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Multimodality approach towards individualized non-small cell lung cancer treatment

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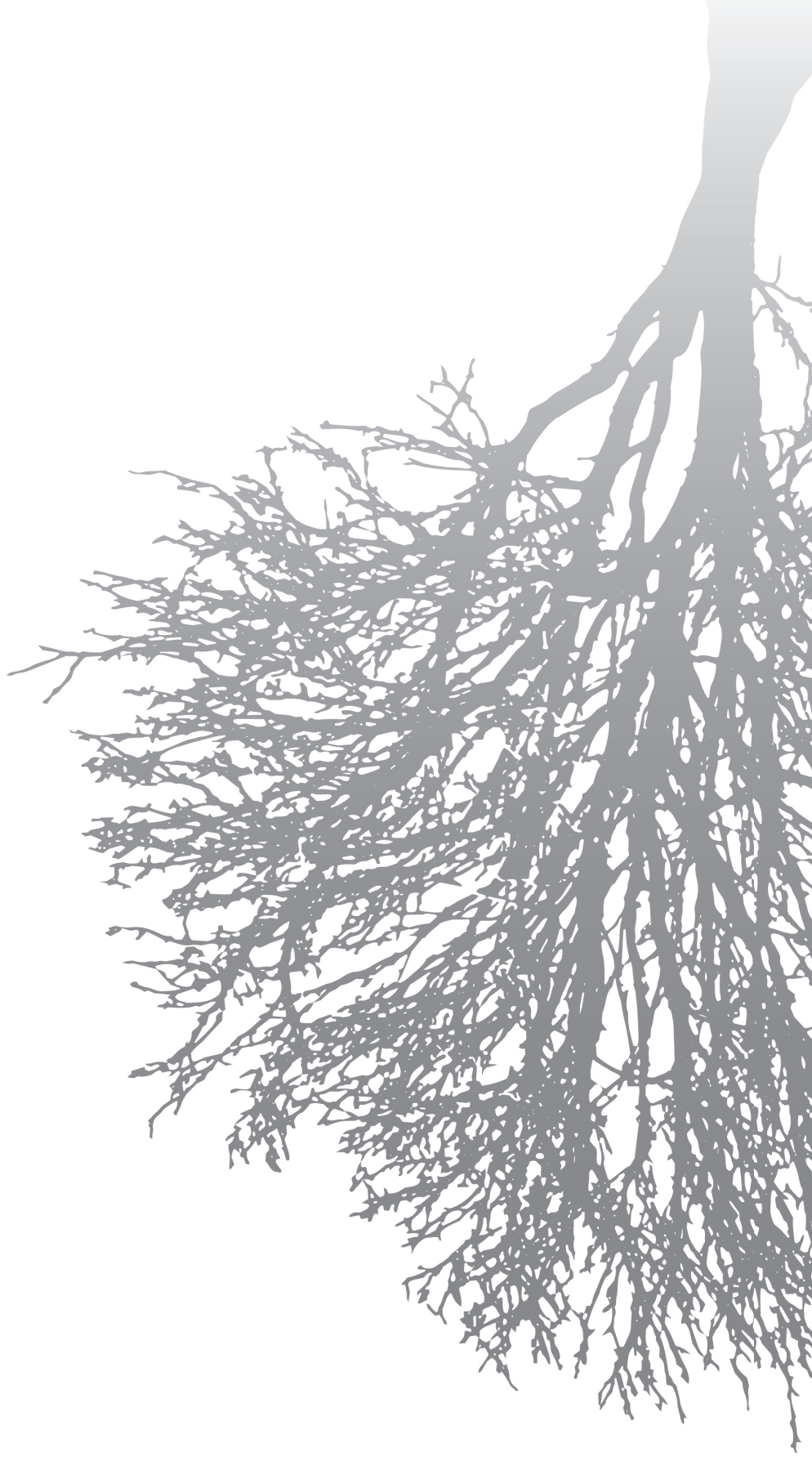
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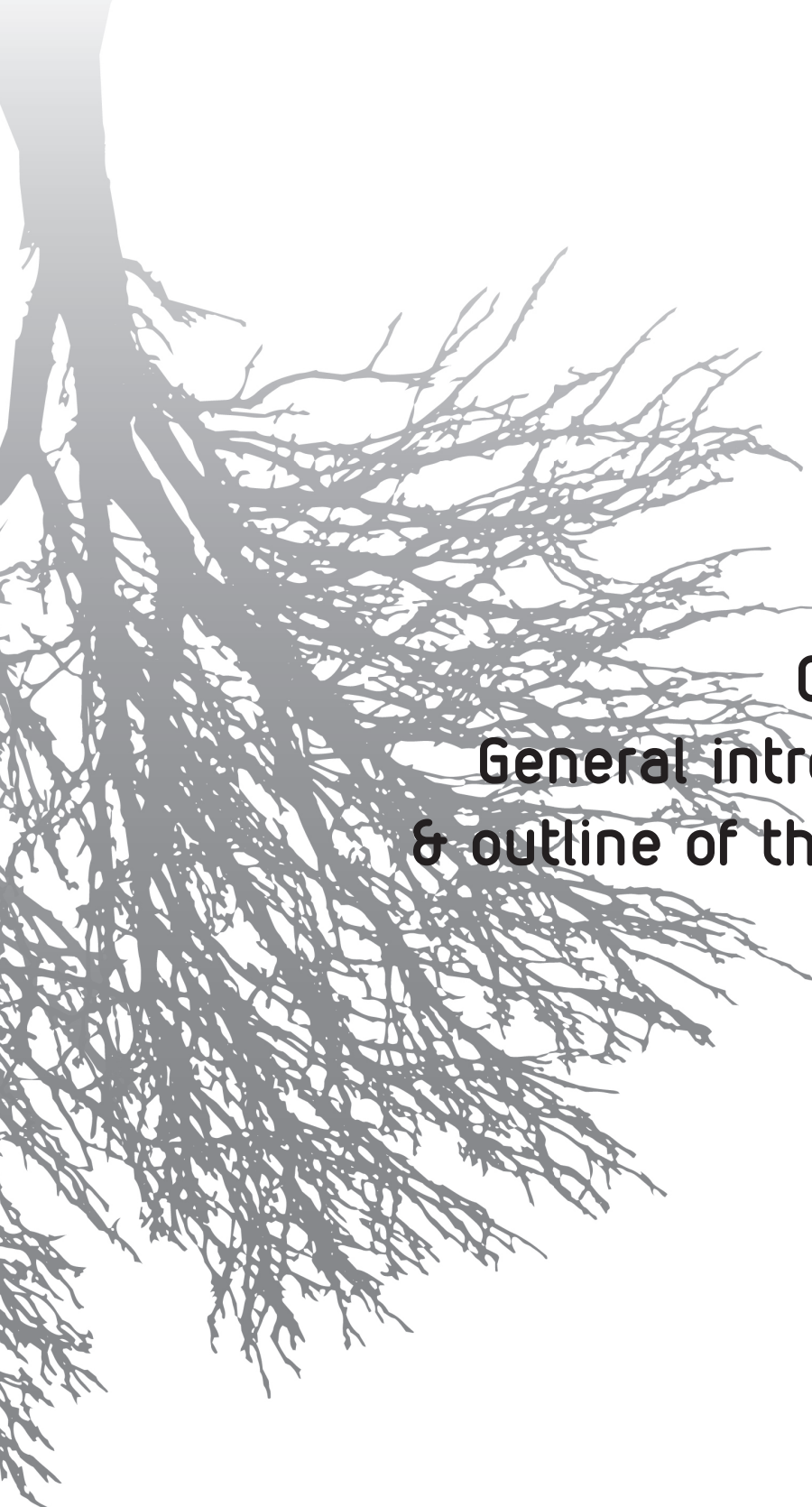
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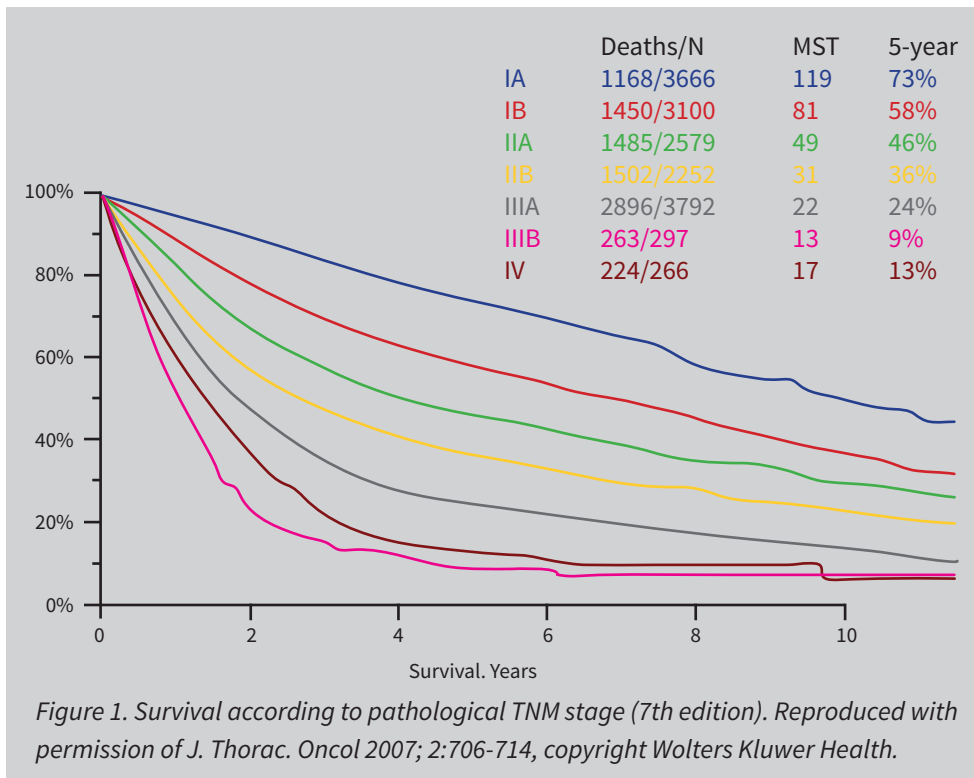
Chapter I
General introduction
& outline of the thesis

EPIDEMIOLOGY

In recent decades, many novel approaches in cancer treatment have emerged. As a consequence, cure rates of certain tumor types such as breast cancer and non-Hodgkin lymphoma have increased and survival of patients with metastatic disease has been significantly prolonged up to a decade (1, 2). Other tumor entities like lung cancer however, remain difficult to treat with mortality rates at 5 years of 85% for all stages together and a median survival of around 1 year (3). The majority of patients is diagnosed with metastatic disease. Figure 1 depicts the survival curves for the different stages in a staging study.

Yearly 10,350 new patients are being diagnosed with lung cancer in the Netherlands, the majority with locally advanced or metastatic disease (3). Historically lung cancer has been a disease with a higher incidence in male patients. The increased incidence of female lung cancer patients over the last few decades of 80% reflects the changing proportion between men and women in smoking behavior (3).

The incidence of lung cancer is strongly related with the exposure to toxic substances leading to damage to the lungs such as particles in (cigarette) smoke, chemical fumes and tar (4, 5). It can induce mutations at the cellular level within the airways. These



mutations may be carcinogenic and contribute to treatment resistance.

Lung cancer can be subdivided in different types: about 80% of the patients present with non-small cell lung cancer (NSCLC) and 15% with small cell lung cancer (SCLC) and 5% with other infrequent tumors (6). This division in distinct subtypes is important for both staging and accordingly the choice of treatment. SCLC is often (subclinically) metastasized at diagnosis, behaves more aggressively than NSCLC and is mainly treated with a combination of chemotherapy and radiotherapy. NSCLC comprises a range of histological subtypes that in early stages can be treated with surgery, in locally advanced stages with chemoradiation and in metastatic setting with platinum based chemotherapy. To a large extent, the different histological subtypes of NSCLC are currently treated the same way. However, more individualized treatment is emerging with growing knowledge about the molecular basis of the different subtypes. Indeed, in recent years new targeted agents have become available, expanding the oncological armamentarium for selected cases.

DIAGNOSTICS AND STAGING

For staging NSCLC the revised, 7th edition of the TNM staging system is used (7). Recent addition of FDG-PET/CT scanning to the diagnostic work-up has created a shift in staging, identifying more patients with pre-clinical loco-regional and distant metastases (8). Therefore, the recent survival shift in various tumor stages is not only reflecting improvement in treatment but also stage migration, (or the so called Will Rogers phenomena (9)) due to more accurate staging.

Despite the important contribution of FDG-PET/CT scan to accurate staging of lung cancer, histological proof of the disease extension is still needed for complete staging, histopathological and molecular characterization and subsequent treatment. The tumor can be accessed by bronchoscopy or ultrasound/CT guided trans-bronchial biopsy (TBNA). Different lymph node stations can be assessed with endobronchial ultrasound (EBUS) fine needle biopsy or via trans esophageal ultrasound fine needle biopsy (EUS-FNA) (10).

GENETIC MARKERS IN NSCLC

In the last decades extensive research has been performed to identify genetic markers that differentiate high- and low-risk patients, eventually leading to improved individual treatment efficacy. With the discovery of the mutations and deregulated signaling pathways involved, a better understanding of tumor types within NSCLC is evolving, possibly leading to new targets for individualized patient treatment. Signals, sent out by stromal factors, can induce or inhibit growth, cell division or cell migration, contributing to tumor development and progression. Disturbed signal regulation is often due to one or multiple mutations in specific oncogenes or tumor-suppressor genes. Most mutations found in NSCLC are found in the RAS-RAF-MEK-ERK-MAPK signaling

pathway, mediating various cellular responses, including proliferation, growth signaling and cell survival (11). In this pathway the over-expression of the epidermal growth factor receptor (EGFR) and KRAS mutations represents the most prominent molecular alterations with 12% and 20% prevalence in NSCLC respectively, in a Caucasian population. KRAS mutation often predicts for negative survival without adequate therapeutic implications, while certain EGFR mutated tumors can have a prolonged average survival when targeted by specific agents. Activating mutations lead to overstimulation of the transmembrane glycoprotein of EGFR, in NSCLC often caused by the deletion of exon 19 or a point mutation in exon 21 (12). EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib or gefitinib are small molecules, which bind reversibly to the intracellular adenosine triphosphate (ATP) binding site of the EGFR cascade. Normally ATP causes transphosphorylation assembling protein complexes, transducing signaling cascades and activating various biochemical processes. The ATP inhibition by erlotinib or gefitinib hampers the protein assembling and thus signaling cascades and process activation are not initiated (13). Cetuximab is a monoclonal antibody that binds to EGFR specifically. By this binding ligands of EGF and transforming growth factor (TGF) are prevented from interaction and therefore block specific ligand induced phosphorylation of EGFR (14).

Transmembrane receptors have an extracellular ligand-binding domain. The ligands of EGFR include epidermal growth factor (EGF), amphiregulin (ARG), epiregulin and TGF α (15). EGFR activation causes phosphorylation of specific sites of the tyrosine kinase domain and thereby activates different pathways including the mitogen-activated protein kinase pathway (MAPK) enhancing angiogenesis, anti-apoptotic signaling and proliferation (16). Therefore EGFR, if over stimulated, as occurs in certain cancer types, can cause pro-survival activities and treatment resistance (16, 17). Recent developments indicate that in the future, patients might be classified based on the specific molecular profile of their tumors. Recently developed targeted agents affect different elements of the RAS-RAF-MEK-ERK-MAPK signaling pathway, with many studies ongoing.

CURRENT TREATMENT IN STAGE I-IIIB NSCLC

Early stage NSCLC

Surgery is the preferred treatment in early stage (I- IIb) NSCLC. Only a minority of 20% of the patients is suitable for radical surgery at diagnosis. About 50% of these patients will be cured. A lobectomy with lymph node sampling and/or dissection is the standard treatment and is associated with less morbidity compared to a pneumonectomy. For elderly or inoperable patients, with comorbidity, stereotactic irradiation can be a good alternative to radical resection in early stage- lymph node negative patients (18).

The 5-year survival after radical resection for patients with lymph node negative disease is 54-73% and for lymph node positive (N1) patients is 38-48% (19, 20). Neoadjuvant chemotherapy has contributed little to survival and postpones the radical resection,

leaving probability for disease progression in the mean time (21). Adjuvant radiotherapy is indicated if the tumor resection was irradical or after unforeseen positive lymph nodes have been diagnosed (22). In patients with positive mediastinal lymph at histopathology, adjuvant cisplatin based chemotherapy is advised to improve survival by 4% at 5 years (23).

Locally advanced NSCLC

About one third of the patients have locally advanced disease without distant metastasis, stage IIIa or IIIb, at the time of diagnosis. In locally advanced NSCLC a tumor can extend in surrounding vascular or bony structures and/ or a tumor is accompanied with mediastinal and/or hilair and/or supraclavicular lymph node spread. The preferred treatment is a multimodal approach, consisting of concurrent platinum-based chemotherapy and high dose radiotherapy. This approach has been studied in the eighties and early nineties of the last century. Cisplatin concurrently added to radiotherapy has improved survival with low and manageable toxicity. This improvement is related to higher loco-regional control rates (24). Later on, concurrent combinations were compared with sequential combinations (25). In a meta-analysis the concurrent treatment appeared to be superior to the sequential treatment (26). The data of the 5-year survival rates range from 19-38%. In our institute concurrent low dose daily cisplatin as radio-sensitizing chemotherapy is the treatment of choice. The low toxicity opens possibilities for adding new agents to further improve the overall survival.

Radiotherapy in locally advanced NSCLC

The technology of delivering radical radiotherapy is rapidly evolving with improved imaging for position verification and adaptation, allowing for higher treatment and dose delivery precision. Four dimensional CT scanning (27) has given more insight into respiratory motion of the tumor during the treatment planning phase and a (4D) Cone Beam CT (CBCT) scan integrated within the linear accelerator provides insight in the mobility over the course of treatment (28, 29). Detection of anatomical changes during treatment such as tumor regression and shifts of the target volume permits treatment plan adaptation (30). While such geometric variability of the primary tumor has been studied since the clinical introduction of in room imaging, reliable information on the position variability of the lymph nodes in the mediastinum is still lacking. As no contrast is administered for daily CBCT the lymph nodes cannot be discriminated from surrounding tissue. Therefore, current safety margins used for mediastinal lymph nodes to correct for different uncertainties during treatment have been very generous.

NOVEL TREATMENT ENTITIES

Recently the development of new therapeutic entities such as erlotinib and gefitinib has led to increased progression free survival, mainly in stage III and IV disease (31-33). Patients who benefited were selected on a molecular base (34, 35). Compared to traditional chemotherapy the targeted agents have a favorable toxicity profile, existing mainly of skin rash and diarrhea (32).

Little is known about these agents in treatment of early stage NSCLC. The new combinations of existing and novel treatments have to be tested. The advantage of neoadjuvant use of these agents is that it allows verifying whether they reach their target at sufficient concentration. In this context, it is important to emphasize that targeted agents should be administered at Biologically Effective Doses, whereas conventional chemotherapeutics are usually dosed at maximal tolerated levels.

Predictive tests for different treatment modalities would be useful tools for individualized treatment. The question is what predicts the patients' sensibility and response for erlotinib. So far clinical selection criteria included: adeno carcinoma, female gender, Asian origin and non-smoking. These patients benefit most from TKI-EGFR treatment (31, 34, 36, 37). While exploring patient specific predictive markers, both serum and tumor tissue contain valuable individual information on tumor behavior. Serum concentrations of erlotinib may explain differences in treatment efficacy, while specific serum markers as biomarkers from the tyrosine kinase domain may be an index of disease expression and - during treatment - of treatment effect. Serum EGFR and other markers as transforming growth factor (TGF α), insulin like growth factor (IGF) or amphireguline (ARG) can be measured as predictive indicators.

Information on RNA, gene mutation status and kinase activity from tumor tissue is emerging. However, retrieving sufficient tumor tissue in patients who do not undergo surgical resection is often challenging. Therefore both predictive serum tests and additional information retrieved from tumor cells remain an important focus in identifying response predicting biomarkers to new treatment agents.

In summary: the current management of NSCLC faces challenges in predictive testing as well as in the optimization of current and combinations with novel treatment entities. In this thesis various aspects of these challenges are investigated as outlined below.

OUTLINE OF THIS THESIS

The different studies described in this thesis focus on better understanding of individualized diagnostics, response evaluation and multi modality treatments in NSCLC patients. In **part I** the novel biological agents erlotinib and cetuximab are evaluated in a new, multimodality treatment setting in resectable and locally advanced patients, respectively. **Part II** focuses on improving radiotherapy by mediastinal lymph node position variability analysis and image guided corrections, in locally advanced NLCLC.

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

A phase II study has been conducted on the effect of erlotinib, in a neoadjuvant setting in patients with early stage, resectable NSCLC. **Chapter II** reports the toxicity and response evaluation of this phase II study. **Chapter III** describes the validation of a method to determine the concentration of erlotinib in serum and the primary lung tumor, while **chapter IV** this method is applied for patients from the neoadjuvant erlotinib trial. **Chapter V** shows the value of predictive serum markers during and after treatment with neoadjuvant erlotinib. **Chapter VI** presents the results of a newly developed tyrosine kinase inhibition profile, predicting response to neoadjuvant erlotinib. In **chapter VII** the addition of cetuximab to our current clinical standard of radical irradiation concurrently combined with daily low dose cisplatin tested in a pilot setting is described. Response evaluation and toxicity are reported in a feasibility study.

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

In **Chapter VIII** it is demonstrated that gold fiducial markers capture considerable mediastinal lymph node position variability during radical radiotherapy in repeat CBCT scans. This is a proof-of-principle study including 15 patients. **Chapter IX** continues with the complete and mature results of this study including 52 evaluable patients. The effects of lymph node position variability, differential motion between lymph nodes and primary tumor and adapted margins to account for this variability are described. **Chapter X** provides a general discussion and future perspectives on the multimodality approach towards individualized non-small cell lung cancer treatment.

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