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Multimodality approach towards individualized non-small cell lung cancer treatment

Schaake, E.E.

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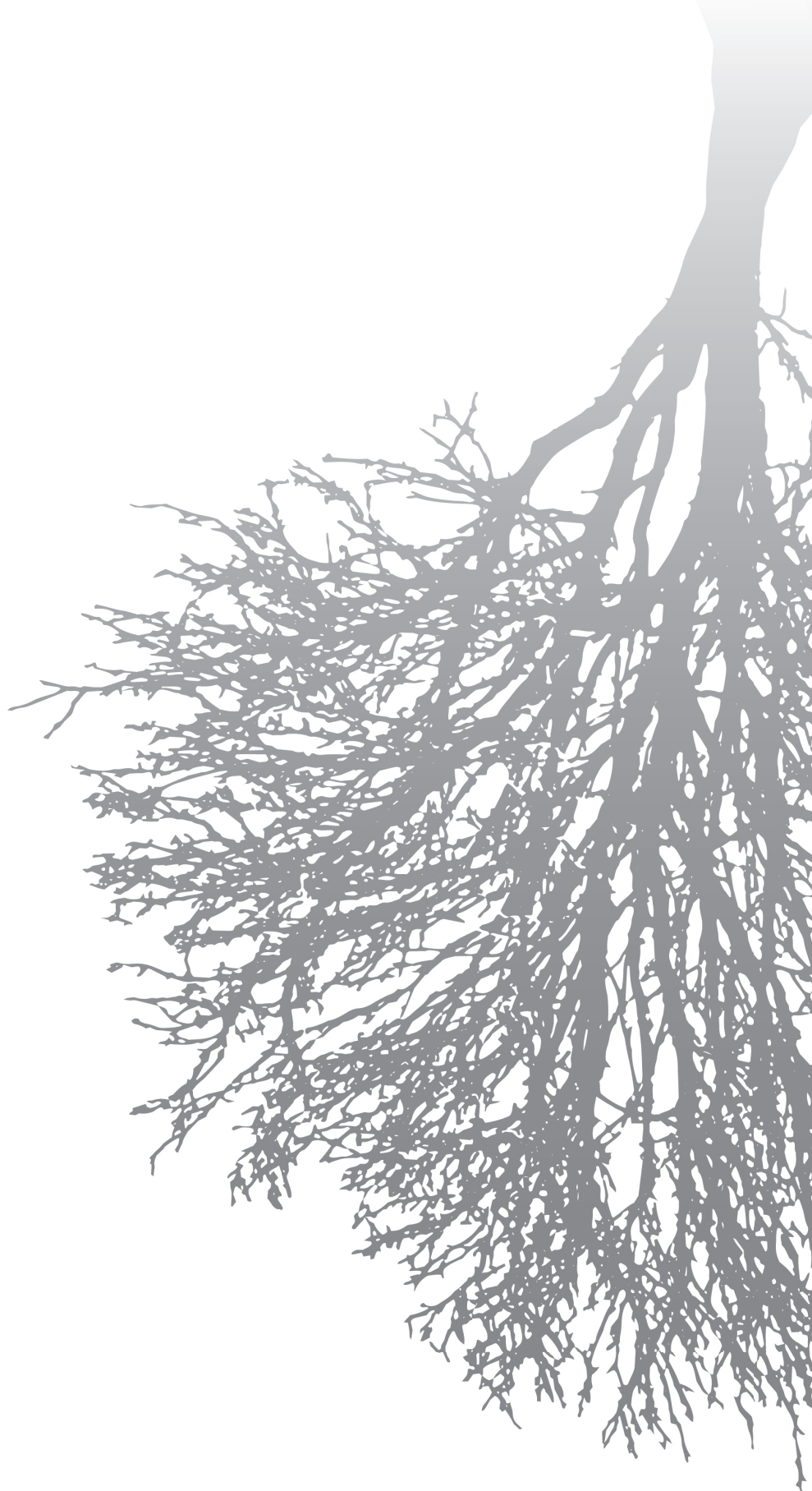
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Summary

This thesis focuses on different aspects of the multimodality treatment in non-small cell lung cancer (NSCLC) patients. **Chapter I** is a general introduction on the current treatment and developments in NSCLC. NSCLC is a smoking related and aggressive disease that covers 80% of the lung cancer subtypes. With most patients being diagnosed with metastasized disease and a life expectancy under a year researchers are facing many challenges for treatment improvement. The main aspects of diagnostics and treatment for early stage and locally advanced NSCLC are being discussed, as well as new developments in individualized treatment through response prediction and the addition of novel agents. The outlines of this thesis are set out and addressed at the end of the introduction (**Chapter 1**).

PART I: EXPLORING THE EGFR PATHWAY; NOVEL AGENTS ERLOTINIB AND CETUXIMAB IN A MULTI MODALITY TREATMENT SETTING

Part I focuses on the application of new agents erlotinib and cetuximab, epidermal growth factor receptor (EGFR) inhibitors. The discovery of EGFR mutations led to a cascade of developments in treatment of advanced NSCLC. Patients harboring an EGFR mutation receiving agents targeting the EGFR receptor or antibodies benefit with increased progression free survival. But also a subgroup of patients without an EGFR mutation can show treatment response. In this thesis novel agents are newly combined with the standard treatment of either resection in early stage NSCLC or chemoradiation in locally advanced NSCLC. Besides the toxicity and treatment response different predictive markers have been tested to improve patient selection.

In **chapter II** the results are shown of a 'window of opportunity' study, in which for the first time, NSCLC patients were treated with neoadjuvant erlotinib during the preparation time to radical surgery. The objective of this prospective study was to investigate the safety of preoperative erlotinib treatment and the (in vivo) response in patients with early stage resectable NSCLC. Initially patients meeting enriched criteria were included as they were more likely to respond to erlotinib. These criteria were female gender, non-smokers, Asian ethnicity and non-squamous histology. Sixty patients were included of whom half of the study cohort met the enrichment criteria. After three weeks of treatment with erlotinib toxicity was generally mild consisting of acneiform skin rash and diarrhea. Treatment evaluation was performed through CT scans, FDG-PET/CT scans and histology and their outcomes are compared. Changes on the FDG-PET/CT and/or necrosis above 50% were the best way for response evaluation. A metabolic partial or complete response was observed in 27% of the patients while radiological CT evaluation showed a response in 5% of the patients. After these three weeks the tumor was resected through lobectomy and lymphadenectomy. No unexpected pre- or post-operative complications occurred. Histological examination showed >50% necrosis in 23%, of whom 5% of the all patients had >95% tumor necrosis. The response rate in the enriched population was 34%. The treatment evaluation indicated that for short term evaluation of erlotinib used in this setting the

volume of the tumor might not decrease while the metabolic activity clearly decreases and necrosis evolves.

In **chapter III** an accurate and sensitive method for the determination of erlotinib and N-desmethyl erlotinib in human EDTA plasma and tumor tissue of NSCLC patients treated with erlotinib is analyzed. To increase knowledge of the plasma and tissue levels a method was established to perform these assays for different studies in NSCLC using high-performance liquid chromatography and detection with tandem mass spectrometry. This method was validated over a linear range from 5 to 2,500 ng/mL in plasma and from 5.0 to 500 ng/mL for human lung tumor tissue homogenate. Calibration curves in plasma were used to quantify the analytes in lung tumor tissue homogenate samples. Results from the validation study demonstrated a good intra- and inter-assay accuracy and precision in both matrices.

Subsequently in **chapter IV** the results of the exploratory study in which erlotinib and des-o-methyl erlotinib concentration determination are presented in plasma and tumor tissue of patients treated with 3 weeks of neoadjuvant erlotinib. The mean plasma and lung tumor tissue erlotinib levels were 1222 ng/mL (standard deviation (SD) 678) and 149 ng/g (SD 153), respectively. No strong accumulation of erlotinib in lung tumor tissue was observed. Nevertheless, extrapolated intra-tumoral concentrations during erlotinib therapy were above the IC50 of wild-type EGFR.

In **chapter V** different serum markers were tested for their predictive value during and after treatment with neoadjuvant erlotinib. The markers are ligands of the EGFR pathway and could therefore play a role in mechanisms of treatment response. The markers soluble-EGFR (s-EGFR), transforming growth factor alpha (TGF α), and amphiregulin (ARG) and two ligands of the insulin-like growth factor (IGF) receptor interacting with the EGFR pathway through IGF and IGF binding protein 3 (IGFBP3) were measured in serum before and during treatment. The concentration of the serum markers were tested for their predictive value for metabolic response. One marker, s-EGFR, showed a trend towards treatment outcome prediction. A high baseline level of s-EGFR (>54.95 μ g/l) was predictive for a response on PET/CT ($p=0.04$). In all responding patients the level of s-EGFR was decreased during treatment. The other markers did not show a correlation with response.

In **chapter VI** the development and results of kinase activity profiles in NSCLC tumor tissue are described in the presence and absence of erlotinib. The assay is used to relate this ex vivo response to clinical response in patients treated with 3 weeks of neoadjuvant erlotinib. A classifier was obtained that distinguished erlotinib responders and non-responders in the training set, using a Leave-One-Out Cross Validation and resulted in misclassification of two samples out of the 30. Application of the classification algorithm to 15 blinded samples from an independent validation set resulted in correct prediction of outcome for 12 samples.

Chapter VII focuses on a different combination of a new drug combined with the standard treatment for NSCLC patients with irresectable or locally advanced disease without metastases. Cetuximab, a monoclonal antibody that selectively binds to the

epidermal growth factor receptor, has demonstrated activity in patients with metastatic NSCLC. This pilot study assessed whether combining cetuximab with concurrent chemoradiation (CCRT) is safe and effective in locally advanced NSCLC patients. Twelve patients were enrolled. Ten patients completed protocol treatment. Although generally well tolerated, two patients were unable to complete treatment according to the protocol. Acneiform rash and dysphagia were the most common side effects (grade ≤ 3 according to CTCAE v 3.0). No unexpected toxicities were observed. Early response monitoring using FDG-PET/CT revealed a metabolic response in 8 (out of 10) patients. CT-scan evaluation showed a partial response in 8 patients. Four (out of 12) patients showed progressive disease after 12 months of follow-up. The addition of cetuximab to CCRT in patients with NSCLC was generally well tolerated and early clinical responses were observed with this new therapy combination. A randomized phase II study comparing CCRT with CCRT and cetuximab followed thereafter.

PART II: IMPROVING IMAGE GUIDED RADIOTHERAPY FOR NON-SMALL CELL LUNG CANCER PATIENTS

Part II of the thesis focuses on motion of the mediastinal lymph nodes during irradiation of locally advanced NSCLC. During irradiation cone beam CT (CBCT) scans are used for position verification of the lung tumor and the organs at risk. Lymph nodes are not well visible on CBCT scan. Therefore gold fiducial markers were used to track the position of the mediastinal lymph nodes during the course of treatment.

In **chapter VIII** the feasibility is analyzed of using these markers as a surrogate for lymph node position variability. The markers were placed during diagnostic endoscopic ultra sound guidance through the esophagus or bronchial wall. No complications occurred during or after marker placement. Substantial position variability was observed, mainly in cranial-caudal direction. The trial continued and the results of in total 51 patients are analyzed

in **chapter IX**. The larger prospectively treated cohort showed that there is substantial motion of the mediastinal lymph nodes. There was no correlation between the baseline shift of the lymph nodes and of the primary tumor. The margin recipe was adapted to the application of two individual targets, while the current margins are based on a single target calculation. By using a carina based correction protocol instead of a bony anatomy based margins can be reduced up to 27% for the lymph nodes and 15% for the primary tumor.

Chapter X contains the discussion of the thesis. Non-small cell lung cancer, often smoking related, remains an aggressive disease that proves difficult to control. Future research will be aimed at slowing the disease down and to seize metastatic disease. These efforts will likely result in greater understanding of oncogen mutations, signaling pathways and drug development for higher percentages of survival benefit. Current treatment challenges, new developments with the use of targeted therapy and the

need for patient selection are discussed. A standard for response to (neoadjuvant) targeted therapy has to be developed and validated as current response criteria for chemotherapy and irradiation do not suffice. Optimizing treatment efficacy while reducing toxicity is the main challenge in locally advanced NSCLC treated with (concurrent) chemoradiation. This concerns the chemotherapy, radiotherapy and their combination. By adding a targeted agent to concurrent chemoradiation toxicity can unexpectedly be increased. The addition and timing of new agents as erlotinib and cetuximab therefore have to be optimized, while simultaneously improving the efficacy and precision of the current treatments. Concluding: Further individualizing treatment by better patient selection, using predictive markers and tests, short term treatment response evaluation and adaptive radiotherapy have the potential to improve treatment outcome in the near future.