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Multimodality approach towards individualized non-small cell lung cancer treatment

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Publication date
2014

[Link to publication](#)

Citation for published version (APA):

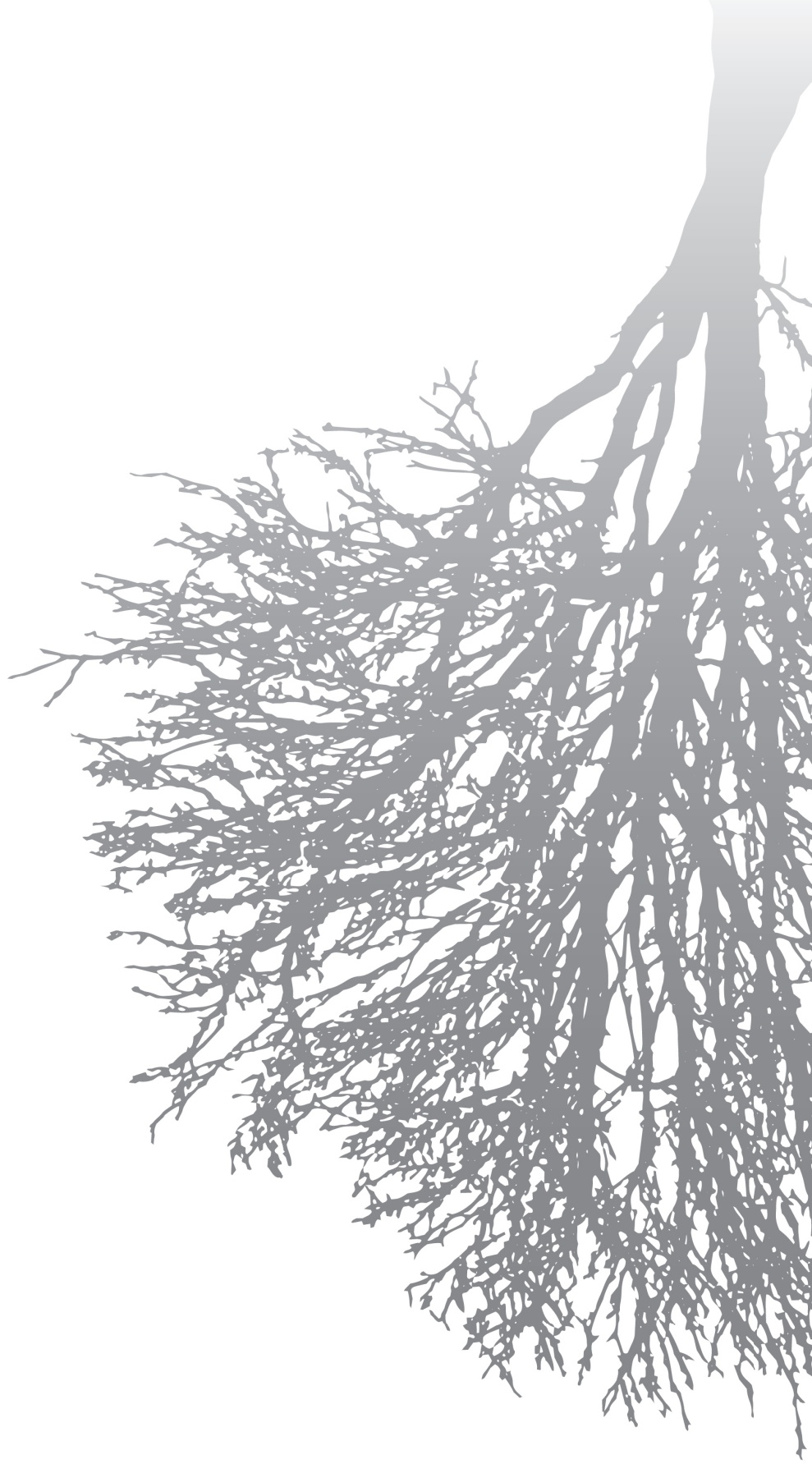
Schaake, E. E. (2014). *Multimodality approach towards individualized non-small cell lung cancer treatment*. [Thesis, externally prepared, Universiteit van Amsterdam].

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Chapter X
Discussion &
future perspectives

Non-small cell lung cancer (NSCLC) remains a malignant disease associated with many diagnostic and therapeutic challenges. The majority of patients die due to the disease, caused by loco-regional tumor progression and/or distant metastases. Radical resection and radical irradiation remain the only curative treatments, but are only applicable for a minority of the patients who are diagnosed with limited and localized disease. Concurrent chemoradiation is the standard of care in locally advanced non-metastasized NSCLC, with a radical radiotherapy schedule and - in our institute - daily low dose cisplatin (1).

Over the last decades combined modality treatment has slightly increased overall survival especially in Stage III disease. This improvement often comes at the expense of more toxicity, which should be weighted against each other on an individual basis.

This thesis has two main subjects: the first focuses on the effect of novel agents combined with standard treatment and its response prediction in early stage and locally advanced NSCLC, the second on measuring lymph node motion during radical radiation and its effect on treatment margins in locally advanced NSCLC.

In the recent years many prognostics tests have been developed and give insight in risk factors for poor and/or improved survival or tumor progression. Although this information does not yet translate into specific treatment options for specific risk groups in lung cancer, it will contribute to a better understanding of tumor behavior and from there lead to new targets for treatment in the future. Predictive tests, on the other hand, directly focus on treatment effects and are therefore of high value for daily clinical practice. By adjusting treatment to its outcome, toxicity and treatment costs can be reduced, especially if these tests are minimally invasive, fast in read-out and individually available. To validate such tests definitive phase III studies are needed. In the currently available treatment options, however, little differentiation can be made for different patient groups. With newly developed agents aimed at different prognostic and predictive genetic mutations treatment benefit can be obtained in subgroups. The new agents are finding their way and place in combination with the current established treatment modalities. One of these agents is erlotinib, a small molecule that binds reversibly to the adenosine triphosphate (ATP) binding site intracellular of EGFR.

Toxicity and response after neoadjuvant erlotinib in early stage NSCLC patients are reported in **Chapter II**. The first aims of our study are to observe the safety and treatment effect of neoadjuvant erlotinib in tumors to be resected. This study shows it is safe to administer erlotinib prior to surgery; toxicity is mild and does not lead to more surgery related complications. Impressive responses are observed in several patients after three weeks of treatment, with a metabolic partial response observed in 27%. Before sensitivity to new (targeted) agents can be predicted by a minimal invasive test, tumor response should be clearly defined and a new standard has to be developed, as the current response evaluation criteria in solid tumors (RECIST) do not suffice to identify responders shortly after treatment (2). CT evaluation does not show any near-complete

responders in this neoadjuvant erlotinib study, while FDG-PET/CT and histology indicate near-complete responses in 3 out of 60 patients. Changes in tumor volume often follow alterations in tumor activity, indicating that CT evaluation is less useful for short-term treatment evaluation. With early FDG-PET/CT scanning it has been studied that a larger percentage of the erlotinib responders can already be identified during the neoadjuvant setting (3). Specific PET tracers, for instance labeled antibodies as cetuximab or labeled erlotinib, indicate tumor penetration and possibly increased response can be objectified in the future as well (4, 5).

After the tumor is resected the histological response can be evaluated. Besides tumor necrosis no other features of treatment induced tumor degenerations are visible at histopathology in our current study. Other tests focusing on cellular and molecular functions may give a more accurate index of tumor response.

In conclusion: new short-term treatment response criteria for targeted agents have to be developed as RECIST evaluation is not functional and both PET- and histological evaluation until now provide insufficient information. Therefore possible evaluation- and response prediction criteria are examined using the trial data of neoadjuvant erlotinib in the **chapters III-VI**, taking advantage of the availability of both imaging and histological data.

The method to measure the concentration of erlotinib in plasma during and after treatment and resected tumor tissue is validated in **chapter III**. In **chapter IV** these measurements are performed in the neoadjuvant erlotinib study population. Plasma concentrations and tumor penetration by erlotinib are variable, and no correlations between the plasma-and/or tumor concentration and treatment response have been observed.

Ideally selection before start of treatment identifies the responders. Predictive serum markers are minimally invasive and available at all time points of treatment to test for drug sensitivity and effects of response. In **chapter V** however only one out of 5 tested serum markers, s(oluble)-EGFR shows predictive quality. A high baseline concentration of s-EGFR is predictive for response ($p=0.04$). Besides, all metabolic responding patients show a significant decrease of s-EGFR during treatment. The other serum markers, amphireguline, transforming growth factor α , insulin like growth factor and insulin-like growth factor binding protein-3, are not related to metabolic treatment response to erlotinib.

In **chapter VI** a kinase inhibition profile has been tested. After optimizing and validating the kinase inhibition profile for the current patient group a test group has been used to assess the predictive value of this profile. This resulted in correct response prediction in 12 out of 15 patients in the test group. For both the validation and test groups ($n=31$) 7 additional responding patients have been identified compared to mutation analyses based selection. After further optimization such a test can contribute to more accurate patient selection in phase III trials.

It has been investigated that EGFR contributes to the repopulation after irradiation of epithelial cells (6, 7). By blocking EGFR the repopulation can be inhibited and therefore enhance the effect of radiotherapy as demonstrated by Bonner et al in head and neck cancer patients (8). Therefore it was hypothesized that a similar effect could be achieved in NSCLC patients.

In **chapter VII** the monoclonal antibody against EGFR cetuximab has been added to the institute's standard concurrent chemoradiation with daily low dose cisplatin for locally advanced NSCLC. In this proof of principle part of the trial, feasibility and treatment response were the primary endpoints. Treatment response was evaluated by CT- and PET/CT-scans. Twelve patients have been included, 8 showing a metabolic partial response. This feasibility study did not show increased toxicity. Acneiform rash and dysphagia were the most common but mild side effects. The consecutive randomized phase II trial concludes that the addition of cetuximab does not improve survival in these patients. Toxicity, however, mainly dysphagia, is increased (9). The differences between the feasibility study and the phase II trial are due to statistical power. The differences in toxicity do not decrease dramatically but statistically significantly. A recently presented randomized study of the Radiotherapy Oncology Group confirms that there is no survival benefit by adding cetuximab to chemoradiation in two different radiotherapy arms (10). Therefore, addition of cetuximab to concurrent chemoradiation does not seem of additional value. In head and neck cancer cetuximab is given combined with radiotherapy alone and proves safe and effective (8), suggesting that the combination with cisplatin mainly increases toxicity.

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. In radiation oncology, toxicity is caused in part by irradiating larger volumes than the tumor to account for geometrical uncertainties. To improve the precision of radiotherapy, in-room cone beam CT (CBCT) has been clinically implemented that allows to capture a time resolved volumetric image of the patient just prior to treatment, assess misalignments and make corrections accordingly. However, the CBCT image quality is insufficient to distinguish the involved mediastinal lymph nodes in locally advanced lung cancer patients from the surrounding tissues. Therefore the position variability of these lymph nodes relative to organs at risk and primary tumor is not exactly known.

Chapter VIII reports on a proof-a-principle study utilizing implanted gold markers for the analyses of lymph node position and amplitude variability based on repetitive daily 4-Dimensional CBCTs acquired during treatment. Lymph node motion variability is larger than anticipated, mainly in cranial-caudal direction. In **chapter IX** a detailed analysis on a larger cohort has been performed investigating differential motion between involved mediastinal lymph nodes and the primary lung tumor. Margins to account for the observed geometrical uncertainties are calculated. Moreover it has been demonstrated that carina registration based correction strategy allows for considerable

margin reduction compared to the traditionally applied bony anatomy based correction.

The carina match has been clinically implemented at the Department of Radiation Oncology of the Netherlands Cancer Institute. With the improved correction strategy and the detailed knowledge of the geometrical uncertainties, margins reduction seems feasible. However it is not yet known what effect margin reduction has on toxicity and tumor control. The latter can unintentionally decrease by inadequate coverage of subclinical, microscopic disease. Therefore a prospective cohort study, comparing reduced margins versus reduced toxicity and tumor control is currently under design. To further improve treatment precision, adaptive radiotherapy is the next step. Plans tailored to the patients' specific deviations and variabilities observed in the first part of treatment can be accounted for with deformable registration creating new planning CT images with usually smaller treatment volumes leading to less toxicity and/or higher tumor doses. Adaptive radiotherapy can also be applied in patients with anatomical changes such as tumor regression or resolving atelectasis. To that end daily in-room imaging can be used to monitor such changes. Thereafter dose recalculation quantifies the dosimetric impact of these changes. Future research should develop automated decision rules, balancing workload and treatment efficacy. Improved precision by image guided and adaptive radiotherapy is an enabling tool to deliver heterogeneous dose distributions tailored to the heterogeneous tumor characteristics. An ongoing study is investigating the effect of integrated boosts on FDG-PET elevated tumor areas (11).

Lung cancer remains an aggressive disease that proves difficult to attack. 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. Individualized multimodality treatment will emerge providing a patient tailored and mutation tailored standard. With both genetic and histological predictive and prognostic assays patient selection will improve. More subgroups will be distinguished with tailored treatment available. If disease reduction can be induced by neoadjuvant treatment while microscopic or metastatic disease will be diminished with adequate chemotherapeutics, more patients can be resected, increasing survival rates and decreasing toxicity. The addition and timing of new agents as erlotinib and cetuximab will be optimized while the efficacy and precision of the current treatments will increase. Margin reduction and adaptive radiotherapy will further increase the effect of individualized NSCLC therapy.

Finally with all this research being performed in the past, present and future millions of Euros of grants and funds have to be invested to move ahead in tiny steps. The largest decrease of incidence and increase of survival, however, can be made outside of the laboratories and hospitals. Ninety percent of the lung cancer cases are smoking related and can therefore be prevented. To stop the production and consumption of tobacco would be the biggest gain. So far we are better at maintaining the disease than curing it.

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