Summary

Non-small cell lung cancer (NSCLC) is the primary cause of cancer-related death and is the second most diagnosed form of cancer in men and women, following prostate cancer and breast cancer respectively. These two facts underpin the importance to search for a cure, or at the very least for improvements in survival and the patients’ quality of life.

During the last decade, a major shift in the treatment paradigm in cancer is to improve cure and care through personalized medicine. New, and often expensive, personalized treatment options become available at a rapid pace. Health care resources are likely to become increasingly constrained while overall costs of oncology are expected to rise. Therefore, decision makers ask for evidence of the cost effectiveness of new treatments before agreeing to their general reimbursement, or before implementation in standard care.

To begin to understand the impact of new treatments in NSCLC care, it is important to first assess what is done in clinical practice at present. This will be addressed in the first part of this thesis, which is dedicated to the assessment of treatment patterns, health outcomes, resource use, and costs, in clinical daily practice. The second part of the thesis is dedicated to the assessment of the cost-effectiveness of individualized radiotherapy treatment strategies, and the related methodological issues in health economic modeling. According to the literature, the selection of the best available evidence for model input, the quantification of a micro-simulation model, model validation and the presentation of uncertainty are relevant items for critical appraisal of modeling studies.

Chapter 2 provides a systematic overview of the available literature comparing the third generation agents docetaxel, gemcitabine, paclitaxel, pemetrexed, vinorelbine and the targeted drug erlotinib with respect to health effects, costs and cost-effectiveness. The evidence from reviews published between 2001 and 2010 showed that all third generation agents were found cost-effective compared to best supportive care. Reviews that included studies comparing erlotinib with best supportive care or pemetrexed in second- or third line treatment showed that erlotinib provided equivalent or additional effectiveness. Due to oral administration of erlotinib (compared to intravenous administration of pemetrexed) erlotinib was cost-saving as well.

The cost-effectiveness studies that were published between 2001 and 2010 showed reasonable consensus between studies with respect to the direction of differences in costs and health effects for a number of drug comparisons. In first-line treatment, the combined therapy gemcitabine+cisplatin seems a cost-effective treatment option, although pemetrexed+cisplatin performs better in a nonsquamous population. In second-line treatment, docetaxel is a cost-effective option compared with best supportive care. Erlotinib may be a cost-effective alternative to docetaxel.

With respect to the quality of the model-based cost-effectiveness studies, the estimates of the input parameters, the model assumptions and calculations were often poorly reported. Due to this lack of transparency, the small number of studies included in this review, and the heterogeneity between studies, strong conclusions could not be drawn.
Chapter 3 and 4 describe the results of a retrospective study to capture treatment patterns, resource use, and costs in the management of all stages of NSCLC in The Netherlands. Within the patient population of four Dutch teaching hospitals, a random sample of unselected patients newly diagnosed with NSCLC between 31 January 2009 until 31 January 2011 was identified. Data was obtained on patient characteristics, tumor characteristics, treatments, survival outcomes, adverse events and resource use, and was manually abstracted from medical records by trained data assistants. Survival outcomes were compared with survival outcomes of the Dutch population, for patients that were eligible for surgery, patients that were ineligible for surgery with nonmetastatic disease and for patients with metastatic disease.

In all patient groups survival was increased for patients treated in one of the four teaching hospitals included in the study. In addition, the reported treatment patterns showed a large variety in treatment options, especially for systematic treatment.

New technologies in medical imaging and radiotherapy show promising steps forward. With the shift towards individualized treatment, cost-effectiveness models need to incorporate patient and tumor characteristics that may be relevant to treatment planning. Chapter 5 describes the development of a micro-simulation model for cost-effectiveness analysis of individualized radiotherapy in lung cancer in detail.

Four clinical states were included in the model: ‘Alive without progression’, ‘Local Recurrence’, ‘Metastasis’, and ‘Death’. Individual patients were simulated by repeatedly sampling a patient profile, consisting of patient and tumor characteristics. The model tracks clinical events over time and takes patient and tumor features into account. The transitioning of patients between the health states is governed by personalized time dependent hazard rates, which were obtained from multi-state statistical modeling (MSSM).

The model simulations for both the individualized and conventional radiotherapy strategies demonstrated internal and external validity. Therefore, MSSM is a useful technique for obtaining the correlated individualized transition rates that are required for the quantification of a micro-simulation model. Moreover, we have used the hazard ratios, their 95% confidence intervals and their covariance to quantify the parameter uncertainty of the model in a correlated way.

The obtained model of Chapter 5 was used to evaluate the cost-effectiveness of individualized radiotherapy treatment, including the uncertainty of input parameters. Chapter 6 describes the evaluation of long-term health effects, costs, and cost-effectiveness of positron emission tomography (PET)-based isotoxic accelerated radiation therapy treatment (PET-ART) compared with conventional fixed-dose CT-based radiation therapy treatment (CRT) in non-small-cell lung cancer (NSCLC).

Primary model outcomes were the difference in life-years (LYs), quality-adjusted life-years (QALYs), costs, and the incremental cost-effectiveness and cost/utility ratio (ICER and ICUR) of PET-ART versus CRT. Model outcomes were obtained from averaging the predictions for 50,000 simulated patients. A probabilistic sensitivity analysis and scenario analyses were carried out.

The average incremental costs per patient of PET-ART were €569 (95% confidence interval (CI))
€5327, €6936) for 0.42 incremental LYs (95% CI 0.19, 0.61) and 0.33 QALYs gained (95% CI 0.13, 0.49). The base-case scenario resulted in an ICER of €1360/LY gained and an ICUR of €1744/QALY gained. The probabilistic sensitivity analysis gave a 36% probability that PET-ART improves health outcomes at reduced costs and a 64% probability that PET-ART is more effective at slightly higher costs. On the basis of the available data, individualized PET-ART for NSCLC seems to be cost-effective compared with CRT.

In Chapter 7, the model was used again in a cost-effectiveness study, this time to evaluate chemo-radiation treatment strategies. We compared four strategies: PET-CT based isotoxic accelerated sequential chemo-radiation (SRT2) and concurrent chemo-radiation with daily low-dose cisplatin (CRT2) to standard sequential (SRT1) and concurrent chemo-radiation (CRT1). Since the model was not developed for the evaluation of concurrent strategies, data from a meta-analysis and a single study were used to obtain the model input parameters for health effects and toxicities. To estimate the strategies SRT1 and SRT2, the model showed a reasonable fit with the data when applied in the subgroup of sequentially treated patients. Costs, utilities and resource use estimates were obtained from literature. Primary outcomes were the ICER and the ICUR of each strategy compared to the reference strategy (SRT1). Compared to the reference strategy SRT1, the ICER and ICUR were €29814/LY and €38024/QALY for CRT1, €4708/LY and €6249/QALY for SRT2, and €263/LY and €346/QALY for CRT2. CRT2 was highly cost-effective compared to SRT1. Moreover, CRT2 was more effective and less costly than CRT1 and SRT2. Therefore, these strategies were dominated by CRT2. Based on our model, optimized sequential and concurrent chemo-radiation strategies are more effective and cost-effective than the current conventional sequential and concurrent strategies. Concurrent chemo-radiation with a daily low dose cisplatin regimen is the most cost-effective treatment option for locally advanced inoperable NSCLC patients.

The studies in this thesis have shown that a more individualized radiotherapy treatment strategy is likely to be a cost-effective alternative to conventional treatment as recommended in the guidelines. This is an important message for clinicians and decision makers, and may support further diffusion into clinical practice. Individualized treatment is of all times. Current developments in technologies such as PET imaging, and improvements in treatment schemes have increased individuality to a detailed level. With resources becoming more constrained, it is extremely important to weigh the benefits of new treatment options against the costs. Individualized care is often perceived as expensive. The results of this thesis show that this does not apply to individualized chemo-radiotherapy treatment.

These results were robust when testing for different scenario analyses. In addition, it was concluded that a concurrent scheme with daily low-dose cisplatin and daily radiation was cost-effective compared to the alternative treatment strategies in two separate patient cohorts that were different in their case-mix. In addition, a sequential isotoxic accelerated chemo-radiation scheme is a better alternative for a
subgroup of patients with a relatively good patient profile (100% had a WHO performance status of 0-1, 75% had two or less lymph nodes affected, and a mean gross tumor volume of 100 cc) than conventional concurrent chemo-radiotherapy.

These results provide strong indications that individualizing chemo-radiotherapy is a promising trend, with increased survival at acceptable costs. As technologies develop rapidly, and treatment regimens are further optimized, model-based cost-effectiveness studies provide a tool to directly or indirectly compare the new optimized strategies with each other, and with conventional treatment. In the light of constrained resources, it is more and more important to weigh the benefits and cost of new individualized treatment strategies.

The results of this thesis may have an important clinical impact as the results indicate that there are circumstances under which individualized care can be delivered at acceptable costs. In addition, there are methodological lessons learned from the studies in this thesis that are equally important.

- Selection of data that reflects true clinical practice is a challenge: randomized controlled trials are considered as the best available evidence for modeling, but may not reflect the resource use and effectiveness in the real-world clinical setting. In addition, trials have a short follow-up time. Registry data may reflect true clinical practice, but a prospective and systematic data collection is highly recommended to avoid missing or poorly reported data. Caution is warranted when combining registry data and trial data, as important events may have been registered according to different protocols and patients may differ in their case-mix.
- Multi-state statistical modeling is a suitable technique for quantifying a micro-simulation model when data from a single source is available. Once the micro-simulation model is quantified and validated, it is a basic model for the evaluation of many therapies. However, the flexibility to include new parameters is limited. With the trend towards the systematic collection of data, multi-state statistical tool is an interesting tool for health economic modeling.
- To use a previously developed micro-simulation model in multiple settings as a comparator for the evaluation of future treatment strategies, external validation by using external datasets is highly recommended.
- Patient heterogeneity and parameter uncertainty both need to be evaluated, preferably in combined double loop PSA. However, this recommendation depends on the level of heterogeneity and random variation included in the model. If a double loop PSA becomes too computationally intensive, alternative uncertainty analyses may be considered.

To conclude, this thesis shows that individualized treatments are cost-effective treatment options compared to standard care once they are properly evaluated accounting for aforementioned recommendations.