Discussion

This thesis assessed the cost-effectiveness of new (chemo-)radiotherapy treatment strategies in NSCLC. Furthermore, the literature on cost-effectiveness of chemotherapeutic and targeted agents was systematically reviewed and critically assessed. In addition, data was collected to gain insight in the current NSCLC care and resource use in the Netherlands. Throughout these studies several methodological challenges in modeling were encountered.

In the following section, these challenges will be addressed. Next, the clinical implications of the results presented in this thesis for NSCLC treatment in Dutch daily clinical practice will be discussed. Finally, based on the lessons learned from this thesis, recommendations for future NSCLC disease modeling and cost-effectiveness studies are given.

Methodological challenges

The systematic review (Chapter 2) showed that targeted drug therapies, although more expensive, can be promising new treatment options compared to docetaxel in a second-line treatment setting. When taking mutation status into account, the ICER in the subgroup of EGFR positive patients changed from over Can$ 94,638 (€ 66,204) to Can$ 33,353 (€ 23,332)

1. This shows the importance of assessing cost-effectiveness within relevant subgroups in addition to an assessment of the cost-effectiveness in the patient population as a whole.

The included studies were critically assessed according to checklists by Drummond et al. and Philips et al. Based on this appraisal, it was found that the included modeling studies reported poorly on the items concerning transparency in the estimation of input parameters. It was not reported how data sources were used to estimate the input parameters, nor the exact calculations that were used for implementation in the model. Moreover, model assumptions were poorly reported.

The following challenges were partly identified in the systematic review, and are widely recognized in the literature:

1. The selection of the best available evidence for model input
2. The quantification of a simulation model
3. Model validation
4. The presentation of uncertainty

1. The selection of the best available evidence for model input

Data and real clinical practice

Randomized controlled trials are regarded as the golden standard for evaluating the effectiveness of new interventions. Health economic models have traditionally been used to extrapolate trial data to long-term clinical and economic outcomes. While health
economic models are used to inform decision making, effectiveness of a new treatment may be different once it is disseminated in broader patient populations. Models would provide valuable additional information if they are used to extrapolate evidence beyond the controlled environment of the experimental randomized controlled trial1. Furthermore, data on resource use and costs obtained from clinical trials often reflect the resource use and costs of the trial protocol. Within a clinical trial, patients are usually far more intensively monitored. As a consequence, resource use of trial patients may not reflect the resource use of actual real-world patients.

The demand for real-world evidence has increased, as decision makers recognize its value in providing information on real-world treatment effectiveness and value for money for reimbursement decisions7. For this reason, data on resource use and treatment patterns that reflect clinical practice in the Netherlands was collected in this project. A retrospective data collection was conducted (Chapter 3 and 4), considering data on treatment patterns, survival and resource use. However, some challenges were encountered.

Since the data was collected retrospectively and was subtracted from medical charts, the resulting data was dependent on the patient information obtained by the hospital and on the registration in medical charts. For example, WHO performance status of patients was often not reported. Moreover, data on occurrence of intermediate events, recurrence of disease or metastasis were also regularly missing.

In addition, the study was performed in four hospitals. Once patients were referred back to their regional hospital they were ‘lost’ to follow-up in this study, and consequently, only snap shot data was available for each patient. This means that information on the entire disease course was often lacking. Moreover, the follow-up time of this study was relatively short. Extra information on survival was obtained through the Netherlands Cancer Registry. However, the collected data on health effects was not suitable for mathematical modeling as complete data on the course of disease was missing.

If the data is collected prospectively, these problems can be avoided. When a clear study protocol is available and is adhered to, variables may still be unknown, but are at least registered as unknown. Since this process can be time-consuming for clinicians, software tools may be developed that help the systematic registration of all relevant data and serve as a clinical tool for clinicians as well. Moreover, patients should be followed during their disease course, even when multiple hospitals are visited for diagnosis and treatment. The aim of the costing study (Chapter 4) was to present the costs of the complete disease course of NSCLC patients, based on real-world data. However, the same issues as mentioned by the data on health effects apply to the resource use data. Since patients were included in the study if they were diagnosed within a specified two-year time frame, we collected relatively more data on the early phases of the disease. In general, it is believed that health care costs are higher in advanced phases of disease. To minimize this bias, the Bang and Tsiatis estimator8 was used to correct the estimated mean costs per patient.

For new developments in cancer care, data from randomized controlled trials is not always available. Imaging techniques have improved staging, radiotherapy planning, and have helped to reduce futile treatment. However, randomized controlled trials that evaluate imaging techniques are scarce, as it is considered unethical to withhold the control arm the information obtained by imaging that is needed for optimal treatment planning10. True clinical equipoise is then generally considered unattainable, as new technologies are theoretically superior11.

An example of the novel use of an imaging technique for which no randomized trial data was available concerns Chapter 6: an additional PET-CT scan to allow for isotonic treatment planning12. For this evaluation, only registry data was available. However, observational studies and cost-effectiveness studies are mentioned as the next best option for the evaluation of such technologies11, despite of the bias that may occur due to possible systematic differences in the patient population. This bias was eliminated by using a statistical regression model to inform the micro-simulation model13. Patient heterogeneity with respect to the risk of disease progression is captured in a statistical model by including covariates that are relevant for the disease progression. The covariates of the regression model were selected carefully14. The most relevant covariates for the outcomes of interest were included. However, the model may not have been able to correct for all relevant patient features.

The registry data that was used for the CEAs in this thesis contains data on patient and tumor features, detailed information on treatment, such as fraction and dosing of radiotherapy, and the follow-up of patients in terms of intermediate outcomes such as the occurrence of recurrences and metastases. The data was systematically and prospectively collected, including all patients receiving radiotherapy between 2002 and 2009. Treatment assignment was based on year of diagnosis, with patients before 2005 receiving CT-based radiotherapy once daily, and patients diagnosed from 2005 onwards receiving PET-CT-based isotonic radiotherapy treatment twice daily. This data was considered to reflect daily clinical practice for the health effects. Since a protocol was used to collect the data, resource use may not reflect true clinical practice. However, for the CEAs in this thesis resource use was not obtained from this data source. The micro-simulation model was developed using the health effects of this data and can therefore simulate daily clinical practice in the Netherlands. As such, it may serve as a reference for assessing the cost-effectiveness of new developments in chemo-radiotherapy.

Challenges in combining multiple data sources

The above described micro-simulation model was also used in a cost-effectiveness study that assessed optimized chemo-radiation schemes (Chapter 7)15. The original model was extended with other data sources to evaluate two additional strategies: concurrent conventional chemo-radiotherapy and concurrent chemo-radiotherapy with a low-dose daily cisplatin administration. The model input was obtained from a meta-analysis16, and from a single study17.
This means that different data sources, namely registry data, a meta-analysis and a single study were combined in one model. These types of data sources differ in their patient mix. Clinical trials and meta-analyses tend to include relatively physically fit patients compared to patients in daily clinical practice, the ‘real-world’ patients. However, this bias was minimized through aforementioned regression modeling.

The problem with combining these different data sources lies within the registration of disease events. The event ‘death’ is a clear clinical outcome, easy to report or to obtain via linked national data sources, and therefore, a reliable outcome across all data sources. For intermediate disease events however, the problem of registering such events arose. For example, although the data from the Maastro Clinic was collected prospectively, intermediate events were registered once detected at follow-up visits, or when patients had symptoms. In addition, these events were only registered for patients that were diagnosed and treated in that hospital, and not for patients that were referred to the Maastro Clinic by other hospitals and were lost to follow-up for further treatment. However, the survival curve of patients that were lost to follow-up was similar to the curve of patients that were kept under surveillance by the Maastro Clinic. Still, in trial studies, patients are more intensively monitored than when data is collected for a registry. This has lead to an unreliable comparison of the occurrence of intermediate events across the data sources and hence, across the optimized and current care chemo-radiation strategies that were evaluated in Chapter 7. The local recurrence rate in the strategies that were informed by clinical trial data, either through meta-analysis or a single study, is higher. It is too straightforward to think that this is an actual clinical finding, as it is more likely that a higher recurrence rate is the consequence of the intensive monitoring of such events in a trial setting compared to the more ‘random’ monitoring of such events in registry data. Since costs and disutilities of intermediate events can have an impact on the ICER, an incremental comparison of the four strategies would be biased. For this reason, the local recurrence and metastasis rates were ignored in this evaluation. Overall survival estimates between the four strategies were considered reliable, as the registry data was linked with the Municipal Personal Records Database.

2. The quantification of a simulation model

Model-based cost-effectiveness studies in cancer care traditionally use relatively simple health economic models in which a homogeneous cohort of patients is simulated. With treatments being increasingly tailored to the specific features of a patient and a tumor, an estimated input parameter for a homogeneous cohort of patients will not reflect the differences in clinical disease progression between patients as a result of differences in patient and tumor features. To obtain clinical predictions that accurately estimate patient outcomes, integration of the clinical, molecular and imaging information on patient and tumors in is needed18. In health economic modeling, this means that for a proper evaluation of long-term costs and effects of individualized strategies, models need to incorporate patient and tumor features that may affect treatment decisions, disease progression, survival, adverse events and quality of life.

For the assessment of the cost-effectiveness of individualized radiotherapy treatment, a micro-simulation model was developed by using multi-state statistical modeling (Chapter 5)19. This chapter showed that multi-state statistical modeling is a feasible method to inform the transitioning of individual patient profiles over multiple health states. Multi-state modeling is an extension of the widely used Cox proportional hazards model for survival19. Using this survival regression technique allowed the inclusion of prognostic factors, such that predictions can be obtained for relevant subgroups of patients14.

In the last decade, parametric models were introduced as a tool to quantify the transitions of a decision model20. The most popular form is the Weibull model. Alternatively, other parametric survivor functions can be employed, depending on which distribution fits best to the data21. The advantage of parametric modeling is that it explicitly models the functional form of the event times using various statistical distributions. In addition, one can test which distribution fits the data, which can be different over the transitions of the decision model. The Cox model is semi-parametric, which means that the baseline hazard is distribution-free. Although the baseline hazard can be obtained through the data, it does not take a functional form. Consequently, the baseline hazard cannot be used to extrapolate to individual patient predictions that can be applied in a nomogram, for example.

In addition, once a baseline hazard that is obtained directly from the data is used for modeling, the baseline hazard is very specific to the data source it is derived from. Since a baseline hazard is estimated for each time interval, that is, for each occurring event in the data, the model becomes data-driven. Therefore, it is recommended that future models use a function to estimate the baseline hazard.

While survival models are used to estimate the time to one specific event, which is often death, intermediate events describing disease progression may also be relevant in modeling. For instance, in the case of lung cancer a local recurrence or distant metastasis may occur. Thus, decision models that have to reflect the course of disease have usually more than one state. An advantage of multi-state modeling is that it can take the same structure as a micro-simulation model. This means that the micro-simulation model can be informed by one statistical model, where all transitions can be quantified simultaneously. Integration of separate statistical models into a micro-simulation model may cause problems, as the statistical models are not interrelated. This is an issue when subsequent events depend on the patient history, that is, previous events. In some studies, this was solved by including the timing of the first events as a factor to predict the timing of the second event22. However, joint correlation of input parameters over transitions cannot be included in the model. In uncertainty analyses, this results in the independent evaluation of uncertainty of the parameters while in fact the uncertainty of parameters may be correlated.

The use of multi-state statistical modeling to inform decision models requires patient-level data from one single data source. In many settings, patient level data may not be available, or specific intermediate events are simply not observed. This was the case
for the CEA that assessed chemo-radiation schemes (Chapter 7), where for two of the treatment strategies under study data from a single source was available, but not for the other two strategies. For these two strategies, a calibration technique was used to derive parameter estimates. Model calibration is described as the process to identify values for unobservable parameters that produce model outputs that best predict observed data. The challenge in calibration is to define a proper goodness-of-fit-measure (GOF), to ensure that the full parameter space (i.e. all possible combinations of parameters) is searched and to define a criterion for when the calibration procedure is considered successful. Model calibration is emerging as a new tool that may generate important fundamental knowledge about the underlying disease process. In contrast to input parameters obtained from a statistical model, calibration does not provide point estimates as the most likely values for model input. Consequently, the uncertainty of the calibrated parameters is unknown. In the CEA in Chapter 7 calibration was applied, and as a result of the correlation between parameters, multiple combinations of parameters led to similar model output that fitted with the data. Hence, it is not known what values can be considered as most likely values for model input. The parameters values can still be used as model input parameters, however, accurate quantification of uncertainty in parameters is not evident.

3. Model validation
Preferably, a model is validated against external data. However, often a model is only internally validated against the dataset used for model building. Not all datasets are suitable for external validation, as important variables may be missing, are not registered or have not been collected at all. In the retrospective data that was used for Chapter 3 and 4, WHO performance was often not reported, and information on intermediate events was not available. The micro-simulation model in Chapter 5 was not only internally but also externally validated before it was used for the evaluation of the cost-effectiveness of PET-based isotoxic accelerated radiotherapy treatment compared to conventional CT-based fixed dose radiotherapy treatment. For this purpose, data from the Dutch Cancer Registry was used. In addition, the model was internally validated for different subgroups of patients. The external validation resulted in a good model fit for the conventional CT-based radiotherapy treatment strategy and in a reasonable fit for the PET-CT isotoxic accelerated radiotherapy treatment strategy. For subgroups, the model output was reasonably close to the data. The model was initially developed to evaluate aforementioned radiotherapy strategies for patients that received either sequential chemo-radiotherapy or radiotherapy alone. The model was thus externally validated for a patient cohort consisting of a mixture of patients that received either radiotherapy alone or sequential chemo-radiotherapy. In Chapter 7, however, the model was used to obtain predictions for patients receiving either sequential chemo-radiotherapy only or concurrent chemo-radiotherapy. This means that the external validation of the original model was not necessarily valid within these two patient populations. With respect to the patient subgroup receiving sequential treatment, a subgroup analysis was carried out to confirm that the model performed reasonably well in this subgroup. For the concurrent strategies, however, validation could not be obtained, as the model output was the result of a calibration procedure. Although the best fitting parameters sets were able to produce model outputs that fitted the data, this does not necessarily reflect a valid model.

4. The presentation of uncertainty
The evaluation of uncertainty is needed to consider whether existing evidence is sufficient, whether model output is robust to uncertainty of input parameters, and to assess the probability that a new treatment is cost-effective. Uncertainty as well as patient heterogeneity are important challenges in decision modeling. More specifically, it is a challenge to evaluate both parameter uncertainty and patient heterogeneity in a micro-simulation model.

Parameter uncertainty
By using multi-state statistical modeling, the joint correlation among all covariate effects of all transitions is easily obtained as the covariance among parameters in a regression framework is known, in contrast to other model types where the covariance structure is unknown and parameters are assumed to be independent. In probabilistic sensitivity analyses (PSA), this assumption may lead to parameter sets with combinations of randomly drawn values that cannot exist. Hence, the uncertainty that is presented is partly introduced by the assumption of independent parameters. When combining a statistical model with calibration, the actual uncertainty of the calibrated parameters is unknown. As previously discussed, two well fitting parameter sets can be completely different due to underlying correlation between calibrated parameters. When combining statistical estimation with partial calibration, probabilistic sensitivity analysis taking correlation among parameters into account is no longer possible. To gain insight in the uncertainty, alternative scenario analyses were carried out in Chapter 7 instead. For example, the impact of using the lower and upper band of the confidence interval for survival for each treatment strategy was assessed.

Patient heterogeneity
Model-based cost-effectiveness studies that were reviewed in Chapter 2 did not include patient heterogeneity. One paper used risk stratification, as pemetrexed was believed to be beneficial in a squamous cell population. However, this study used a separate model for a squamous cell population rather than including patient heterogeneity in the main model. In practice, patient heterogeneity is often ignored, and an average value of the patient population is used instead. However, the average patient does not exist, and results may not be useful for decision makers. Subgroup analysis or risk stratification is proposed as an alternative for dealing with heterogeneity, however, the number of patients in the data set and the number of included covariates for relevant subgroups may be restrictive.
By using a multi-state regression model we were able to include covariates that are relevant for survival and the timing of intermediate events, such as a recurrence. These covariates were patient and tumor features, such as WHO performance status and gross tumor volume. Patient heterogeneity was included in the micro-simulation model by drawing patient profiles and calculating the timing of events for each individual. This allows the evaluation of treatment strategies for specific target groups, or to simulate a randomized controlled trial, thereby eliminating bias due to differences in baseline characteristics between the two treatment groups. However, it should be noted that caution is warranted as regression techniques can lead to statistical chance findings if many subgroups are investigated or if subgroups are not specified before looking at the data.

The combined analysis of patient heterogeneity and parameter uncertainty

Compared to more conventional methods to quantify Markov-like micro-simulation models, multi-state statistical modeling allows for the assessment of both patient heterogeneity and parameter uncertainty. The PSA that was carried out in the CEA that assessed the PET-based strategy is rarely used in health economic models. Recently, the method was described in Vemer et al. They proposed a ‘nested Monte Carlo simulation’ for the evaluation of treatment strategies for specific target groups, or to simulate a randomized controlled trial, thereby eliminating bias due to differences in baseline characteristics between the two treatment groups. However, it should be noted that caution is warranted as regression techniques can lead to statistical chance findings if many subgroups are investigated or if subgroups are not specified before looking at the data.

In this thesis, studies 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. European and Dutch guidelines provide a detailed description of many new technologies and treatment schemes to individualize chemo-radiotherapy treatment, and describe the level of scientific evidence that is obtained through studies. Current developments in technologies such as PET imaging, and improvements in treatment schemes have increased individuality to a detailed level. Apart from beneficial dosimetric outcomes, such as an increased therapeutic ratio, survival and quality of life are increased at acceptable costs. 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.

In this thesis, it was shown that individualized (chemo-)radiotherapy treatment is cost-effective compared to standard treatments. These results were robust when testing for different scenario analyses. Probabilistic sensitivity analyses in the PET-ART cost-effectiveness study showed that at a threshold value of 18,000 Euro per QALY gained, the probability that PET-based isotoxic accelerated treatment was cost-effective was 95%. In addition, we showed 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.

Lessons learned and future implications

The results of this thesis may have an important clinical impact as we showed 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.

**Concluding remarks**

This thesis provides an overview of the challenges of assessing the cost-effectiveness of individualized chemo-radiotherapy treatment in lung cancer. In addition, trial data and data on resource use and treatment patterns were collected, providing useful input for future models. Despite the described methodological challenges, the thesis has presented valuable evaluations of the cost-effectiveness of several new technologies and treatment schemes in chemo-radiotherapy treatment in lung cancer.

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.


