Chapter 1

General Introduction
General introduction

Non-small cell lung cancer (NSCLC) comprises 85% of all lung cancers, and is the primary cause of cancer-related death. Moreover, it 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, while health care resources become more and more constrained. Therefore, it is important to assess not only the effectiveness, but also the cost-effectiveness of new treatment options in NSCLC compared to standard care.

Prognosis and current treatment approach in NSCLC

Patients in early stage of disease (stage I-II) that are eligible for surgery have a relatively good prognosis. Even so, the estimated 5-year survival for early stage patients is still only between 45% and 50%. Unfortunately, only 20% of the patients is eligible for a tumor resection. For patients that are ineligible for resection, stereotactic radiotherapy is the best alternative for surgery, that is, if no locoregional metastases are present and if the tumor is located centrally. Alternatively, concurrent chemo-radiotherapy is the standard treatment option for inoperable nonmetastatic patients. There is evidence from a meta-analysis that radiotherapy with concurrent chemotherapy reduces locally recurrent disease and mortality compared to sequential chemo-radiotherapy. In the absence of distant metastases these patients have a 5-year survival of 5%-30%. Patients in advanced stage of disease (stage IV) are treated with combinations of chemotherapeutic agents or targeted therapy. The 5-year survival is 1%.

Inequality in treatment of NSCLC over hospitals and regions is widely recognized. Variation in treatment is only partly explained by differences in case mix or accessibility of care, but also by differences in guideline adherence. In addition, treatment options are increasing. For example, advances in technologies in radiotherapy treatment are developing at a rapid pace.

While resources become increasingly constrained and overall costs of oncology are expected to rise, further innovations in radiotherapy may be restrained. Before agreeing to the general reimbursement or before implementation in standard care, decision makers ask for evidence of the cost effectiveness of new treatments. The general view is that personalized care is expensive, caused by the high prices for targeted drugs in the metastatic phase. Innovations in radiotherapy are probably less expensive, however actual costs of radiotherapy are unknown.
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 daily clinical practice.

A new era of personalized medicine

Personalized medicine has become an important part of treatment planning for NSCLC patients. Personalized medicine is often described as “the tailoring of medical treatment to the individual characteristics, needs, and preferences of a patient during all stages of care, including prevention, diagnosis, treatment, and follow-up”. Although it is long recognized that patients with lung cancer differ from each other in clinical presentation, prognosis, tumor response and tolerance to treatment, it is only recently that technologies enable better understanding of the underlying biological mechanism of cancer. An example is to test the tumor for specific molecular characteristics. Such biomarker tests may be used to predict increased sensitivity to a drug that is developed to target specific molecular pathways. The development of targeted drugs has provided more treatment options to improve survival for patients with metastatic disease. Where stage IV patients used to be treated with one-size-fits-all systematic therapy, nowadays patients can be selected according to the probability to benefit from a specific targeted treatment. Examples of biomarkers in NSCLC are the epidermal growth factor receptor (EGFR) and the KRAS mutational status, and ALK rearrangements. For both EGFR and ALK status, targeted therapeutic agents are available that attack the specific molecular pathway involved, the Tyrosine-Kinase-Inhibitors (TKI)’s.

For patients with non-metastatic disease, the concept of personalized medicine refers to individualizing chemo-radiation by determining the optimal dose of radiation per tumor area, and to minimizing radiation-induced toxicity to healthy tissue, also called high-precision radiation. Individualized radiotherapy can be obtained through optimal treatment planning by using advanced imaging (PET-imaging) and through the use of modified chemo-radiation schemes. An additional PET-CT-scan in treatment planning allows for selective lymph node irradiation. In addition, based on this PET-CT-scan isotoxic therapy can be administrated, whereby doses of radiotherapy are individualized according to the constraints of the organs at risk. Consequently, patients receive individual dosing that saves the healthy tissue. Individualizing therapy through isotoxic treatment planning has been shown to improve tumor coverage, decrease the isolated nodal failure rate and reduce the volume of healthy tissues irradiated compared to CT alone. Long-term health effects and cost-effectiveness of isotoxic therapy has not previously been addressed. In the search for optimizing radiotherapy treatment, also modified schemes were studied such as hyperfractionated and accelerated radiation schemes. In the latter scheme, patients receive lower doses Gray (Gy) per fraction (hyperfractionated) twice daily, in a shorter overall treatment time (accelerated). The 8 hour treatment interval between doses allows the healthy tissue to recover, thereby decreasing toxicity. Accelerated schemes have shown small reductions in mortality15, and were shown to be more effective but also more costly than conventional radiotherapy16.

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.

Cost-effectiveness of new therapies

Cost-effectiveness analysis (CEA) involves a comparative analysis of the health and cost consequences of alternative courses of action13. To date, CEAs in cancer care are most often applied to evaluate pharmaceutical interventions, facilitated by pharmaceutical companies as well as by (inter)national health authorities. Less evidence is available for other types of interventions, such as medical devices, surgery and radiotherapy14. The association between CEAs and drug therapy may be reinforced by the fact that personalized medicine is associated with biomarkers and targeted drugs rather than with other developments that also tailor treatment, such as advanced imaging techniques to individualize tumor radiation.

In general, there is a dearth of up-to-date, robust evidence on the cost-effectiveness of radiotherapy in cancer. The number of published economic evaluations of radiotherapy using outcomes as QALYs or LYs saved is quite low14. The available literature illustrates that economic evaluations of radiotherapy have mainly focussed on specific area’s of radiotherapy treatment15–19, such as particle therapy, while a comparison of new technologies with each other and with conventional schemes would be useful for decision making.

New technologies in medical imaging and radiotherapy show promising steps forward. These technologies, such as advanced PET-imaging for treatment planning, are typically introduced under the assumption that better dose distribution or more accurate dose delivery will ultimately yield better outcomes for patients. However, generally little or no evidence is available about to what extent these technologies lead to improved clinically relevant outcomes, such as survival and quality of life. This is not a problem as long as new technologies yield at least similar outcomes to similar or less costs as standard technologies19. However, some new technologies are significantly more costly16–20. Cost-effectiveness studies aim to assess the increased benefits and costs of such technologies to support decisions regarding implementation.

Disease Modeling

To support treatment decisions, it is essential to use the best available evidence on health effects and costs of treatments. The best available evidence of treatment effects may be derived from randomized controlled trials, which are recognized as the gold standard for establishing health effects. However, evidence from a clinical trial may not
always be available. PET-imaging for radiotherapy treatment planning is an example of a development that can change the management of cancer, but is not an actual treatment. As such, randomized controlled trials are scarce. In addition, randomized controlled trials operate in an idealized environment and can only measure treatment effects in selected populations. For these reasons, mathematical models are widely used for economic evaluations of populations. Mathematical models incorporate assumptions that allow a simpler representation of complex reality. These models synthesize data from multiple sources and estimate the effects and costs of interventions over an extended time horizon. In the context of cost-effectiveness of cancer care these models are referred to as ‘disease models’. Other situations when modeling is useful include those where intermediate outcome measures are used rather than effect on survival or quality of life, where relevant comparators have not been jointly assessed in a single trial or where trials do not include evidence on relevant subgroups. Since the evidence required to compare all relevant options with respect to all relevant outcomes in the relevant subpopulations is rarely extractable from one single data source, models synthesize evidence on health effects and costs from many different sources, including clinical trials, observational studies, registries, claim databases or expert opinion.

Traditionally, cost-effectiveness studies in cancer care are either health-economic evaluations alongside clinical trials or relatively simple health-economic models in which a homogeneous cohort of patients is simulated. Decision trees and Markov models are commonly used models to study decision problems. These models are easy to understand for decision makers, transparent and relatively easy to build. However, as decision making in health care is becoming increasingly complex, disease models need to include more detail.

With the shift towards individualized therapy, treatments are increasingly tailored to the specific characteristics of a patient and a tumor. To obtain clinical predictions that accurately estimate patient outcomes, integration of the clinical, molecular and imaging information on patient and tumors in is needed. Likewise, in the field of cost-effectiveness assessment, this means that for a proper evaluation of long-term costs and effects of individualized strategies, cost-effectiveness models need to incorporate patient and tumor features that may affect treatment decisions, disease progression, survival, adverse events and quality of life.

Important challenges in disease 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. The cost-effectiveness studies in this thesis attempted to deal with these challenges.

In modeling studies, it is crucial that the best available evidence is used. Although randomized controlled trials are considered to be the golden standard, patients included in trials may not be representative for the population of interest for a specific intervention. Moreover, trial data is not always available. Recently, decision makers and health authorities are interested in the use of Real World Evidence data, as evidence from trials is obtained in a highly controlled environment.

For radiotherapy treatment in NSCLC, clinical evidence on new therapies is mainly available through small clinical studies that evaluate short term outcomes, such as tumour coverage or local failure rate. Evidence on costs or resource use is hardly available. There is one study in the Dutch setting that explored resource use and costs of advanced stage NSCLC, presenting total mean costs of €32,000 per patient per year. Thus, more Real World Evidence data on resource use and costs is needed for model-based CEAs in radiotherapy treatment for lung cancer in the Netherlands.

Once the data source(s) that reflect the best available evidence are selected, the next challenge is to obtain input parameters from the data that inform the disease model. This is referred to as the quantification of the disease model. Models that have to reflect the natural course of disease have usually more than one state. Intermediate events may occur that are relevant for the outcomes of a cost-effectiveness study. For instance, in the case of lung cancer a local recurrence or distant metastasis may occur. The challenge is how to quantify the entire disease model with occurrence of multiple events, either subsequent or competing events.

Model validation is another important issue in modeling. The model structure should reflect important health states of a patient. During all phases of model development, clinical experts should critically assess the model and the model predictions. The internal validation of a model is performed by comparing the predictions of the model with the observations in the data. However, it is not sufficient to show that a model can successfully reproduce the outcomes of interest in the sample data. When applied to a different patient group, the performance of the model is expected to be lower than the performance observed in the population used for model development. Therefore, models should be validated in external patient groups before they can be used for the evaluation of treatment in a different patient population. External model validations are not frequently done in model-based CEAs.

In CEAs of radiotherapy in cancer treatment, some essential methodological standards were generally not met, especially in the identification of the data sources used for model input. Consequently, the full uncertainty associated with estimation of the long-term clinical benefits of interventions, was rarely captured. Guidelines for cost-effectiveness studies require that a measure of uncertainty is presented in addition to point estimates.

Parameter uncertainty and patient heterogeneity are two types of uncertainty. Parameter uncertainty reflects the uncertainty of each input parameter. In a base-case scenario, the
input parameters are the values that were considered the most likely estimates for that parameter. When the input parameter is directly estimated from data, a distribution around the point estimate is available that reflects the uncertainty of that point estimate. When the input parameter is not directly estimated from data, a distribution can be assigned to the input parameter. These distributions can be used in probabilistic sensitivity analyses (PSA). PSA is an evaluation of the uncertainty of all input parameters combined. At each iteration, a new set of input parameters is randomly drawn from the distributions specified for the input parameters. Model output is generated for a patient cohort based on this new parameter set. This process is repeated for a large number of iterations, whereby a new parameter set is drawn at each iteration.

Another approach to present parameter uncertainty is by carrying out scenario analyses or univariate sensitivity analyses. Each input parameter is varied one-by-one over a plausible range, and the resulting variation in the model output shows the sensitivity of the output to that parameter.

Patient heterogeneity refers to actual differences between patients. In contrast to parameter uncertainty, patient heterogeneity cannot be reduced by better data. Patient heterogeneity can be modeled by using subgroups in cohort simulations, and can be modeled by including covariates in statistical models. Using subgroups in cohort simulations will lead to different model results for each subgroup. Including covariates in a statistical model will lead to one model result that is averaged over all patients, but allows for extrapolation to any subgroup, depending on the selection of included covariates.

To assess all these types of uncertainty within one disease model is considered a methodological challenge.

**Aim of this thesis**

The aim of this thesis is to provide insight in current NSCLC care and costs in The Netherlands, and to assess the cost-effectiveness of a number of new treatment strategies in (chemo-)radiotherapy. The thesis focuses on challenges in disease modeling and cost-effectiveness that were encountered during this research.

**Outline of this thesis**

This thesis is structured as follows. Part 1 focuses on current care in NSCLC. Chapter 2 provides an overview of the cost-effectiveness literature with respect to currently used systemic and targeted therapies for metastatic NSCLC patients. Cost-effectiveness studies that were included in this review were critically appraised according to a checklist for cost-effectiveness studies and a checklist for model-based cost-effectiveness studies by Philips et al. This has led to the identification of a number of challenges in conducting model-based cost-effectiveness studies that were addressed in part 2 of this thesis. Both Chapters 3 and 4 describe the current care in the Netherlands as observed in our large retrospective study on NSCLC care in four large Dutch hospitals. Chapter 3 describes the treatment patterns and survival of patients over different stages of disease, while Chapter 4 describes the real-world resource use and costs of patients over different stages of disease.

Part 2 of the thesis focuses on the evaluation of the cost-effectiveness of individualized strategies for chemo-radiotherapy treatment. Chapter 5 describes the development and validation of a flexible micro-simulation model that can be used for the evaluation of new strategies in (chemo-)radiotherapy treatment. This model calculates the individual disease pathways with multiple events, thereby accounting for patient heterogeneity and parameter uncertainty. The model is used for the cost-effectiveness studies carried out in Chapter 6 and 7. In Chapter 6 the cost-effectiveness of PET-CT-based treatment planning with an isotoxic and accelerated radiation scheme compared to CT-based treatment planning with a fixed dose radiation scheme was assessed. Chapter 7 is an evaluation of the cost-effectiveness of optimized concurrent and sequential chemo-radiation schemes compared to standard concurrent and sequential chemo-radiation schemes.
Chapter 1

References


