LUCIS

Lung Cancer Imaging Studies

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LIST OF PAPERS
This PhD is based on the following papers:

1) Harders SW, Madsen HH, Rasmussen TR, Hager H, Rasmussen F. High resolution spiral CT for determining the malignant potential of solitary pulmonary nodules: Refining and testing the test. ActaRadiologica 2011 May 1;52(4):401-9.

2) Harders SW, Madsen HH, Hjorthaug K, Arveschoug AK, Rasmussen TR, Meldgaard P, Andersen JB, Pilegaard HK, Hager H, Rehling M, Rasmussen F. Characterisation of pulmonary lesions in patients with suspected lung cancer. CT versus F-18-FDG PET/CT. Cancer Imaging 2012 In press.

3) Harders SW, Madsen HH, Nellemann HM, Rasmussen TR, Thygesen J, Hager H, Andersen NT, Rasmussen F. DCE-CT in suspected lung cancer. Dissenting results. Submitted.

4) Harders SW, Madsen HH, Hjorthaug K, Arveschoug AK, Rasmussen TR, Meldgaard P, Andersen JB, Pilegaard HK, Hager H, Rehling M, Rasmussen F. Mediastinal staging in Non-Small-Cell Lung Carcinoma. CT versus F-18-FDG PET/CT. Submitted.

ABBREVIATIONS

ACCP	American College of Chest Physicians
AUC	Area Under the ROC Curve
CT	Computed Tomography
CTP	CT Perfusion
DCE-CT	Dynamic Contrast-Enhanced Computed Tomography
EBUS	Endobronchial Ultrasound
ELCAP	Early Lung Cancer Action Program
EUS	Endoscopic Ultrasound
FNR	False Negative Rate
FPR	False Positive Rate
GGO	Ground-Glass Opacity
HRCT	High Resolution Computed Tomography
HU	Hounsfield Units
MDCT	Multiple-row Detector Computed Tomography
NPV	Negative Predictive Value
NSCLC	Non-Small-Cell Lung Carcinoma
PACS	Picture Archiving and Communication System
PET/CT	Positron-Emission Tomography and Computed Tomography
PPV	Positive Predictive Value
ROC	Receiver Operating Characteristic
ROI	Region of Interest
SCLC	Small Cell Lung Carcinoma
SPN	Solitary Pulmonary Nodule
TMIP	Time-averaged Maximum Intensifier Projection
TPR	True Positive Rate

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1. BACKGROUND

1.1 PULMONARY NODULES

Pulmonary nodules are of high clinical importance, given they may prove to be an early manifestation of lung cancer. Pulmonary nodules are small, focal, radiographic opacities that may be solitary or multiple. A solitary pulmonary nodule *(SPN)* is a single, small (≤ 30 mm in diameter) opacity (1, 2) (Figure 1). Larger opacities are called masses and are often malignant (3) (Figure 2).

Pulmonary nodules and masses are also known as pulmonary lesions.

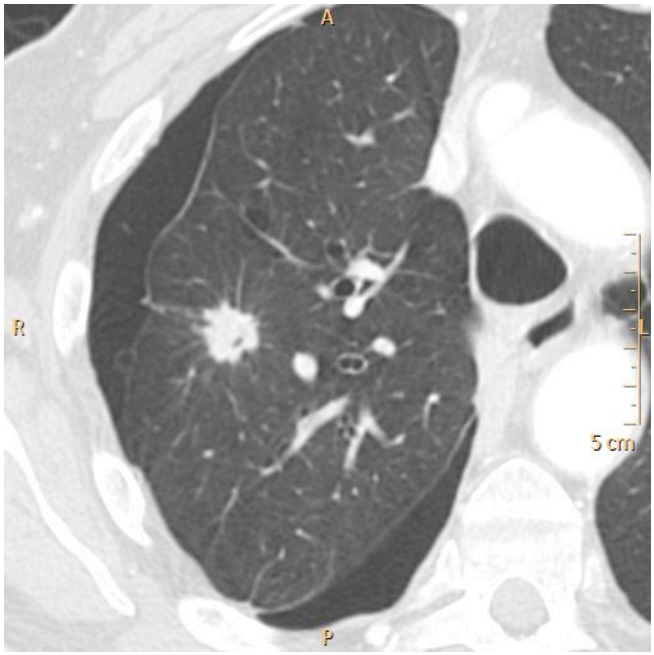

Figure1
A solitary pulmonary nodule; this nodule represented an adenocarcinoma.

In studies of F-18-FDG PET/CT imaging, most of which were performed in the United States[1], the most common causes of malignant SPNs are adenocarcinoma (47%), squamous cell carcinoma (22%) and solitary metastasis (8%) (4-12). The most common causes of benign SPNs are healed or nonspecific granulomas (25%), active granulomatous infections (15%) and hamartomas (15%) (4-12).

[1] Unfortunately, data on the causes of pulmonary nodules in Denmark is not available. Instead, data from the United States is used.

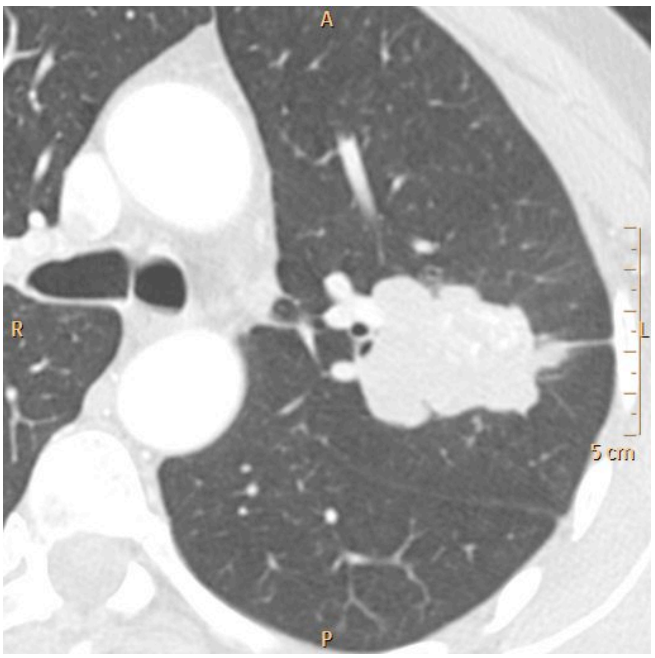

Figure2
A pulmonary mass; this mass represented a large cell carcinoma.

1.1.1 Prevalence of pulmonary nodules

Although the prevalence of pulmonary nodules depends on the studied population, the last decades have seen a significant rise in this prevalence due to improved imaging techniques, especially the utilization of CT. In a study from the 1950s, an SPN was found in 0.2% of all chest radiographs obtained in community settings (13). In the 1990s that prevalence had risen to 7% of all chest radiographs obtained as part of the Early Lung Cancer Action Program *(ELCAP),* an American screening study (14). However, the prevalence was as high as 23% in the ELCAP study when utilizing low-dose CT. In general, the prevalence of pulmonary nodules is reported to be 8% to 51% in CT screening studies (3).
The prevalence of malignancy in patients with SPNs varies widely across studies. In screening studies with low-dose CT, the prevalence of malignant SPN has been reported to be roughly 1% to 12% in those with nodules (3). However, in a study of patients with either screening detected or incidentally detected lung nodules, the prevalence of malignancy was 33% to 60% in nodules that measured 11 to 20 mm in diameter and 64% to 82% in nodules that measured > 20 mm in diameter (3).
This variation in prevalence of malignancy is reflected in this PhD. In the HRCT study, where size was limited to ≤ 30 mm in diameter for inclusion, the prevalence of malignancy was 48%. On the other hand, in the CT versus F-18-FDG PET/CT (1) study and in the DCE-CT study, where size was not a limiting factor, the prevalence of malignancy was approximately 80%.

1.1.2 Imaging of pulmonary nodules

As imaging techniques improve and more nodules are detected, the optimal management of pulmonary nodules remains unclear. However, the question of malignancy of any given nodule remains the same. Current assessment strategies include: no follow-up in low-risk patients and imaging follow-up in high-risk patients with very small nodules (< 4 mm); imaging follow-up in low-risk pa-

tients and imaging as well as tissue sampling in high-risk patients with small nodules (4 mm to 8 mm); and imaging as well as tissue sampling in all patients regardless of risk class with larger nodules and masses. This is irrespective of whether the nodules are incidental findings or if they are found in patients with suspected lung cancer (15).

Imaging plays an important role in the assessments of patients with suspected lung cancer and in the assessment of patients with incidentally discovered pulmonary nodules. Usually the first imaging examination is a chest radiograph. This is followed by contrast-enhanced CT of the thorax and upper abdomen and, dependant on local arrangements, by whole body integrated F-18-FDG Positron-Emission Tomography and CT *(F-18-FDG PET/CT)*. Other imaging examinations are optional and include Magnetic Resonance Imaging *(MRI)* of the thorax and, as in this PhD, Dynamic Contrast-Enhanced CT (DCE-CT) of the thorax.

Over the years, political decisions based on scientific advances have increased the number of patients referred for CT significantly. Thus, the first patient with suspected lung cancer was CT scanned at our department in 1998. In 1999 that number had increased to 200 patients per year and, little more than 10 years later, in 2011 it has increased to more than 1,200 patients per year. In the same period the number of patients diagnosed with lung cancer in Denmark has increased from 3,400 per year to 4,300 per year.

Modern imaging algorithms are based on combinations of technical performance, diagnostic performance, diagnostic impact and therapeutic impact. However, the impact of imaging on the patients' health remains unclear. The technical performances and especially the diagnostic performances of the individual modalities will be described later. Typical effective radiation doses are: chest radiograph, 0.1 mSv; low dose CT of the thorax and upper abdomen, 1.0 to 2.0 mSv; standard CT of the thorax and upper abdomen, 8.0 to 10.0 mSv; F-18-FDG PET (400 MBq), 8.0 to 10.0 mSv; F-18-FDG PET (400 MBq) and low dose CT of the thorax and upper abdomen, 8.0 to 10.0 mSv; F-18-FDG PET (400 MBq) and standard CT of the thorax and upper abdomen, 16.0 to 20.0 mSv (16, 17).

The participants in this PhD were all sampled from a population of patients with suspected lung cancer. Most had received a chest radiograph prior to the examinations that are part of this PhD. This is described in detail in the "participants" section.

1.2 LUNG CANCER

In the western world, lung cancer remains the leading cause of cancer death in both men and women (18). The predominant cause of lung cancer is exposure to tobacco smoke, with active smoking causing most cases, but passive smoking also contributing to the lung cancer burden.

Cigarette smoking is by far the leading cause of lung cancer, accounting for approximately 90% of lung cancer cases in the United States and other countries where cigarette smoking is common (19). Compared with never smokers, smokers have approximately a 20 times the risk of others for lung cancer. Few exposures to environmental agents convey such increased risks of any disease. In general, lung cancer trends closely reflect smoking patterns, but rates of occurrence lag after smoking rates by approximately 20 years. Analyses using statistical modelling techniques show a close association between national mortality rates and smoking (20). The unequivocal role of cigarette smoking in causing lung cancer is one of the most thoroughly documented causal relationships in biomedical research (21, 22). Minor causes of lung cancer include occupational exposures to carcinogens, radon (23) and outdoor air pollution (24).

1.2.1 Survival from lung cancer

In Denmark the observed 5-year survival rate from lung cancer was 11% for patients diagnosed in 2003 to 2006. The survival rate has slowly, but steadily been rising since 2000 (25).

1.2.2 Staging of Non-Small-Cell Lung Carcinoma (NSCLC)

Staging is used to predict survival and to guide the patient toward the most appropriate treatment regimen or clinical trial. The most significant division is between those patients who are candidates for surgery and those who may benefit from chemotherapy, radiation therapy or both. Distinguishing malignant involvement of the ipsilateral or contralateral mediastinal lymph nodes (N2 or N3) from the ipsilateralhilar lymph nodes or no lymph nodes (N0 or N1) is critical, because malignant involvement of N2 or N3 lymph nodes usually indicates non–surgically resectable disease. The basis for staging Non-Small-Cell Lung Carcinoma *(NSCLC)* is the TNM system (26, 27) (Figure 3). Patients with stage IA, IB, IIA and IIB disease can benefit from surgical resection. Patients with stage IIIA, IIIB and IV disease almost never meet the criteria for surgery. The role of chemotherapy and radiation therapy followed by surgery for stage IIIA and IIIB disease is controversial (28).

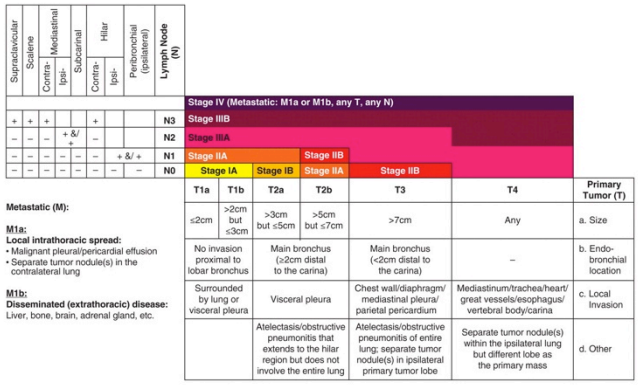

Figure3
This chart illustrates the descriptors from the 7th edition of the TNM staging system for lung cancer. With permission(141).

A variety of imaging modalities are applied for mediastinal staging of NSCLC. However, in the studies in this PhD only the most commonly used imaging modalities are used and thus only CT and F-18-FDG PET/CT are covered in detail.

2. AIM AND HYPOTHESES

2.1 AIM

In 2008 when this PhD was commenced, patients with suspected lung cancer received standard contrast-enhanced CT of the thorax and upper abdomen and HRCT of the thorax; only selected patients received F-18-FDG PET/CT. However, based on increasing international experience with F-18-FDG PET/CT, it was about to be part of the standard clinical work-up of patients with suspect-

ed lung cancer and patients with NSCLC. DCE-CT was used in patients with suspected lung cancer on an experimental basis. Patients who were subsequently diagnosed with lung cancer were invasively staged using mediastinoscopy and eventually mediastinotomy.
3 of the papers of this PhD concerns the characterisation of pulmonary lesions in patients with suspected lung cancer; 2 of these papers, the HRCT paper and the F-18-FDG PET/CT (1) paper, evaluate the diagnostic performance of the imaging modalities in a selected population of cancer suspect patients. Thus, these papers are concerned with the ability of the involved methods to identify disease correctly and therefore measure sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the methods. The last paper concerning the characterisation pulmonary lesions in patients with suspected lung cancer, the DCE-CT paper is more experimental. None the less, it measures the diagnostic performance of a qualitative as well as a quantitative approach to Dynamic Contrast-Enhanced CT, only this time the quantitative approach use numerical values and p-values to examine the performance. The fourth paper of this PhD evaluates the diagnostic performance of CT and F-18-FDG PET/CT for mediastinal staging in patients with NSCLC. That study was a substantial part of the entire CT versus F-18-FDG PET/CT study. Therefore the paper is also a part of the PhD.
Thus, the aim of this PhD was to examine and validate modern imaging modalities used to characterise pulmonary lesions in patients with suspected lung cancer, to aid in the ability of modern methods to replace older established methods and to aid in the development of new methods. The desire was to safely distinguish between malignant and benign lesions without the need for invasive procedures. This would have a significant diagnostic impact on patient management.

2.2 HYPOTHESES

The hypotheses for each study were as follows:

1) HRCT study: The pathological basis of a pulmonary nodule is reflected in its attenuation, morphology and certain other characteristics. By using High Resolution CT *(HRCT)* to review these, radiologists can distinguish between malignant and benign nodules with high to excellent reproducibility.

2) CT versus F-18-FDG PET/CT (1) study: Integrated F-18-FDG Positron-Emission Tomography and low dose Computed Tomography *(F-18-FDG PET/CT)* is as sensitive and specific as CT for characterising pulmonary nodules and masses in patients with suspected lung cancer.

3) DCE-CT study: The angiogenesis of a pulmonary nodule or mass can be depicted by its perfusion, peak enhancement intensity, time to peak or blood volume. By using Dynamic Contrast-Enhanced CT *(DCE-CT)* to review this, radiologists can distinguish between malignant and benign nodules. However, concerns have been raised regarding the reproducibility of these measurements.

4) CT versus F-18-FDG PET/CT (2) study: Integrated F-18-FDG Positron-Emission Tomography and low dose Computed Tomography *(F-18-FDG PET/CT)* is more sensitive and more specific than CT for staging the mediastinum in patients with NSCLC.

Approximately 500 patients with suspected lung cancer, were included into one retrospective or one of three prospective studies. All participants received a standard contrast-enhanced CT. Besides this standard CT, the participants in study 1) also received an HRCT; the participants in study 2) also received an F-18-FDG PET/CT; the participants in study 3) also received a DCE-CT and the participants in study 4) also received an F-18-FDG PET/CT. Reference standard consisted primarily of tissue sampling and in few cases on CT follow-up (Table 1).

Table 1. Overview of this PhD

	Study 1)	Study 2)	Study 3)	Study 4)
Aim	Characterisation of pulmonary nodules; reproducibility	Characterisation of pulmonary lesions; reproducibility	Characterisation of pulmonary lesions; reproducibility	Mediastinal staging in NSCLC; reproducibility
Participants	213	168	59	114
Population	Patients with suspected lung cancer	Patients with suspected lung cancer	Patients with suspected lung cancer	Patients with NSCLC
Study design	Retrospective cohort	Prospective cohort	Prospective cohort	Prospective cohort
Imaging modality	HRCT	CT; F-18-FDG PET/CT	DCE-CT	CT; F-18-FDG PET/CT
Reference standard	Tissue sampling (90%); CT follow-up (10%)	Tissue sampling (91%); CT follow-up (9%)	Tissue sampling (100%)	Tissue sampling (100%)

Abbreviations: DCE-CT: Dynamic Contrast-Enhanced CT; F-18-FDG PET/CT: F-18-FDG Positron-Emission Tomography and CT; HRCT: High Resolution CT; NSCLC: Non-Small-Cell Lung Carcinoma.

3. METHODS

In the following section, the methods used in this PhD will be described. The section is divided into subsections relating to Participants, Test methods and Statistical methods.

3.1 PARTICIPANTS

In all studies in this PhD, participants were sampled from a population of patients with suspected lung cancer. All patients were referred from their general practitioner to the department of pulmonology at hospital. Once there, all patients were thoroughly questioned about their predictors for lung cancer, including their smoking history; they also received a physical examination and a chest radiograph. Based on individual predictors and physical examinations, patients at an increased risk for lung cancer were referred for a standard contrast-enhanced CT of the chest and upper abdomen.
However, it is recognised that although it is based on a standard clinical algorithm, this approach with the initial use of CT introduces a selection bias into the studies. This selection is responsible for the high prevalence of malignancy in the studies, and in the CT versus F-18-FDG PET/CT (1) study it may favour CT. As such, it may also be a possible cause for discrepancies between our studies and previous works on the subject.

3.1.1 HRCT study (a retrospective[2] cohort[3] study)

Patients with suspected lung cancer, which were referred to a tertiary sector hospital for diagnosis, were identified for potential inclusion through medical records and through Picture Archiving and Communication System *(PACS)* records. Only those patients with pulmonary nodules < 30 mm were included. The search was limited to the last 5½ years, as this was the time when the department introduced digital imaging techniques. 1,988 consecutive patients were referred for CT, but only 213 of these patients had nodules < 30 mm.

As data was collected after the patients were examined, the study was defined as a retrospective cohort study.

3.1.2 CT versus F-18-FDG PET/CT (1) study (a prospective cohort study)

Patients with suspected lung cancer, which were referred to a tertiary sector hospital for diagnosis, were prospectively identified for inclusion over a 1 ¼ - year study period. All patients received standard contrast-enhanced CT of the chest and upper abdomen as part of their clinical work-up. Based on the CT results the patients were subjects to a multidisciplinary decision. If there were no pulmonary lesions, or at least no malignancy suspect pulmonary lesions on CT, the patients were either discharged without follow-up or received CT follow-up after 3, 6, 12, 24 months or longer. On the other hand, if there were indeterminate lesions or malignancy suspect lesions on CT, they furthermore received whole body F-18-FDG PET/CT.

Consecutive patients who received both a CT of the thorax and upper abdomen, and an F-18-FDG PET/CT of the whole body were included in the study. To ensure equal review terms between CT and F-18-FDG PET/CT, all examinations made as part of the clinical work-up were blinded, and were reviewed all over as part of the study. 182 consecutive patients received a CT as well as an F-18-FDG PET/CT. However, 14 patients were excluded due to discrepancy between CT and F-18-FDG PET/CT nodule location, incomplete F-18-FDG PET/CT data or incomplete CT data, leaving 168 patients for final analysis. Patient sampling preceded both imaging and reference standard. Therefore the study design was prospective.

3.1.3 DCE-CT study (a prospective cohort study)

Patients with suspected lung cancer and pulmonary nodules or masses on a chest radiograph, which were referred to a tertiary sector hospital for diagnosis, were over a 2½-year period prospectively identified for inclusion. They all received standard contrast-enhanced CT of the chest and upper abdomen. Those who signed an informed consent form to participate in the study also received DCE-CT. 67 patients signed the informed consent form and were included in the study. However, due to technical difficulties only 59 of these patients were included in the final analysis.

[2] In a retrospective study, disease status is determined from medical records produced prior to the beginning of the study but after identification of the cohorts. Conversely, in a prospective study, investigators follow up subjects after study inception to collect information about development of disease.

[3] A cohort is a group of individuals. The term is derived from roman military tradition; according to this tradition, legions of the army were divided into 10 cohorts.

3.1.4 CT versus F-18-FDG PET/CT (2) study (a prospective cohort study)

Patients, who were recently diagnosed with NSCLC and were ready for staging, were prospectively identified for inclusion over a 2-year study period. All 114 consecutive patients received CT as well as F-18-FDG PET/CT and tissue sampling was obtained on all patients. As patient inclusion preceded both imaging and reference standard, the study design was prospective.

3.2 TEST METHODS

As mentioned in the introduction, imaging plays an important role in the assessments of patients with suspected lung cancer and in the assessment of patients with incidentally discovered pulmonary nodules. Usually, the first imaging examination is a chest radiograph. This is followed by a standard CT of the thorax and upper abdomen and, dependant on local arrangements, by an integrated F-18-FDG PET/CT of the whole body. Other imaging examinations are optional and include a DCE-CT of the thorax.

3.2.1 Chest radiography

The majority of lung nodules are first identified on chest radiographs. Depending on the location of lung nodules and the sharpness of their borders, nodules as small as 5 or 6 mm can sometimes be identified by chest radiography (29).

The main disadvantage of chest radiographs is that even peripherally located, large nodules are often missed on chest radiographs by radiologists and in fact a chest radiograph has low sensitivity, specificity and positive predictive value for lung nodules (30, 31). This has been confirmed in several studies.

The Mayo Clinic screened high-risk patients with chest radiography every four months. Of 50 detected peripheral bronchogenic carcinomas, 45 could be identified earlier when reviewed in retrospect and with the exception of one, all were larger than 10 mm before they could be identified (32). In a more recent report, 19% of all detected bronchogenic carcinomas could be identified earlier when reviewed in retrospect (33). These nodule miss rates have been reported to be significantly higher in some studies. Finally, in a study of 40 patients with NSCLC that initially were missed on chest radiographs, the median diameter of the missed nodules was 1.9 cm and 85% of the lesions were peripheral in location (30). To this should be added that there is a lower detection limit of 0.8 to 1.0 cm for lung nodules. Nodules smaller than that limit may be missed in as many as 71% of the cases (33, 34). Due to these considerations chest radiography should always be followed by CT in patients with suspected lung cancer and in patients with pulmonary nodules discovered incidentally.

3.2.2 CT

Currently CT is the de facto standard examination for patients with suspected lung cancer and for patients with incidentally discovered pulmonary nodules.

There are three main predictors for malignancy: nodule size, edge morphology and attenuation.

Nodule size measured as the greatest axial diameter on CT: Screening trials have shown, that for nodules smaller than 5 mm in diameter, the prevalence of malignancy is extremely low (<1%); for nodules larger than 5 mm, the prevalence is higher (3).

Edge morphology: Studies have shown that the risk for malignancy is low (20% to 35%) in nodules with smooth edges; in nodules

with irregular or spiculated edges the risk is higher, but varies from 33% to 100% (3).
Attenuation: Lung nodules should be classified as solid nodules, partly solid nodules or Ground-Glass Opacities *(GGOs).* In two Asian studies, almost 70% of all GGOs were malignant (35, 36). However, in the ELCAP study this number was lower (18%) (37). Similarly, the prevalence of malignancy was high (50% to 60%) in partly solid lesions, but much lower (< 10%) in solid nodules (35, 37).
Currently, the vast majority of CT studies for characterisation of pulmonary nodules are carried out using contrast enhancement, as this has been found to be highly sensitive, albeit nonspecific, for identifying malignant nodules (3). In a multicentre study (38), Swensen et al enrolled 356 participants with noncalcified nodules that measured 0.5 to 4 cm in diameter, 48% of which were malignant. Using an enhancement threshold of 15 HU, the sensitivity and specificity of contrast-enhanced CT were 98% and 58%, respectively.
The main disadvantages of CT for characterisation of pulmonary nodules include radiation exposure and adverse effects as a result of the administration of iodinated contrast media. The magnitude of the risk associated with radiation exposure from a single CT scan is likely to be small, but in patients who require multiple follow-up scans, low-dose techniques[4] should be used whenever possible to minimize the uncertain risk associated with repeated radiation exposure (17).

3.2.2.1 CT for staging NSCLC

CT is the most widely available and commonly used non-invasive modality for evaluation of the mediastinum in lung cancer. The vast majority of reports evaluating accuracy of CT scanning for mediastinal lymph node staging have employed the administration of iodinated contrast media. Furthermore, the majority of these reports use a short-axis diameter of ≥ 1 cm on a transverse CT scan image as a threshold for abnormal nodes.
Thirty-five studies evaluating the accuracy of CT scanning for staging the mediastinum were analysed in the American College of Chest Physicians *(ACCP)* guidelines from 2007 (28). The pooled sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis were 47% to 54% (median, 51%) and 84% to 88% (median, 86%), respectively. Although the combined estimates should be interpreted with caution as the studies were statistically heterogeneous, these findings closely mirrored previous analyses addressing the accuracy of CT scanning for staging the mediastinum in NSCLC by Gould et al (39) and by Dwamena et al (40).
While it remains the best overall anatomic study available for the thorax, CT scanning is clearly an imperfect means of staging the mediastinum. First, approximately 20% of all benign nodes are falsely deemed to be malignant by CT scan criteria (False Positive Rate or 1 - specificity) *(FPR).* Second, approximately 20% of all malignant nodes are deemed to be benign by CT scan criteria (False Negative Rate or 1 - sensitivity) *(FNR).* CT scanning can thus overstage as well as understage the mediastinal nodes. Given these limitations, it is usually inappropriate to rely solely on CT to determine mediastinal lymph node status in patients with NSCLC. Nonetheless, CT continues to play an important and necessary role in the evaluation of these patients.

3.2.3 F-18-FDG PET and F-18-FDG PET/CT

Unlike chest radiography and CT, which are both anatomical imaging modalities, F-18-FDG-PET is a non-invasive functional imaging test that is widely used in clinical oncology for tumour diagnosis, disease staging, and evaluation of treatment response (41, 42). F-18-FDG is taken up selectively by malignant tumour cells, which overexpress the glucose transporter protein. Inside the cell, F-18-FDG is phosphorylated once by hexokinase, generating F-18-FDG-6-phosphate, which is not metabolized further. The combination of increased uptake of F-18-FDG and a decreased rate of dephosphorylation by glucose-6-phosphatase in malignant cells results in an accumulation of F-18-FDG-6-phosphate in these cells (43, 44). F-18-FDG is a positron-emitting radionuclide that undergoes an annihilation reaction after colliding with a nearby electron, resulting in the simultaneous release of two high-energy (511 kilo electron volts) photons in opposite directions. Annihilation photons are coincidentally detected by a ring of crystals in the PET scanner. Electronic circuits and computer software subsequently localize the abnormality, register the intensity of uptake, and reconstruct cross-sectional images for display (45).
F-18-FDG PET aids in differentiating malignant and benign nodules if these are > 10 mm in diameter (46-48). For this purpose sensitivity has been reported to be 80% to 100% (median, 87%) and specificity to be 40% to 100% (median, 83%) for malignancy of lung nodules (3). These results are slightly less optimistic than those reported previously on the subject (49). However, due to large numbers of false negatives, the use of F-18-FDG PET outside clinical trials is discouraged for nodules < 10 mm (50). Besides the risk of false negatives in nodules < 10 mm, F-18-FDG PET is also reported to give false negatives in highly differentiated adenocarcinomas and other slow growing cancers as well (6, 51). In theory, uncontrolled hyperglycaemia can also disguise malignant lung nodules (52). This considerable risk of false negatives means that, although F-18-FDG PET has been reported to have a consistently high negative predictive value, the modality cannot be used to rule out lung nodule malignancy. F-18-FDG PET is also reported to be false positive in infections and inflammation of all kinds (12, 53).
Modern F-18-FDG PET scanners are integrated with CT scanners in a single gantry (F-18-FDG PET/CT scanner). The purpose of this is to couple the functionality of an F-18-FDG PET scanner with the resolution of a CT scanner, thereby increasing the value of both. However, there are only few published studies on the matter of characterisation of pulmonary nodules using integrated F-18-FDG PET/CT scanners (54-56).

3.2.3.1 F-18-FDG PET and F-18-FDG PET/CT for staging NSCLC

F-18-FDG PET has a higher sensitivity and a higher specificity than CT for the evaluation of mediastinal lymph nodes and it can provide important information regarding the presence of metastatic disease outside the thorax (28, 39). This holds true even though standardised quantitative criteria for abnormal F-18-FDG PET findings in the mediastinum are lacking. Clinical assessments are

[4] Although there is no strict definition of low-dose CT techniques, a hint of what this means can be obtained by closely examining the methods used in the on-going National Lung Screening Trial *(NLST)* in the United States. In this trial, the CT radiation dose is reduced to 1.5 mSv per examination. This is achieved through the regulation of the tube voltage and the tube current. In comparison, the average radiation dose of a diagnostic CT of the chest and upper abdomen varies widely, but is approximately 8 to 10 mSv. Other methods to achieve a lower radiation dose are the use of multiple tubes, multiple energies, filters and data reiteration.

usually based on a qualitative assessment of uptake in the lesion or structure in question compared to the background activity of the lung or liver (57). Despite the lack of standardised criteria defining positive findings, F-18-FDG PET has proved useful in differentiating neoplastic from normal tissues.

Forty-four studies evaluating the accuracy of F-18-FDG PET scanning for identifying mediastinal lymph node metastases were analysed in the ACCP guidelines from 2007 (28). All studies were interpreted in conjunction with patients' CT findings so that the F-18-FDG PET findings were correlated with the anatomic location of the lesion seen on CT. In all studies, F-18-FDG was the radiopharmaceutical used for imaging. Estimates of sensitivity and specificity for identifying mediastinal metastases were 69% to 79% (median, 74%) and 82% to 88% (median, 85%), respectively. As was the case for characterisation of pulmonary nodules, our results are slightly less optimistic than those previously reported (39).

Some studies have pointed out that the accuracy of F-18-FDG PET imaging in the mediastinum is dependent on the size of the nodes identified on CT (39, 58-60). Indeed, F-18-FDG PET is more sensitive (but less specific) when enlarged nodes can be identified on CT (39, 59). In a meta-analysis evaluating the conditional test performance of F-18-FDG PET and CT, Gould et al reported sensitivity and specificity of F-18-FDG PET of 90% to 100% (median, 100%) and 68% to 100% (median, 78%), respectively, in patients with enlarged lymph nodes (39). F-18-FDG PET is thus very accurate in identifying malignant nodal involvement when nodes are enlarged. However, F-18-FDG PET will falsely identify malignancy in approximately one fourth of patients with nodes that are enlarged for other reasons (e.g. inflammation or infection). Positive F-18-FDG PET findings in this situation should be confirmed by biopsy. Failure to do so could result in patients with surgically resectable disease being denied curative surgery. Conversely, F-18-FDG PET is less sensitive (but more specific) in patients with normal-sized mediastinal nodes seen by CT. In the meta-analysis by Gould and colleagues, the sensitivity and specificity of F-18-FDG PET were 65% to 100% (median, 82%) and 92% to 100% (median, 93%), respectively, in patients with normal-sized lymph nodes (39). These data indicate that nearly 20% of patients with normal-sized nodes, but with malignant involvement, had falsely negative F-18-FDG PET scan findings. This, in turn, addresses the controversial question of whether a negative PET scan in patients with normal-sized lymph nodes on CT can obviate the need to perform further invasive mediastinal evaluation prior to thoracotomy.

F-18-FDG PET may provide an additional benefit in that it is a whole-body study. F-18-FDG PET is able to provide information about the primary site in the chest as well as intra-thoracic and extra-thoracic metastases using a single study. Several studies have reported on the ability of F-18-FDG PET scanning to identify extra-thoracic metastases in patients whose tumours had been deemed resectable by conventional imaging (61-63). The rate of detection of unanticipated M1 disease by F-18-FDG PET scanning has been reported as 1% to 8% in patients with clinical stage I disease and 7% to 18% in patients with clinical stage II disease (61, 62). The identification of unanticipated distant metastases by F-18-FDG PET scanning in such patients should result in the avoidance of unwarranted thoracotomies, but all positive findings in surgical candidates should be confirmed by biopsy unless there is overwhelming evidence of distant metastasis (64).

3.2.4 Dynamic Contrast-Enhanced CT

Dynamic Contrast-Enhanced CT *(DCE-CT),* also known as perfusion CT, is a functional imaging modality that reflects angiogenesis and is applied to the imaging of patients with suspected or known cancer (65-67). In DCE-CT the perfusion of tissues is quantified using dedicated software (68-70).

The basic principle of DCE-CT is based on the temporal changes in tissue density following intravenous administration of iodinated contrast media. The chronological changes in tissue density are dependent on the iodine concentration and are a reflection of the tissue vascularity. By rapid sequential acquisition of images during the passage of contrast in the tissues, DCE-CT allows quantification of the tissue vascularity.

Following intravenous injection of the contrast media, the contrast distributes within the tissues resulting in increasing tissue density on CT. The tissue enhancement seen following contrast administration can be divided into two phases based on its distribution in the intra vascular or the extra vascular compartment (67). In the initial phase following contrast injection, the enhancement is mainly due to the contrast within the intravascular space (67). Later in the second phase as contrast passes from the intravascular to the extra vascular compartment across the capillary basement membrane, enhancement results from contrast distribution in both intravascular and extravascular compartments (67). Thus in the initial phase, the enhancement is determined to a great extent by the blood flow while in the second phase the enhancement depends on the blood volume and the permeability of capillaries to the contrast medium (67).

By obtaining a series of image in quick succession in the region of a particular tissue it is possible to record the temporal changes in the tissue attenuation occurring after intravenous injection of contrast. The quantification of perfusion recorded by CT is done using mathematical modeling techniques, which use data from the tissue and the vascular system. The two most commonly used analytical methods for quantifying various perfusion parameters from the dynamic CT data are: Compartmental analysis and Deconvolution analysis (71, 72). Both the analytical methods require obtaining time attenuation data from the arterial input for estimation of tissue vascularity and to correct for inter patient variations in bolus geometry (71, 72).

Compartmental analysis is based on single compartment model or the two-compartment model (66, 71, 72). The single compartmental model is used to estimate the tissue perfusion and as the name suggests it considers the intravascular and extra-vascular spaces as a single compartment. This model, which is based on Fick's principle, calculates tissue perfusion based on conservation of mass within the system (66, 71). It estimates the perfusion either from the maximal slope or the peak height of the same tissue concentration curve normalized to the arterial input function (66, 71, 73). The two compartmental model is used for the evaluation of capillary permeability and blood volume (66, 71, 73). This model assumes the intravascular and extra vascular spaces as separate compartments and measures perfusion parameters using a technique called Patlak analysis.

Deconvolution analysis is based on the use of arterial and tissue time-concentration curves to calculate the impulse residue function (IRF) for the tissue. Impulse residue function is a theoretical tissue curve that is obtained from the direct arterial input assuming that the concentration of contrast material in the tissue is linearly dependent on the input arterial concentration when the blood flow is constant (66, 71, 72). After flow correction, the height of this curve gives the tissue perfusion and the area under the curve will decide the relative blood volume (71).

Preliminary results have shown that both the techniques are broadly equivalent. However they differ in terms of their theoretical assumptions, susceptibility to noise and motion (71). Compartmental analysis is based on the assumption that the bolus of contrast media has to be retained within the organ of interest at the time of measurement, which may result in underestimation of perfusion values in organs with rapid vascular transit or with large bolus injection (71). While deconvolution assumes that the shape of IRF is a plateau with a single exponential washout.
One of the important considerations for adequate assessment of perfusion of a tissue is the contrast medium bolus used for the intravenous injection (71, 72). A short sharp bolus is essential for adequate perfusion assessment with compartment method and hence a small bolus of 40-50 ml is administered with a higher injection rate between 5 to 7 ml/sec (71, 72). Though deconvolution can tolerate lower injection rates, higher rates (up to 7 ml/sec) are still beneficial to maximize tissue enhancement and to improve signal to noise ratio (71, 72). Due to linear relationship of iodine concentration and tissue enhancement a higher concentration of contrast media is preferred (370mg Iodine/ ml) (71, 72).
A consideration in patients with suspected lung cancer is respiratory motion, which is of considerable significance during image acquisition as it can lead to image misregistration and errors in calculation of perfusion values. Respiratory motion can be restricted to a certain extent by proper instruction to patients regarding breathholding and/or shallow breathing.
Finally, the analytical methods used and the acquisitions protocols vary from scanners to scanner and between commercial vendors. Whereas Philips and Siemens use the slope method, GE uses the deconvolution approach.

DCE-CT results for lung cancer have thus far been promising (74-78). However, there is a continued demand for research and development before DCE-CT can classify lesions with sufficient accuracy and reproducibility as to be used in a clinical setting, thus reducing the need for interventional procedures (77).
According to Zhang et al (78) and Yi et al (65), perfusion and peak enhancement intensity measurements are higher for malignant and inflammatory lesions than for benign lesions. The diagnostic accuracy of DCE-CT, DCE-MRI, F-18-FDG PET and ^{99m}Tc Depreotide Single-Photon Emission-CT *(SPECT)* for the evaluation of solitary pulmonary nodules was shown to be comparable, with only negligible differences in performance between the tests (79). Sensitivity of DCE-CT was 89% to 100% (median, 93%) and specificity was 54% to 90% (median, 76%) for differentiating between malignant and benign nodules.
In studies using intra-class correlation coefficients *(ICCs)*,it has been shown that the reproducibility of DCE-CT for early stage lung cancer is very high (99%) (75, 76). However, ICCs can be misleading and may not reveal the clinical utility of given measurements (80-82). Thus, Ng et al, in a study regarding late stage lung cancer, concluded that the broad 95% limits of agreement could potentially be of concern (83, 84).
DCE-CT measurements may contribute valuable clinical information and have been found to correlate with other clinicopathologic parameters, including tumour size, F-18-FDG uptake value and nodal status. In 46 patients with surgically resected lung cancer, tumour perfusion, peak enhancement and blood volume were significantly higher in tumours < 3 cm compared with larger tumours (76). Similar findings were reported in advanced lung cancer (85, 86) and may be explained by the central tumour necrosis often found in larger tumours (87). A complex relationship between tumour glucose metabolism and tumour perfusion has been hypothesized (88). In a study of Standardised Uptake Value *(SUV)* measured using F-18-FDG PET and Standardised Perfusion Value *(SPV)* measured using DCE-CT, , Miles et al reported a positive correlation between the ratio of SUV to SPV in lung cancer with higher values found in larger tumours. They also reported a significant correlation between SUV and SPV for tumours smaller than 4.5 cm^2 (85). Additionally, DCE-CT has been studied as a means of identifying patients at risk for nodal infiltration. However, results in this area have yet to be published.
Although DCE-CT seems promising, in theory as well as in practice, a number of challenges still remain, of which the most important relate to standardisation of practice and quality assurance.

3.2.5 HRCT study

HRCT included only slices with nodules and were performed immediately following the end of standard CT. HRCT was performed with a Multiple-Row Detector CT *(MDCT)* scanner (Philips MX 16-channel scanner or brilliance CT 64-channel scanner; Philips Healthcare, Best, The Netherlands). The acquisition parameters were: 16 x 0.625 mm collimation or 64 x 0.625 mm collimation. No contrast medium was administered. Raw picture data sets were transferred to a Philips Extended Brilliance™ Workspace workstation v4.02 and were reviewed with the application CT-viewer.
Two consultant radiologists reviewed the studies. Blinded images were reviewed in four ways: 1) based on attenuation, all nodules were categorised into solid nodules, partly solid nodules or GGOs; 2) based on morphology, solid nodules were rated as low-risk nodules (smooth edges), intermediate-risk nodules (irregular edges) or high-risk nodules (spiculated edges); 3) Calcifications and other specific signs of malignancy were described and 4) an overall “potential of malignancy” rating was assigned using the following rating scale: 1) definitely benign, 2) probably benign, 3) indeterminate, 4) probably malignant and 5) definitely malignant. Both radiologists reviewed all participants' images side by side, to obtain consensus results for the study. They also reviewed the images individually, to assess reproducibility.

3.2.6 CT versus F-18-FDG PET/CT (1) study

CT including the chest and the upper abdomen was performed with an MDCT scanner (Philips Brilliance CT 64-channel scanner; Philips Healthcare, Best, The Netherlands). CT acquisition parameters were: 64 x 0.625 mm collimation, section thickness 2.0 mm, increment 1.0 mm. Iodixanole 270 mg/ml (Visipaque® 270; GE Healthcare, Oslo, Norway) or iohexole 300 mg/ml (Omnipaque® 300; GE Healthcare, Oslo, Norway), was injected intravenously in weight-adjusted doses of 2 ml/kg body weight to compensate for differences in distribution volume. A bolus tracking technique was used to compensate for differences in cardiac output. The trigger ROI was placed in the Aorta and when it exceeded 200 HU, the patients were scanned from the root of the neck to the upper abdomen including the liver and adrenals. CT was performed after a delay of 15 seconds for the chest and 65 seconds for the upper abdomen and raw picture data sets were transferred to a Philips Extended Brilliance™ Workspace workstation v4.02, where they were reviewed with the application CT-viewer.
Two consultant radiologists reviewed the studies. The reviewers were blinded to patient name, patient ID and clinical data. They assessed three well-documented predictors of malignancy (3): 1)

lesion size, measured as the greatest axial diameter on CT; 2) lesion morphology, assessed as smooth, irregular or spiculated and 3) lesion attenuation assessed as solid, partly solid or GGO. Although no formalised score system was used, these predictors were considered as the reviewers assigned each lesion an overall "potential of malignancy" rating. The following rating scale was used: 1) definitely benign, 2) probably benign, 3) indeterminate, 4) probably malignant and 5) definitely malignant (Figure 4). Both radiologists reviewed all participants' images side by side, to obtain consensus results for the study. Six months later, they reviewed the first 100 participants' images again, individually, to assess reproducibility.

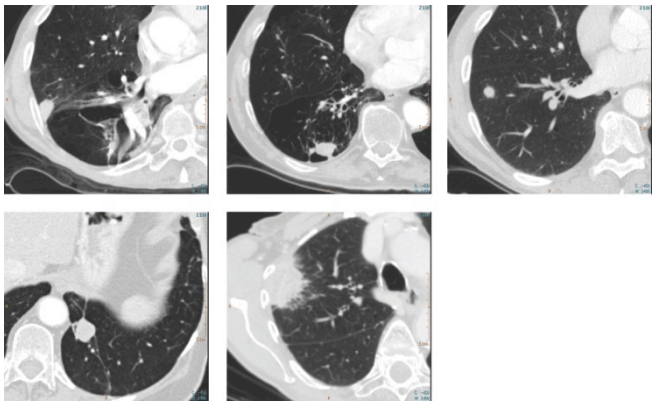

Figure4
Examples of the 5 CT ratings. From top left to bottom right, these specific lesions were rated: definitely benign, probably benign, indeterminate, probably malignant and definitely malignant.

As a part of a fast-track work-up for suspected lung cancer, the patients received CT and F-18-FDG PET/CT within few days, immediately followed by tissue sampling. Whole body F-18-FDG PET/CT including the head except for the brain, neck, thorax, abdomen, pelvis and thighs was performed with an integrated PET/CT scanner (Siemens Biograph w. 40-slice CT scanner; Siemens Healthcare, Erlangen, Germany). Participants were instructed to fast for 6 hours prior to the examination. Approximately 400 MBq F-18-FDG was injected intravenously. F-18-FDG PET/CT scans were performed after a delay of 60 minutes. The F-18-FDG PET images were corrected for scatter and iteratively reconstructed. CT acquisition parameters were: 40 x 3.0 mm collimation, section thickness 5.0 mm, increment 3.0 mm. No contrast medium was administered. F-18-FDG PET/CT picture data sets were transferred to a Hermes Gold 3™ workstation, where they were reviewed with the application Hermes Hybrid Viewer.
Two consultants in nuclear medicine did the F-18-FDG PET/CT reviews. The reviewers were blinded to patient names, patient IDs and clinical data. According to international guidelines (89, 90), F-18-FDG uptake was compared to the background uptake of the liver. Thus, lesion uptake was rated on a scale of 1 to 4: 1) no uptake, 2) mildly increased uptake (i.e. below liver level uptake), 3) moderately increased uptake (i.e. at or slightly above liver level uptake) and 4) intensely increased uptake (i.e. substantially above liver level uptake) (Figure 5). Low dose CT images were used for attenuation correction, lesion location and measuring purposes only. Both nuclear medicine consultants reviewed all participants' images side by side to obtain consensus results for the study. Six months later, they reviewed the first 100 participants' images again, individually, to assess reproducibility.

The consultant radiologists had no access to F-18-FDG PET/CT images and the consultants in nuclear medicine had no access to CT images. Thus, the reviewers were completely blinded.

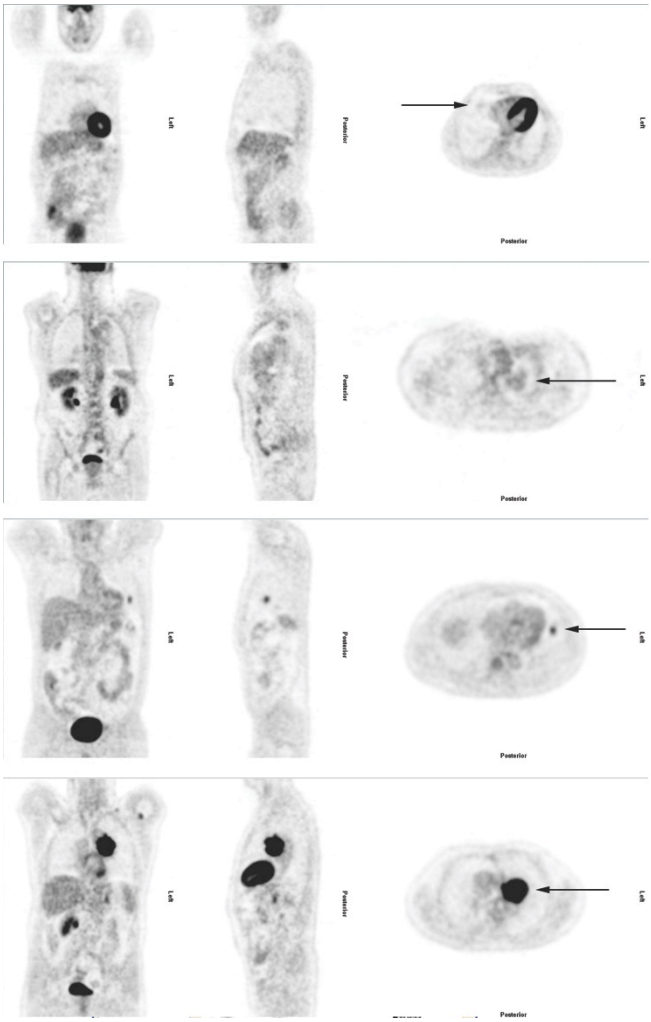

Figure5
Examples of the 4 F-18-FDG PET/CT ratings. From top to bottom these specific lesions were rated: negative, with mildly increased uptake, with moderately increased uptake and with intensely increased uptake.

3.2.7 DCE-CT study

DCE-CT examinations included only slices with nodules. DCE-CT was performed with an MDCT scanner (Philips Brilliance CT 64-channel scanner; Philips Healthcare, Best, The Netherlands). The acquisition parameters were: 64 x 0.625 mm collimation. A short sharp bolus injection of 60 ml iodixanole 270 mg/ml (Visipaque® 270; GE Healthcare, Oslo, Norway) was administered to all patients at a rate of 6 ml/second. Patients were scanned every two seconds for a period of 80 seconds (40 seconds active scan time). Raw picture data sets were transferred to a Philips Extended Brilliance™ workspace workstation v4.02 and were reviewed with the application Functional CT v. 4.5.2.
Blinded images were reviewed. The primary software input consisted of an arterial ROI placed in the aorta. This yielded two images: a time averaged, morphological image (c40, w350) (78) and time averaged Maximum Intensifier Projection *(tMIP)* perfusion maps. Based on this, the qualitative approach to DCE-CT was

examined (Figure 6). First, perfusion intensities were categorised into three categories: 1) less than 25%, 2) 25% to 50% or 3) 50% to 100% perfused. Second, perfusion patterns were categorised into five categories: no perfusion, partial rim perfusion, complete rim perfusion, heterogeneous perfusion or homogenous perfusion. Third, three well documented predictors of malignancy were assessed (3): 1) lesion size, measured as the greatest axial diameter on CT; 2) lesion morphology, assessed as smooth, irregular or spiculated and 3) lesion attenuation assessed as solid, partly solid or GGO. Although there was no formalised score system, these predictors were considered as the reviewers assigned each lesion an overall "potential of malignancy" rating using the following rating scale: 1) definitely benign, 2) probably benign, 3) indeterminate, 4) probably malignant and 5) definitely malignant.

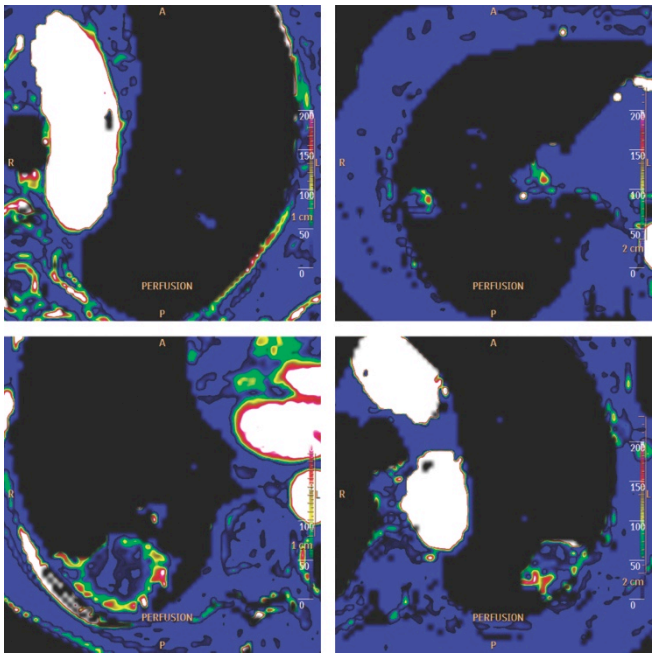

Figure6
Examples of perfusion patterns using the qualitative approach: (Top left) No perfusion; the lesion represents a squamous cell carcinoma. (Top right) Partial rim perfusion; the lesion represents an adenocarcinoma. (Bottom left) Complete rim perfusion; the lesion represents an adenocarcinoma. (Bottom right) Heterogeneous perfusion; the lesion represents a squamous cell carcinoma.

Secondary software input consisted of multiple tissue ROIs placed in the pulmonary lesions. Using the slope technique, the computer analysed the tissue ROIs voxel by voxel. This yielded four perfusion parameter measurements: perfusion (measured in ml/min/100 ml), peak enhancement intensity (measured in Hounsfield Units *(HU)*), time to peak (measured in seconds) and blood volume (measured in ml/100 g). Based on this, the quantitative approach to DCE-CT was examined (Figure 7). First, a tissue ROI was placed over the entire lesion using a morphological image and with the time set to the end of the arterial first pass *(large ROI(1))* (91). Second, a tissue ROI was placed over the entire lesion using perfusion maps with options set to default values *(large ROI(2))*. Third, a tissue ROI was placed in the maximally perfused parts of the lesion using perfusion maps with options set to default values *(small ROI)*. This process was repeated for each contiguous axial level of each lesion to ensure complete coverage of the lesion. The vendor specific default values were: Bone 300 HU (everything higher than 300 HU was whitened); Air -500 HU (everything below -500 HU was blackened) and Vessels deactivated. Finally, medians of the large ROI(1) measurements, large ROI(2) measurements and small ROI measurements of each lesion were computed in order to ensure that each lesion was represented by only one set of large ROI(1) measurements, only one set of large ROI(2) measurements and only one set of small ROI measurements. Medians were chosen to avoid extreme outliers.

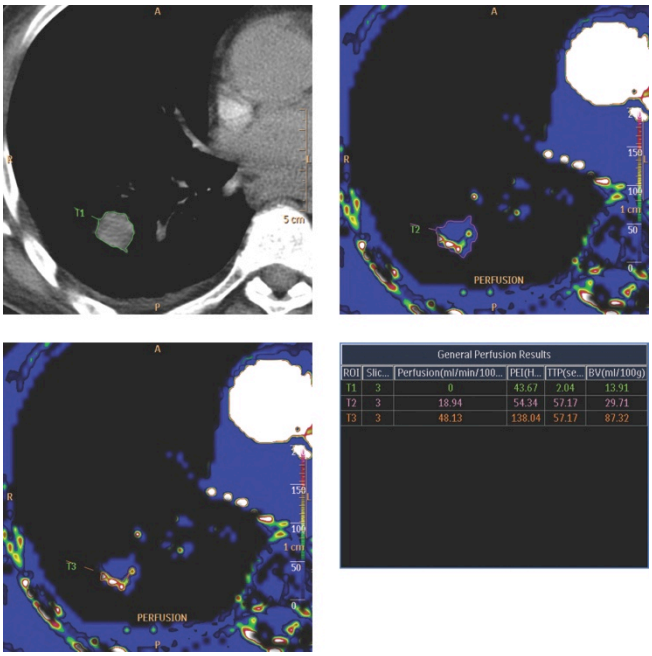

Figure7
Examples of ROI placements using the quantitative approach: T1, Large ROI(1); T2, Large ROI(2); and T3, Small ROI; the lesion represented an adenocarcinoma.

3.2.8 CT versus F-18-FDG PET/CT (2) study

CT including the chest and the upper abdomen was performed with an MDCT scanner (Philips Brilliance CT 64-channel scanner; Philips Healthcare, Best, The Netherlands). CT acquisition parameters were: 64 x 0.625 mm collimation, section thickness 2.0 mm, increment 1.0 mm. Iodixanole 270 mg/ml (Visipaque® 270; GE Healthcare, Oslo, Norway) or iohexole 300 mg/ml (Omnipaque® 300; GE Healthcare, Oslo, Norway), was injected intravenously in weight-adjusted doses of 2 ml/kg body weight to compensate for differences in distribution volume. A bolus tracking technique was used to compensate for differences in cardiac output. The trigger ROI was placed in the Aorta and when it exceeded 200 HU, the patients were scanned from the root of the neck to the upper abdomen including the liver and adrenals. CT was performed after a delay of 15 seconds for the chest and 65 seconds for the upper abdomen and raw picture data sets were transferred to a Philips Extended Brilliance™ Workspace workstation v4.02, where they were reviewed with the application CT-viewer.
Two consultant radiologists reviewed the studies. The reviewers were blinded to patient name, patient ID and clinical data. Lymph nodes were characterised as normal-sized or enlarged; a short axis diameter ≥ 1 cm on a transverse CT scan was considered enlarged. Mediastinal staging was done on a per-patient basis, in accordance to the seventh edition of the TNM classification of

malignant tumours (92). Both radiologists reviewed all participants' images side by side, to obtain consensus results for the study. Six months later, they reviewed the first 100 participants' images again, individually, to assess reproducibility.

As a part of a fast-track work-up for suspected lung cancer, the patients received CT and F-18-FDG PET/CT within few days, immediately followed by tissue sampling. Whole body F-18-FDG PET/CT including the head except for the brain, neck, thorax, abdomen, pelvis and thighs was performed with an integrated PET/CT scanner (Siemens Biograph w. 40-slice CT scanner; Siemens Healthcare, Erlangen, Germany). Participants were instructed to fast for 6 hours prior to the examination. Approximately 400 MBq F-18-FDG was injected intravenously. F-18-FDG PET/CT scans were performed after a delay of 60 minutes. The F-18-FDG PET images were corrected for scatter and iteratively reconstructed. CT acquisition parameters were: 40 x 3.0 mm collimation, section thickness 5.0 mm, increment 3.0 mm. No contrast medium was administered. F-18-FDG PET/CT picture data sets were transferred to a Hermes Gold 3™ workstation, where they were reviewed with the application Hermes Hybrid Viewer.
Two consultants in nuclear medicine did the F-18-FDG PET/CT reviews. The reviewers were blinded to patient names, patient IDs and clinical data. According to international guidelines (89, 90), F-18-FDG uptake was compared to the background uptake of the liver. Thus, lymph node uptake was rated on a scale of 1 to 3: 1) no uptake, 2) probably increased uptake and 3) definitely increased uptake. A rating of 1 was considered normal, a rating of 2 or 3 was considered abnormal. Mediastinal staging was done on a per-patient basis, in accordance to the seventh edition of the TNM classification of malignant tumours (92). Low dose CT images were used for attenuation correction, lesion location and measuring purposes only. Both nuclear medicine consultants reviewed all participants' images side by side to obtain consensus results for the study. Six months later, they reviewed the first 100 participants' images again, individually, to assess reproducibility. The consultant radiologists had no access to F-18-FDG PET/CT images and the consultants in nuclear medicine had no access to CT images. Thus, the reviewers were completely blinded.

3.2.9 Reference standard

In general in this PhD, tissue sampling was the preferred reference standard. As such, all malignant diagnoses were verified by tissue sampling and all non-malignant diagnoses were sought verified by tissue sampling. In this manner three separately obtained non-malignant diagnoses were accepted as a definitely benign result.
In most cases pulmonary lesion material was obtained by fluoroscopy-guided or CT-guided Transthoracic Needle Aspiration Biopsies *(TNAB).*However, in selected cases material was obtained by bronchoscopy or by Video-Assisted Thoracic Surgery*(VATS).* That way, definitive diagnoses were obtained in more than 90% in all three studies in this PhD.
Few studies of fluoroscopy-guided TNAB have limited enrolment to participants with pulmonary nodules < 4 cm in diameter. In one study with a very high prevalence of malignancy, a diagnosis was made by fluoroscope-guided needle aspiration biopsy in 84% of patients with nodules that measured 2 to 4 cm in diameter (93). However, in two other studies with a lower prevalence of malignancy, the diagnostic yield was only 36% to 43% (94, 95). On the other hand, several studies of CT-guided TNAB have limited enrolment to patients with pulmonary nodules < 4 cm in diameter. In 11 studies of CT-guided diagnostic biopsy results, sensitivity ranged from 82% to 100% (median, 97.5%) (3). However, when non-diagnostic biopsy results were included in the false negative column, sensitivity ranged from 65% to 94% (median, 90%). Non-diagnostic results were recorded in 4% to 41% of cases (median, 21%): in 0% to 22% of patients with malignant nodules (median, 8%) and in 0% to 89% of patients with benign nodules (median, 44%).
Bronchoscopy has traditionally been used for sampling central airway lesions, mediastinal lymph nodes and parenchymal masses. However, bronchoscopy's role in the management of SPNs has been small due to very low diagnostic yields. For malignant nodules < 20 mm, diagnostic yields have been as low as 10% - 50% (96-98). For benign nodules, diagnostic yields have been even lower.
VATS may be used to diagnose peripheral SPN. It is a minimally invasive technique with a sensitivity and specificity approaching 100% (99-101) and with an associated mortality of approximately 1% (102-107). Thoracotomy is sometimes necessary to make the diagnosis. The rate of conversion to thoracotomy is approximately 12%. If the nodule proves to be a primary lung malignancy, then therapeutic resection and staging are often completed in a single operative procedure.
In cases where it was inappropriate to do an invasive procedure to achieve a definitive diagnosis CT follow-up was accepted as reference standard. Studies have shown that solid nodules that have been stabile for at least 2 years usually do not require further evaluation (108-110), Therefore, CT follow-up was done at 3, 6, 12 and 24 months. Partly solid nodules and GGOs should be followed for at least 36 months. However, as the validity of the follow-up rules has been questioned (111), the follow-up period was longer if necessary. Follow-up ceased prematurely if lesions resolved entirely. The follow-up time was 8 to 28 months (median, 12 months) in the HRCT study and 5 to 30 months (median, 18 months) in the CT versus F-18-FDG PET/CT (1) study. All patients received tissue sampling in the DCE-CT study.
In the CT versus F-18-FDG PET/CT (2) study, mediastinal tissue sampling was obtained in all cases. This was accomplished primarily through mediastinoscopy with lymph node sampling from nodal stations 2R/L, 4R/L and 7 or through anterior mediastinotomy from nodal stations 3A, 5 and 6. In patients who received surgery, tissue sampling was obtained by complete lymph node resection.
Mediastinoscopy is performed in the operating room under general anaesthesia. In most centres, patients are discharged from the hospital the same day (112-114). The procedure involves an incision just above the suprasternal notch, insertion of a mediastinoscope alongside the trachea and biopsy of the mediastinal nodes. Rates of morbidity and mortality as a result of this procedure are low (2% and 0.08%, respectively) (115). Ideally, nodal stations 2R/L, 4R/L and 7 should routinely be examined, with at least one node sampled from each station. In 19 studies of cervical mediastinoscopy in lung cancer patients, sensitivity of mediastinoscopy to detect mediastinal node involvement from cancer was 40% to 97% (median, 78%) and the False Negative Rate *(FNR)* was 3% to 20% (median, 11%) (116).

This reflects our clinical setup as it was in 2008/2009. In our current clinical setup, mediastinoscopy is replaced by Endobronchial Ultrasound with Transbronchial Needle Aspiration (EBUS-TBNA) and Endoscopic Ultrasound with Needle Aspiration (EUS-FNA):

EBUS-TBNA is a relatively new technique for mediastinal staging, which can be performed on an outpatient basis. EBUS-TBNA can be used to sample nodal stations 1, 2R/L, 4R/L, 7, 10R/L, 11R/L and 12R/L. In eight studies of EBUS-TBNA of the mediastinum, the sensitivity was 79% to 95% (median, 90%) and the FNR was 1% to 37% (median, 24%) (116).
EUS-FNA of mediastinal lymph nodes through the wall of the oesophagus can also be performed on an outpatient basis. No mortality has been reported. EUS-FNA is particularly useful for nodal stations 4L, 5, 7, 8 and 9. In 16 studies of EUS-FNA of the mediastinum, the sensitivity was 45% to 100% (median, 84%) and the FNR was 0% to 61% (median, 19%) for the detection of N2 or N3 malignant mediastinal lymph nodes (116).

3.3 STATISTICAL METHODS

3.3.1 Estimates and confidence intervals

A confidence interval produces a move from a single value estimate - such as the sample mean, difference between sample means, etc. - to a range of values that are considered to be plausible for the population. The width of a confidence interval based on a sample statistic depends partly on its standard error and hence on both the standard deviation and the sample size.
The investigator can select the degree of confidence associated with a confidence interval, though 95% is the most common choice. If greater or less confidence is required different intervals can be constructed: 99%, 95% and 90% confidence intervals.

3.3.2 Measures of diagnostic accuracy

3.3.2.1 Receiver Operating Characteristic (ROC) curves

A Receiver Operating Characteristic *(ROC)* curve is a plot of test True Positive Rate *(TPR)* (or sensitivity) (plotted on the y axis) versus its False Positive Rate *(FPR)* (or 1 - specificity) (plotted on the x axis).
A popular measure of the accuracy of a diagnostic test is the Area Under the ROC curve *(AUC).* The ROC curve area can take on values between 0.0 and 1.0. A test with an area under the ROC curve of 1.0 is perfectly accurate because the sensitivity is 1.0 when the FPR is 0.0. In contrast, a test with an area of 0.0 is perfectly inaccurate.

3.3.2.2 Sensitivity, specificity, False Positive Rate and False Negative Rate

The sensitivity and specificity are often used to describe test performance. The result of a test can be classified as a True Positive *(TP) (sensitivity),* a True Negative *(TN) (specificity),* a False Positive *(FP) or* a false negative *(FN)* (Table 2). The test can have two types of errors, false positive errors and false negative errors. An ideal test has no false positives and no false negatives.

Table 2. Classification of test results by disease status

	Disease = 1	Disease = 0
Test result = 1	True positive *(TP)*	False positive *(FP)*
Test result = 0	False negative *(FN)*	True negative *(TN)*

Sensitivity is a measure of the conditional probability that a person having a disease will be correctly identified by a clinical test. It is defined as the number of true positive results divided by the total number of those with the disease. Sensitivity is calculated as TP/(TP + FN).
Specificity is a measure of the conditional probability that a person not having a disease will be correctly identified by a clinical test. It is defined as the number of true negative results divided by the total number of those without the disease. Specificity is calculated as TN/(FP + TN).
False Positive Rate (FPR) is defined as the rate of occurrence of positive test results in subjects known to be free of a disease for which an individual is being tested. FPR is calculated as (1 - specificity).
False negative Rate (FNR) is defined as the rate of occurrence of negative test results in subjects known to have a disease for which an individual is being tested. FNR is calculated as (1 - sensitivity).

3.3.2.3 Positive and negative predictive values

Because sensitivity and specificity provide an incomplete picture of the clinical usefulness of an imaging examination, two additional measurements that have much greater clinical relevance and intuitive appeal will also be discussed: positive and negative predictive values.
The Positive Predictive Value *(PPV)* indicates the likelihood of disease given a positive examination. PPV is defined, as the probability of disease in a patient whose examination result is abnormal: TP/(TP + FP). This value is sometimes referred to as “post-test likelihood” or “post-test probability of disease” because the predictive value simply reflects the probability of disease after the examination result is known.
The Negative Predictive Value *(NPV)* indicates the likelihood of no disease given a negative examination. NPV is defined, as the probability that disease is absent in a patient whose examination result is negative: TN/(FN + TN).
Although predictive values have substantial clinical usefulness, a short discussion of their weaknesses is warranted. The most important weakness is the dependence of predictive values on the pre-examination probability or the prevalence of disease in the imaged population: the higher the pre-examination probability of disease, the higher the post-examination probability of disease.

3.3.3 Observer agreement

Cohen’s kappa is a dominant technique for evaluating reader agreement in the radiology literature. Another technique is Bland and Altman’s 95% Limits of Agreement.

3.3.3.1 Kappa

Kappa is a technique for estimating paired inter-rater agreement for nominal and ordinal-level data (117). Kappa is a coefficient that represents agreement obtained between two readers beyond that which would be expected by chance alone (118). Key assumptions for using kappa include that the raters as well as the rated elements must be independent of each other (119).
Weighted kappa is used when the magnitude of disagreements is important. The observed and expected proportions of each cell are multiplied by a weight before using them to calculate kappa (120).
Kappa has the advantage that it is corrected for agreement with statistical chance and that there is an accepted method for com-

puting confidence intervals. The main disadvantage of κ is that the scale is not free of dependence on disease prevalence or the number of rating categories. As a consequence, it is difficult to interpret the meaning of any absolute value of κ, although it is still useful in experiments in which a control is used for prevalence and for the number of categories.
A κ of 1.00 means that there is perfect agreement and a κ of zero means that there is no agreement beyond chance. Interpretations of intermediate values are subjective, but an often-used range of κ values was suggested by Landis and Koch (118).

3.3.3.2 95% Limits of agreement
95% limits of agreement is a method to describe the agreement between methods of measurement (81, 82).
In order to describe the agreement between two methods of measurement, the difference between the measurements by the two methods, one minus the other, is calculated. Having obtained a set of numbers, the mean and standard deviation *(sd)* can be calculated. 95% of the differences can then be found in the interval mean ± 1.96 sd. The differences (plotted on the y axis) against the averages (plotted on the x axis) of the two methods are then plotted. The mean and the limits of agreement can be added as horizontal lines in the difference versus average plot, which should then include approximately 95% of the observations.
The 95% limits of agreement depend on some assumptions about the data: that the mean and sd of the differences are constant throughout the range of measurements and that these differences are from an approximately normal distribution.

3.3.4 Statistical methods in this PhD
As this PhD deals with studies of diagnostic performance, in general three statistical methods were used to describe the data: the area under the ROC curve was used to describe the overall diagnostic accuracy; sensitivity and specificity were used to describe the classification probabilities; and kappa or 95% limits of agreement were used to describe the reproducibility. Furthermore, according to accepted scientific standard, all data were reported using 95% confidence intervals. Exact measures were used whenever possible.
Sample test statistics was used when appropriate; in these instances Fisher's exact test was used to test for correlation between categorised (nominal) variables, and Spearman's rho was used to test for correlation between ordered categorised (ordinal) variables. The chi-square test was used to test for non-independence of the areas under the ROC curves of CT and F-18-FDG PET/CT. P-values < 0.05 were considered statistically significant, and p-values < 0.001 were considered highly statistically significant.
The licensed statistical software package STATA/IC 10 (STATAcorp LP, College Station, Texas, United States) or STATA/SE 11 (STATAcorp LP, College Station, Texas, United States), was used.
Pulmonary lesions were rated on an ordinal scale from 1 to 5 (CT) or from 1 to 4 (F-18-FDG PET/CT), with higher values being indicative of malignancy (121). In all studies, diagnostic accuracy was defined as the area under the fitted ROC curve and was computed using the ratings with a maximum-likelihood ROC model assuming bivariate normal distributions (122). Sensitivity, specificity, positive predictive value and negative predictive value were computed from the resulting 2x2 contingency tables. Two different clinical situations relating to CT's role as the first examination in a line of examinations, were addressed: 1) What were the sensitivity, specificity and positive predictive value if CT was used to identify patients with lung cancer? In this situation it was important to achieve a high positive predictive value. Therefore CT ratings 1 to 3 were considered benign results, and CT ratings 4 and 5 were considered malignant results. 2) What were the sensitivity, specificity and negative predictive value if CT was used to rule out cancer? In this situation it was important to achieve a high sensitivity and a high negative predictive value. Therefore CT ratings 1 and 2 were considered benign test results, and CT ratings 3 to 5 were considered malignant test results. In both situations F-18-FDG PET/CT rating 1 was considered a benign test result, and F-18-FDG PET/CT ratings 2 to 4 were considered malignant test results. The reproducibility of the results was assessed with weighted kappa of the original ratings.
In the quantitative part of the DCE-CT study, three different methods of measurement were compared. Only the first measurement by each method was used to compare the methods; the second measurement was used to study the reproducibility. Analyses were made on the logarithmic scale due to non-normal distribution of the individual measurements, as well as due to variance inhomogeneity of the differences between the methods of measurement. After logarithmic transformation, the individual measurements approached the normal distribution and the variance of the differences between the methods of measurement approached homogeneity. Log scale means and mean differences between methods of measurement were computed and paired t-tests were used to assess whether there were statistically significant differences between the methods of measurement. Results were presented as medians and median ratios and with 95% limits of agreement. All transformations were done according to the mathematical relationship log (b) - log (a) = log (b/a) → exp [log (b) – log (a)] = b/a
Log scale means and mean differences between malignant and benign nodules were computed and unpaired t-tests were used to assess whether any of the perfusion parameters could be used to distinguish between malignant and benign lesions. Results were presented as medians and illustrated by box and whiskers plots. Log scale agreement plots were used to assess the reproducibility of the three methods. Results were presented as median ratios and with 95% limits of agreement as described by Bland and Altman (81, 82).
In the CT versus F-18-FDG PET/CT (2) study, according to the significance of involvement of N2 or N3 lymph nodes, all participants were classified as having either positive (N2 or N3) or negative (N0 or N1) staging results and as having or not having mediastinal lymph node involvement as determined by the reference standard. Again, diagnostic accuracy, defined as the area under the fitted ROC curve, was computed using the ratings with a maximum-likelihood model assuming bivariate normal distributions (122). Sensitivity and specificity were computed from the resulting 2x2 contingency tables. The reproducibility of these results was assessed with weighted kappa of the original ratings.

4. RESULTS
4.1 HRCT STUDY
First, all nodules were categorised by their attenuation: 92% (196/213) were solid nodules, 7% (15/213) were partly solid nodules and 1% (2/213) were GGOs. 57% (112/196) of the solid nodules, 73% (11/15) of the partly solid nodules and 50% (1/2) of the GGOs were malignant; reproducibility was substantial (κ =

0.73). Second, all solid nodules were rated by their edge morphology: 53% (59/112) of the malignant, solid nodules were categorised as high-risk nodules, 38% (43/112) as intermediate-risk nodules and only 9% (10/112) as low-risk nodules (Spearman's rho = 0.54; p < 0.001); reproducibility was substantial (κ = 0.67) (Figure 8). Third, all solid nodules with calcifications were rated by the calcification patterns: all malignant nodules were rated as "malignant" or "indeterminate" and all benign nodules were rated "benign" (Spearman's rho = 0.92; p < 0.001); reproducibility was substantial (κ = 0.74). Fourth, all solid nodules with one or more specific morphological features were identified: one specific feature, retraction of the pleura, was highly associated with malignancy (p < 0.001); reproducibility was substantial (κ = 0.56). Other specific features were also identified, but these were either insignificantly associated to malignancy or had poor reproducibility.

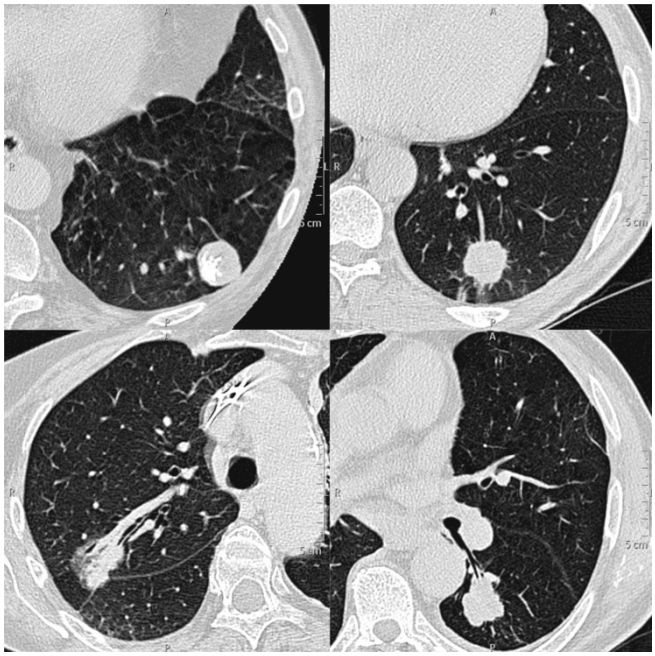

Figure8
(Top left) Solid nodule with smooth edges (low-risk nodule) and benign calcifications; this nodule represented a hamartoma. (Top right) Solid nodule with spiculated edges (high-risk nodule); this nodule represented a squamous cell carcinoma. (Bottom left) Partly solid nodule (partly solid nodules and GGOs were not risk rated); this nodule represented an adenocarcinoma. (Bottom right) Solid nodule with irregular/lobulated edges (intermediate-risk nodule); this nodule represented an adenocarcinoma. (All: C-425 to W1400)

Overall accuracy was 87% (83% to 92%). If HRCT was used to identify patients with lung cancer, sensitivity, specificity, positive predictive value and negative predictive value were 82% (74% to 89%), 72% (61% to 81%), 80% (72% to 87%) and 74% (64% to 83%), respectively; FPR was 28%. If HRCT was used to rule out cancer, sensitivity, specificity, positive predictive value and negative predictive value were 98% (94% to 100%), 23% (14% to 33%), 64% (57% to 71%) and 91% (71% to 99%), respectively; FNR was 1.6%. Reproducibility of these results was substantial (κ = 0.76). HRCT ratings are presented in Table 3.

Table 3. HRCT ratings (Spearman's rho = 0.62; p < 0.001)

	Def. benign	Prob. benign	Indeterminate	Prob. malignant	Def. malignant	Total
Benign	8	12	44	18	7	89
Malignant	0	2	20	21	81	124
Total	8	14	64	39	88	213

4.2 CT VERSUS F-18-FDG PET/CT (1) STUDY

4.2.1 Overall results

89 males and 79 females ages 34 to 88 years (mean, 66 years) participated in the study. Each participated with a single pulmonary lesion. 81% (136/168) of the lesions were malignant and 19% (32/168) were benign. The malignant lesions had the following distribution: 47% (64/136) adenocarcinomas, 30% (41/136) squamous cell carcinomas, 4% (6/136) large cell carcinomas, 9% (12/136) other or undifferentiated NSCLCs, 8% (11/136) Small Cell Lung Carcinomas *(SCLCs)* and 1% (2/136) metastases from extrathoracic cancers.
There was no significant difference between the areas under the ROC curves of CT and F-18-FDG PET/CT (χ^2 = 0.07; p = 0.80) (Figure 9). Although based on different criteria, CT and F-18-FDG PET/CT ratings were both highly associated to malignancy (both p < 0.001). Likewise, the overall accuracy was higher than 80% for both imaging modalities. This was irrespective if whether CT was used to identify lung cancer or to rule out cancer.

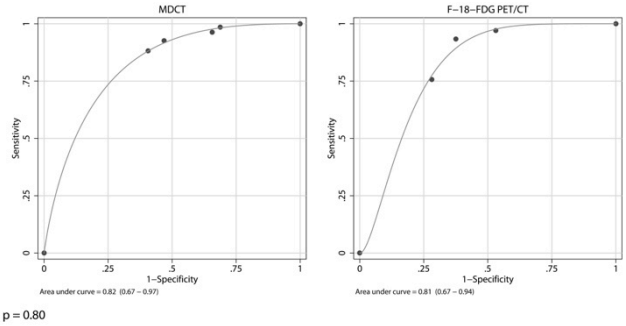

Figure9
These two parametric ROC curves illustrate the overall lesion characterisation results for CT (left) and F-18-FDG PET/CT (right). In this study the overall diagnostic accuracy of CT and of F-18-FDG PET/CT was defined as the area under the parametric ROC curves. The two ROC curves were compared using the chi-square test.

The sensitivity of CT did not vary significantly, irrespective of whether the imaging modality was used to identify lung cancer (93%) (126/136) or to rule out cancer (96%) (131/136). However, specificity was almost 20 percentage points higher if CT was used to identify lung cancer (53%) (17/32) than to rule out cancer (34%) (11/32) (Table 5). Reproducibility of the CT ratings was substantial (κ = 0.62 (0.41 to 0.76)).
F-18-FDG PET/CT results were very similar to CT results; sensitivity for F-18-FDG PET/CT was 97% (132/136), specificity was 47% (15/32) (Table 5). Reproducibility of the F-18-FDG PET/CT ratings was substantial (κ = 0.73 (0.43 to 0.89)).
When the false positives and false negatives were reviewed, the modalities also yielded very similar results (Table 5, Figure 10 and Figure 11). The false positive rate (or 1 – specificity), at approxi-

mately 50%, was clearly too high; this was irrespective of imaging modality and of the clinical situation. On the other hand, the false negative rate (or 1 – sensitivity) was well below 5% in rule out instances. Of special note, the false negative lesions of F-18-FDG PET/CT were comprised of three adenocarcinomas and a transitional cell carcinoma metastasis. The size of these lesions ranged from 7 mm to 24 mm (median, 17 mm).

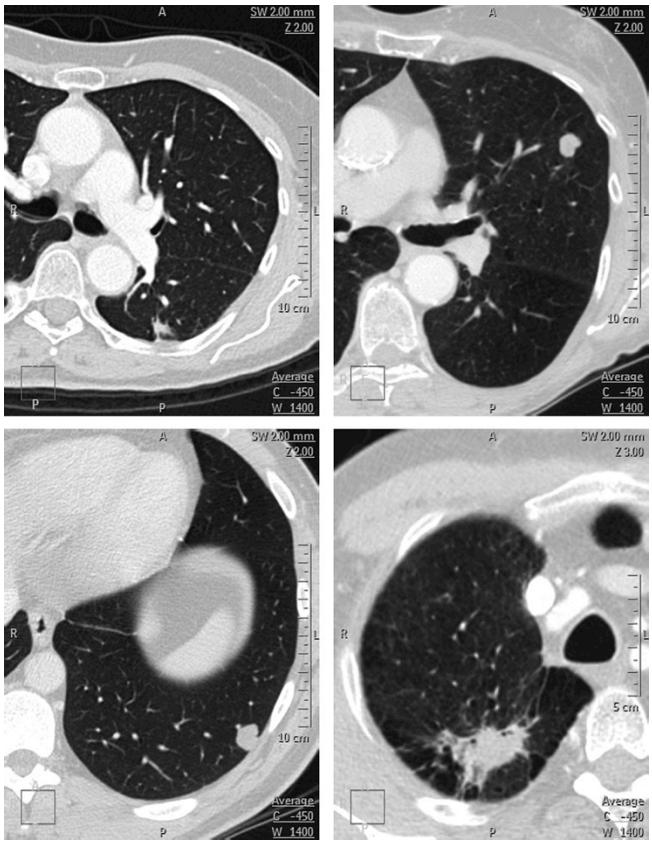

Figure10
This figure illustrates four false negative lesions on CT. Both nodules in the top row were rated "definitely benign" and both nodules in the bottom row were rated "probably benign". Both nodules in the top row and the nodule in the bottom left represent adenocarcinomas; the nodule in the bottom right represents a large cell carcinoma (bottom right). In retrospect, the large cell carcinoma could have been rated differently. (All: C-450; W1400).

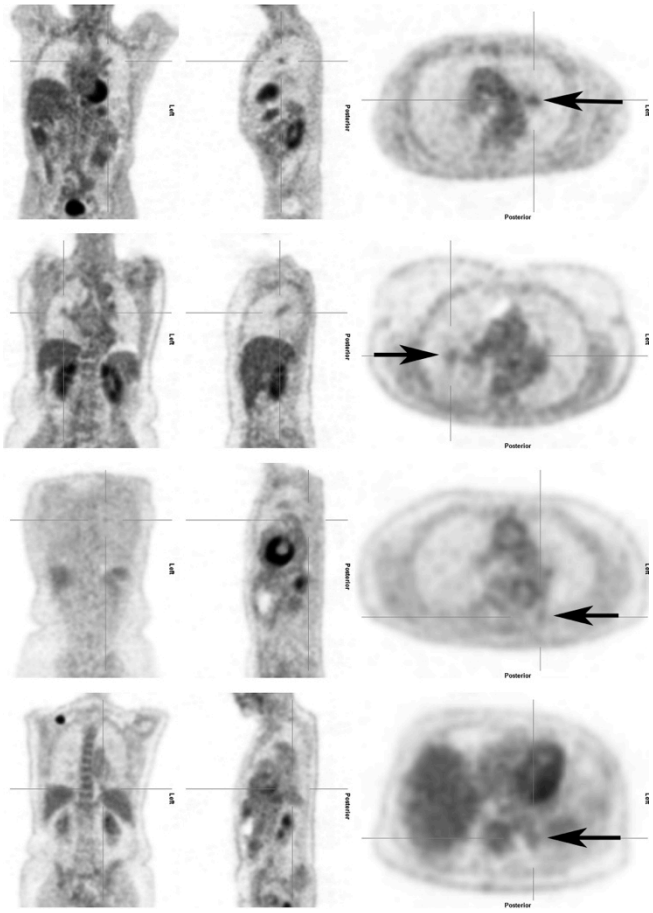

Figure11
This figure illustrates four false negative lesions on F-18-FDG PET/CT: The lesions in rows 1 to 3 represent adenocarcinomas; the lesion in row 4 represents a transitional cell carcinoma metastasis.

CT and F-18-FDG PET/CT ratings are presented in “wide” layout in Table 4 (123). Derived classification probabilities and predictive values are presented in Table 5 and Table 6.

Table 4a. CT and F-18-FDG PET/CT ratings

Reference std. benign	Def. benign	Prob. benign	Indeterminate	Prob. malignant	Def. malignant	Total
No uptake	6	1	4	1	3	15
Mildly increased uptake	2	0	0	1	2	5
Moderately increased uptake	0	0	1	0	2	3
Intensely increased uptake	2	0	1	0	6	9
Total	10	1	6	2	13	32

Paired CT (columns) and F-18-FDG PET/CT (rows) ratings when the reference std. was indeed benign.

Table 4b. CT and F-18-FDG PET/CT ratings

Reference std. malignant	Def. benign	Prob. benign	Indeterminate	Prob. malignant	Def. malignant	Total
No uptake	1	0	0	1	2	4
Mildly increased uptake	0	1	1	0	3	5
Moderately increased uptake	0	1	0	1	22	24
Intensely increased uptake	1	1	4	4	93	103
Total	2	3	5	6	120	136

Paired CT (columns) and F-18-FDG PET/CT (rows) ratings when the reference std. was indeed malignant.

Table 5. Overall results of CT and F-18-FDG PET/CT

	CT used to id lung cancer	CT used to rule out cancer	F-18-FDG PET/CT
Sensitivity	93% (87% to 96%)	96% (92% to 99%)	97% (93% - 99%)
Specificity	53% (35% to 71%)	34% (19% to 53%)	47% (29% - 65%)
PPV	89% (83% to 94%)	86% (80% to 91%)	89% (82% - 93%)
NPV	63% (42% to 81%)	69% (41% to 89%)	79% (54% - 94%)
FPR	47%	66%	53%
FNR	7.3%	3.7%	2.9%

Note: the positive predictive value always reflects the likelihood of disease given a positive examination. Likewise, the negative predictive value always reflects the likelihood of no disease given a negative examination. This is irrespective of whether CT is used to id lung cancer or if it used to rule out cancer. Derived from Table 4.

4.2.2 Stratified results

Next, CT results were used to stratify F-18-FDG PET/CT results into subgroups.

If CT was used to identify patients with lung cancer *(i.e. lesions reviewed as being probably malignant or definitely malignant on CT (n = 141)),* a positive F-18-FDG PET/CT examination would make the likelihood of malignancy even higher. For this purpose, sensitivity and specificity of F-18-FDG PET/CT were 98% (123/126) and 27% (4/15), respectively; the false positive rate was 73% (Table 6).

If CT was used to rule out cancer *(i.e. lesions reviewed as being probably benign or definitely benign on CT (n=16)),* obviously the clinical issue would be to rule out cancer. For this purpose, sensitivity and specificity of F-18-FDG PET/CT were 80% (4/5) and 64% (7/11), respectively; the false negative rate was 20% (Table 6).

Finally, if CT was indeterminate *(i.e. lesions reviewed as being indeterminate on CT (n = 11)),* sensitivity and specificity of F-18-FDG PET/CT were 100% (5/5) and 67% (4/6), respectively; the false positive rate was 33%. There were no false negatives (Table 6).

Table 6. Stratified results of F-18-FDG PET/CT, if

	CT was used to id lung cancer	CT was used to rule out cancer	CT was indeterminate
Sensitivity	98% (93% to 100%)	80% (28% to 100%)	100% (48% to 100%)
Specificity	27% (8% to 55%)	64% (31% to 89%)	67% (22% to 96%)
PPV	92% (86% to 96%)	50% (16% to 84%)	71% (29% to 96%)
NPV	57% (18% to 90%)	88% (47% to 100%)	100% (40% to 100%)
FPR (1-spec)	73%	36%	33%
FNR (1-sens)	2%	20%	0%

Derived from Table 4.

4.3 DCE-CT STUDY

4.3.1 Qualitative approach

Using the qualitative approach, a statistically significant correlation was established between perfusion patterns and malignancy ($p = 0.022$). Overall accuracy was 89% (81% to 98%). If DCE-CT was used to identify patients with lung cancer, sensitivity, specificity, positive predictive value and negative predictive value were 83% (69% to 92%), 83% (52% to 98%), 95% (84% to 99%) and 56% (31% to 79%), respectively. If DCE-CT was used to rule out cancer, sensitivity, specificity, positive predictive value and negative predictive value were 96% (86% to 100%), 33% (10% to 65%), 85% (72% to 93%) and 67% (22% to 96%), respectively.

4.3.2 Quantitative approach

Using the quantitative approach, three separate sets of tissue ROIs were placed: large ROIs(1) placed using morphological images, large ROIs(2) placed using perfusion maps and small ROIs placed using perfusion maps. This yielded a plethora of results, as follows.

First, because of their non-normal nature, DCE-CT measurements must be analysed using the log scale. Second, there were no measurable differences between large ROIs(1) and large ROIs(2). On the other hand, there were measurable differences between large ROIs(2) and small ROIs. In general, small ROI measurements were higher. This was supported by median ratios and by 95% limits of agreement and was highly significant for perfusion ($p < 0.001$), peak enhancement intensity ($p < 0.001$) and blood volume ($p < 0.001$). Third, neither perfusion, peak enhancement intensity, time to peak, nor blood volume could be used to distinguish between malignant and benign lesions. This was irrespective of the method of quantification [large ROI(1), ($0.13 < p < 0.96$); large ROI(2), ($0.13 < p < 0.76$); and small ROI, ($0.084 < p < 0.73$)]. Fourth, although there were no indications of systematic reproducibility bias, the 95% limits of agreement were so broad, that the risk of disagreement could potentially affect the clinical utility of the measurements. This was irrespective of the method of quantification.

4.4 CT VERSUS F-18-FDG PET/CT (2) STUDY

4.4.1 Overall results

114 patients participated in the study. 89 of these patients received surgery with complete lymph node resection; 25 received mediastinoscopy/-tomy only. The nodal stage distribution was 61% (69/114) N0, 13% (15/114) N1, 23% (26/114) N2 and 4% (4/114) N3.

There was no significant difference between the areas under the ROC curves of CT and F- 18-FDG PET/CT ($\chi^2 = 0.53$; $p = 0.47$) (Figure 12). However, whereas CT results were significantly associated to reference standard results ($\rho = 0.29$; $p = 0.002$), F-18-FDG PET/CT results were not ($\rho = 0.16$; $p = 0.08$).

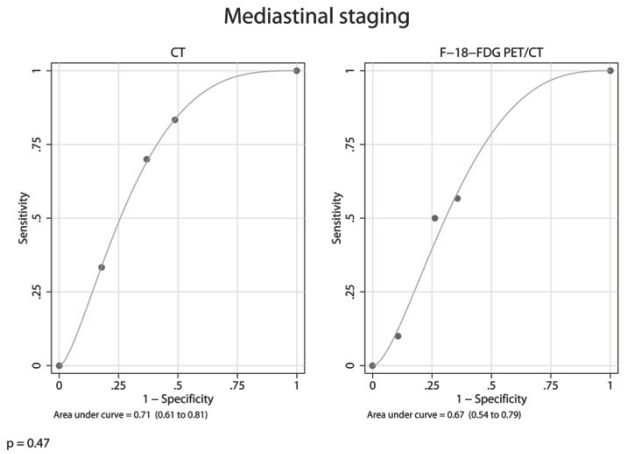

Figure12
These two parametric ROC curves illustrate the overall mediastinal staging results of CT (left) and F-18-FDG PET/CT (right). In this study the overall diagnostic accuracy of CT and of F-18-FDG PET/CT was defined as the area under the parametric ROC curves. The two ROC curves were compared using the chi-square test.

CT and F-18-FDG PET/CT ratings are presented in "wide" layout in Table 7 (123). Derived classification probabilities and predictive values are presented in Table 8 and Table 9.

Table 7a. CT and F-18-FDG PET/CT ratings

Reference std. N0/N1	N0 (CT)	N1 (CT)	N2 (CT)	N3 (CT)	Total
N0 (F-18-FDG PET/CT)	31	7	8	8	54
N1 (F-18-FDG PET/CT)	5	2	0	1	8
N2 (F-18-FDG PET/CT)	3	1	7	2	13
N3 (F-18-FDG PET/CT)	4	0	1	4	9
Total	43	10	16	15	84

Paired CT (columns) and F-18-FDG PET/CT (rows) ratings when the reference std. was indeed N0/N1.

Table 7b. CT and F-18-FDG PET/CT ratings

Reference std. N2/N3	N0 (CT)	N1 (CT)	N2 (CT)	N3 (CT)	Total
N0 (F-18-FDG PET/CT)	4	3	3	3	13
N1 (F-18-FDG PET/CT)	1	0	1	0	2
N2 (F-18-FDG PET/CT)	0	1	7	4	12
N3 (F-18-FDG PET/CT)	0	0	0	3	3
Total	5	4	11	10	30

Paired CT (columns) and F-18-FDG PET/CT (rows) ratings when the reference std. was indeed N2/N3.

CT correctly classified 65% (74/114) of the cases. 27% (31/114) were falsely overstaged and 7% (9/114) were falsely understaged. The overall sensitivity and specificity of CT for mediastinal staging were 70% (21/30) and 63% (53/84), respectively (Table 8). Reproducibility of the CT stagings was substantial (κ = 0.63 (0.47 to 0.77))
F-18-FDG PET/CT correctly classified 68% (77/114) of the cases. 19% (22/114) were falsely overstaged and 13% (15/114) were falsely understaged. The overall sensitivity and specificity of F-18-FDG PET/CT for mediastinal staging were 50% (15/30) and 74% (62/84), respectively (Table 8). Reproducibility of the F-18-FDG PET/CT stagings was moderate (κ = 0.57 (0.39 to 0.72))
The false positive rates (or 1 – specificity) of CT and F-18-FDG PET/CT were 37% and 26%, respectively; the false negative rates (or 1 – sensitivity) were 30% and 50%, respectively. The false negative lymph nodes were located at stations 3A, 4R/L and 7, irrespective of imaging modality.

Table 8. Overall results of CT and F-18-FDG PET/CT

	CT	F-18-FDG PET/CT
Sensitivity	70% (51% to 85%)	50% (31% to 69%)
Specificity	63% (52% to 73%)	74% (63% to 83%)
Positive predictive value	40% (27% to 55%)	41% (25% to 58%)
Negative predictive value	86% (74% to 93%)	81% (70% to 89%)
False positive rate	37%	26%
False negative rate	30%	50%

Derived from Table 7.

4.4.2 Stratified results

Next, CT results were used to stratify F-18-FDG PET/CT results into subgroups.
In patients with enlarged lymph nodes on CT (n = 52), the sensitivity and specificity of F-18-FDG PET/CT were 67% (14/21) and 55% (17/31), respectively; the false positive rate was 45% (Table 9).
In patients without enlarged lymph nodes on CT (n = 62), the sensitivity and specificity of F-18-FDG PET/CT were 11% (1/9) and 85% (45/53), respectively; the false negative rate was 89% (Table 9).

Table 9. Stratified results of F-18-FDG PET/CT, in patients

	with enlarged lymph nodes on CT	without enlarged lymph nodes on CT
Sensitivity	67% (43% to 85%)	11% (0% to 48%)
Specificity	55% (36% to 73%)	85% (72% to 93%)
Positive predictive value	50% (31% to 69%)	11% (0% to 48%)
Negative predictive value	71% (49% to 87%)	85% (72% to 93%)
False positive rate	45%	15%
False negative rate	33%	89%

Derived from Table 7.

4.4.3 Metastases

CT identified a total of 29 patients with metastases. Most of these metastases were located to the pleural or pericardial fluid or the contralateral lung. 8 of the metastases were verified by biopsy.
F-18-FDG PET/CT identified a total of 44 patients with metastases. Most of these metastases were located to the bones or the contralateral lung. 9 of the metastases were verified by biopsy.

5. DISCUSSION

The discussion will evolve around the main question of this PhD: The performance characteristics of the standardized imaging modalities chest radiography, CT and F-18-FDG PET/CT for characterisation of pulmonary lesions, followed by a discussion of the experimental imaging modality DCE-CT. The performance characteristics of CT and F-18-FDG PET/CT for mediastinal staging in NSCLC are also discussed. Finally, general limitations of the studies and comments on the evolvement of the imaging algorithms in the past few years are discussed.

5.1 CHARACTERISATION OF PULMONARY NODULES

5.1.4 HRCT study

The distribution of solid nodules, partly solid nodules and GGOs in our study did not match that of the ELCAP study. Like in the ELCAP study however, there was an overweight of malignancy among the partly solid nodules. The first part of our study was based on a previous study in which Furuya et al cross-tabulated edge morphology with malignancy and came to highly significant

results (124). However, these results have later been questioned (125). In our study, focus was on edge morphology of solid nodules only. These were organised into categories according to patient risk. On that basis, a highly significant association with malignancy was achieved with clinically acceptable reproducibility. Similarly, for calcification patterns, a highly significant association with malignancy was found and also this time with an acceptable reproducibility. In addition, a highly significant association was found between retraction of the pleura and malignancy.
This study confirmed that attenuation and edge morphology are easy to apply in clinical practice, although certain types of edges are hard to discriminate (Figure 13). However, data from this study show that when further organised by their inherent risk of malignancy, the clinical impact of these discrepancies is of minor importance and that the reproducibility of dividing patients into risk of malignancy groups is high. Calcification patterns and pleural retraction are also easy to apply in the daily clinical practice and these features have high reproducibility as well.

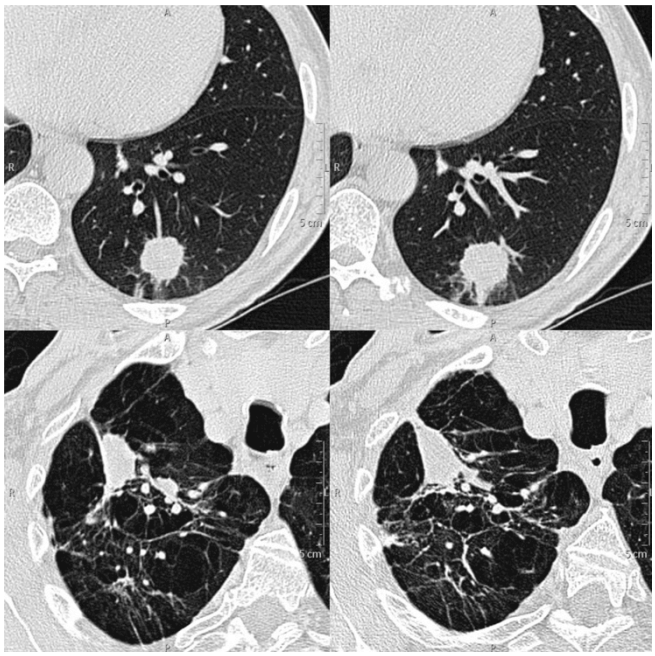

Figure13
(Top row) Two HRCT images of the same SPN on two different slices 4 mm apart. (Bottom row) Two HRCT images of another SPN on two different slices 5 mm apart. These images illustrate that the same nodule can look very different on slices closely apart. Naturally, this affects the reproducibility of edge morphology and is the reason behind the need to organize nodules into risk categories. (All: C 425 to W1400)

The second part of the study dealt with the diagnostic accuracy of using HRCT to identify patients with lung cancer or to rule out cancer. Although it was not possible to identify previous studies applying HRCT in this way, the sensitivity and specificity of our study closely matched international reports in which standard contrast-enhanced CT were used to identify patients with lung cancer (3, 49). It was not possible to identify previous reports in which CT was used specifically to rule out cancer.
One issue remains, however. In the identification of patients with lung cancer, a strategy intended to maximize the positive predictive value was chosen. In spite of this strategy, there was a false positive rate of 28%. Thus, there is a substantial risk of overdiagnosis of cancer-free individuals. In contrast, a strategy intended to maximize the negative predictive value was applied to rule out cancer. In this case there was a false negative rate of 2%. These numbers indicate that HRCT is in fact best suited to rule out cancer.
In conclusion, HRCT of a solitary pulmonary nodule, assessed using attenuation and morphological criteria is fast, widely available and effective method for diagnosing lung cancer correctly, and especially for ruling out cancer.

5.1.5 CT versus F-18-FDG PET/CT (1) study

Previous studies by our research group have indicated that the prevalence of lung cancer is 15% to 20% in the population referred to CT (126, 127). However, in this study the “pre-study” standard contrast-enhanced CT raised the prevalence of malignancy to more than 80%, a significant result in itself. It was obvious from the overall results, that standard contrast-enhanced CT is better suited to diagnose patients with lung cancer, than to rule out cancer; all other things being equal, the specificity for the former purpose was 20 percentage points higher than for the latter one. On the other hand, there was strikingly little difference between overall CT and F-18-FDG PET/CT results.
These results raised a need for stratification according to CT results in order to mimic the setup in the daily practice. When reviewing the stratified results, it appeared that F-18-FDG PET/CT could be an effective examination for patients, if these were previously identified with lung cancer on CT or if the CT was indeterminate. However, in a clinical setting, these patients would already be considered highly suspicious for malignant disease and though F-18-FDG PET/CT might make the likelihood of lung cancer even higher, the need to obtain a lesion biopsy would in most cases make further diagnostic imaging redundant. Thus, in this context, F-18-FDG PET/CT would make no difference to these patients. The next question was whether F-18-FDG PET/CT should be offered to patients, if these were previously deemed cancer-free on CT. Obviously, for these patients the major clinical issue would be to rule out cancer. However, the low prevalence of malignancy in these patients combined with the rather significant false negative rate of F-18-FDG PET/CT indicates that the chance of finding an additional lung cancer in this group would be so low that it would hardly justify further workup. Therefore, clinically, it would make more sense to follow these patients with CT.
The results of this study are fairly close to those previously reported on the subject, further bolstering these. In the present study, the prevalence of malignancy was 81%. If CT was used to identify patients with lung cancer, sensitivity and specificity were 93% and 53%, respectively; F-18-FDG PET/CT sensitivity and specificity were 97% and 47%, respectively. In comparison, in analysis by Wahidi et al from 2007 (3), the prevalence of malignancy was 48% to 73% in 8 studies of CT imaging. In the same analysis, the prevalence of malignancy was 46% to 82% in 17 studies of F-18-FDG PET imaging. CT sensitivity was 98% to 100% (median, 100%) and specificity was 54% to 95% (median, 75%); F-18-FDG PET/CT sensitivity was 80% to 100% (median, 87%) and specificity was 40% to 100% (median, 83%). In turn, those results were slightly less optimistic than those of 40 studies of F-18-FDG PET analysed by Gould et al in 2001 (49).
There were some limitations to the design of this study, the most significant of which was whether it was justifiable to let the outcome of one imaging test determine whether the next should be carried out. However, as mentioned above, this trial was per-

formed in the clinical setting and represented everyday imaging algorithms and problems. Clinically, it would not be feasible to suggest F-18-FDG PET/CT as the first examination for patients with suspected lung cancer due to cost-benefit analyses as well as due to radiation exposure considerations.
Conversely, our study's strengths must also be mentioned. Patient sampling preceded both imaging and reference standard. This prospective design, as well as the blinding procedure conforms to the STARD statement from 2003, which dictates that these are both natural requisites in studies of diagnostic accuracy (128). Furthermore, there was the large study size: 168 participants with pulmonary lesions were included. This should be compared to an average study size of 37 to 66 participants per study for both CT and for F-18-FDG PET/CT in most studies (3, 49), making our study comparably strong. In addition, all results in this study were controlled for reproducibility. Though this has been standard for CT since the STARD statement, to the best of our knowledge, reproducibility has not previously been controlled for F-18-FDG PET/CT.
In conclusion, this study was initiated to compare CT with F-18-FDG PET/CT for characterisation of pulmonary lesions in patients with suspected lung cancer. When used early in the work-up of the lesions, CT raised the prevalence of lung cancer in the population to the point at which further diagnostic imaging examination could be considered redundant. Standard contrast-enhanced CT seems better suited to identify patients with lung cancer than to rule out cancer. Finally, the overall diagnostic accuracy as well as the classification probabilities and predictive values of the two modalities were not significantly different. The reproducibility of the above results was substantial.

5.3.6 DCE-CT study

To our knowledge, a qualitative approach to DCE-CT has not previously been reported. In that sense, these results are unique. However, we had to conclude, that although we established a connection between perfusion patterns and malignancy, and although we achieved acceptable overall accuracy, sensitivity, and specificity, these results were less impressive when compared to our previous studies of CT alone (126), as well as of CT with an additional HRCT (127). In fact, we had to conclude that this new qualitative approach to DCE-CT does not contribute anything new in patients with suspected lung cancer.
If we turn to the quantitative approach to DCE-CT, the last decade has seen positive reports of the benefits of DCE-CT in the diagnosis of colorectal cancer (129-131), head and neck cancer (132, 133) and lung cancer (74-78). So far, however, logarithmic scale data transformation prior to analysis has not been standard in quantitative approaches; none the less, our data was unambiguously in favour of data transformation. Logarithmic scale data transformation lowered variance and made analyses as well as results more robust. Therefore, it seems reasonable that logarithmic scale data transformation should be used in other DCE-CT studies as well.
We were not able to distinguish between malignant and benign lesions; this is despite the fact that we examined three different ROI methods. At least for small ROIs this came as a surprise to us, as small ROIs, in theory, only reflect viable lesion tissue. On that basis, we find it somewhat difficult to recommend DCE-CT for patients with suspected lung cancer, and thus, find ourselves in dissent to previous studies on the matter. As reported in the methodology section, Zhang et al (78), and Yi et al (65) reported that perfusion and peak enhancement intensity measurements are higher for malignant and inflammatory lesions than for benign lesions. However, in none of these reports did the authors use log scale data transformation of data prior to analysis; and, as they furthermore did not discriminate between malignant and inflammatory lesions, these results are of little clinical value and will remain so until valid cut-offs can be established that can discriminate between malignant lesions and all types of benign lesions.
The reproducibility was also troublesome. The more specific the tissue ROIs got, the more the reproducibility fell, along with the validity of the results. Although there were no indications of systematic reproducibility bias, the 95% limits of agreement were too broad. Unfortunately, as long as no current software suites automatically draw reliable ROIs and propagate them throughout the sequences, lack of reproducibility must be expected. This has been experienced for all functional modalities that rely on the application of tissue ROIs. We consider this lack of reproducibility another setback for the clinical utility of DCE-CT for patients with suspected lung cancer (123). In that sense, we tend to agree with Ng et al, who, in a study regarding late stage lung cancer, concluded that the broad 95% limits of agreement could potentially be of concern (83, 84). In our study, lack of reproducibility represented a setback for DCE-CT.
This study's strengths must also be mentioned. As patient sampling preceded both imaging and reference standard, the study design was prospective, and as in both CT versus F-18-FDG PET/CT studies, this design is follows the STARD statement. It is also essential to mention that most of the preliminary studies cited in this report have included 15 to 30 participants, whereas the more thorough studies have included approximately 60 participants, making this study, with its 59 participants comparatively strong.
In conclusion, the results of the qualitative approach were acceptable in their own right. They did not, however, add anything new when compared to standard CT. The quantitative approach gave rise to several conclusions concerning DCE-CT analysis as well as the use of DCE-CT in the diagnosis of lung cancer: First, that DCE-CT is best analysed using logarithmic scale data transformation; second, that irrespective of the ROI method applied, it was not possible to discriminate malignant and benign; and, third, that the lack of reproducibility should be addressed.

5.2 Mediastinal staging in NSCLC

Staging is used to predict survival and to guide the patient toward the most appropriate treatment regimen or clinical trial. The most important distinction is between those patients who are candidates for surgery and those who may benefit from chemotherapy, radiation therapy or both. Distinguishing malignant involvement of the ipsilateral or contralateral mediastinal lymph nodes (N2 or N3) from the ipsilateralhilar lymph nodes or no lymph nodes (N0 or N1) is critical, because malignant involvement of N2 or N3 lymph nodes usually indicates non–surgically resectable disease.

5.2.3 CT versus F-18-FDG PET/CT (2) study

The overall prevalence of N2 or N3 disease was 26% in our study population. There was no significant difference between CT and F-18-FDG PET/CT staging results. As such, approximately two-thirds of the patients were correctly staged using either CT or F-18-FDG PET/CT; the remaining one-third of the patients were incorrectly staged. Whereas CT tended to overstage the mediastinal nodes, F-18-FDG PET/CT tended to overstage as well as understage. The sensitivity and specificity of CT were 70% and 63%,

respectively and the sensitivity and specificity of F-18-FDG PET/CT were 50% and 74%, respectively. When the false positives and false negatives were reviewed, it was noteworthy that the false positive rates of both CT and F-18-FDG PET/CT were approximately 30% to 33%, while the false negative rate of F-18-FDG PET/CT was as high as 50%. Two important messages emerged from these results. First, approximately one-third of all benign nodes are falsely deemed to be malignant, irrespective of the imaging modality. Second, as many as half of all malignant nodes are falsely deemed to be benign on F-18-FDG PET/CT. Thus, both imaging modalities overstage*and* understage the mediastinal nodes.

Next, the presence of enlarged lymph nodes on CT was used to stratify F-18-FDG PET/CT results into subgroups. If there were enlarged lymph nodes on CT, the number of true positives (sensitivity) and false positives of F-18-FDG PET/CT increased. Thus, in patients with enlarged lymph nodes, F-18-FDG PET/CT is more likely to reveal true positive findings that are due to lymph node metastasis as well as false positive findings that are due to infection or inflammation. However, because the negative consequences of false positives are so serious, a positive F-18-FDG PET/CT should not automatically "rule in" N2 or N3 disease and these patients should receive mediastinoscopy, EBUS-TBNA and/or EUS-NA, unless distant metastases were proven beforehand. Failure to do so could result in patients with surgically resectable disease being denied curative surgery. In fact, in that context, F-18-FDG PET/CT made no clinical difference in this group of patients. Conversely, if there were no enlarged lymph nodes on CT, the numbers of true negatives (specificity) of F-18-FDG PET/CT rose substantially, but there were 89% false negatives! Thus, according to our results, a negative F-18-FDG PET/CT would not obviate the need for mediastinoscopy, EBUS-TBNA and/or EUS-NA in these patients. In that context, an F-18-FDG PET/CT examination would not make any difference to these patients either.

These results are somewhat controversial, considering the present general agreement on F-18-FDG PET/CT being highly accurate for mediastinal staging of NSCLC *and* being superior to CT. In two large meta-analyses of relevant articles published since the mid 1990s (28, 39), F-18-FDG PET sensitivity and specificity for mediastinal staging of NSCLC have been found to be almost 90%. Although the overall prevalence of N2 and N3 disease of our study (26%) is almost exactly identical to the prevalence in these meta-analyses (29% and 32%, respectively), we are nowhere near their results. Most likely some or all of the studies included in the meta-analyses represent highly selected study participants, whereas our study is set in our everyday clinical population. Thus, our results seem to resemble the results from some newer studies on the matter in which F-18-FDG PET/CT results are less optimistic (134-139).

There are some limitations to our study, the most important being whether all mediastinal lymph node metastases were detected by the reference standard. Especially in the patients that were only examined with mediastinoscopy/-tomy, this could be an issue. The diagnostic yield of mediastinoscopy/-tomy is operator dependent and the false negative rate is estimated to be between 3% and 20% (28). However, considering that these procedures were only used to confirm N2 or N3 disease, they were accepted as reference standard.

Conversely, our study's strengths must be mentioned. Patient sampling preceded both imaging and reference standard. This prospective design as well as the blinding procedure conforms to the STARD statement from 2003, which dictates that these are both natural requisites in studies of diagnostic accuracy (128). Furthermore, there is the large study size: 114 participants with NSCLC were included in our study and all participants were examined both with CT and with F-18-FDG PET/CT. This should be compared to an average study size of 118 participants for CT (28), 65 participants for F-18-FDG PET (28) and 51 participants for both CT and F-18-FDG PET (39), making our study comparably strong. In addition, all results in this study were controlled for reproducibility. Though this has been standard for CT since the STARD statement, to the best of our knowledge, reproducibility has not previously been controlled for F-18-FDG PET/CT.

In addition to the mediastinal staging, we also examined whether the modalities could contribute to the detection of distant metastases. Thus, all detected metastases were noted and some were biopsied. However, in cases where more than one metastasis was detected, only the most accessible was biopsied. 29 patients with metastases were identified by CT and 44 patients with metastases were identified by F-18-FDG PET/CT. However, as not all of these metastases were biopsy verified, we found it inappropriate to analyse these results further, just as it would be inappropriate to use these results to comment on the future of F-18-FDG PET/CT. It must be mentioned however, that F-18-FDG PET/CT is increasingly used to identify otherwise unexpected metastases and thereby to avoid futile thoracotomies. It is also increasingly used to facilitate oncological treatment decisions and for treatment monitoring.

In conclusion, no measureable difference could be found between the CT and the F-18-FDG PET/CT mediastinal staging results; overall two-thirds of the participants in the study were correctly staged and almost one-third of the participants were falsely staged. However, the false positives and false negatives were balanced in CT, whereas the false negatives were predominant in F-18-FDG PET/CT. Furthermore, according to the stratified results of F-18-FDG PET/CT, the need for further investigations prior to thoracotomy could not be avoided, no matter the size of the mediastinal lymph nodes.

In our current clinical setting, all patients are invasively examined with either Endobronchial Ultrasound (EBUS) or with Endoscopic Ultrasound (EUS). An exception to this rule is patients that are found to have metastatic disease.

5.3 LIMITATIONS

The discussion of the limitations of this PhD are mainly related to study design, study population and statistical power.

As previously mentioned, the initial use of CT introduces a strong selection bias into the studies. This selection is responsible for the high prevalence of malignancy in the studies, and in the CT versus F-18-FDG PET/CT (1) study it may favour CT. As such, it may also be a possible cause for discrepancies between our studies and previous works on the subject. However, it should also be recognised that although the population is selected, it represents our standard clinical work-up for patients with suspected lung cancer in 2008. We consider this selection a strength, and notice that it raises the prevalence of disease in the examined population to more than 80%. This is a significant result in itself.

Obviously, the optimal trial setting would be either an observational study, or even better, a multicentre, Randomized Controlled Trial *(RCT)* comparing CT with HRCT or CT with CT plus HRCT, or comparing CT with F-18-FDG PET/CT or CT with CT plus

F-18-FDG PET/CT in patients with suspected lung cancer. With such studies it would be possible to measure the diagnostic performance CT, HRCT and F-18-FDG PET/CT, and to address the false positives and false negatives of each modality more closely. Furthermore, in an RCT it would be possible to address the diagnostic, therapeutic and even the health impact of the modalities. However, the implication of these study designs would be a significant increase in radiation exposure to the patients as well as a significant increase in health related costs. This is especially relevant when considering that only 20% to 25% of the patients with suspected lung cancer are eventually diagnosed with cancer. For those reasons it would not have been possible in 2008 to setup an RCT comparing CT, HRCT and F-18-FDG PET/CT for characterisation of patients suspected with lung cancer. In 2012 on the other hand, an RCT could be interesting. This could be a perspective for future research.

Statistical power is the probability that a statistical test will indicate a significant difference when there truly is one. In a study comparing two groups of individuals, the power of a statistical test must be sufficient to enable detection of a statistically significant difference between the two groups if a difference is truly present. This issue becomes important if the study results were to demonstrate no statistically significant difference. If such a negative result were to occur, there would be two possible interpretations. The first is that the results of the statistical test are correct and that there truly is no statistically significant difference (a true-negative result). The second is that the results of the statistical test are erroneous and that there is actually an underlying difference, but the study was not powerful enough to find the difference, yielding a false-negative result. In statistical terminology, a false-negative result is known as a type II error. In studies, which measure certain characteristics of a single group against a reference standard (descriptive studies), power calculations are of little use. Thus, statistical power is relevant in the CT versus F-18-FDG PET/CT studies.

However, before discussing the statistical power of the studies, the preliminary sample size assessments of these studies should be mentioned: In 2007 a series of comprehensive meta-analyses on the performance characteristics of CT and F-18-FDG PET/CT for diagnosis and staging of lung cancer were published in Chest (3, 28). According to the sensitivities and specificities reported in these analyses, sample size calculations were made. In the study on suspected lung cancer 96 patients (sensitivity) and 55 patients (specificity) should be included in each group (95% confidence, 90% power). In the study on mediastinal staging 74 patients (sensitivity) and 21,232 patients (specificity) should be included in each group (95% confidence, 90% power). These sample size assessments were discussed in the research group and since most of the sample sizes were definitely obtainable it was decided to initiate the study.

After finishing the studies, it is obvious that study power represents a challenge. Nobody expected the sensitivities and specificities of CT and F-18-FDG PET/CT would be so alike. Using a two-tailed power test, the power of the first study is 39% (sensitivity) and 20% (specificity) if CT is used to id lung cancer. If, on the other hand CT is used to rule out cancer the power is 7.9% (sensitivity) and 68% (specificity). In the mediastinal staging study the statistical power is 87% (sensitivity) and 43% (specificity). In fact, these percentages make it possible that both these studies suffer from a type II error.

In the words of the Statistician John Eng, a conclusion on this increased risk of a type II error could be that: “One could argue that it is as wasteful and inappropriate to conduct a study with inadequate power as it is to obtain a diagnostic test of insufficient sensitivity to rule out a disease.” (140). On the other hand, one could also argue that our studies are among the largest studies published on the matter. As such, 168 patients in the CT versus F-18-FDG PET/CT (1) study should be compared to an average of 37 to 66 participants in other similar studies (3, 49). In the CT versus F-18-FDG PET/CT (2) study 114 included participants should be compared to an average study size of 118 for CT (28), 65 participants for F-18-FDG PET/CT (28) and 51 participants for both CT and F-18-FDG PET/CT (39). Thus, there appears to be a continuing need for large clinical studies, just as more meta-analyses are required before evidence based guidelines can be established. However, instead of dismissing the studies as the innocent victims of flawed study designs and poor statistical power, they should be recognised for their inherent quality: they represent the diagnostic setup in 2008 and they question the value of new modalities, which are supposed to replace older established ones. Despite the flaws, the results of the studies stand and, more than anything else, these results indicate that more research is needed. Thus, the studies should be considered indicators of where to go next and to the perspectives of more complex randomised studies comparing CT with other modalities.

6. CONCLUSION AND PERSPECTIVES

In daily clinical practice, the work-up of pulmonary nodules and masses is a challenge in both the numbers of referred patients and in the complexity. A standard contrast-enhanced CT is often the first examination, followed by a number of other examinations.

In Aarhus, Denmark the first patient with suspected lung cancer received CT in 1998. Though based on 5-10 mm slices, this was immediate success. Already the next year, in 1999, as many as 200 patients with suspected lung cancer received CT. Since then, the number of these patients receiving CT has just kept increasing and presently as many as 1,200 of these patients receive CT each year. Today, standard CT is the mainstay of cancer imaging worldwide.

Not surprisingly, this increase in patients receiving CT has led to a significant increase in the prevalence of patients diagnosed with pulmonary lesions as well as increase in the number of patients diagnosed with lung cancer. However, the survival of these patients has only increased marginally. According to the Danish Lung Cancer Database, the survival of the patients is statistically significantly increasing, but it is unclear whether this is caused by improved diagnosis and staging, by improved treatment, or by both. Obviously, the implications of this are unclear.

Questions regarding the safety and cost-effectiveness of aggressively examining a selected population at an increased risk for lung cancer with CT are not unlike those asked regarding low dose CT screening of symptom-free individuals. However, it should be stressed that the two populations are not identical and some of the adverse health considerations, which should be taken in a screening population, are of less importance in patients at an increased risk of lung cancer.

Thus, the point of aggressively examining these risk patients with CT is to increase the number of lung cancer patients identified at early disease stages. Treatment of patients with early-stage lung cancer should decrease the number of patients identified at late disease stages, resulting in a stage shift toward earlier disease for the population as a whole and thus, in turn decrease the mortali-

ty from lung cancer. However, it should be noted that the diagnosis of early-stage lung cancer and thus the prolongation of life with lung cancer is not an aim in itself, as this may be representative of lead-time bias. Also the diagnosis of more cancers is not an aim in itself, as this may be representative of length time bias and/or overdiagnosis. Thus, the aim is to reduce the mortality from lung cancer, and subsequently to demonstrate this reduction.

HRCT using thin slices and a special edge enhancing reconstruction was introduced to patients with suspected lung cancer in 2000, to determine the precise location and characteristics of lung nodules. Being highly sensitive, HRCT was used for almost a decade and was only abandoned recently, when HRCT-like reconstructions with thin slices and edge enhancement were possible from standard CT raw data.
Though F-18-FDG PET had existed for years as an experimental imaging modality in oncology, it was not systematically introduced to patients with suspected lung cancer at our hospital prior to 2008. However, internationally F-18-FDG PET had for years been recognized for its superior ability to characterise pulmonary lesions in patients with suspected lung cancer, but especially for its ability to stage the mediastinum in patients with NSCLC. Thus, there was a growing awareness of the need to systematically introduce F-18-FDG PET locally. However, due to lack of evidence-based guidelines on the use of F-18-FDG PET in suspected lung cancer, it was unclear how. Considering the expected diagnostic and therapeutic impact of the modality, F-18-FDG PET/CT was initially offered to patients, who were expected to receive surgical treatment. The hope was that F-18-FDG PET could improve the mediastinal staging of the patients, detect metastases and prevent futile thoracotomies. That way, F-18-FDG PET (as part of the dual modality F-18-FDG PET/CT) was introduced into our standard clinical algorithm. However, due to an increasing awareness of the inadequacies of F-18-FDG PET/CT in patients with suspected lung cancer, since then our clinical algorithm has been altered. F-18-FDG PET/CT is no longer used to characterise pulmonary lesions in patients with suspected lung and to a lesser extent to stage the mediastinum in patients with NSCLC. Instead it is now mainly used to detect distant metastases and to guide oncological therapy, that is chemotherapy and radiation therapy. However, this has not diminished the use of F-18-FDG PET/CT. On the contrary, more patients than ever receive F-18-FDG PET/CT.
DCE-CT was, and remains, experimental.
As already briefly mentioned, the clinical algorithm has changed, making some of the results of this PhD redundant. However, instead of regretting this fact, it could be claimed that the combined results of this PhD provide qualified validations of modern international trends. Thus, according to our results HRCT was fast, widely available and effective. Although HRCT has been abandoned as an individual examination, it is replaced by iterative reconstructions with thin slices and edge enhancement from the raw scan data. This is possible because of modern computer power. Likewise, the results of this PhD support an increasing number of modern clinical studies diminishing the superiority of F-18-FDG PET/CT for lesion characterisation in patients with suspected lung cancer and for mediastinal staging in patients with NSCLC. Thus, our studies along with these international studies have changed the main indications for F-18-FDG PET/CT in these patients. Whereas the main indications in 2008 were characterisation of pulmonary lesions in patients with suspected lung cancer and mediastinal staging in patients with NSCLC, today the main indications are mediastinal staging in patients with NSCLC, detection of distant metastases in patients with NSCLC and guidance of oncological therapy in patients with NSCLC. Finally, this PhD questions the value of DCE-CT in suspected lung cancer. These studies reflect the setting in which they were initiated in 2008. That fact that time has made some of the results redundant is simply a product of scientific advances.

Thus, the aim of this PhD was to examine and validate modern imaging modalities used to characterise pulmonary lesions in patients with suspected lung cancer, to aid in the ability of modern methods to replace older established methods and to aid in the development of new methods. The desire was to safely distinguish between malignant and benign lesions without the need for invasive procedures. This would have a significant diagnostic impact on patient management. The technical and diagnostic performance and validity of the standard contrast-enhanced CT for patients with suspected lung cancer was examined, along with that of three other imaging modalities, HRCT, F-18-FDG PET/CT, and DCE-CT. Standard contrast-enhanced CT and F-18-FDG PET/CT were also examined for mediastinal staging in patients with NSCLC.

1) 213 participants with pulmonary nodules on CT were examined with an additional HRCT. It was concluded that HRCT of a solitary pulmonary nodule, assessed using attenuation and morphological criteria is fast, widely available and effective method for diagnosing lung cancer correctly, and especially for ruling out cancer.

2) 168 patients with pulmonary lesions on CT were examined with an additional F-18-FDG PET/CT. It was concluded that when used early in the work-up of the lesions, CT raised the prevalence of lung cancer in the population to the point at which further diagnostic imaging examination could be considered redundant. Standard contrast-enhanced CT seems better suited to identify patients with lung cancer than to rule out cancer. Finally, the overall diagnostic accuracy as well as the classification probabilities and predictive values of the two modalities were not significantly different. The reproducibility of the above results was substantial.

3) 59 patients with pulmonary lesions on chest radiography were examined with an additional DCE-CT. A qualitative as well as a quantitative assessment method was examined. It was concluded that although the results of the qualitative approach were acceptable in their own right, they did not, however, add anything new when compared to standard CT. The quantitative approach gave rise to several conclusions concerning DCE-CT analysis as well as the use of DCE-CT in the diagnosis of lung cancer: First, that DCE-CT is best analysed using logarithmic scale data transformation; second, that irrespective of the ROI method applied, it was not possible to discriminate malignant and benign; and, third, that the lack of reproducibility should be addressed. These results show us that DCE-CT is currently not a clinically feasible method for analysing pulmonary lesions. This does not necessarily mean that DCE-CT should be abandoned, but it does signify the need for further development of the current DCE-CT methods.

4) 114 patients with NSCLC were examined with both a CT and with an additional F-18-FDG PET/CT. It was concluded that there was no significant difference in the overall diagnostic accuracy of the two modalities when imaging the mediastinum for staging purposes.

After carrying out these studies, the hypotheses of the studies, as they were expressed in the Hypotheses section, may be answered as follows:

1) HRCT study:

HRCT was useful to assess attenuation, morphology and special features of pulmonary nodules. There was an overweight of malignancy among the partly solid nodules. There was also an overweight of malignancy among the nodules with pleural retraction. Based on an assessment of these features, HRCT had a high sensitivity, a high negative predictive value and a low false negative rate for ruling out lung cancer. All these results were highly reproducible.

Naturally, the high sensitivity, high negative predictive value and low false negative rate had to have consequences. As such, based on our results, we could highly recommend the continued used of HRCT of pulmonary nodules. However, in the few years that have passed since the study data was collected, reality has overtaken our results. When the study was initiated, a spiral HRCT of the slices with pulmonary nodules was performed. Today, however, the technology has evolved, and all patients with suspected lung cancer are scanned once. Images are reconstructed with both standard CT and HRCT algorithms and raw image data is stored in PACS. These reconstructions are useful not only for the characterisation of pulmonary nodules, but also for further assessment of pulmonary interstitial disease. Although this involves the storage of huge amounts of data, the technical developments within the last half-decade now make this possible. For this, we use 256 row scanners, computers with minimal reconstruction times and a huge PACS storage. This was not possible only a few years ago when this PhD was initiated.

2) CT versus F-18-FDG PET/CT (1) study:

CT and F-18-FDG PET/CT were equally sensitive and specific for identifying lung cancer. Furthermore, CT and F-18-FDG PET/CT results were equally reproducible.

Based on the results of previous studies on the matter, the demand for F-18-FDG PET/CT has been overwhelming. It has been suggested by physicians as well as by several patient organisations that F-18-FDG PET/CT should be the first examination for patients with suspected lung cancer. Our results suggest otherwise.

Considering that CT and F-18-FDG PET/CT were equally sensitive and specific for identifying lung cancer, the decision of which modality should be the first should be determined by other considerations. Special advantages/disadvantages, radiation exposure and cost-benefit of CT versus F-18-FDG PET/CT should be considered.

In that sense, the most important advantage of F-18-FDG PET/CT is the fact that it is a whole body examination. As such, it is generally accepted that it is a major advantage that F-18-FDG PET/CT may detect unsuspected distant metastases, thereby relieving inoperable patients the distress of a futile thoracotomy. On the other hand, the high number of false positives as well as false negatives is considered to be a big disadvantage of the modality. As such, there are arguments both for and against the initial use of F-18-FDG PET/CT in suspected lung cancer.

The radiation exposure associated with a standard CT of the thorax and upper abdomen, and the radiation exposure associated with an F-18-FDG PET/low dose CT is approximately the same, as mentioned in the background section. Thus, this consideration should not play a role. However, this also means that an integrated F-18-FDG PET/diagnostic CT involves twice the radiation exposure of each of the individual examinations. As such, F-18-FDG PET/diagnostic CT cannot be recommended.

In the light of cost-benefit, CT is clearly the preferable alternative. Currently, a standard CT of the thorax and upper abdomen is performed in a few minutes, whereas an F-18-FDG PET/CT takes hours; both these time estimates include patient preparation. Furthermore, for practical reasons, CT can be performed almost everywhere and at all times; this is contrary to F-18-FDG PET/CT, which is a more specialised examination that furthermore depends on the proximity of a cyclotron. Due to these considerations, CT should still be considered workhorse of initial lung cancer assessment and as such, the gatekeeper to further examinations.

In perspective, a few aspects of future developments of CT and F-18-FDG PET/CT must be mentioned. Recognizing that the most serious disadvantage of CT is radiation exposure, CT vendors are currently putting much effort into reducing this. Currently the buzzword is iterative reconstruction. Although this reconstruction technique has been used in nuclear medicine for years, it has only recently found its way to radiology and CT. A new generation of CT scanners using iterative reconstruction is now commercially available. Along with other radiation dose reduction techniques, these CT scanners are able to lower the radiation dose of a chest CT to less than 1 mSv without significant losses in image quality. Although still scientifically unverified, the technique holds the promise of reconstructing even very low dose CT scans to the point where they cannot be distinguished from regular dose CT scans.

For F-18-FDG PET/CT, the future holds less promise. After being widely heralded when it was first introduced, the imaging modality is now mainly used to detect distant metastases in malignancies in general and to diagnose, stage and monitor haematological malignancies. The development of a super-sensitive and specific tracer for use with PET/CT or SPECT could be a game changer, however, but this is speculative and as of yet, no such tracer exists yet.

3) DCE-CT study:

We found that perfusion, peak enhancement intensity, time to peak and blood volume could not be used to distinguish between malignant and benign pulmonary nodules or masses; this was irrespective of the ROI method. We also found that the lack of reproducibility could be a serious challenge for the method if used clinically.

Naturally, the perspectives of this study relate to the future use of DCE-CT.

DCE-CT is an interesting imaging modality, especially in theory. However, in our study we found that although we could identify patients with lung cancer with reasonable accuracy by a qualitative assessment of colour maps, this was not the case when using the quantitative method. Furthermore, we found the results to be troubled by a lack of reproducibility. On that basis, we could not recommend the modality for clinical use in suspected lung cancer, but concluded that significant modifications were needed before this was an option. These modifications should preferably include the development of automatic segmentation of and quantification of entire tumours with a reasonably acceptable reproducibility, and tools to reduce motion artefacts. Until then, DCE-CT remains experimental and should only be used as such.

4) CT versus F-18-FDG PET/CT (2) study:

Controversially, according to our results, CT was superior to F-18-FDG PET/CT for mediastinal staging of NSCLC in more ways than one. We found that the sensitivity of CT was higher than for F-18-FDG PET/CT, and more importantly, that the number of false negatives of CT was lower than for F-18-FDG PET/CT. However, we also found that neither CT nor F-18-FDG PET/CT could obviate the need for further invasive staging prior to thoracotomy in patients with NSCLC; for that purpose, the results of both modalities were too meagre. Finally, we found that F-18-FDG PET/CT was not clinically feasible - regardless of whether the patients had or did not have enlarged lymph nodes on CT.
The clinical perspective of this study relates to whether CT or F-18-FDG PET/CT can obviate the need for invasive staging prior to thoracotomy.
According to our results neither CT nor F-18-FDG PET/CT, individually or in combination, can obviate the need for invasive staging prior to thoracotomy. This is regardless of whether the patients to be staged are unselected or if they are initially CT scanned, and then F-18-FDG PET/CT scanned. There are too many false positives and especially too many false negatives. Therefore, these patients still depend on invasive staging methods. In our study, invasive staging was accomplished by mediastinoscopy. However, today this is increasingly overtaken by EBUS or EUS, which have both shown promising results and have been included in our daily clinical algorithm (116).

In conclusion, although standard contrast-enhanced CT has brought us far in the characterisation of pulmonary nodules and masses, the last decade has seen a constant move away from strictly anatomical approaches to imaging, towards more functional or analytical approaches. The desire has been to be able to safely distinguish between malignant and benign nodules without the need for invasive procedures. Though this was also the aim of this PhD, the conclusions are somewhat away from that goal and should lead to reflections over the future practise in these patients.

6.1 THOUGHTS ON A FUTURE WORKFLOW

Considering the results of these studies, standard contrast-enhanced CT must be recommended as the first examination in patients with suspected lung cancer. As concluded in the HRCT study and in the CT versus F-18-FDG PET/CT (1) study, CT is fast, widely available and has high to very high sensitivity for even very small lung nodules. Besides these cost-effective considerations, the radiation exposure of CT is lower than that of other imaging modalities. Finally, CT using thin slices is anatomically highly accurate and therefore ideal as a lesion biopsy guide.
Patients at an increased risk for lung cancer after CT should be subject to invasive methods, both to establish the diagnosis of lung cancer, but also to subclassify the cancer and thereby facilitate eventual chemotherapeutic treatment. Which invasive method is used to diagnose the cancer depends on the anatomic location and could be either fluoroscopically guide needle biopsy, CT guided needle biopsy or Ultrasound guided biopsy or other. However, a thorough discussion of invasive methods is beyond the scope of this PhD.
When lung cancer is diagnosed, patients should receive F-18-FDG PET/CT to aid in the mediastinal staging and more importantly to detect distant metastases and to guide subsequent invasive staging. Although, as concluded in the CT versus F-18-FDG PET/CT (2), F-18-FDG PET/CT is limited by both false positives and by false negatives, F-18-FDG PET/CT is a whole body examination, which has proved itself through numerous clinical studies. Although matched by CT for lesion characterisation in patients with suspected lung cancer and for mediastinal staging in patients with NSCLC, no imaging modality comes close to matching F-18-FDG PET/CT in metastases detection and thus in the prevention of unnecessary thoracotomies. This means that the diagnostic impact and also the therapeutic impact of F-18-FDG PET/CT are unparalleled in patients with metastases.
According to our results in the DCE-CT study, with limited diagnostic performance and poor reproducibility, DCE-CT should only be used in protocolled clinical trials.
Finally, all patients with no sign of distant metastases should receive EUS/EBUS to clarify the clinical stage and determine the next therapeutic procedure. Although not a part of this PhD, it seems logical that the modern invasive methods EUS-FNA and EBUS-TBNA replace the established methods mediastinoscopy/-tomy. The modern methods have a higher diagnostic performance, and thus a higher diagnostic impact and therapeutic impact than mediastinoscopy/-tomy and are gentler on patients. Considering the lack of clinical studies as well as of evidence-based guidelines, MRI is not recommended for patients with suspected lung cancer.
Using this workflow, the diagnostic performance and also the diagnostic and therapeutic impact would be high on all levels of decision while maintaining a high degree of cost-effectiveness. A positive side effect for the patients would be quick diagnosis and staging and a strong basis for initiation of surgery or oncological treatment.

7. SUMMARY

Pulmonary nodules are of high clinical importance, as they may prove to be an early manifestation of lung cancer. Pulmonary nodules are small, focal opacities that may be solitary or multiple. A solitary pulmonary nodule *(SPN)* is a single, small (≤ 30 mm in diameter) radiographic opacity. Larger opacities are called masses and are often malignant. As imaging techniques improve and more nodules are detected, the optimal management of SPNs remains unclear. Current strategies include tissue sampling or CT follow-up.
The aim of this PhD was to examine current non-invasive methods used to characterise pulmonary nodules and masses in patients with suspected lung cancer and to stage NSCLC. In doing so, this PhD helps to validate the existing methods used to diagnose and stage lung cancer correctly and, hopefully, aids in the development of new methods.
In the first study, 213 participants with pulmonary nodules on CT were examined with an additional HRCT. In this study, it was concluded that HRCT of a solitary pulmonary nodule, assessed using attenuation and morphological criteria is fast, widely available and effective method for diagnosing lung cancer correctly, and especially for ruling out cancer.
In the second study, 168 patients with pulmonary lesions on CT were examined with an additional F-18-FDG PET/CT. It was concluded that when used early in the work-up of the lesions, CT raised the prevalence of lung cancer in the population to the point at which further diagnostic imaging examination could be considered redundant. Standard contrast-enhanced CT seems better suited to identify patients with lung cancer than to rule out cancer. Finally, the overall diagnostic accuracy as well as the classification probabilities and predictive values of the two modal-

ities were not significantly different. The reproducibility of the above results was substantial.

In the third study, 59 patients with pulmonary nodules or masses on chest radiography were examined with an additional DCE-CT. A qualitative as well as a quantitative assessment method was examined. It was concluded that although the results of the qualitative approach were acceptable in their own right, they did not, however, add anything new when compared to standard CT. The quantitative approach gave rise to several conclusions concerning DCE-CT analysis as well as the use of DCE-CT in the diagnosis of lung cancer: First, that DCE-CT is best analysed using logarithmic scale data transformation; second, that irrespective of the ROI method applied, it was not possible to discriminate malignant and benign; and, third, that the lack of reproducibility should be addressed. These results show us that DCE-CT is currently not a clinically feasible method for analysing pulmonary lesions. This does not necessarily mean that DCE-CT should be abandoned, but it does signify the need for further development of the current DCE-CT methods.

Finally, in the fourth study, 114 patients with NSCLC were examined with both a CT and with an additional F-18-FDG PET/CT. It was concluded that there was no significant difference in the overall diagnostic accuracy of the two modalities when imaging the mediastinum for staging purposes.

In conclusion, although standard contrast-enhanced CT has brought us far in the characterisation of pulmonary nodules and masses, the last decade has seen a constant move away from strictly anatomical approaches to imaging, towards more functional or analytical approaches. The desire is, of course, to be able to safely distinguish between malignant and benign nodules without the need for invasive procedures.

8. REFERENCES

1. Ost D, Fein AM, Feinsilver SH. Clinical practice. the solitary pulmonary nodule. N Engl J Med. 2003 Jun 19;348(25):2535-42.
2. Tuddenham WJ. Glossary of terms for thoracic radiology: Recommendations of the nomenclature committee of the fleischner society. AJR Am J Roentgenol. 1984 Sep;143(3):509-17.
3. Wahidi MM, Govert JA, Goudar RK, Gould MK, McCrory DC, American College of Chest Physicians. Evidence for the treatment of patients with pulmonary nodules: When is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):94S-107S.
4. Prauer HW, Weber WA, Romer W, Treumann T, Ziegler SI, Schwaiger M. Controlled prospective study of positron emission tomography using the glucose analogue [18f]fluorodeoxyglucose in the evaluation of pulmonary nodules. Br J Surg. 1998 Nov;85(11):1506-11.
5. Orino K, Kawamura M, Hatazawa J, Suzuki I, Sazawa Y. Efficacy of F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scans in diagnosis of pulmonary nodules. Jpn J Thorac Cardiovasc Surg. 1998 Dec;46(12):1267-74.
6. Lowe VJ, Fletcher JW, Gobar L, Lawson M, Kirchner P, Valk P, Karis J, Hubner K, Delbeke D, Heiberg EV, Patz EF, Coleman RE. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol. 1998 Mar;16(3):1075-84.
7. Dewan NA, Shehan CJ, Reeb SD, Gobar LS, Scott WJ, Ryschon K. Likelihood of malignancy in a solitary pulmonary nodule: Comparison of bayesian analysis and results of FDG-PET scan. Chest. 1997 Aug;112(2):416-22.
8. Gupta NC, Maloof J, Gunel E. Probability of malignancy in solitary pulmonary nodules using fluorine-18-FDG and PET. J Nucl Med. 1996 Jun;37(6):943-8.
9. Duhaylongsod FG, Lowe VJ, Patz EF,Jr, Vaughn AL, Coleman RE, Wolfe WG. Detection of primary and recurrent lung cancer by means of F-18 fluorodeoxyglucose positron emission tomography (FDG PET). J Thorac Cardiovasc Surg. 1995 Jul;110(1):130,9; discussion 139-40.
10. Dewan NA, Reeb SD, Gupta NC, Gobar LS, Scott WJ. PET-FDG imaging and transthoracic needle lung aspiration biopsy in evaluation of pulmonary lesions. A comparative risk-benefit analysis. Chest. 1995 Aug;108(2):441-6.
11. Patz EF,Jr, Lowe VJ, Hoffman JM, Paine SS, Burrowes P, Coleman RE, Goodman PC. Focal pulmonary abnormalities: Evaluation with F-18 fluorodeoxyglucose PET scanning. Radiology. 1993 Aug;188(2):487-90.
12. Dewan NA, Gupta NC, Redepenning LS, Phalen JJ, Frick MP. Diagnostic efficacy of PET-FDG imaging in solitary pulmonary nodules. potential role in evaluation and management. Chest. 1993 Oct;104(4):997-1002.
13. HOLIN SM, DWORK RE, GLASER S, RIKLI AE, STOCKLEN JB. Solitary pulmonary nodules found in a community-wide chest roentgenographic survey; a five-year follow-up study. Am Rev Tuberc. 1959 Apr;79(4):427-39.
14. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness G, Miettinen OS, Libby DM, Pasmantier MW, Koizumi J, Altorki NK, Smith JP. Early lung cancer action project: Overall design and findings from baseline screening. Lancet. 1999 Jul 10;354(9173):99-105.
15. MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, Patz EF,Jr, Swensen SJ, Fleischner Society. Guidelines for management of small pulmonary nodules detected on CT scans: A statement from the fleischner society. Radiology. 2005 Nov;237(2):395-400.
16. Mettler FA,Jr, Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: A catalog. Radiology. 2008 Jul;248(1):254-63.
17. Mayo JR, Aldrich J, Muller NL, Fleischner Society. Radiation exposure at chest CT: A statement of the fleischner society. Radiology. 2003 Jul;228(1):15-21.
18. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK. SEER Cancer Statistics Review, 1975-2008 [Internet]. Bethesda, MD: National Cancer Institute
19. Peto, R, Imperial Cancer Research Fund, World Health Organization. Mortality from smoking in developed countries, 1950-2000: indirect estimates from national vital statistics. Oxford ; New York: Oxford University Press; 1994. 103, 553 p.
20. Greenwald, P, Kramer, BS, Weed, DL. Cancer prevention and control. New York: M. Dekker; 1995. 803 p.
21. United States. Public Health Service. Office of the Surgeon General, United States. Office on Smoking and Health. Reducing the health consequences of smoking: 25 years of progress : a report of the Surgeon General : 1989 executive summary. Rockville, Md.: U.S. Dept. of Health and Human Services, Public Health Service, Cen-

ters for Disease Control, Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health; 1989. 703 p.
22. Zaridze, DG, Peto, R, International Agency for Research on Cancer, Vsesoiuznyĭ onkologicheskiĭ tsentr. Tobacco: a major international health hazard : proceedings of an international meeting organized by the IARC and co-sponsored by the All-Union Cancer Research Centre of the Academy of Medical Sciences of the USSR, Moscow, USSR, held in Moscow, 4-6 June 1985. Lyon: International Agency for Research on Cancer ; New York : Distributed in the USA by Oxford University Press; 1986. 324 p.
23. National Research Council . Committee on Health Risks of Exposure to Radon. Health effects of exposure to radon. Washington, D.C.: National Academy Press; 1999. 500 p.
24. Holgate, ST. Air pollution and health. San Diego: Academic Press; 1999. 1065 p.
25. Palshof, T, Jakobsen, E. Lungecancer årsrapport 2011. Dansk Lunge Cancer Gruppe; 2010.
26. Mountain CF. Revisions in the international system for staging lung cancer. Chest. 1997 Jun;111(6):1710-7.
27. Mountain CF. A new international staging system for lung cancer. Chest. 1986 Apr;89(4 Suppl):225S-33.
28. Silvestri GA, Gould MK, Margolis ML, Tanoue LT, McCrory D, Toloza E, Detterbeck F, American College of Chest Physicians. Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):178S-201.
29. SPRATT JS, JR., TER-POGOSSIAN M, LONG RTL. The detection and growth of intrathoracic neoplasms: The lower limits of radiographic distinction, the antemortum size, the duration, and the pattern of growth as determined by direct mensuration of tumor diameters from random thoracic roentgenograms. AMA Arch Surg. 1963 February 1;86(2):283-8.
30. Shah PK, Austin JH, White CS, Patel P, Haramati LB, Pearson GD, Shiau MC, Berkmen YM. Missed non-small cell lung cancer: Radiographic findings of potentially resectable lesions evident only in retrospect. Radiology. 2003 Jan;226(1):235-41.
31. Austin JH, Romney BM, Goldsmith LS. Missed bronchogenic carcinoma: Radiographic findings in 27 patients with a potentially resectable lesion evident in retrospect. Radiology. 1992 Jan;182(1):115-22.
32. Muhm JR, Miller WE, Fontana RS, Sanderson DR, Uhlenhopp MA. Lung cancer detected during a screening program using four-month chest radiographs. Radiology. 1983 Sep;148(3):609-15.
33. Quekel LG, Kessels AG, Goei R, van Engelshoven JM. Miss rate of lung cancer on the chest radiograph in clinical practice. Chest. 1999 Mar;115(3):720-4.
34. Kundel HL. Predictive value and threshold detectability of lung tumors. Radiology. 1981 Apr;139(1):25-9.
35. Li F, Sone S, Abe H, Macmahon H, Doi K. Malignant versus benign nodules at CT screening for lung cancer: Comparison of thin-section CT findings. Radiology. 2004 Dec;233(3):793-8.
36. Takashima S, Sone S, Li F, Maruyama Y, Hasegawa M, Matsushita T, Takayama F, Kadoya M. Small solitary pulmonary nodules (< or =1 cm) detected at population-based CT screening for lung cancer: Reliable high-resolution CT features of benign lesions. AJR Am J Roentgenol. 2003 Apr;180(4):955-64.
37. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS, ELCAP Group. CT screening for lung cancer: Frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol. 2002 May;178(5):1053-7.
38. Swensen SJ, Viggiano RW, Midthun DE, Muller NL, Sherrick A, Yamashita K, Naidich DP, Patz EF, Hartman TE, Muhm JR, Weaver AL. Lung nodule enhancement at CT: Multicenter study. Radiology. 2000 Jan;214(1):73-80.
39. Gould MK, Kuschner WG, Rydzak CE, Maclean CC, Demas AN, Shigemitsu H, Chan JK, Owens DK. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: A meta-analysis. Ann Intern Med. 2003 Dec 2;139(11):879-92.
40. Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non-small cell lung cancer: Mediastinal staging in the 1990s--meta-analytic comparison of PET and CT. Radiology. 1999 Nov;213(2):530-6.
41. Lowe VJ, Naunheim KS. Current role of positron emission tomography in thoracic oncology. Thorax. 1998 Aug;53(8):703-12.
42. Cook GJ, Maisey MN. The current status of clinical PET imaging. Clin Radiol. 1996 Sep;51(9):603-1.
43. Wahl RL, Hutchins GD, Buchsbaum DJ, Liebert M, Grossman HB, Fisher S. 18F-2-deoxy-2-fluoro-D-glucose uptake into human tumor xenografts. feasibility studies for cancer imaging with positron-emission tomography. Cancer. 1991 Mar 15;67(6):1544-50.
44. WEBER G, CANTERO A. Glucose-6-phosphatase activity in normal, pre-cancerous, and neoplastic tissues. Cancer Res. 1955 Feb;15(2):105-8.
45. Patz EF,Jr, Goodman PC. Positron emission tomography imaging of the thorax. Radiol Clin North Am. 1994 Jul;32(4):811-23.
46. Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midthun DE, Nathan MA, Lowe VJ. Lung cancer screening experience: A retrospective review of PET in 22 non-small cell lung carcinomas detected on screening chest CT in a high-risk population. AJR Am J Roentgenol. 2005 Jul;185(1):126-31.
47. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K, Uno K. Evaluation of F-18 fluorodeoxyglucose (FDG) PET scanning for pulmonary nodules less than 3 cm in diameter, with special reference to the CT images. Lung Cancer. 2004 Jul;45(1):19-27.
48. Pastorino U, Bellomi M, Landoni C, De Fiori E, Arnaldi P, Picchio M, Pelosi G, Boyle P, Fazio F. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet. 2003 Aug 23;362(9384):593-7.
49. Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: A meta-analysis. JAMA. 2001 Feb 21;285(7):914-2.
50. Herder GJ, Golding RP, Hoekstra OS, Comans EF, Teule GJ, Postmus PE, Smit EF. The performance of(18)F-fluorodeoxyglucose positron emission tomography in small solitary pulmonary nodules. Eur J Nucl Med Mol Imaging. 2004 Sep;31(9):1231-6.

51. Higashi K, Ueda Y, Seki H, Yuasa K, Oguchi M, Noguchi T, Taniguchi M, Tonami H, Okimura T, Yamamoto I. Fluorine-18-FDG PET imaging is negative in bronchioloalveolar lung carcinoma. J Nucl Med. 1998 Jun;39(6):1016-20.
52. Langen KJ, Braun U, Rota Kops E, Herzog H, Kuwert T, Nebeling B, Feinendegen LE. The influence of plasma glucose levels on fluorine-18-fluorodeoxyglucose uptake in bronchial carcinomas. J Nucl Med. 1993 Mar;34(3):355-9.
53. Fletcher JW. PET scanning and the solitary pulmonary nodule. Semin Thorac Cardiovasc Surg. 2002 Jul;14(3):268-74.
54. Quaia E, Tona G, Gelain F, Lubin E, Pizzolato R, Boscolo E, Bussoli L. Integrated fluorine-18 fluorodeoxyglucose (18F-FDG) PET/CT compared to standard contrast-enhanced CT for characterization and staging of pulmonary tumors eligible for surgical resection. Acta Radiol. 2008 Nov;49(9):995-1004.
55. Lardinois D, Weder W, Hany TF, Kamel EM, Korom S, Seifert B, von Schulthess GK, Steinert HC. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med. 2003 Jun 19;348(25):2500-7.
56. Antoch G, Stattaus J, Nemat AT, Marnitz S, Beyer T, Kuehl H, Bockisch A, Debatin JF, Freudenberg LS. Non-small cell lung cancer: Dual-modality PET/CT in preoperative staging. Radiology. 2003 Nov;229(2):526-33.
57. Schelbert HR, Hoh CK, Royal HD, Brown M, Dahlbom MN, Dehdashti F, Wahl RL. Procedure guideline for tumor imaging using fluorine-18-FDG. society of nuclear medicine. J Nucl Med. 1998 Jul;39(7):1302-5.
58. Spiro SG, Porter JC. Lung cancer--where are we today? current advances in staging and nonsurgical treatment. Am J Respir Crit Care Med. 2002 Nov 1;166(9):1166-9.
59. Dietlein M, Weber K, Gandjour A, Moka D, Theissen P, Lauterbach KW, Schicha H. Cost-effectiveness of FDG-PET for the management of potentially operable non-small cell lung cancer: Priority for a PET-based strategy after nodal-negative CT results. Eur J Nucl Med. 2000 Nov;27(11):1598-609.
60. Scott WJ, Shepherd J, Gambhir SS. Cost-effectiveness of FDG-PET for staging non-small cell lung cancer: A decision analysis. Ann Thorac Surg. 1998 Dec;66(6):1876,83; discussion 1883-5.
61. Reed CE, Harpole DH, Posther KE, Woolson SL, Downey RJ, Meyers BF, Heelan RT, MacApinlac HA, Jung SH, Silvestri GA, Siegel BA, Rusch VW, American College of Surgeons Oncology Group Z0050 trial. Results of the american college of surgeons oncology group Z0050 trial: The utility of positron emission tomography in staging potentially operable non-small cell lung cancer. J Thorac Cardiovasc Surg. 2003 Dec;126(6):1943-51.
62. MacManus MP, Hicks RJ, Matthews JP, Hogg A, McKenzie AF, Wirth A, Ware RE, Ball DL. High rate of detection of unsuspected distant metastases by pet in apparent stage III non-small-cell lung cancer: Implications for radical radiation therapy. Int J Radiat Oncol Biol Phys. 2001 Jun 1;50(2):287-93.
63. Pieterman RM, van Putten JW, Meuzelaar JJ, Mooyaart EL, Vaalburg W, Koeter GH, Fidler V, Pruim J, Groen HJ. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. N Engl J Med. 2000 Jul 27;343(4):254-61.
64. van Tinteren H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA, van Velthoven PC, Comans EF, Diepenhorst FW, Verboom P, van Mourik JC, Postmus PE, Boers M, Teule GJ. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: The PLUS multicentre randomised trial. Lancet. 2002 Apr 20;359(9315):1388-93.
65. Yi CA, Lee KS, Kim EA, Han J, Kim H, Kwon OJ, Jeong YJ, Kim S. Solitary pulmonary nodules: Dynamic enhanced multi-detector row CT study and comparison with vascular endothelial growth factor and microvessel density. Radiology. 2004 Oct;233(1):191-9.
66. Miles KA, Charnsangavej C, Lee FT, Fishman EK, Horton K, Lee TY. Application of CT in the investigation of angiogenesis in oncology. Acad Radiol. 2000 Oct;7(10):840-5.
67. Miles KA. Tumour angiogenesis and its relation to contrast enhancement on computed tomography: A review. Eur J Radiol. 1999 Jun;30(3):198-205.
68. Miles, K, Dawson, PH, Blomley, M. Functional computed tomography. Miles K, Dawson PH, Blomley M, editors. Oxford: Isis Medical Media; 1997.
69. Miles KA, Hayball MP, Dixon AK. Functional images of hepatic perfusion obtained with dynamic CT. Radiology. 1993 Aug;188(2):405-11.
70. Miles KA, Hayball M, Dixon AK. Colour perfusion imaging: A new application of computed tomography. Lancet. 1991 Mar 16;337(8742):643-5.
71. Miles KA. Perfusion CT for the assessment of tumour vascularity: Which protocol? Br J Radiol. 2003;76 Spec No 1:S36-42.
72. Miles KA. Functional CT imaging in oncology. Eur Radiol. 2003 Dec;13 Suppl 5:M134-8.
73. Miles KA, Griffiths MR. Perfusion CT: A worthwhile enhancement? Br J Radiol. 2003 Apr;76(904):220-31.
74. Li Y, Yang ZG, Chen TW, Yu JQ, Sun JY, Chen HJ. First-pass perfusion imaging of solitary pulmonary nodules with 64-detector row CT: Comparison of perfusion parameters of malignant and benign lesions. Br J Radiol. 2010 Sep;83(993):785-90.
75. Li Y, Yang ZG, Chen TW, Deng YP, Yu JQ, Li ZL. Whole tumour perfusion of peripheral lung carcinoma: Evaluation with first-pass CT perfusion imaging at 64-detector row CT. Clin Radiol. 2008 Jun;63(6):629-35.
76. Li Y, Yang ZG, Chen TW, Chen HJ, Sun JY, Lu YR. Peripheral lung carcinoma: Correlation of angiogenesis and first-pass perfusion parameters of 64-detector row CT. Lung Cancer. 2008 Jul;61(1):44-53.
77. Sitartchouk I, Roberts HC, Pereira AM, Bayanati H, Waddell T, Roberts TP. Computed tomography perfusion using first pass methods for lung nodule characterization. Invest Radiol. 2008 Jun;43(6):349-58.
78. Zhang M, Kono M. Solitary pulmonary nodules: Evaluation of blood flow patterns with dynamic CT. Radiology. 1997 Nov;205(2):471-8.
79. Cronin P, Dwamena BA, Kelly AM, Carlos RC. Solitary pulmonary nodules: Meta-analytic comparison of cross-sectional imaging modalities for diagnosis of malignancy. Radiology. 2008 Mar;246(3):772-8.
80. Bland JM, Altman DG. Measurement error and correlation coefficients. BMJ. 1996 Jul 6;313(7048):41-2.

81. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986 Feb 8;1(8476):307-10.
82. Bland JM, Altman DG. Measurement in medicine: The analysis of method comparison studies. Statistician. 1983;32:307-1.
83. Ng QS, Goh V, Fichte H, Klotz E, Fernie P, Saunders MI, Hoskin PJ, Padhani AR. Lung cancer perfusion at multidetector row CT: Reproducibility of whole tumor quantitative measurements. Radiology. 2006 May;239(2):547-53.
84. Ng QS, Goh V, Klotz E, Fichte H, Saunders MI, Hoskin PJ, Padhani AR. Quantitative assessment of lung cancer perfusion using MDCT: Does measurement reproducibility improve with greater tumor volume coverage? AJR Am J Roentgenol. 2006 Oct;187(4):1079-84.
85. Miles KA, Griffiths MR, Keith CJ. Blood flow-metabolic relationships are dependent on tumour size in non-small cell lung cancer: A study using quantitative contrast-enhanced computer tomography and positron emission tomography. Eur J Nucl Med Mol Imaging. 2006 Jan;33(1):22-8.
86. Kiessling F, Boese J, Corvinus C, Ederle JR, Zuna I, Schoenberg SO, Brix G, Schmahl A, Tuengerthal S, Herth F, Kauczor HU, Essig M. Perfusion CT in patients with advanced bronchial carcinomas: A novel chance for characterization and treatment monitoring? Eur Radiol. 2004 Jul;14(7):1226-33.
87. Yamashita K, Matsunobe S, Tsuda T, Okuda K, Matsumoto K, Oyanagi H, Konishi J. Intratumoral necrosis of lung carcinoma: A potential diagnostic pitfall in incremental dynamic computed tomography analysis of solitary pulmonary nodules? J Thorac Imaging. 1997 Jul;12(3):181-7.
88. Miles KA, Williams RE. Warburg revisited: Imaging tumour blood flow and metabolism. Cancer Imaging. 2008 Mar 25;8:81-6.
89. Boellaard R, O'Doherty MJ, Weber WA, Mottaghy FM, Lonsdale MN, Stroobants SG, Oyen WJ, Kotzerke J, Hoekstra OS, Pruim J, Marsden PK, Tatsch K, Hoekstra CJ, Visser EP, Arends B, Verzijlbergen FJ, Zijlstra JM, Comans EF, Lammertsma AA, Paans AM, Willemsen AT, Beyer T, Bockisch A, Schaefer-Prokop C, Delbeke D, Baum RP, Chiti A, Krause BJ. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: Version 1.0. Eur J Nucl Med Mol Imaging. 2010 Jan;37(1):181-200.
90. Delbeke D, Coleman RE, Guiberteau MJ, Brown ML, Royal HD, Siegel BA, Townsend DW, Berland LL, Parker JA, Hubner K, Stabin MG, Zubal G, Kachelriess M, Cronin V, Holbrook S. Procedure guideline for tumor imaging with 18F-FDG PET/CT 1.0. Journal of Nuclear Medicine. May 2006 May 2006;47(5):885-9.
91. Petralia G, Bonello L, Viotti S, Preda L, d'Andrea G, Bellomi M. CT perfusion in oncology: How to do it. Cancer Imaging. 2010 Feb 11;10:8-19.
92. Sobin, LH, Gospodarowicz, MK, Wittekind, C, International Union against Cancer. TNM classification of malignant tumours. 7th ed. Chichester, West Sussex, UK ; Hoboken, NJ: Wiley-Blackwell; 2009.
93. Berquist TH, Bailey PB, Cortese DA, Miller WE. Transthoracic needle biopsy: Accuracy and complications in relation to location and type of lesion. Mayo Clin Proc. 1980 Aug;55(8):475-81.
94. Levine MS, Weiss JM, Harrell JH, Cameron TJ, Moser KM. Transthoracic needle aspiration biopsy following negative fiberoptic bronchoscopy in solitary pulmonary nodules. Chest. 1988 Jun;93(6):1152-5.
95. Wallace JM, Deutsch AL. Flexible fiberoptic bronchoscopy and percutaneous needle lung aspiration for evaluating the solitary pulmonary nodule. Chest. 1982 Jun;81(6):665-71.
96. Baaklini WA, Reinoso MA, Gorin AB, Sharafkaneh A, Manian P. Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. Chest. 2000 Apr;117(4):1049-54.
97. Reichenberger F, Weber J, Tamm M, Bolliger CT, Dalquen P, Perruchoud AP, Soler M. The value of transbronchial needle aspiration in the diagnosis of peripheral pulmonary lesions. Chest. 1999 Sep;116(3):704-8.
98. Cortese DA, McDougall JC. Biopsy and brushing of peripheral lung cancer with fluoroscopic guidance. Chest. 1979 Feb;75(2):141-5.
99. McCormack PM, Bains MS, Begg CB, Burt ME, Downey RJ, Panicek DM, Rusch VW, Zakowski M, Ginsberg RJ. Role of video-assisted thoracic surgery in the treatment of pulmonary metastases: Results of a prospective trial. Ann Thorac Surg. 1996 Jul;62(1):213,6; discussion 216-7.
100. Mack MJ, Hazelrigg SR, Landreneau RJ, Acuff TE. Thoracoscopy for the diagnosis of the indeterminate solitary pulmonary nodule. Ann Thorac Surg. 1993 Oct;56(4):825,30; discussion 830-2.
101. Allen MS, Deschamps C, Lee RE, Trastek VF, Daly RC, Pairolero PC. Video-assisted thoracoscopic stapled wedge excision for indeterminate pulmonary nodules. J Thorac Cardiovasc Surg. 1993 Dec;106(6):1048-52.
102. Lewis RJ, Caccavale RJ. Video-assisted thoracic surgical non-rib spreading simultaneously stapled lobectomy (VATS(n)SSL). Semin Thorac Cardiovasc Surg. 1998 Oct;10(4):332-9.
103. Yim AP, Izzat MB, Liu HP, Ma CC. Thoracoscopic major lung resections: An asian perspective. Semin Thorac Cardiovasc Surg. 1998 Oct;10(4):326-31.
104. McKenna RJ,Jr, Fischel RJ, Wolf R, Wurnig P. Video-assisted thoracic surgery (VATS) lobectomy for bronchogenic carcinoma. Semin Thorac Cardiovasc Surg. 1998 Oct;10(4):321-5.
105. Brown WT. Video-assisted thoracic surgery: The miami experience. Semin Thorac Cardiovasc Surg. 1998 Oct;10(4):305-12.
106. Kaseda S, Aoki T, Hangai N. Video-assisted thoracic surgery (VATS) lobectomy: The japanese experience. Semin Thorac Cardiovasc Surg. 1998 Oct;10(4):300-4.
107. Walker WS. Video-assisted thoracic surgery (VATS) lobectomy: The edinburgh experience. Semin Thorac Cardiovasc Surg. 1998 Oct;10(4):291-9.
108. Friberg S, Mattson S. On the growth rates of human malignant tumors: Implications for medical decision making. J Surg Oncol. 1997;65(4):284-97.
109. Weiss W. Tumor Doubling Time and Survival of Men with Bronchogenic Carcinoma. ; 1974. 3 p.
110. Nathan MH, Collins VP, Adams RA. Differentiation of Benign and Malignant Pulmonary Nodules by Growth Rate. ; 1962. 221 p.

111. Yankelevitz DF, Henschke CI. Does 2-year stability imply that pulmonary nodules are benign? AJR Am J Roentgenol. 1997 Feb;168(2):325-8.
112. Cybulsky IJ, Bennett WF. Mediastinoscopy as a routine outpatient procedure. Ann Thorac Surg. 1994 Jul;58(1):176-8.
113. Vallieres E, Page A, Verdant A. Ambulatory mediastinoscopy and anterior mediastinotomy. Ann Thorac Surg. 1991 Nov;52(5):1122-6.
114. Selby JH,Jr, Leach CL, Heath BJ, Neely WA. Local anesthesia for mediastinoscopy: Experience with 450 consecutive cases. Am Surg. 1978 Oct;44(10):679-82.
115. Detterbeck, FC. Diagnosis and treatment of lung cancer: an evidence-based guide for the practicing clinician. Philadelphia: W.B. Saunders Co.; 2001. 480 p.
116. Detterbeck FC, Jantz MA, Wallace M, Vansteenkiste J, Silvestri GA, American College of Chest Physicians. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):202S-20.
117. Fleiss, JL, Levin, BA, Paik, MC. Statistical methods for rates and proportions. 3rd ed. Hoboken, N.J.: J. Wiley; 2003. 760 p.
118. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977 Mar;33(1):159-74.
119. Cyr L, Francis K. Measures of clinical agreement for nominal and categorical data: The kappa coefficient. Comput Biol Med. 1992 Jul;22(4):239-46.
120. Cohen J. Weighted kappa: Nominal scale agreement with provision for scaled disagreement or partial credit. Psychol Bull. 1968 Oct;70(4):213-20.
121. Weinstein S, Obuchowski NA, Lieber ML. Clinical evaluation of diagnostic tests. AJR Am J Roentgenol. 2005 Jan;184(1):14-9.
122. Obuchowski NA. ROC analysis. AJR Am J Roentgenol. 2005 Feb;184(2):364-72.
123. Pepe, MS. The statistical evaluation of medical tests for classification and prediction. Oxford ; New York: Oxford University Press; 2003. 302 p.
124. Furuya K, Murayama S, Soeda H, Murakami J, Ichinose Y, Yabuuchi H, Katsuda Y, Koga M, Masuda K. New classification of small pulmonary nodules by margin characteristics on high-resolution CT. Acta Radiol. 1999 Sep;40(5):496-504.
125. Xu DM, van Klaveren RJ, de Bock GH, Leusveld A, Zhao Y, Wang Y, Vliegenthart R, de Koning HJ, Scholten ET, Verschakelen J, Prokop M, Oudkerk M. Limited value of shape, margin and CT density in the discrimination between benign and malignant screen detected solid pulmonary nodules of the NELSON trial. Eur J Radiol. 2008 Nov;68(2):347-52.
126. Harders SW, Madsen HH, Hjorthaug K, Rehling M, Rasmussen TR, Pedersen U, Pilegaard HK, Meldgaard P, Baandrup UT, Rasmussen F. Limited value of 99mTc depreotide single photon emission CT compared with CT for the evaluation of pulmonary lesions. British Journal of Radiology. 2012 July 01;85(1015):e307-13.
127. Harders SW, Madsen HH, Rasmussen TR, Hager H, Rasmussen F. High resolution spiral CT for determining the malignant potential of solitary pulmonary nodules: Refining and testing the test. Acta Radiol. 2011 May 1;52(4):401-9.
128. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Lijmer JG, Moher D, Rennie D, de Vet HC, Standards for Reporting of Diagnostic Accuracy. Towards complete and accurate reporting of studies of diagnostic accuracy: The STARD initiative. BMJ. 2003 Jan 4;326(7379):41-4.
129. Goh V, Halligan S, Hugill JA, Bartram CI. Quantitative assessment of tissue perfusion using MDCT: Comparison of colorectal cancer and skeletal muscle measurement reproducibility. AJR Am J Roentgenol. 2006 Jul;187(1):164-9.
130. Goh V, Halligan S, Hugill JA, Bassett P, Bartram CI. Quantitative assessment of colorectal cancer perfusion using MDCT: Inter- and intraobserver agreement. AJR Am J Roentgenol. 2005 Jul;185(1):225-31.
131. Sahani DV, Kalva SP, Hamberg LM, Hahn PF, Willett CG, Saini S, Mueller PR, Lee TY. Assessing tumor perfusion and treatment response in rectal cancer with multisection CT: Initial observations. Radiology. 2005 Mar;234(3):785-92.
132. Rumboldt Z, Al-Okaili R, Deveikis JP. Perfusion CT for head and neck tumors: Pilot study. AJNR Am J Neuroradiol. 2005 May;26(5):1178-85.
133. Hermans R, Meijerink M, Van den Bogaert W, Rijnders A, Weltens C, Lambin P. Tumor perfusion rate determined noninvasively by dynamic computed tomography predicts outcome in head-and-neck cancer after radiotherapy. Int J Radiat Oncol Biol Phys. 2003 Dec 1;57(5):1351-6.
134. Bille A, Pelosi E, Skanjeti A, Arena V, Errico L, Borasio P, Mancini M, Ardissone F. Preoperative intrathoracic lymph node staging in patients with non-small-cell lung cancer: Accuracy of integrated positron emission tomography and computed tomography. Eur J Cardiothorac Surg. 2009 Sep;36(3):440-5.
135. Kim BT, Lee KS, Shim SS, Choi JY, Kwon OJ, Kim H, Shim YM, Kim J, Kim S. Stage T1 non-small cell lung cancer: Preoperative mediastinal nodal staging with integrated FDG PET/CT--a prospective study. Radiology. 2006 Nov;241(2):501-9.
136. Halpern BS, Schiepers C, Weber WA, Crawford TL, Fueger BJ, Phelps ME, Czernin J. Presurgical staging of non-small cell lung cancer: Positron emission tomography, integrated positron emission tomography/CT, and software image fusion. Chest. 2005 Oct;128(4):2289-97.
137. Takamochi K, Yoshida J, Murakami K, Niho S, Ishii G, Nishimura M, Nishiwaki Y, Suzuki K, Nagai K. Pitfalls in lymph node staging with positron emission tomography in non-small cell lung cancer patients. Lung Cancer. 2005 Feb;47(2):235-42.
138. Verhagen AF, Bootsma GP, Tjan-Heijnen VC, van der Wilt GJ, Cox AL, Brouwer MH, Corstens FH, Oyen WJ. FDG-PET in staging lung cancer: How does it change the algorithm? Lung Cancer. 2004 May;44(2):175-81.
139. Gonzalez-Stawinski GV, Lemaire A, Merchant F, O'Halloran E, Coleman RE, Harpole DH, D'Amico TA. A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. J Thorac Cardiovasc Surg. 2003 Dec;126(6):1900-5.
140. Eng J. Sample size estimation: How many individuals should be studied? Radiology. 2003 May;227(2):309-13.
141. UyBico SJ, Wu CC, Suh RD, Le NH, Brown K, Krishnam MS. Lung cancer staging essentials: The new TNM stag-

ing system and potential imaging pitfalls. Radiographics. 2010 Sep;30(5):1163-81.