SUMMARY

Patients with locally advanced non-small cell lung cancer (NSCLC), who are in a good general condition, are preferably treated with concomitant radiotherapy and chemotherapy. This combination treatment results in the highest overall survival rates: 32%–40% of patients are alive after 5 years. However, by combining these two treatment modalities the rates of (serious) side effects, such as swallowing complaints (dysphagia), are also high.

The aim of this thesis is to be able to better predict the survival and recurrence rates of locally advanced NSCLC-patients, as well as further improvement of the radiotherapy treatment. Chapter 1 contains a general introduction and describes the current state of affairs in the field of NSCLC. The epidemiology and standard treatment are described. A conventional radiation regimen for patients with a locally advanced NSCLC consists of 60 Gy in 30 fractions, resulting in an overall treatment time of six weeks. At the Antoni van Leeuwenhoek hospital, these patients are treated with a (mild) hypofractionated radiation regimen, which shortens the total duration of the treatment by one week. The rationale is discussed extensively in this chapter. Various challenges are also described, which can lead to a better prognosis or fewer side effects. An overview of the structure of this thesis is given at the end of the chapter.

Part I
Predicting the outcomes of patients with locally advanced lung cancer

Part I focuses on a better prediction of the outcomes of patients with locally advanced NSCLC who are being treated with concomitant radiotherapy and chemotherapy. Despite this intensive treatment, for about a third of patients the tumor recurs within the thorax. It is important to know which patients have a high risk of a recurrence and whether there are certain prognostic characteristics. A number of characteristics have already proven to be prognostic, such as the general condition (scored according to WHO and/or Karnofsky), weight loss and the tumor volume (GTV). Regarding the tumor volume, generally no distinction was made between the GTV of the primary tumor and the GTV of the involved lymph nodes. It was also unclear what the likelihood was of a local recurrence (the recurrence of the primary tumor) and a regional recurrence (the recurrence of the tumor in an irradiated lymph node) after radiotherapy and chemotherapy. It turned out that the regional recurrence rate was much smaller than the local recurrence rate. In chapter 2, possible differences in prognostic factors between local and regional control were investigated after radiotherapy and chemotherapy. The primary tumor and the involved lymph nodes were separately contoured and analyzed. This study included 226 patients, of which 92% had stage IIIA-B NSCLC. All patients were treated with concurrent radiotherapy and chemotherapy. The median follow-up was 29 months. The local recurrence rate was 16% after 1 year and 26% after 2 years; this was twice as high as the regional recurrence rate of 8% after 1 year and 14% after 2 years. In the multivariate analysis, no patient or tumor-specific characteristics were found to be associated with a local or regional recurrence. The only prognostic factor was the volume of the primary tumor or the volume of the lymph nodes before the start of the treatment. This study provided the rationale for a subsequent study, namely reducing the radiation dose to the mediastinal lymph nodes. The results of this analysis are described in chapter 6.
FDG-PET-scans are indispensable in staging lung cancer patients because the sensitivity for assessing the extent of the tumor is better than that of a CT-scan. FDG-PET-scans are also essential for determining the GTV for radiotherapy. A CT-thorax is generally performed a few weeks after the treatment is completed. The role of FDG-PET-scans in evaluating the treatment is less clear. In addition, it is important to know if there is a difference in response after treatment between the primary tumor and the lymph nodes. Chapter 3 investigated the additional value of FDG-PET-scans performed just weeks after completing the treatment for patients treated in the Raditux-study. The randomized phase II Raditux-study investigated the addition of cetuximab, an EGFR-inhibitor, in patients with locally advanced NSCLC who were treated with concurrent radiotherapy and chemotherapy. All 102 patients underwent an FDG-PET-scan before the start of the treatment. An FDG-PET-scan was performed in 47 patients approximately 4 weeks after treatment. Multiple PET-parameters were investigated (maximum and mean standardized uptake value, metabolic tumor volume, tumor lesion glycolysis; SUV$_{\text{max}}$, SUV$_{\text{mean}}$, MTV, TLG) as well as specific patient and tumor characteristics such as tumor volume. The PET-parameters measured before and after the treatment as well as the relative difference between the two scans was tested. In this study too, the primary tumor and the involved lymph nodes were separately contoured and analyzed. Performing an FDG-PET-scan 4 weeks after treatment turned out to have prognostic value. In particular the PET-parameters of the primary tumor were associated with the outcomes. Both the volumetric PET-parameters (MTV, TLG) and the intensity PET parameters (SUV$_{\text{max}}$, SUV$_{\text{mean}}$) were valuable.

Part II

Optimizing the treatment of patients with locally advanced lung cancer

Part II investigates the improvement of the radiotherapy of locally advanced NSCLC-patients. As described in chapter 2, lung cancer recurs more often in the primary tumor than in the involved lymph nodes. To increase the local control, research is focused on increasing the dose to the primary tumor. In the Antoni van Leeuwenhoek hospital, a hypofractionated radiation regimen is used, which means that a higher fraction dose (2.75 Gy/day) is given than the conventional fractionation of 2 Gy/day. In part II this radiotherapy scheme is further investigated in relation to the dose to the heart as well as by adapting the dose to the primary tumor or to the involved lymph nodes.

In chapter 4, the relationship between the radiation dose to the heart and the overall survival was investigated in 469 patients who were treated with radiotherapy and chemotherapy. The $V_{0.5}/V_{45}$ (the volume of the heart that received a minimum of 0.5 Gy to 45 Gy) were associated with overall survival. The $V_2$ showed the highest probability with a HR 1,008, meaning that if the volume of the heart treated with $\geq 2$ Gy increased, the probability of death increased by 0.8%. The median volume irradiated with 2 Gy was 59.7%. The group of patients with a $V_2$ higher than 59.7% showed a median survival of 17 months, while this was 30 months in the group of patients with a $V_2$ lower than 59.7%. Other factors associated with survival in the multivariate analysis were age and tumor volume. It was remarkable that the mean lung dose (MLD) was not significantly associated with overall survival.

In 2010 the PET-boost trial opened, an international randomized phase II study in which the value of a higher radiation dose to the primary tumor was investigated. Patients were treated with a higher dose either to the entire tumor or to the FDG-active areas within the tumor. The aim was to investigate whether local control improved after one year due to the higher radiation dose. Consequently, the acute and late adverse events may also have increased. Chapter 5 described the
adverse events of the PET-boost trial. The pre-defined limits were not exceeded. For example, the number of patients with severe (> grade 3) dysphagia was 14.3% when treated with concomitant chemotherapy. Because the patients treated in this study had large tumors (> 4 cm) that were often located near or around the large blood vessels, we expected in advance that up to 10% could die from a fatal pulmonary hemorrhage or a fistula between the esophagus and the bronchi. Ultimately, 5 patients (4.7%) died from a pulmonary hemorrhage and 4 patients (3.7%) from a fistula. Most of them, however, had an active tumor at the time of death, which may also have been the reason for the pulmonary hemorrhage or fistula. After a thorough analysis of all patients, it was concluded that although the increased radiation dose caused more side effects, it was tolerable.

There were two reasons to reduce the dose to the mediastinal lymph nodes for all lung cancer patients receiving radiotherapy at the Antoni van Leeuwenhoek hospital. First, the phase III RTOG 0617 trial, published in 2015, showed that 74 Gy in 2 Gy per day with a treatment duration of 7.5 weeks versus 60 Gy in 6 weeks caused a poorer survival. Possible causes for this were severe (> grade 3) dysphagia, the irradiated heart volume, the extended overall treatment time and the consolidation chemotherapy that was given. Secondly, the involvement of mediastinal lymph nodes increases the radiation field resulting in an increased dose to the organs at risk, such as the heart and esophagus. Chapter 2 demonstrated that the regional recurrence rate is lower than the local recurrence rate, caused by a difference in tumor volume. It was therefore decided to reduce the dose to the lymph nodes to 60 Gy. Previous research also showed that the margins for both the primary tumor and the involved lymph nodes could be reduced due to an improved image-guidance procedure consisting of a daily online carina based correction strategy. Chapter 6 described the results of these two implementations: (1) reduced dose to 60 Gy to the involved lymph nodes while maintaining the 66 Gy/24 fractions dose for the primary tumor and (2) reduced margins due to the carina based correction strategy. We compared a reduction-cohort (N = 138) in which these adaptations were introduced with a reference-cohort (N = 170). The severe (> grade 3) dysphagia rates decreased significantly: from 12.9% to 3.6%. Furthermore, the adverse events of the lungs (> grade 3) consisting of cough, dyspnea and radiation pneumonitis decreased from 4.1% to 0%. The local and regional recurrence rates did not increase due to the reduced dose to the lymph nodes and the reduced margins. The overall survival, however, improved significantly even after adjusting for the mean lung dose and the > grade 3 pulmonary adverse events. At present, the reduced radiation dose to the involved lymph nodes and the reduced margins due the implementation of the online carina based correction strategy are standard of care for patients with locally advanced NSCLC at the Antoni van Leeuwenhoek hospital.

Chapter 7 contains the general discussion of this thesis.