to double in volume. Nodule matching was either done automatically by the NELSON management system (NMS), a web-based application for storing and managing all NELSON trial data, or manually. Based on the fact if a nodule was new or previously detected, the nodule was assigned a nodule category or a growth category. The screen result was based on the largest or fastest growing nodule detected in a screened participant. In case of referral, any histological specimens acquired were reassessed by NELSON’s chief pathologist.

Equipment and analysis
To obtain the CT-images, 16-detector multidetector CT (MDCT) scanners were used in a low-dose setting without intravenous contrast. All scans were realized in about 12 s in spiral mode with 16mmx0.75 mm collimation and 15mm table feed per rotation (pitch = 1.5), in a cranial-caudal scan direction. Depending on the body weight (<50, 50-80 and >80 kg), the kVp settings were 80-90, 120 and 140 kVp respectively. To achieve a CTDIvol of 0.8, 1.6 and 3.2 mGy the mAs settings were adjusted accordingly dependent on the machine used. To minimize breathing artefacts, scans were performed in inspiration.

During the first rounds, the CT images were read twice independently. First readings were done by radiologists with a varying degree of experience in reading thoracic CT scans, ranging from zero to twenty years, second readings were done by radiologists with six years of experience(36). In case of a discrepancy between the first and second reader,
a third radiologist with more than 15 years of experience in lung CT made the final decision (37). Lung windows were assessed at a width of 1500 and a level of -650 Hounsfield units. The nodule volume was analyzed with software for semi-automated volume measurement (Lungcare, Siemens Healthcare, Erlangen, Germany). The same software was used for calculating the mean CT density of the nodule. This software was used in addition to double reading to aid the readers in measuring and characterizing nodules. During later rounds double reading was replaced by a single reader combined with CAD, as this was proven to be more accurate. (19,20)

**Purpose**

The goal of the NELSON trial is to show a 25% reduction in lung cancer mortality after 10 years of follow-up. In substudies, the screening protocol as it has been used in the trial is being analyzed retrospectively, and patient data is used to look for more efficient and precise screening methods. The final mortality results are pending, but evaluation of the first three screening rounds of the NELSON study showed that the NELSON approach has resulted in a more favorable cancer stage distribution at diagnosis, indicating an effective strategy so far (38).

**Nodule features**

As mentioned before, the rate of false positives in lung cancer CT screening is high. For example, in the NLST trial, only 3.6% of the positive CT scans with indeterminate or suspicious nodules represented lung cancer, whereas the percentage of false positives was 26.6% (39). Note that this percentage false positives is a lot higher than it was in the NELSON trial (1.2%) (40). The NLST team did not use volumetric analysis but instead opted for a 2D measurement-based nodule management protocol, which could explain the difference in this percentage (21,39).

While MDCT has increased the amount of detected nodules, it is of major importance to develop better strategies for differentiation between benign and malignant nodules. Because the majority (up to 99%) of the CT-detected pulmonary nodules is benign, a good discriminative method can help avoid unnecessary surgery and invasive diagnostic procedures, thus reducing possible harm, patient anxiety and health care costs.

The evaluation of pulmonary nodules revolves around assessing the probability of cancer. Nodule size and growth rate are the most important parameters to estimate the risk of malignancy. So far the NELSON trial has extensively studied assessment by size and growth rate. In the past, suspicious nodules detected in the NELSON study have been evaluated with regards to shape, margin, density and the potential of these characteristics to discriminate between malignant and benign nodules. The results were limited, but this analysis was performed before the trial was concluded and thus had a smaller sample size of only 16 respectively 59 malignant nodules (37,41).

The NELSON team was not alone in this endeavor: research on CT morphology in lung cancer screening is mostly focused on features seen on CT that are relevant in differentiating between benign and malignant nodules. A list of features often associated with malignant nodules is stated below, as the current study revolved around these features. As this particular study was exclusively about the malignant nodules found during the trial, features associated with benignity have been left out of this summary.

**Size and growth**

The risk of malignancy is strongly related to nodule size, which is measured by its maximal transversal diameter or by semi-automated volume measurements. Risk
assessment as based on nodule size can be seen in Table 2, although risk estimations for nodules greater than 20 mm vary from 20% to 80% (16,42-47). A 2D image has its drawbacks, as it does not allow one to fully appreciate the dimensions of a nodule, thus increasing the risk of misjudging the size. Ideally, 3D measurements are acquired to estimate nodule volume instead of 2D size. This can be challenging in non-solid lesions and lesions with inappropriate segmentation, such as pleural-based lesions (48). Nodule volume greater than 500 mm³ is considered suspicious for malignancy. Apart from nodule size, growth rate has proven to be a good predictor of malignancy. This is usually measured in terms of volume-doubling time (VDT). The VDT is calculated with an algorithm that uses the change in a nodule’s size between the first CT-scan and the most recent follow-up scan to calculate how many days it would take the tumor to double in size, based on its recent growth pattern. A VDT <30 days is most likely infectious. Nodules with <30<VDT<400 days are most likely malignant. A VDT >400 days is typically associated with benign growth. The absence of growth in a lesion over a two year period of time is generally accepted as a sign of benignity. However, some malignant lesions can grow very slowly with a VDT of over 400 days (15,42).

### Attenuation

Noncalcified, nonfat attenuation pulmonary nodules may be classified into solid, non-solid and partially solid attenuation. Solid nodules completely obscure the lung parenchyma within it. Non-solid nodules have a focal area of increased lung attenuation through which the lung parenchymal architecture is visible and undisturbed. Part solid nodules are nodules containing components of both (49,50). The risk of malignancy is said to be highest in part-solid nodules, lowest in solid nodules and intermediate in non-solid nodules (17,42,51-55). Nodule density cannot be used to discriminate between benign and malignant solid indeterminate pulmonary nodules, but a perceived increase in density is suggestive enough to merit shorter follow-up (17,37).

### Location and attachment

The majority of primary tumors is found in the right upper lobe of the lung, followed by the left upper lobe. This is not a coincidence: when inhaling, the first airflow is most powerful towards the right upper lobe bronchus. As a result, the depositions of particles in tobacco smoke, and their carcinogenic effects, are the largest in the right upper lobe (56). Nodules in the lower lobes are more often associated with inflammatory processes and metastases (15,38,47,51,52). Perifissural nodules have not shown malignant potential so far (47,57,58). Vessel attachment is defined as a pulmonary vessel leading to the pulmonary nodule. Vessel attachment is seen significantly more, but not exclusively, in malignant pulmonary nodules (59). Non-small cell lung cancers, especially adenocarcinomas, are more often found peripherally or attached to the pleura than in the central and middle two thirds of the lung (38). Small cell lung cancer and carcinoid are both predominantly centrally located (60-63).

### Shape and margins

Categories vary between studies, and the distinction between shape and margin is not always made. As the classification in these categories is based on subjective observation,
this can make comparison of various studies difficult. Indeed, the lack of standardized terminology has hindered firm conclusions on the predictive value of margins (18). For this article the most commonly used categories are described. The consensus in current literature is that purely by themselves, margin characteristics are not specific enough to rely on for differentiation between benign and malignant nature. However, combined with other findings such as size and attenuation, a prediction can be made (16,18,64). The margin of a tumor is thought to be related to the degree of aggressive growth, wherein non-smooth margins are caused by an uneven, malignant growth pattern (65). Nodules with irregular, lobulated or spiculated borders are associated with a progressively higher probability of malignancy than those with a smooth border (16-18,47,54,59,66,67). A spiculated margin is defined as strands extending from the tumor margin into the lung parenchyma without reaching the pleural surface. A lobulated margin is defined as an irregular undulation of the nodule margin. CT images of these different types of margins can be found in the addendum to this paper. A spherical shape is relatively often benign in solid lesions, whereas a non-spherical shape is more often associated with malignancy (68). When a spherical shape is encountered in subsolid lesions the probability of malignancy increases (67).

**Calcification.** Although calcification itself is not a sign of malignancy, certain patterns of calcification are highly suggestive for malignancy. Malignant patterns of calcification tend to be punctate, diffuse, amorphous and eccentric (15,16,59,64).

**Pleural retraction.**
Pleural retraction is seen significantly more, but not exclusively, in malignant pulmonary nodules (54,59).

**Bronchus sign or air bronchogram.**
Defined as a pattern of air-filled (and therefore low attenuation) bronchi against a background of an airless (and therefore opaque) lung. This pattern is seen significantly more, but not exclusively, in malignant pulmonary nodules, especially in adenocarcinomas (52,54,59,69).

**Cavitation.**
Cavitation is defined as an air-filled space within a nodule, visible as a low-attenuation area. It is most commonly seen in nodules >3cm (16). It is seen significantly more, but not exclusively, in necrotic malignant pulmonary nodules, such as squamous cell carcinomas (45). The wall thickness can be somewhat useful in aiding the discrimination between benign and malignant nodules, as malignant lesions with cavitations have thicker walls compared to benign ones. However, since there is considerable overlap, wall thickness alone cannot discriminate between the two (65).

**Morphology and histology**
Although the potential use of morphologic features on CT for distinguishing between benign and malignant nodules is extensively discussed in literature, little is said about distinguishing between different types of lung cancer. Some articles do discuss radiological features of specific types of cancer, but these articles often lack comparison with other types. Squamous cell carcinoma and large cell carcinoma are especially underrepresented on this subject. There have been many studies on CT features of adenocarcinoma useful in distinguishing between adenocarcinoma subtypes (70-74). Neuro-endocrine carcinoma has been studied quite a lot as well, but these articles focus more on distinguishing subtypes of neuro-endocrine cancers from each other as well
Different types of non-small cell lung cancers share many similarities: the majority is found in the periphery (47), as opposed to carcinoid and small cell lung carcinoma, which are usually found centrally (60,61,77). Carcinoid and small cell carcinoma, while both central cancers, can generally be distinguished from one another because carcinoid is often well-demarcated, while small cell lung carcinoma is often poorly demarcated and perihilar (61,63).

Two retrospective studies on screen-detected lung cancers both showed a generic malignant appearance, with no margins specific for any type of cancer (51)(78). Unfortunately neither article discusses the implications of its findings, merely describing the results. A recent retrospective study of 106 peripheral solid lung cancer nodules found in a clinical setting concluded that the only characteristic feature predicting histology (in this case adenocarcinoma) was the presence of an air bronchogram. Other morphologic features assessed (spiculation and lobulation) became more prominent and prevalent as the tumor increased in size but did not have a predictive value of their own (69).

It is hypothesized that screen-detected lung cancers differ from lung cancers found in a clinical setting in terms of morphology, histology and prognosis (51,69). Although there is plenty of literature on both CT morphology in the general population and in screen-detected cancers, there seems to be little literature comparing the two. Exploring the differences and similarities between screen-detected lung cancers first, and screen detected lung cancers versus lung cancers detected in a clinical setting second, could be useful in furthering the diagnostic approach to pulmonary nodules.

**Purpose**

The purpose of this study was to give insight in the radiological characteristics of screen detected lung cancers, including margins, shape and size, and investigate whether these characteristics can be linked to specific subtypes of lung cancer. Furthermore a comparison between the morphology of screen-detected cancers and cancers detected in the general population was made, to assess whether there are shared features that can be used to increase diagnostic accuracy.

**II: Materials and methods**

**Lung cancers**

- 259 lung cancers
- 246 lung cancers
- 224 lung cancers
- 197 lung cancers

16 cases excluded: missing data.
3 cases added: double tumors counted once.
22 cases excluded: no diagnosis or incidental discovery.
27 cases excluded: sublobar nodules.
Among the 7,915 participants randomized to the screening arm of the NELSON trial, a total of 259 lung cancers were diagnosed in 244 participants. Cases in which histological diagnosis could not be obtained were excluded from further analysis. This was caused mainly by biopsies that were unsuccessful, not performed, or had inconclusive results. Lung cancers that were incidentally discovered after a patient was referred because of another screen-detected nodule were excluded from further analysis, as these specific nodules were not screen-detected. Furthermore, as the predictive value of morphological features varies with nodule solidity, only solid nodules were included in the study. After applying these criteria a total of 197 lung cancers in 192 patients remained (Figure 1).

**Nodule features**

Morphological categories studied were nodule shape, margin, location, volume, and VDT. Only features described by the readers were included in this analysis, which means not all morphologic information described in the introduction has been used. Calcification is not a separate category, however, the pattern of calcification (benign vs non-benign) was used to decide whether a tumor screened positive or not. To facilitate comparison with other studies, margin definition was reduced to four subcategories: smooth, lobulated, spiculated and irregular. All features were tested for association with histopathological diagnosis. Shape was divided into spherical and non-spherical. In the cases where shape was not recorded in the database, it was calculated according to the following rule: if, at time of diagnosis, the maximal diameter was smaller than twice the minimal diameter, the nodule was considered spherical. If not, the nodule was considered non-spherical. Attachment was divided into vessel-attached and intraparenchymal. Location was determined both by lobe and distance to costal pleura. The distance to costal pleura was less than one-third of the total distance to hilum-costal pleura for peripheral nodules, more than two-thirds for central nodules and the intermediate nodules were—as the name implies—in the middle third part. Although some nodule features changed over time, for every characteristic the features last recorded, i.e. at the time of positive screening, were used for analysis.

**Nodule detection**

For each nodule it was determined whether detection was based on volume, volume-doubling time (VDT), visual (but not measurable) growth or suspicious morphology. This was determined as followed: A nodule screened positive at baseline was considered positive for baseline volume. As, at this point, nothing can be said about its growth rate or behavior, these baseline cancers were not considered as standard volume positive cancers. Any tumor positive at first detection (but not baseline) was automatically categorized as detected by volume (as VDT calculation is based on repeat measurements). A nodule detected during follow-up was interpreted as detected by VDT, unless specified otherwise, for instance when a nodule was new in a follow-up round, or when VDT was below threshold and volume above. When a nodule was positive for VDT and volume both (VDT <400 days, volume >500 mm³), it was considered to be detected based on growth, so on positive VDT. Nodules that were initially missed in previous scans but were retrospectively detected based on increase in size were also classified as screen-detected due to positive VDT. Nodules classified as GROWCAT C (the highest growth category, reserved for nodules...
with a VDT<400 days or a partially-solid nodule that had become more solid since the last scan) without specification of nodule volume were considered detected by VDT. New nodules manually measured and included based on growth were classified as screen detected by growth. Nodules referred because of a suspicious appearance, although not positive for volume or VDT, were classified as screen detected based on suspicious appearance. In ten cases it was not clear what prompted the readers to screen a nodule as positive, these cases were classified as ‘other’.

Pathology

Some types of lung cancer were diagnosed only once or twice in this study. To increase the power of the analysis, several histologically related subtypes of lung cancer were pooled together into four larger groups: Adenocarcinoma, squamous cell carcinoma, neuro-endocrine carcinoma and large cell carcinoma. Bronchioloalveolar carcinoma was pooled with adenocarcinoma. The large cell group was formed by large cell carcinoma, mixed non-small cell lung carcinoma/ small cell lung carcinoma, non-small cell lung carcinoma (not otherwise specified), and adenosquamous carcinoma. The neuro-endocrine cancer group consisted of large cell neuro-endocrine carcinoma, carcinoid and small-cell lung cancer. Neuro-endocrine cancers of the lung share common morphological, immunohistochemical and molecular characteristics. They are considered to be part of a continuum, with carcinoid at the lowest grade with the least aggressive behavior, and small-cell lung carcinoma the highest grade with the most aggressive behavior (63,75,76,79).

Statistics

The data was analyzed using SPSS 20 software. Normality of continuous variables was assessed by means of the Shapiro-Wilk test. In samples with N>30, normality was assumed according to the Central Limit Theorem. Before comparing means, equal variance was tested with Levene’s test. Parametric data was analyzed with the student’s t-test or ANOVA with a post-hoc Tukey test, non-parametric data was analyzed with the Mann-Whitney U or Kruskal-Wallis test.

A Chi-square test of independence was performed on all nominal data. If sample sizes were too small to allow Chi-square tests, Fischer’s exact was used, as this test allows lower counts per cell.

Ethics

The NELSON trial was approved by the Dutch Ministry of Health and the Ethics Committees of all participating centers. All participants have given written informed consent for participation and the evaluation of personal data from hospital charts.

III: Results

Participants

A total of 197 lung cancers in 192 participants could be included (see Table 3). The mean age of the participants was 61.34 years (SD: 6.20) and 16.7% were female. Study participants had a median 43.7 pack-years and 60.4% were current smokers at the time of inclusion. Stage distribution differed between genders, with women having a more
favorable cancer stage distribution than men (p=0.045).

<table>
<thead>
<tr>
<th>Gender (n of cases)</th>
<th>Mean age (±SD)</th>
<th>Median pack years (IQR)</th>
<th>Current smokers</th>
<th>Stage I-II cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (160)</td>
<td>61.3 (5.97)</td>
<td>49.5 (26.0)</td>
<td>97 (60.6%)</td>
<td>108 (72.0%)</td>
</tr>
<tr>
<td>Female (32)</td>
<td>60.5 (6.98)</td>
<td>35.8 (18.3)</td>
<td>19 (59.4%)</td>
<td>26 (89.7%)</td>
</tr>
</tbody>
</table>

**Table 3: Age and gender of participants**

Of the 197 solid nodules, the distribution of histological diagnosis, pack years, and cancer stage is shown in Table 3. There was no statistically significant difference in median pack years found between the different histological types of cancer, but there was a statistically significant difference found in median pack years between stage I-II cancers (M=43.7, IQR 23) and stage III-IV cancers (M=53.2, IQR 22.3, p=0.049). Age and cancer stage were not associated (p=0.38).

Fourteen cases were missing data on pathological staging. Histological subtype and stage distribution were associated (p<0.001). Adenocarcinoma and squamous cell carcinoma had a relatively favorable stage distribution, with 84.3% respectively 78.4% of the cancers being diagnosed at stage I or II. Large cell carcinoma and neuro-endocrine carcinoma had a less favorable distribution, with 50% respectively 42.9% stage I-II cancers.

**Margin**

Data on margin characteristics was lacking in two cases. The most obvious result was the high frequency of lobulated and spiculated lung cancers compared to the other margin characteristics (Table 4). The presence of lobulated and spiculated nodules is high in all four categories. Neuro-endocrine cancers are a slight exception, with a slightly higher percentage of smooth than spiculated nodules. However, no statistically significant association between histological diagnosis and nodule margins (p=0.42) or margin characteristics and cancer stage (p=0.342) was found.

**Shape**

Data on nodule shape was lacking in eleven cases. The majority of cancers was spherical (Table 4), but squamous cell carcinoma had a higher percentage of non-spherical nodules than the other groups. Shape and histological diagnosis were statistically significantly associated (p=0.011).

**Location**

Most cancers (64.0%) were localized in the right lung with a large proportion (42.1%) in the right upper lobe. As analyzing data for each separate lobe would yield too little data, two separate analyses were performed. Location in the left and right upper lobe, compared to the middle and lower lobes, was statistically significantly associated with histological diagnosis (p=0.04). Adenocarcinoma appeared more often in the upper lobes than squamous cell carcinoma (p=0.005). Comparison of the right and left lung did not yield a significant association between location and histological diagnosis (p=0.53).

**Distance to pleura**

For this analysis tumors were grouped as peripheral and pleural on the one hand, and middle and central on the other (Table 4). The results showed no statistically significant association with histological diagnosis (p=0.48). All cancer types were predominantly
Peripheral.

Attachment
For the attachment category, four nodules described as atypical were not included in the analysis. The majority of tumors was intraparenchymal, with the exception of squamous cell carcinoma, which was slightly more often vessel attached than not. No statistically significant association between nodule attachment and histological diagnosis (p=0.074) was found.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adenocarcinoma</th>
<th>Squamous cell carcinoma</th>
<th>Large cell carcinoma</th>
<th>Neuroendocrine cancer</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cancers</td>
<td>114</td>
<td>37</td>
<td>28</td>
<td>18</td>
<td>0.42</td>
</tr>
<tr>
<td>Margin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smooth</td>
<td>10 (8.9%)</td>
<td>6 (16.2%)</td>
<td>6 (21.4%)</td>
<td>5 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Lobulated</td>
<td>51 (45.5%)</td>
<td>17 (45.9%)</td>
<td>11 (39.3%)</td>
<td>8 (44.4%)</td>
<td></td>
</tr>
<tr>
<td>Spiculated</td>
<td>38 (33.9%)</td>
<td>12 (32.4%)</td>
<td>10 (35.7%)</td>
<td>4 (22.2%)</td>
<td></td>
</tr>
<tr>
<td>Irregular</td>
<td>13 (11.6%)</td>
<td>2 (5.4%)</td>
<td>1 (3.6%)</td>
<td>1 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>Shape</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Spherical</td>
<td>101 (91.0%)</td>
<td>24 (70.6%)</td>
<td>23 (95.8%)</td>
<td>14 (82.4%)</td>
<td></td>
</tr>
<tr>
<td>Non-spherical</td>
<td>10 (9.0%)</td>
<td>10 (29.4%)</td>
<td>1 (4.2%)</td>
<td>3 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Upper lobes</td>
<td>81 (71.1%)</td>
<td>17 (45.9%)</td>
<td>16 (57.1%)</td>
<td>11 (61.1%)</td>
<td></td>
</tr>
<tr>
<td>Middle and lower</td>
<td>33 (28.9%)</td>
<td>20 (54.1%)</td>
<td>12 (42.9%)</td>
<td>7 (38.9%)</td>
<td></td>
</tr>
<tr>
<td>Distance to pleura</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>Peripheral and pleural</td>
<td>85 (74.6%)</td>
<td>23 (62.2%)</td>
<td>21 (75%)</td>
<td>12 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Middle and central</td>
<td>29 (25.4%)</td>
<td>14 (37.8%)</td>
<td>7 (25%)</td>
<td>6 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>Attachment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Vessel-attached</td>
<td>42 (38.2%)</td>
<td>19 (51.4%)</td>
<td>6 (21.4%)</td>
<td>5 (27.8%)</td>
<td></td>
</tr>
<tr>
<td>Intraparenchymal</td>
<td>68 (61.8%)</td>
<td>18 (48.6%)</td>
<td>22 (78.6%)</td>
<td>13 (72.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Nodule detection
Of the 197 tumors, 65 tumors were excluded from this part of analysis, since they were no incidence cancer (N=55), because of undisclosed reason for referral (N=7), or because of not fitting the criteria for positive referral, even though being screen-detected (N=3).

Detection method
Histology and detection method were statistically significantly associated (p=0.045). As shown in Table 5, the majority of adenocarcinomas and large cell carcinomas was detected by VDT, while the majority of neuro-endocrine cancers were detected based on volume. Squamous cell carcinomas were slightly more often detected by volume.

Volume doubling time
Of the 79 VDT-detected lung cancers, sixteen cancers had incomplete or no measurements recorded in the database, and therefore these were excluded from the next analysis. A statistically significant difference in VDT value between the four histological
subtypes was found (p=0.010). Adenocarcinoma had a higher mean VDT (mean = 211.1) than large cell carcinoma (mean = 96.83, p=0.033). Comparisons between the other groups showed no statistically significant differences.

**Volume**

Of the 50 cancers screened positive based on volume, fifteen had incomplete or no measurements recorded in the database, and therefore could not be included for further analysis on detection. The 35 remaining cancers showed no statistically significant difference in median volume across the four groups (p=0.88).

Of the 92 cancers not detected by volume, in sixteen cancers the semi-automated volumetry could not be performed, for instance because the nodule volume was too big for the measurement. As can be seen below, the median volume is drastically lower for the group of cancers not detected by volume, with the exception of neuro-endocrine cancers. The volume of neuro-endocrine cancers not detected by volume was roughly 75% of those that were volume-detected. Meanwhile, the other histological groups had a volume closer to 25% of the volume of volume detected tumors. The difference in volume was statistically significant for all histological groups (p<0.001 for adenocarcinoma; p=0.001 for squamous cell carcinoma; p=0.048 for large cell), except for neuro-endocrine cancers (p=0.27). There was no statistically significant association between tumor margins and tumor volume (p=0.57). Tumor margins were not statistically significantly associated with detection mechanism (p=0.72).

**Table 5: Detection method, volume and VDT of the histological subgroups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Adenocarcinoma</th>
<th>Squamous cell carcinoma</th>
<th>Large cell carcinoma</th>
<th>Neuro-endocrine cancer</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection mechanism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDT</td>
<td>50 (66.7%)</td>
<td>13 (46.4%)</td>
<td>13 (65.0%)</td>
<td>3 (25.0%)</td>
<td>0.045</td>
</tr>
<tr>
<td>Volume</td>
<td>21 (28.0%)</td>
<td>15 (53.6%)</td>
<td>6 (30.0%)</td>
<td>8 (66.7%)</td>
<td></td>
</tr>
<tr>
<td>Visual growth</td>
<td>2 (2.7%)</td>
<td>0</td>
<td>1 (5%)</td>
<td>1 (8.3%)</td>
<td></td>
</tr>
<tr>
<td>Suspect appearance</td>
<td>2 (2.7%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Median volume (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Detected by volume</td>
<td>850.7 (713)</td>
<td>1347 (1349)</td>
<td>1232 (2319)</td>
<td>1027 (2249)</td>
<td></td>
</tr>
<tr>
<td>Not detected by volume</td>
<td>344 (516)</td>
<td>362 (409)</td>
<td>312 (829)</td>
<td>842 (586)</td>
<td></td>
</tr>
<tr>
<td>Mean VDT (±SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.010</td>
</tr>
<tr>
<td>Detected by VDT</td>
<td>211.1 (±92.98)</td>
<td>149.2 (±109.1)</td>
<td>96.83 (±77.26)</td>
<td>104.7 (±50.92)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>344.6 (±361.1)</td>
<td>149.2 (±109.1)</td>
<td>173.9 (±160.9)</td>
<td>209.5 (±213.7)</td>
<td></td>
</tr>
</tbody>
</table>
IV: Discussion
This study suggests that, for malignant nodules detected in CT lung cancer screening, the only morphological features associated with histopathological diagnosis are shape and location in the upper versus lower lobes. The morphological features of the cancers found in this study were compared with those of lung cancers found in the general population. While different types of lung cancer can sometimes be distinguished from one another based on CT-morphological features, there are enough similarities to limit the usability of these features (47,60,61,77). No such distinctive features could be found for the nodules in this study, which mostly had a generic malignant appearance.

Nodule features
The distribution of histopathological diagnoses was according to current literature, in which adenocarcinoma often constitutes around 50% of the cancers found (21,51,78). The stage distribution per diagnosis found in the NELSON study was more favorable than those found in the NLST study, especially for neuro-endocrine cancers (39). Although the majority of neuro-endocrine cancers in this study was detected at an advanced stage, the percentage of advanced staged cancers of this type was still lower than is found in a clinical setting (3). The unfavorable cancer stage in which these tumors were discovered should serve as a reminder that lung cancer screening in its current form might not yet be viable for all types of lung cancer, especially the fast-growing cancers such as neuro-endocrine and large cell carcinoma (80).

The lack of difference in pack years between histological subtypes is not as expected. Since squamous cell and especially small cell lung carcinoma are associated with smoking, participants diagnosed with these types of cancer were expected to have a higher average number of pack years smoked than the other cancer types (81). The difference in pack years between early and late stage lung cancer is as expected, since more advanced cancer stage has been shown to be associated with longer duration of
smoking (82).
This study has not shown an association between nodule margin and histological subtype of cancer. The high prevalence of lobulated and spiculated margins is as expected, since this is a known feature of malignant tumors. The global distribution of margin characteristics mostly matches other studies on screen-detected lung cancers, in which no margin characteristic was found to be specific for one type of cancer, yet most cancers had a generic malignant appearance, which is to say the majority of the cancers in these studies had either lobulated or spiculated margins (51,78). As was discussed earlier, lobulation and spiculation have been found to become more pronounced as tumors increase in size (69). This could not be reproduced in this study, likely due to the relatively early stage of the cancers found. An association between nodule margins and cancer stage could not be found. One would have expected to see more spiculation and lobulation at higher stages, but the small number of cancers at a high stage could have contributed to a lack of result here.
The majority of nodules had a spherical shape, although squamous cell carcinoma had a lower percentage of spherical nodules than the other categories. Although the majority of subsolid spherical nodules are malignant, the same has not been shown for solid nodules (67). While there is a statistically significant association between shape and histology, this is attributable to the large difference between spherical and non-spherical nodules. Since all types of cancer were predominantly spherical, the clinical usability of this finding is limited in differentiating between types of cancer.
The high percentage of cancers located in the upper lobes (63.5%) was comparable to that of an earlier NELSON-study with all lung cancers from the first 3 screening rounds (64.1%) (38,56).
Analysis of the lung cancers found in the first three screening rounds of the NELSON trial showed lung cancers to be located predominantly in the periphery of the lungs. This was particularly true for adenocarcinomas, of which 82.2% was located in the periphery and/or attached to the pleura, compared to 17.8% in the middle or central one-third of the lungs. This differed significantly from the other types of lung cancers (38). In the current study the average percentage of peripheral and pleural cancers is comparable to the aforementioned study (71.6% now vs 72.2% then). However, the difference between groups is not as pronounced now. Although the majority of all cancers was located either peripherally or attached to the pleura, none of the cancers appeared here significantly more often than the others.
In this study the majority of neuro-endocrine carcinomas were located peripherally. However, in clinical settings, both small cell lung carcinoma and carcinoid tumors are predominantly centrally located (63). Large cell neuro-endocrine carcinoma is the exception, with the majority of tumors located in the periphery (75,76). An explanation for this location shift could be that centrally located tumors are more likely to cause symptoms due to central airway involvement, prompting diagnostic evaluation in a clinical setting. Peripheral neuro-endocrine tumors, if discovered, are usually found incidentally in an asymptomatic patient (62). The high percentage of peripheral neuro-endocrine cancers detected in this screening study could be partially explained by indolent tumors. In a 20-year long population-based study, 24% of typical carcinoids, 7% of atypical carcinoids and 5% of small cell lung cancers found were incidentally diagnosed on autopsy, not contributing to the cause of death (77). Typical carcinoids,
with their relatively low malignant potential, are especially likely to be indolent. This study did not find an association between vessel-attachment and histological subtype. So far in literature, the only attachment that has been associated with histological subtype was an air bronchogram, which was seen more often in adenocarcinoma than in other cancers (69). Unfortunately during the NELSON trial the presence or absence of the air bronchogram was either not recorded or not seen, so this cannot be confirmed for our study.

Adenocarcinoma was the slowest growing type of cancer, as well as the cancer that was most often screened positive for VDT. This was as expected, since adenocarcinomas are generally believed to have a relatively slow growth rate (51,52). The fact that neuroendocrine carcinoma was more often detected by volume than by VDT corresponds with its fast growth rate. The fact that large cell carcinoma had the lowest volume doubling time was somewhat surprising, as generally neuro-endocrine cancers are regarded to be the fastest-growing lung cancer. However, there was no statistical difference between these two, and they have been shown to be tied for fastest growth more often (51). Tumor volume did not differ significantly between the cancer categories.

Participants
With a male:female ratio of 83.4:16.6, this study’s population has a higher percentage of male participants than any other European trial or the NLST, with the exception of the DANTE trial which featured only male participants (10,21,29-32). Whether this gender distribution has had an effect on the results remains to be seen. Although studies have demonstrated that female participants are more often diagnosed with adenocarcinoma, usually diagnosed at a lower cancer stage and at an earlier age than men, those results are not reproduced in this study (82,83). This may be explained by the fact that the cited trials have sampled a national database in which all cancer cases were recorded, whereas our patients are from a select group with stringent age and smoking criteria.

Strengths
One of the biggest strengths of this study was the high amount of screen-detected cancers and screening moments, as well as the long follow-up time of the participants.

Limitations
Since Lungcare software has trouble segmenting subsolid nodules, only solid nodules could be used for this study. This meant excluding 27 nodules from the trial. The 16 cases in which no histological data was obtained limited data collection as well. Pooling histological data together into four groups has increased statistical accuracy, but this has come at the cost of loss of detail. If sample sizes had been bigger across all categories, we could have had data on ten types of lung cancer, instead of the four groups reported now. Perhaps once the EUCT trial data is pooled together, the group sizes will be adequate for analysis of all subtypes of lung cancer. Even with the data pooled together some samples were small. For large cell carcinoma and neuro-endocrine cancer, the sample sizes were low and the difference in sample size with especially adenocarcinoma disproportionate. This limited the power of many of the analyses. Since neuro-endocrine carcinoma is a category composed of a heterogeneous group of tumors, it is difficult to summarize general characteristics for these groups. Although the way the cancers were pooled together was histopathologically justifiable, radiologically this may not have been the most logical decision. Large cell neuro-endocrine carcinoma, while histopathologically one of the neuro-endocrine cancers, does not look like the other
cancers in the group and is indistinguishable from adenocarcinoma or squamous cell carcinoma on CT imaging (61,63,76). The inclusion of large cell neuro-endocrine carcinoma in the neuro-endocrine carcinoma group may be responsible for the lack of morphological differences between neuro-endocrine carcinomas and the other cancers, since it resembles the other cancer categories more than its own. Peculiar is that analysis of tumors in the first three rounds of the NELSON trial did reproduce the findings with regards to sex, age and cancer stage found in population-wide studies, in which women diagnosed with cancer are younger and at an earlier cancer stage than their male counterparts, and are more often diagnosed with adenocarcinoma (38). These results were not reproduces in this study. Perhaps the difference in results was caused by the exclusion of semi-solid and non-solid tumor for this study, while tumors of all attenuation were included in the earlier analysis. However, since no mention of tumor attenuation is made in that article, it is hard to tell (38).

V: Future goals
Due to constraints of time and manpower, reviewing all screen-detected tumors in this study for the presence of an air bronchogram has not been performed as of yet, but this might be interesting for future research.
For this study the focus was on CT morphology at time of diagnosis. However, morphological features have been recorded during each round of screening. It would be interesting to study the development in CT morphology in nodules that have been through more than one screening round, to see if there is a connection between change in appearance and histology and/or behavior. Increasing solidity in partially-solid nodules as well as increasing spiculation and lobulation are seen as suspect (17,37), but this database offers a unique chance to discover if there are more red flags to be found.

VI: References


(55) Lazarus DR, Ost DE. The solitary pulmonary nodule-deciding when to act? Semin Respir Crit Care Med 2013 Dec;34(6):748-761.


(68) van't Westeinde SC, de Koning HJ, Xu DM, Hoogsteden HC, van Klaveren RJ. How to deal with incidentally detected pulmonary nodules less than 10mm in size on CT in a healthy person. Lung Cancer 2008 May;60(2):151-159.

(69) Jiang B, Takashima S, Miyake C, Hakudo T, Takahashi Y, Morimoto D, et al. Thin-section CT findings in peripheral lung cancer of 3 cm or smaller: are there any characteristic features for predicting tumor histology or do they depend only on tumor size? Acta Radiol 2013 Aug 7.


Figure 1: A lung tumor with smooth margins.
Figure 2: A lung tumor with irregular margins.
Figure 3: A lung tumor with lobulated margins.
Figure 4: A lung tumor with spiculated margins.