Summary

Chapter 2 describes outcomes of a multicenter phase II trial (2001 to 2004) investigating the efficacy of more aggressive induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer (NSCLC). The chemotherapy scheme consisted of cisplatin combined with high-dose epirubicin every two weeks for three courses. A radiological partial response, according to response evaluation criteria in solid tumors (RECIST), was observed in 48.3% of patients with acceptable toxicity. However this response rejected further exploration of this regimen in phase III setting as was prespecified in the statistical design of the study. Following induction chemotherapy, surgery or radiotherapy was decided upon results of restaging. The overall survival in this study of 61 patients was 18 months.

In 2003, concurrent chemoradiotherapy (CCRT) was implemented as the routine VUmc treatment strategy for stage III NSCLC patients, on the basis that simultaneous administration of both modalities would have a favourable effect on response and survival, mainly due to the radiosensitizing properties of several chemotherapy regimen. The advantage for a concurrent approach has been confirmed in multiple phase III trials and meta-analyses. **Chapter 3** describes a treatment strategy in which all potentially operable stage III NSCLC patients (n=34) underwent CCRT, followed by surgery if invasive mediastinal restaging showed downstaging in those with mediastinal lymph node involvement. In this time period (from 2003 to 2007), a preoperative radiotherapy dose of 46 to 50 Gy was recommended, whereas definitive or curative radiation doses typically ranged between 60 and 66 Gy. The former approach results in radiation treatment 'splits' for restaging after induction therapy, which in turn may have a negative impact on survival in patients who are not suitable for surgery. This study describes a strategy to prevent such treatment splits but this approach was subsequently not adopted as it was very labor-intensive and required careful coordination. After phase III trials showed no additional value for routine surgery following induction chemo(radio)therapy, and with growing evidence of the beneficial effect from CCRT compared to sequential administration, CCRT became standard of treatment for stage III NSCLC patients. However, due to toxicity concerns when CCRT is applied, patients with comorbidities are often excluded in clinical trials and consequently also by physicians in routine treatment. The cohort analysis described in **Chapter 4** included 89 stage III NSCLC patients treated with CCRT, 28% at an age of 70 or more, 42% having significant comorbidities and 14% were treated previously for lung cancer, illustrating a

general treatment population. Selection criteria required that patients had to be fit enough to undergo cisplatin-based chemotherapy, and achieving a radiation field less than 42% of the total lung volume receiving 20 Gy or more. In this population, toxicity was acceptable and the median overall survival was 18.2 months, a figure comparable to most phase III trials.

In search of a better understanding of patient tolerance of CCRT, we retrospectively investigated in **Chapter 5** the relation between nutritional status and treatment outcomes of 33 consecutive stage III NSCLC patients undergoing CCRT followed by surgery from 2003 to 2007. The results revealed that patients with overweight at diagnosis and losing ≥5% of their weight during CCRT, had a worse prognosis than other groups, implying that nutritional status in every patient has to be carefully monitored and supported when necessary.

Toxicity of CCRT mainly consists of increasing rates of esophagitis and neutropenia, with radiation pneumonitis occurring less frequently. However, we are still unable to predict which patient will develop clinical or symptomatic radiation pneumonitis. Therefore, in **Chapter 6** we studied the radiological changes in lung tissue which might precede the development of clinical radiation pneumonitis after CCRT. Measuring and analyzing changes in Hounsfield Units in different dose regions within the normal lung tissue on follow-up CT scans of 25 stage III NSCLC patients, showed that increases in radiological lung density can be expected only after 3 months of follow-up and stabilizes after 1 year. In addition, lung tissue receiving >30 Gy showed the most evident density changes. There was no significant relation found between radiological density changes and clinical radiation pneumonitis, probably due to small sample size. This study quantifying radiological density changes after CCRT could be helpful in the search of predicting radiation pneumonitis, especially when novel treatment strategies are applied.

Finally, in **Chapter 7** the phenomenon of tumor cavitation is reviewed in a cohort of 87 stage III NSCLC patients treated with CCRT. Pretreatment tumor cavitation was observed in 18% of patients, the majority having squamous cell carcinoma. Half of these latter patients developed severe pulmonary complications during or after treatment, including hemorrhage, embolism and tumor abscess. The findings have implications for the choice of optimal treatment strategy in patients presenting with 'cavitated' tumors. The early detection and treatment of patients with cavitating tumors with intravenous antibiotics will have to be evaluated as an approach to prevent severe toxicity.