General introduction and outline of the thesis
Lung cancer is the leading cause of cancer-related deaths worldwide, with 1.6 million lung cancer deaths each year [1]. In the Netherlands, 10,263 patients died from lung cancer in 2013 [2]. After the age of 45 years, the incidence of lung cancer greatly increases in both males and females. Despite improvements in surgical treatment, chemotherapy and radiotherapy, the long-term survival of lung cancer remains low [3], since lung cancer is usually diagnosed at a late, advanced stage. Most patients with early-stage lung cancer are asymptomatic. More than two-thirds of clinical patients present with regional or distant metastases [4]. Lung cancer survival is strongly related to the stage at time of diagnosis, with five-year survival decreasing from 67% for stage IA disease, which can be treated surgically with good overall survival, to less than 1% for stage IV disease [5].

After the introduction of low-dose multi-detector spiral computed tomography (CT) in the 1990s, several randomized controlled trials were performed to compare the use of CT and chest radiography in early detection of lung cancer as a method for lung cancer screening [6–8]. The largest of these studies, the National Lung Screening Trial (NLST) concluded that annual screening by low-dose CT reduces lung cancer specific mortality by 20%, compared to screening with chest radiography [8]. Other trials compared low-dose CT-screening with no screening [9–11]. Most of these trials are ongoing.

The promising results of the NLST have led to a positive recommendation on lung cancer screening by the United Stated Preventive Services Task Force at the end of 2013, and to the announcement of the U.S. Centers for Medicare and Medicare services for immediate coverage of annual low-dose CT lung cancer screening in a high risk population [12, 13]. Currently, lung cancer screening in the United States is rapidly expanding. Although none of the European trials have shown benefit of lung cancer screening by low-dose CT yet, also in Europe implementation of lung cancer screening is discussed [14, 15].

One of the challenges of lung cancer screening, however, is the high rate of participants (up to 66%) with at least one small-to-indeterminate sized lung nodule. Up to 99% of these nodules has been found to be benign. Differentiation of benign and malignant pulmonary nodules, especially in case of indeterminate size nodules (volume 50-500 mm$^3$, about 4.6-9.8 mm diameter), remains a problem. If it is possible to identify which nodules are less likely malignant, diagnostic workup, or even follow-up CT of these lesions could be avoided, which can reduce invasive procedures, radiation exposure, anxiety and costs.

**Outline of this thesis**

The aim of the studies described in this thesis is to optimize nodule management in CT lung cancer screening, in order to minimize false-positives without affecting the sensitivity and negative predictive value. In **Chapter 2**, the initial results of the European lung cancer screening trials are reviewed. A practical approach to CT lung cancer screening and lung nodule management is described in **Chapter 3**.

The studies described in the remainder of the thesis are based on the Dutch-Belgian lung cancer screening trial (Dutch acronym: NELSON). The NELSON trial is an ongoing multicenter randomized controlled trial comparing CT screening to no screening, launched in September 2003. Primary object is to investigate whether chest CT screening in year 1,
2, 4 and 6.5 will decrease lung cancer mortality by at least 25% in high-risk (ex-)smokers between 50 and 75 years of age compared to a control group receiving no screening. The NELSON trial is the first large lung cancer screening trial in which the nodule management protocol is based on nodule volume, instead of nodule diameter, and on nodule growth of previously detected nodules, in terms of volume-doubling time (VDT). The final results will indicate whether a volumetry- and VDT based CT protocol is more efficient in terms of detection rate, morbidity, mortality, recall rate, and cost-effectiveness, compared to other approaches.

The second part of this thesis focuses on quantitative analyses of NELSON data. It was hypothesized that the volume and VDT cutoff for, respectively, nodules at initial detection, and fast-growing nodules at short-term follow-up CT could be optimized, compared to the cutoff values determined prior to the start of the trial in 2003. In Chapter 4, the optimal VDT cutoff value for fast-growing pulmonary nodules is evaluated. In Chapter 5 optimal volume cutoff values based on cancer probability are described and a volume-based screening guideline is compared to a diameter-based approach. Since a nodule has only one volume, but an unlimited number of diameters, it is likely that nodule management based on nodule volume is far more accurate than diameter-based nodule management. The influence of the use of nodule diameter and nodule volume for the estimation of nodule size is described in Chapter 6. Lung cancer probability of new nodules at incidence screen after baseline, and the question whether or not management should be different for incident lung nodules is addressed in Chapter 7.

Based on theoretical models, exponential growth is expected for lung cancer. For this reason, VDT is used to estimate nodule growth. However, real evidence on lung cancer growth patterns is very limited, because lung cancer usually is an aggressive disease, in which a wait-and-see approach is not an option. Lung cancer screening programs, in which small and intermediate sized nodules are followed by several CT exams, provide a unique opportunity to study lung cancer growth. In Chapter 8, growth curves of solid lung cancers, detected at ≥3 CT exams before lung cancer diagnosis were quantified, to investigate if lung cancers really grow exponentially and if therefore VDT is a good measure to monitor lung cancer growth.

In the last part of this thesis, a qualitative analysis of CT imaging in lung cancer screening is performed. In Chapter 9, the influence of manual adjustments of test result on screen outcome in terms of false-positives and false-negatives is evaluated. Some lung nodules resolve during follow-up, and we hypothesized that if we could identify specific nodule features to predict resolution, unnecessary extra evaluation of these nodules could be avoided. The prevalence of resolving lung nodules, and features predicting the disappearance of a nodule, are described in Chapter 10 and Chapter 11. In Chapter 12, the main results of the studies described in this thesis are discussed, and the relevance of the findings and suggestions for future research are described.

References


