Chapter 1

General introduction

GENERAL INTRODUCTION

Since the introduction of computed axial tomography by Godfrey Newbold Hounsfield in 1971 and the introduction of the whole-body scanner in 1974, computed tomography (CT) has been improved massively. The introductions of the spiral scanner in 1990 and the multidetector-row CT in 1998 have revolutionized CT imaging by making volumetric scanning feasible and limiting the scanning time. These developments have increased the number of applications to for example cardiac CT and CT angiography. As a result of these advances there has been an increase in the number of CT examinations and on average, more and thinner slices are obtained at each examination. In the mean time, the applied radiation dose has increased exponentionally. While CT accounts for about 10% of the radiological procedures, it accounts for about 67% of the medical radiation dose [1].

In contrast to plain X-rays, CT is not hampered by over projection. Although the benefits of more accurate data have been proven, the major disadvantage of CT is the intrinsic risk of radiation dose. With present standard techniques, between 4 and 8 mSv effective dose is delivered (UNSCEAR rapport 2001), which leads to a calculated risk of dying from radiation-induced cancer of 2-4 in 10.000 (30-year old) individuals. The risk, however, is strongly age-dependent and decreases sharply for elderly individuals (up to a factor of 5), while it increases for children (up to a factor of 5).

The exponential increase in applied radiation dose is concerning more and more radiologists [2-6] and has lead to the implementation of the "As Low As Reasonably Achievable" (ALARA) principle [7]. According to this principle, for each patient the applied radiation dose should be kept to the minimum, which is necessary to obtain enough image quality to get the required diagnostic information.

PART 1

In clinical routine, many patients receive a plain chest X-ray for suspected pulmonary diseases. In many cases, this chest X-ray is not conclusive and a chest CT-scan is ordered to get the required diagnostic information. This approach results in more radiation dose applied to the patient. Moreover, many patients with chronic, but benign chest disease receive regular X-rays to follow-up the status of their disease. For these patients a CT-scan could provide more information, but the radiation dose level of CT-scans is a major limiting factor. In chapter 2, we investigate if an ultra-low dose CT-scan can provide the diagnostic information of a standard dose CT-scan at the radiation dose of a plain chest X-ray in two directions. We report the results of a study comparing both plain chest X-ray and ultralow-dose chest CT to the standard dose chest CT performed on the same day, in order to show that ultralow-dose chest CT could be performed in daily practice.

The early detection and the study of the natural progression of emphysema is an other application for low dose CT. Emphysema is anatomically defined as a permanent abnormal enlargement of the alveoli distal to the terminal bronchioles. This anatomical definition makes CT an ideal tool to non-invasively detect the presence and the extent of lung tissue destruction. In 1988, Müller and co-workers described a method to highlight areas within the lungs showing an attenuation below a prefixed threshold [8]. The extent of the highlighted areas can be expressed as percentage of total lung area. They demonstrated that the extent of highlighted low-attenuated areas showed a good correlation with the extent of macroscopic emphysema. The method was originally described and validated for axial images, but Park et al showed a good correlation with three-dimensional data [9]. Since emphysema is a common and debilitating disease, CT could play a role in the early detection and secondary prevention of emphysema. However, also for this purpose the radiation dose should be kept as low as achievable. The detection of emphysema has been shown to be feasible on low dose scans by Shaker et al [10], but the lack of contrast between destructed areas and normal lung parenchyma makes the automated technique sensitive to image noise. In chapter 3, we demonstrate that massive image noise raises emphysema scores, especially for low amounts of lung destruction. For reliable diagnostic results, application of a dedicated noise reduction filter is required before the extent of emphysema can reliably be quantified.

PART 2

For most patients, the benefits of CT will exceed the harms. However, CT is now increasingly being used for screening purposes, being applied to healthy subjects. In this particular setting, the development of low-dose scanning protocols is of importance. With the introduction of the multi-detector row scanners protocols applying low radiation dose have become feasible [2]. The high contrast between air and many pathological structures in the lungs, make the chest an area where substantial dose reduction is achievable. This option is already applied in the lung cancer screening trials performed on several locations around the world [11-13]. In this particular situation the increased noise has been shown to have limited influence on the diagnostic task: the detection and measurement of pulmonary nodules [14].

Part two of this thesis concerns the reproducibility of the semiautomated quantification of the volume of pulmonary nodules, which can show early lung cancer and the management of these nodules. Lung cancer is today the most frequent cause of cancer deaths in the Western world. At time of diagnosis more than two-third of these people have locally advanced or metastatic disease, and their poor prognosis is due to late diagnosis and lack of effective treatment of metastatic disease. Less than 15% of the patients are surviving at least 5 years. However, when lung cancer is diagnosed in early stages and curative treatment is

still possible, 85% of the patients are surviving at least 5 years [15]. The well-described population at-risk, the options to treat lung cancer in early stage and the possibility to detect lung cancer in early stage without doing too much harm, have made screening for lung cancer with low dose CT an attractive way to decrease the lung cancer specific mortality.
The Dutch Belgian Lung Cancer Screening Trial (NELSON) is a population-based randomized multi-center lung cancer screening trial that studies about 16,000 current and former heavy smokers. Selection of participants was performed by sending a questionnaire about smoking history and other health-related issues to citizens between 50 and 75 years of age who lived in the areas around the participating centers. Among the respondents, subjects meeting the inclusion criteria of a minimum of 16 cigarettes/day for 25 years or 11 cigarettes/day for 30 years were asked to participate in the trial. After being informed about, among others, the radiation dose that was exposed to the participants, those who gave written informed consent were equally randomized to either the screening arm or the control arm. Participants with a moderate or poor self-reported health status who were unable to climb two flights of stairs were excluded from participation.
Early lung cancer is detected as small pulmonary nodule. Chapter 4 describes the management of pulmonary nodules detected during the NELSON-trial. Since about 70% of the heavy smoking population show such nodules and only a few of these nodules turn out to be malignant, a simple non-invasive way to distinguish the malignant nodules from the benign ones is mandatory. Therefore, in lung cancer screening trial growth of nodules is used as main feature to detect the nodules with a high suspicion to be malignant. However, measurement errors can interfere with the calculation of growth rates. In chapter 5, we report the influence of the observer on the variability in volume measurements of isolated pulmonary nodules performed with a semiautomated, FDA approved, commercially available and widely used lung nodule volume program. In chapter 6, we quantify the extent of measurement variability of isolated pulmonary nodules caused by variables that are changed when a new CT is performed. This study was performed on patients of the outpatient department of oncology with pulmonary metastases shown on previous imaging.

PART 3

The third part of this thesis concerns the detection of an other major smoking-related disease: chronic obstructive pulmonary disease (COPD). COPD is after cardio-vascular disease the second smoking-induced disease in terms of prevalence of morbidity and mortality [16]. COPD is a heterogeneous disease comprising mucosal thickening of the bronchioles, resulting in airflow limitation and emphysema, anatomically defined as a permanent enlargement of the terminal bronchioles and alveoli [17]. In clinical practice computed tomography (CT) is used to detect emphysema, showing good correlations with histology [18-21].

The population enrolled in lung cancer screening trials is also the population at-risk for developing COPD. Therefore, lung cancer screening trials form a good environment to study the prevalence and the natural course of COPD in an asymptomatic population.
Studies correlating pulmonary pathophysiology examined with function tests and pathology demonstrated on CT, have shown moderate to good results [18;22], but smokers with parenchymal damage demonstrated with computed tomography (CT) often have no reduced airflow function [23;24]. Despite this limitation, the detection of emphysema is still based on the FEV_1 [25].
The method of highlighting voxels with an abnormally low attenuation is hypothesized to be a simple method to monitor lung tissue destruction [5;6], but little is known about the preciseness of automatically obtained results. In chapter 7 the reproducibility of the automated quantification of low-attenuation areas in the heavy current and former smokers participating in the screening arm of the NELSON-trial is reported.
In chapter 8 we describe a study performing pulmonary function tests in a randomly selected sample of the participants of the NELSON-trial who underwent a baseline scan in the University Medical Center in Utrecht. Results were compared to the extent of moderate and severe emphysema detected on CT of these subjects. Diffusion testing is a more dedicated method to detect lung tissue destruction than spirometry, so it was not surprising that D_{CO} turned to be the most sensitive parameter to detect emphysema shown on CT. However, D_{NO} was hypothesized to be even more sensitive, since NO has a stronger affinity for haemoglobin than CO. In chapter 9 we investigate the ability of NO-diffusion to detect emphysema demonstrated on CT and compared the results to capability of D_{CO}/V_A to detect emphysema demonstrated on CT.
Parr et al have shown that the distribution pattern of the lung tissue destruction significantly influences the extent of airflow obstruction and gas exchange impairment in a group of patients with $alpha_1$-antitrypsine deficiency [26]. $Alpha_1$-antitrypsine deficiency is a rare disease, but results in severe emphysema. However, emphysema in these patients results from a different pathophysiologial process than smoking-related emphysema, making the results of this study not simply transferable to the smoking population. We conducted a study investigating the impact of the distribution pattern of smoking-related emphysema on airflow limitation and gas exchange impairment in the population of current and former heavy smokers, participating in the NELSON-project. The results are reported in chapter 10.

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