The use of real-world data in lung and head and neck oncology

Naomi van der Linden

The Use of Real-World Data in Lung and
Head and Neck Oncology

Het gebruik van data uit de dagelijkse praktijk in long- en
hoofd-hals oncologie

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Chapter I

General introduction

ANTICANCER DRUG STUDIES

Over the last 40 years, hundreds of new anticancer drugs have been developed.[1] Part of this progress was driven by an increased understanding of cancer biology, which allowed scientists to develop new classes of drugs.[2] These classes of drugs include therapies aimed at specific molecular targets. Such targeted therapies block the growth and spread of cancer by interfering with molecules involved in tumour progression.[2]

Despite these new types of drugs, for most types of cancer enduring responses are still rare, and cures even rarer.[1] One of the reasons for this is tumour heterogeneity, which means that attributes of tumour cells differ within and between tumours, thereby influencing their susceptibility to treatment.[2] When (part of the) tumour cells are not susceptible to a drug, they can continue to progress during or after treatment. Therefore, responses to anticancer drugs are often temporary and the unmet medical need remains substantial.[3] New drugs or new combinations of drugs may, hopefully, overcome this problem.[4]

Efforts to develop new drugs and other (non-pharmaceutical) treatments continue. This is a lengthy process, usually starting in the laboratory, the pre-clinical phase, and slowly moving to large, randomised controlled trials (RCTs) to assess treatment safety and efficacy (phase III, see Table 1.1). When clinical evidence shows the drug to be safe and efficacious, market licensing authorities can evaluate it and approve the drug for marketing. In the European Union (EU) and the United States (US) this approval is performed by the European Medicines Agency (EMA) and the US Food and Drug Administration.[5]

Table 1.1 Drug development process

				Marketing approval
Preclinical	**Phase I**	**Phase II**	**Phase III**	**Phase IV**
Molecule discovery and characterisation, biological activity, safety	Dosage, safety	Efficacy, safety	Efficacy, safety	Real-world outcomes: (appropriate) use, effectiveness, safety, budget impact, cost-effectiveness

However, after marketing approval, important questions still remain to be answered. While the drug has been extensively tested in the study setting, the real-world (RW) setting may be different. In the real world, the drug may be used differently from how it was used in clinical trials. Furthermore, due to selection, patients included in clinical trials may be

different from the general patient population. In addition, monitoring practices in trials may differ from the real world; they can have a therapeutic effect as such and/or may allow clinicians to respond earlier to changes in a patient's clinical condition. These and other differences can limit the generalisability of trial results to the actual RW patients in need of the drug.

Therefore, in various countries, RW evidence is required in addition to trial results, for example to approve a drug for continued reimbursement. This evidence is often collected in observational studies and may include RW effectiveness and safety evidence, but also information on appropriate use, patient-reported outcomes, budget impact and/or cost-effectiveness.[6] Given the fact that national healthcare budgets are limited, information about RW budget impact and cost-effectiveness is increasingly important to ensure rational allocation of scarce resources.

In this thesis, the value of RW evidence will be evaluated. Observational outcome studies from two clinical areas will be presented: head and neck cancer oncology and lung oncology. In both of these areas, substantial clinical progress has been made over the last decade, including the market approval of targeted therapies. Also in both of these areas, RW evidence has been scarce.

First, in the following paragraphs ("clinical background"), a general overview of head and neck and lung oncology will be provided. Secondly, (in "RW data") various types of RW data and their relevance will be introduced. The last part of the introduction will discuss the aim, research questions and structure of the thesis.

CLINICAL BACKGROUND

The case of head and neck cancer

The term "head and neck cancer" covers malignant tumours of a number of anatomic regions in the body, depicted in Figure 1.1. Head and neck cancer constitutes 5% of the total number of cancer cases worldwide.[3] In the Netherlands the annual incidence of head and neck cancer is approximately 3,000 and mortality is 875 per year.[7] The incidence of squamous cell carcinoma of the oral cavity, oropharynx and hypopharynx has risen in the last decennia in the Netherlands. The incidence of laryngeal carcinoma has decreased in men and remained stable in women.[8] Risk factors for developing head and neck cancer are exposure to tobacco, excessive alcohol use and human papilloma virus (HPV).[9,10]
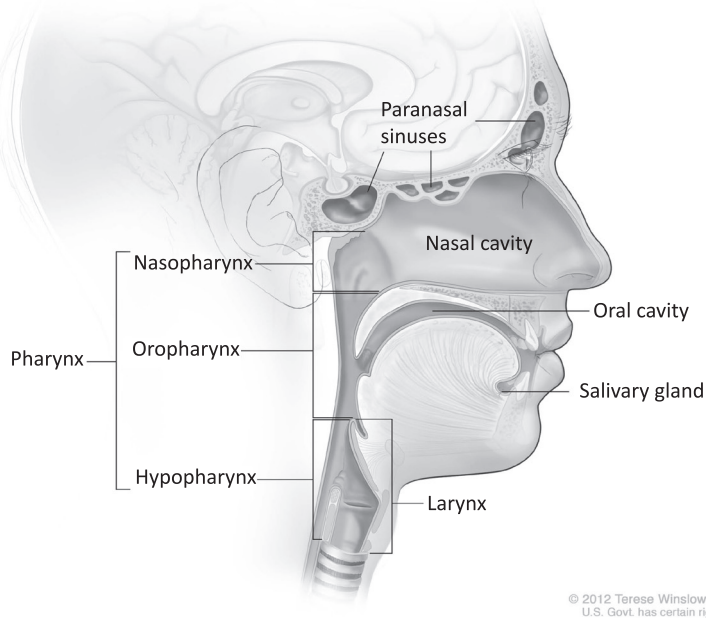
Head and Neck Cancer Regions

Figure 1.1. Head and Neck Cancer Regions.
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Traditionally, treatment of head and neck cancer consists of surgery, radiotherapy, chemo-therapy, or combinations of these, depending on the disease stage. Recently, targeted therapy was added to this range of treatment options. In 2006 and 2008 study results demonstrated the efficacy of cetuximab in locally advanced (LA) and recurrent and/or metastatic (RM) squa-mous cell carcinoma of the head and neck (SCCHN).[11,12] Cetuximab is a monoclonal antibody aimed at the epidermal growth factor receptor (EGFR). In the clinical trials, the overall survival of patients treated with cetuximab in addition to radiotherapy (in LA SCCHN) or chemotherapy (in RM SCCHN), was median 19.7 (LA SCCHN) and 2.6 (RM SCCHN) months longer, respectively, than the overall survival of patients treated with radiotherapy or chemotherapy alone.[11,12] RW use, costs and effects were previously unknown and will be discussed in this thesis.

Head and neck cancer care is relatively well organised in the Netherlands. Approximately 90% of patients with head and neck cancer are treated in specialised head and neck treat-ment centres.[13] Strict standards exist for head and neck treatment centres in order to ensure quality. These standards were drafted by the profession and include minimum treatment volumes and requirements regarding (multidisciplinary) staff composition. For example, each patient should be discussed in a multidisciplinary head and neck working group with

a medical oncologist, radiotherapists, head and neck cancer surgeons, and expertise about reconstructive surgery.[14] The locations of the head and neck treatment centres are indicated in Figure 1.2.[13]

Figure 1.2. Head and neck treatment centres in the Netherlands.

The case of lung cancer

Lung cancer is the most commonly diagnosed cancer (1.8 million cases, 12.9% of the total cancer cases in 2012) and the most common cause of cancer death (1.6 million cases, 19.4% of the total in 2012) worldwide.[3] Also in the Netherlands, lung cancer incidence as well as mortality has remained relatively high, despite medical advances and a reduction in smoking. In 2012, incidence was 66.1 males and 44.5 females per 100,000 person years (European Standardised Rates). Lung cancer mortality was 59.6 males and 35.6 females per 100,000 person years.[15] More than 85% of lung cancers are of the non-small cell type.[7] Figure 1.3 shows a picture of the respiratory anatomy, including the lungs.

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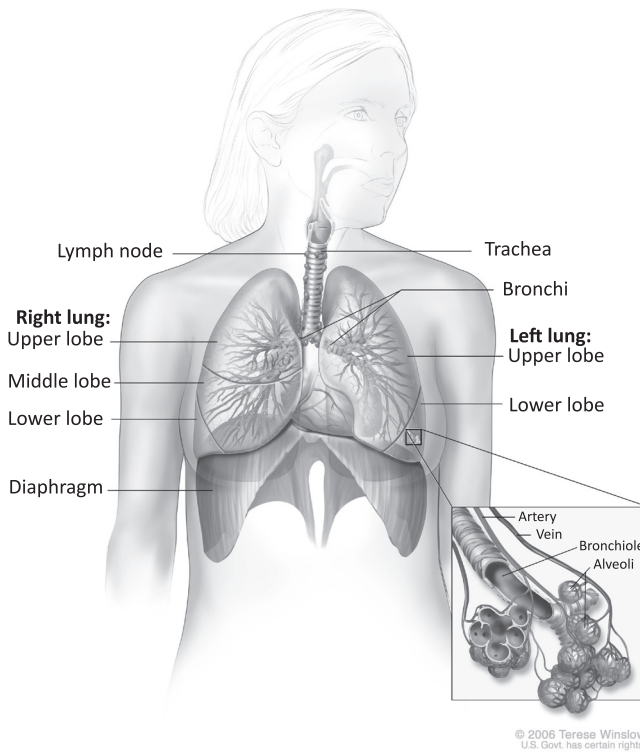
Figure 1.3. Respiratory Anatomy.
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Treatment of lung cancer traditionally consists of surgery, radiotherapy, chemotherapy, or combinations of these, depending on the disease stage. Commonly prescribed chemotherapy regimens include combinations of a platinum agent (cisplatin, carboplatin) with a third-generation agent (paclitaxel, docetaxel, gemcitabine or vinorelbine), or pemetrexed. Furthermore, targeted therapies have recently been added to the range of treatment options. Amongst others, erlotinib and gefitinib are being prescribed, both of which target EGFR. New targeted therapies that target, amongst others, KRAS (Kirsten Rat Sarcoma Viral Oncogene Homolog), ALK (Anaplastic Lymphoma Kinase), HER2 (Human Epidermal Growth Factor Receptor 2) and BRAF (V-Raf Murine Sarcoma Viral Oncogene Homolog B) are being studied extensively.[16] Other advances in lung cancer treatment include the use of new techniques for the planning and administration of radiotherapy, and new surgical approaches.[17] In the last decades, NSCLC treatment has improved and survival has slightly improved as well, within all disease stages.[18,19]

Unlike the treatment of head and neck cancer, NSCLC treatment is not centralised in the Netherlands. However, similarly to head and neck cancer, standards exist for hospitals treating patients with lung carcinoma. These standards were drafted by the profession and include minimum treatment volumes and requirements regarding (multidisciplinary) staff composition and available facilities.[14] Further, a Dutch evidence-based guideline for the diagnosis and treatment of NSCLC exists and (modular) revisions are performed regularly to ensure actuality.[20] However, better compliance with the guideline as well as further centralisation may be needed to further improve NSCLC management.[21]

In this thesis, current NSCLC treatment patterns will be discussed. Furthermore, RW information is provided with regard to clinical outcomes and costs of NSCLC diagnosis and treatment.

RW DATA

Various types of RW data exist, including data on treatment patterns, clinical outcome measures, budget impact and cost-effectiveness.

Treatment patterns / (appropriate) use

Data on treatment patterns can be used to evaluate how a certain treatment is being prescribed. For example, one can measure the uptake of new drugs by looking at how often they are prescribed and how this changed over time, from market access onwards. Also, one can evaluate for which indications a drug is used and which type of patients are receiving it. This can be compared to the drug's label and/or the national or international clinical guidelines to evaluate if the drug is being used appropriately. National reimbursement authorities including the Dutch National Health Care Institute (ZIN, previously called the "College voor Zorgverzekeringen", CVZ) require information on appropriate use (on-label use, use according to guidelines) of certain types of new drugs as a condition for continued reimbursement.

Furthermore, treatment sequences can be evaluated to check, for example, treatment effectiveness and safety dependent on treatment history. Moreover, RW data on treatment patterns can also be used to assess treatment variability between hospitals. Treatment variability can be an important indication of differences in quality of care. In the Netherlands, large differences exist in the proportion of surgeries hospitals perform for (up to 5.5 times difference, for the same indication).[22] The same is likely true for pharmaceutical treatments. Differences can be caused by e.g. patient heterogeneity, undertreatment or overtreatment in some of the hospitals. Comparing treatment patterns and clinical outcomes, corrected

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for differences in patient populations, can point towards best practices and possibilities for improvement.

Clinical outcome measures
Clinical outcomes are valuable for assessing the RW impact of new drugs. There is a difference between treatment efficacy and treatment effectiveness. While the efficacy of a treatment refers to its performance "under ideal and controlled circumstances", the effectiveness of a treatment refers to its performance "under usual or 'real-world' circumstances".[23] As is shown in Table 1.1, treatment efficacy has usually been proven within clinical trials before marketing approval. Effectiveness needs to be measured in daily clinical practice.

Important efficacy and effectiveness measures include overall survival[24], progression-free survival[25] and treatment response.[26] Furthermore, treatments can positively or negatively affect the quality of life of patients. Impact on quality of life can be the result of (an increase or decrease in) adverse events, during and (in the case of long-term or delayed adverse events) after treatment. Furthermore, treatments can impact quality of life by relieving symptoms of the disease. Quality of life is multiplied with overall survival to obtain a composite measure incorporating both the quantity and quality of life: quality-adjusted life years (QALYs).[27]

Overall survival, progression-free survival, response, safety and quality-adjusted life years gained can be compared between treatment alternatives and inform decision making on the individual as well as the macro level.

Budget impact
In order for national healthcare decision makers to approve a drug for reimbursement, they generally also require information regarding budget impact. Since healthcare budgets are limited, payers need to know to what extent new drugs will take up available resources. The number of cancer patients is large and rising, as are the number and prices of new pharmaceuticals. More and more innovative cancer drugs are being developed and their prices have increased from 300-500 euro per month in the nineties to 10,000 euro per month in 2014.[28] Therefore, the budget impact of cancer drugs is increasing.

The total budget impact of a drug should be based on the size and characteristics of the affected population, the current intervention mix without the new intervention, the costs of the current intervention mix, the new intervention mix with the new intervention, the cost of the new intervention mix and the use and cost of other health condition and treatment related healthcare services.[29]

Just like clinical outcome measures, budget impact can be compared between treatment alternatives and inform decision making. Budget impact analyses are usually performed from the perspective of the national healthcare decision maker[29], not the individual clinician or oncology practice. In the Netherlands, economic evaluations (including evidence on budget impact and cost-effectiveness) are required for drugs with an added therapeutic value and for expensive specialist drugs.[30]

Cost-effectiveness

In addition to information about budget impact, national healthcare payers generally require information on drug cost-effectiveness. This is also true for the National Health Care Institute in the Netherlands. Cost-effectiveness is calculated by dividing the cost of a treatment by its effects. A subtype of cost-effectiveness is cost-utility. In this case, effects are expressed in QALYs.

The cost-effectiveness (or cost-utility) of a new treatment can be compared to the cost-effectiveness (or cost-utility) of another treatment alternative to calculate the incremental cost-effectiveness ratio (ICER): (cost of the treatment − cost of the comparator) / (effects of the treatment − effects of the comparator). Usually the ICER is expressed in costs per QALY gained, because this measure can be used generically and allows decision makers to compare treatments for different diseases.

Various methods exist to calculate cost-effectiveness. Generally data from clinical studies is used and health-economic modelling is needed to extrapolate cost and effects over a longer period of time than the study duration (e.g.: a patient's lifetime). Furthermore, cost-effectiveness analyses include various types of sensitivity analyses to quantify the uncertainty of the outcomes. Additionally, scenario analyses can be performed to quantify the impact of alternative assumptions for model inputs.[31]

In the Netherlands, ICERs for new pharmaceuticals are evaluated by the National Health Care Institute. However, no formal cost-effectiveness threshold exists for approving or denying a drug for reimbursement. A threshold range was suggested depending on the severity of the disease (i.e. €10,000-80,000 per QALY gained), but was never confirmed nor endorsed by the Ministry of Health. While the requirement to deliver cost-effectiveness evidence exists in policy procedures, it does not (yet) seem to influence reimbursement decisions in the Netherlands.[30]

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AIM AND RESEARCH QUESTIONS OF THIS THESIS

The aim of this thesis is to assess the value of RW evidence in addition to RCT evidence in lung and head and neck oncology. The following research questions will be answered:
– What are the differences between RW evidence and evidence obtained in RCTs?
– How can the addition of RW evidence to RCT evidence support decision making?
– How can RW cost data improve lung and head and neck cancer care?
– How can RW data on treatment patterns improve lung and head and neck cancer care?
– How can patient registries be used to collect high-quality RW data?
In the discussion of this thesis, the results from the various chapters will be combined and used to answer these research questions.

STRUCTURE OF THIS THESIS

First, in Chapter II-IV of this thesis, several outcome studies in head and neck cancer will be discussed. Chapter II discusses the use of cetuximab in locally advanced squamous cell carcinoma of the head and neck. It compares the RW setting to the pivotal clinical trial setting and stresses the differences. Chapter III builds on these outcomes to model the cost-effectiveness of cetuximab in the locally advanced setting, in order to inform reimbursement decisions. Multiple scenarios are presented, showing the impact of an alternative assumption regarding the prognosis of RW versus clinical trial patients.

The fourth chapter discusses a different indication in head and neck cancer, namely recurrent and/or metastatic disease. It describes RW treatments and costs for a patient group with a poor prognosis and small expected treatment gains.

Chapter V discusses treatment and survival of non-small cell lung cancer patients in the Netherlands. It presents differences in survival between patients treated in different hospital types. Chapter VI and VII discuss the costs of non-small cell lung cancer care. Chapter VI zooms in on the costs for laboratory tests, amongst others genetic biomarker tests to assess eligibility for treatment with targeted therapies. Chapter VII uses these and other costs to provide an overview of all hospital costs associated with non-small cell lung cancer management.

Chapter II to VII all provide practical examples of possible questions to be answered with RW evidence. However, disregarding the question at hand, the value of RW evidence largely depends on the quality of the data. An increasingly popular way to collect RW data is via

patient registries. Chapter VIII therefore provides a practical guide to setting up patient registries for the collection of high-quality RW data for decision making. It provides important prerequisites to ensure proper design and management of the patient registry.

Chapter IX draws together the results of previous chapters in the general discussion. Furthermore, it summarises the limitations of this thesis.

Chapter II

Cetuximab in locally advanced squamous cell carcinoma of the head and neck: generalisability of EMR 062202-006 trial results

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ABSTRACT

In a randomised controlled trial in patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN), treatment with radiotherapy plus cetuximab (RT+C) resulted in improved survival compared to treatment with RT alone. Uncertainty exists about the generalisability of the trial results for the Dutch healthcare setting due to possible discrepancies in treatment allocation.

Retrospective patient chart review was performed for 141 patients treated with first-line RT+C or RT alone, diagnosed in 2007–2010 in two head and neck treatment centres. Combined with aggregated population-based data from the Netherlands Cancer Registry and patient-level clinical trial data, use of cetuximab in Dutch daily practice was assessed through comparison of patient characteristics, treatment characteristics and treatment outcomes between trial and daily practice.

Sixty-one daily practice patients fulfilled the selection criteria. In line with Dutch guidelines, RT+C is prescribed in patients requiring combined therapy unfit to receive traditional platinum-based chemotherapeutics. These patients have unfavourable baseline characteristics, due to selection on—amongst others—high age of the patients. Beyond 1 year after treatment start, patients treated with RT+C in daily practice died earlier than patients treated with RT+C in the trial.

Selective treatment allocation in daily practice limits generalisability of EMR 062202-006 trial results. Evidence is needed about the effectiveness of RT+C compared to other treatments for patients with unfavourable clinical baseline characteristics.

II

INTRODUCTION

Each year in Europe over 130,000 cases of head and neck cancer are diagnosed, associated with high morbidity and 63,000 deaths annually.[15] For decades, the mainstay treatment for locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) consisted of surgery or radiotherapy, alone (RT) or combined with platinum-based chemotherapy (CRT), according to disease stage and clinical characteristics.[32-37] In 2006, Bonner et al. published the results of a phase III study investigating the addition of cetuximab, a chimeric human-murine monoclonal IgG antibody, to RT in three fractionation regimens, to treat oropharyngeal, hypopharyngeal or laryngeal carcinoma (EMR 062202-006). Improved locoregional control (LRC), progression-free survival (PFS) and overall survival (OS) were demonstrated in the study arm receiving cetuximab, effectively expanding the range of treatment modalities.[38] Updated survival figures confirmed efficacy of RT plus cetuximab (RT+C) compared to RT. A median OS of 49.0 months (95% CI 32.8–69.5 months) was observed for RT+C versus 29.3 months (95% CI 20.6–41.4 months) for RT (hazard ratio 0.73, 95% CI 0.56–0.95; p=0.018).[11]

The European Medicines Agency issued marketing authorisation for cetuximab in 2004 for the treatment of patients with squamous cell cancer of the head and neck in combination with radiation therapy for locally advanced disease. The Dutch Association for Medical Oncology (NVMO) in current LA SCCHN treatment guidelines proposes RT, CRT or RT+C, guided by tumour characteristics and medical condition.[34-37] Definitive criteria for prescription of cetuximab in LA SCCHN in the Netherlands have not been specified, although guidelines recommend RT+C in cases where RT is thought to be insufficiently effective and CRT is contraindicated. More research is needed to determine efficacy and effectiveness of RT+C compared to current, standard chemoradiation, as well as for the addition of cetuximab to standard chemoradiation.[39-41]

NVMO's scientific committee (CieBOM) states that although the "Bonner trial" was not powered for subgroup analyses, results suggested cetuximab to be most efficacious when prescribed to patients with oropharyngeal carcinoma and when combined with concomitant boost RT regimen (hyperfractionated RT).[41] CieBOM therefore recommended considering treatment with cetuximab + accelerated and/or hyperfractionated RT, only for the treatment of patients with an oropharyngeal carcinoma and a contraindication to chemoradiation. Subsequently, the Netherlands Healthcare Insurance Board's committee for pharmaceutical aid (CFH) confirmed therapeutic added benefit of the combination of cetuximab and hyperfractionated or accelerated RT over treatment with RT alone, in patients with LA SCCHN with a contraindication to platinum-based chemoradiation, especially for patients with oropharyngeal carcinoma and a good general condition.[42]

These recommendations for treatment allocation can result in dissimilarities between patients receiving RT+C in daily practice and those selected for the "Bonner trial", possibly resulting in limited generalisability of trial results. The extent to which patients receiving RT+C in daily clinical practice match those in the trial has remained unknown. We designed a study to provide insight into the position of RT+C in the Netherlands. Further, we aim to determine applicability of the "Bonner trial" results to Dutch healthcare. In this paper, we present results on patient characteristics, treatment characteristics and clinical effectiveness of RT+C in a sample of the Dutch LA SCCHN patient population, as compared to the trial. In a companion paper, an analysis of cost-effectiveness of RT+C in this indication will be presented.

METHODS

Study design

We performed a retrospective, observational study of LA SCCHN patients in the Netherlands treated with RT+C or RT alone. Although main interest lies with RT+C in daily practice, as such and as compared to the trial, characteristics of patients treated with RT alone, comparator arm in the "Bonner trial", inform on daily practice treatment allocation. The study consisted of retrospective chart review of patients treated with first-line RT+C or RT for oropharyngeal, hypopharyngeal or laryngeal SCC between January 1, 2007 and December 31, 2010 in two university medical centres. No further selection criteria were applied. In contrast, the "Bonner trial" accepted subjects only when the following criteria were fulfilled: an expected survival of C12 months, normal renal, liver and hematopoietic function, no systemic chemotherapy or previously treated malignancy in the last 3 years, and no prior RT to the head and neck or surgery for the tumour. As our study design is not subject to the Medical Research Involving Human Subjects Act, the Medical Research Ethics Committee exempted the study from ethical appraisal. Informed consent was not required for chart review. Charts were obtained from VU University Medical Centre (VUMC) in Amsterdam and University Medical Centre Groningen (UMCG) for all LA SCCHN patients who had received first-line RT+C or definitive RT. Eligible patients were identified from hospital databases by one clinician in each hospital.

Patient charts (n=141 total, 61 RT+C and 80 RT) were manually reviewed. Detailed information was collected about patient characteristics, tumour classification, treatment characteristics, disease progression and survival. Data were recorded onto standardised paper case report forms. For a subsample of these patients (31 patients treated with RT+C and 31 treated with RT), matched by year of treatment start, tumour site and disease stage,

additional data on toxicities and resource use were collected. Aggregated population data from the Netherlands Cancer Registry (NKR), available up to 2009, on disease stage and tumour location were used to inform on representativeness of the observational study data.[43] Observational study results on baseline characteristics and OS were compared to the "Bonner trial" results. Patient-level data from the trial consisted of patient and tumour characteristics, treatment arm, date of randomisation, date of progression and date of death. These were obtained from the marketing authorisation holder.

Data analysis
Patient characteristics consisting of age, sex, and WHO performance status, tumour classification comprising disease stage and tumour site, and treatment characteristics (modality, dosing, adverse events) were compared between patients from the trial and the observational study. In addition to descriptive statistics, differences were assessed by means of the independent samples t-test for variables showing a normal distribution and the Pearson Chi square test for variable fractions. Statistical significance was assumed if the two-tailed probability value was <0.05.

The clinical effectiveness measure reported in this paper is OS, defined as time from treatment start to death. Survival curves were visualised according to the Kaplan Meier methods. OS was not corrected for covariates and compared between groups: the study aims to describe the position of RT+C in daily practice, not to compare its effectiveness between treatment settings. All statistical analyses were performed using the SPSS computer package, version 17.0.

RESULTS

Inclusion
Based on results from the National Cancer Registry (NKR), between January 1, 2007 and December 31, 2009, in the Netherlands 2,111 patients were diagnosed with locally advanced oropharyngeal, hypopharyngeal or laryngeal squamous cell carcinoma (Figure 2.1). Of these patients, 109 had received first-line treatment with RT+C. Forty-four of these patients (40.4%) had been treated in VUMC or UMCG and were therefore included in the observational study. We included an additional 17 patients from VUMC and UMCG diagnosed in 2010, resulting in a patient population of 61 RT+C patients fulfilling the selection criteria. Median follow-up of these patients was 29 months (range 20–38 months).
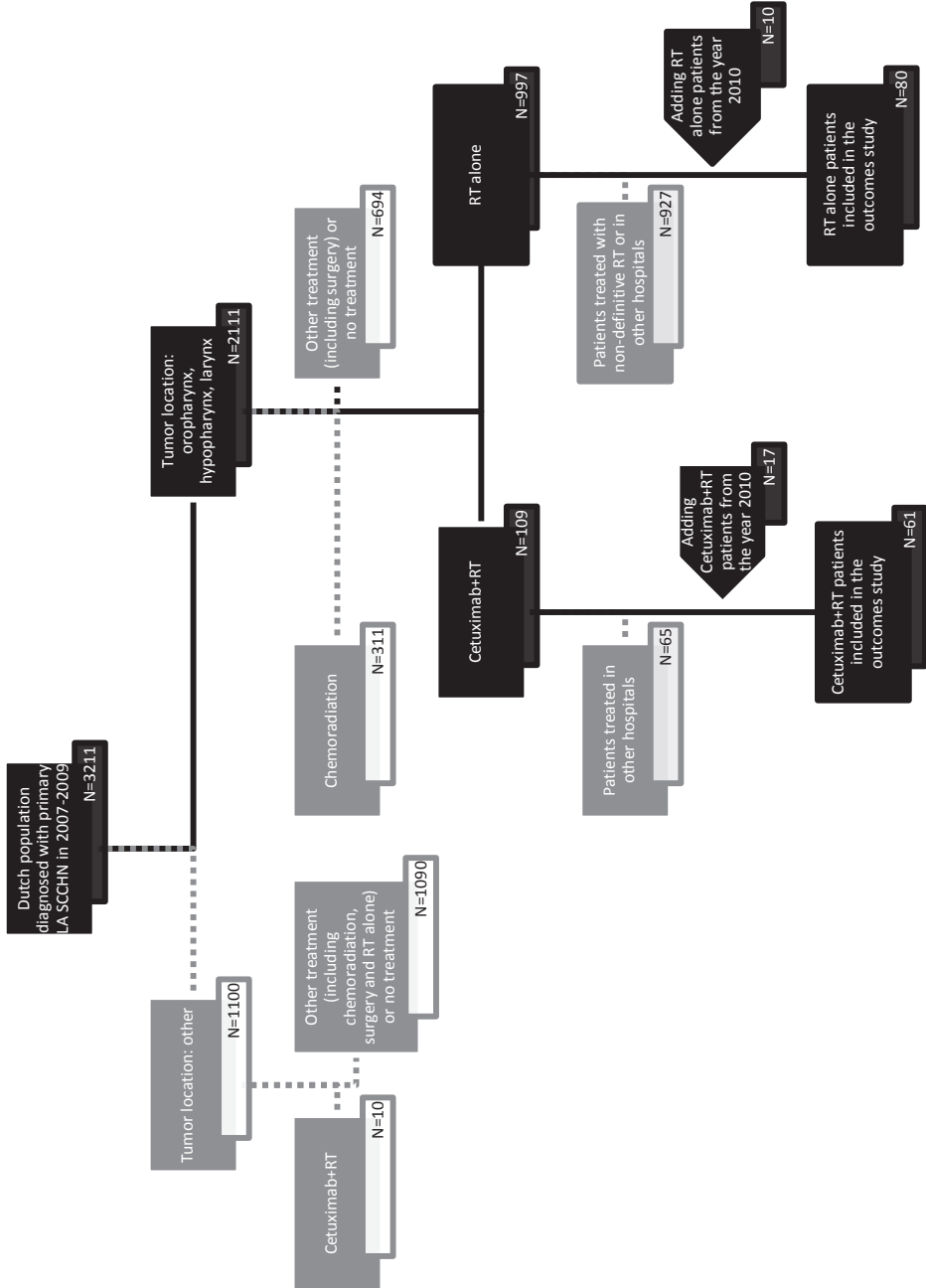
Figure 2.1. Flowchart of the Dutch patient population with locally advanced squamous cell carcinoma of the head and neck.

During this timeframe, the proportion of patients receiving RT+C each year ranged from 4.6 to 6.1% of LA SCCHN patients. Disease stage and tumour site in the sample (n=61) were representative for the population treated with RT+C on a national level as recorded by the NKR (n=109) (Table 2.1).

Table 2.1. Distribution of disease stage and site of primary tumours in patients treated with radio-therapy plus cetuximab (RT+C), observational study versus national

	Observational study: RT + C (n = 61, 2007–2010)	National: RT + C (n = 109, 2007–2009)	p
Disease stage			
III	16 (26%)	22 (20%)	0.36
IV	45 (74%)	87 (80%)	
Tumour site			0.76
Oropharynx	32 (53%)	63 (58%)	
Larynx	6 (10%)	11 (10%)	
Hypopharynx	23 (38%)	35 (32%)	

Patient and tumour characteristics

Demographics and tumour characteristics differed between the population treated in Dutch daily practice and the "Bonner trial" (Table 2.2). For both treatment arms, the patients in the observational study had a higher median age; 65 versus 56 (RT+C, p=0.00) and 62 versus 58 (RT alone, p=0.00). In the RT+C group, the proportion of females was significantly higher in daily practice. For patients treated with RT+C, no statistical differences at baseline were found in disease stage between the trial population and our study sample. Tumours treated with RT+C were more often located in the hypopharynx in our sample (n=23, 38%) than in the "Bonner trial" (n=36, 17%). In patients receiving RT alone in daily practice, 70% (n=56) of carcinomas were laryngeal, compared to 24% (n=51) in the trial.

Treatment

In 38% of our sample, treatment choice was motivated in patients' files. The most common arguments for choosing RT+C over CRT were: weakened condition (n=8, 13%), impaired renal function (n=8, 13%) and high age (n=5, 8%).

Planned radiotherapy and pharmaceutical regimens in patients who had received RT+C were according to label. In 12 patients (39%) planned regimens were abandoned during the course of treatment, primarily for reasons of toxicity (n=8). This included immediate hypersensitiv-

Table 2.2: Baseline characteristics within the 'Bonner trial' versus the observational study

	RT+C			RT alone		
	Trial	Daily practice	P	Trial	Daily practice	P
N =	211	61		213	80	
Age, yr			0.001[1]			0.001[1]
Median	56	65		58	62	
Range	34-81	42-83		35-83	40-87	
Sex, no. (%)			0.00			0.34
Male	171 (81)	37 (61)		169 (79)	61 (76)	
Female	40 (19)	24 (39)		44 (21)	19 (24)	
Disease stage, no. (%)			0.98			0.00
III	55 (26)	16 (26)		52 (24)	35 (44)	
IV	156 (74)	45 (74)		161 (76)	45 (56)	
Tumour site, no. (%)			0.00			0.00
Oropharynx	118 (56)	32 (53)		135 (63)	20 (25)	
Larynx	57 (27)	6 (10)		51 (24)	56 (70)	
Hypopharynx	36 (17)	23 (38)		27 (13)	4 (5)	
Performance status, no. (%)			0.16			0.31
WHO ≤ 1	189 (90)	27 (82)		190 (90)	37 (95)	
WHO 1 – 2	21 (10)	6 (18)		22 (10)	2 (5)	

1 = The p-value is for the comparison between the number of patients less than 60 years of age and those 60 years of age or older.

ity to cetuximab (n=2), fever (n=1), and abnormal liver function tests (n=1). In four patients, cetuximab was planned treatment regimen occurred significantly more often in daily practice than in the "Bonner trial", where deviations were reported in 1% of patients (n=3, p=0.00). RT regimens used in daily practice were diverse. Preferred regimen was accelerated RT, 35 9 2 Gy, total dose 70 Gy, 6 fractions per week, radiobiologically similar to the concomitant boost regimen in the trial. No deviations from RT treatment plans were reported.

Clinical effectiveness

Kaplan Meier curves for both the outcomes study and clinical trial populations show similar patterns of OS (Figure 2.2). This is not the case when survival curves are corrected for treatment modality. Figure 2.3 shows Kaplan Meier curves for patients receiving RT+C in the outcomes study versus the clinical trial. As opposed to the patient group as a whole, patients receiving RT+C demonstrate lower OS in daily practice than in the "Bonner trial", beyond 1 year of follow-up. Conversely, a higher OS was seen for RT alone (not shown).
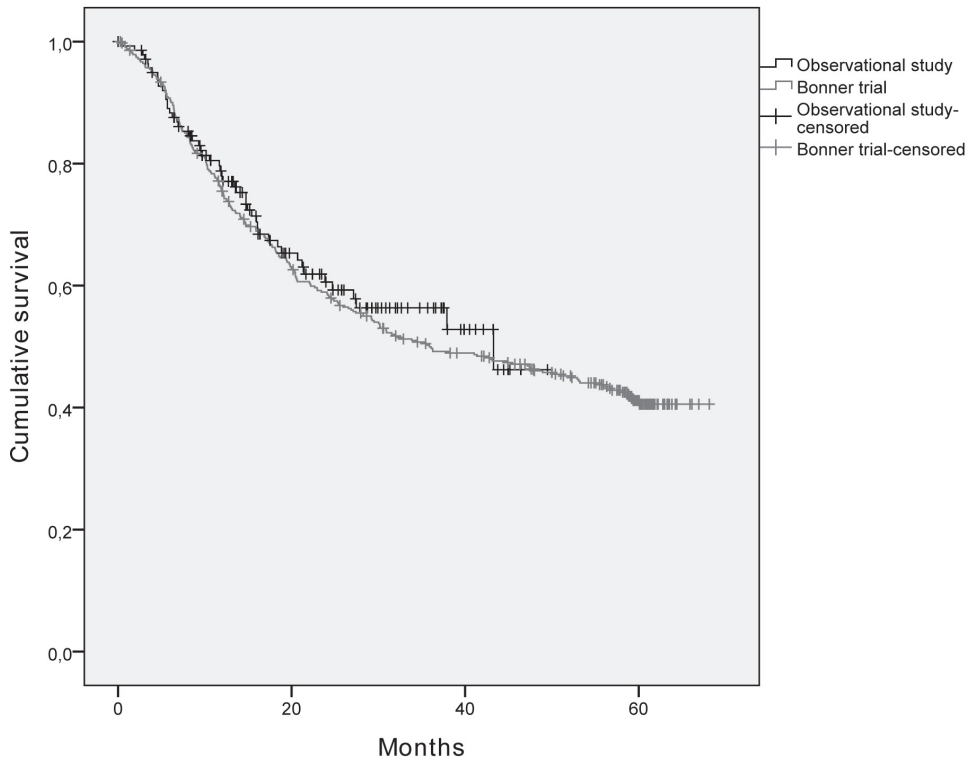
Figure 2.2. Kaplan Meier curves of all patients within the "Bonner trial" versus all patients within the observational study.

DISCUSSION

We demonstrate OS of patients in the daily practice sample matched survival of the "Bonner trial subjects". However, patients treated with cetuximab added to RT in daily practice had less favourable outcomes than their counterparts in the trial. The opposite was true for RT patients. This is likely due to treatment allocation, following differences in baseline characteristics.

Patient selection may influence generalisability of trial results. Two moments in patient selection are relevant. First, "trial patient selection" refers to the inclusion of a group of selected patients to participate in a clinical trial, based on trial protocol in a randomised setting combined with explicit or implicit choices by clinicians enrolling these patients. Second, "daily practice patient selection" refers to non-randomised or planned treatment allocation, based on guidelines or hospital protocols and explicit or implicit choices by patients and clinicians.
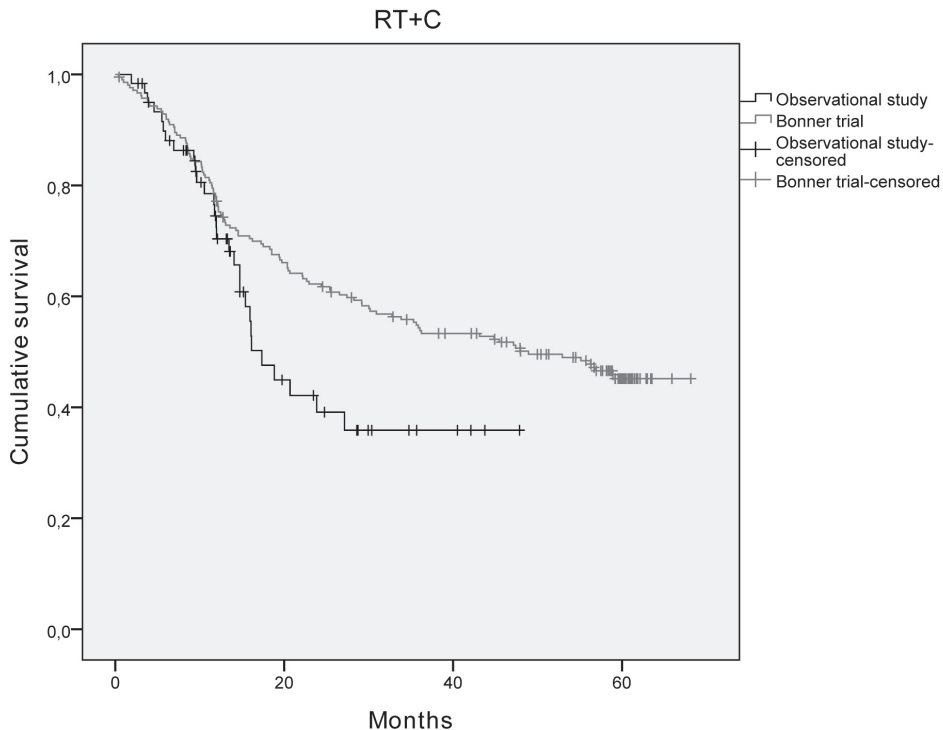
Figure 2.3. Kaplan Meier curves of the patients treated with RT+C (radiotherapy+cetuximab) within the "Bonner trial" versus the patients treated with RT+C in the observational study.

For RT+C, at least "daily practice patient selection" seems to limit the generalisability of the trial results. RT+C is prescribed in Dutch clinical practice to patients requiring combined treatment and who are contraindicated to receive CRT. As a result, patients receiving RT+C in Dutch clinical practice are more likely to have poor prognostic factors at baseline. Their median age has been found to be higher than the median age of patients who receive RT alone in daily practice, and higher than the median age of subjects in the "Bonner trial". Tumour characteristics at baseline were also indicative of poor prognosis. In patients following RT+C, we found a relative underrepresentation of laryngeal tumours, known to respond well to RT alone. Patients diagnosed with hypopharyngeal carcinoma, associated with poorer outcomes, were overrepresented in the patient group receiving RT+C. This is noteworthy since Dutch recommendations advocate use of RT+C mainly for oropharyngeal carcinoma.

Recently, Beijer et al. published a study on feasibility, effectiveness and toxicity of RT+C or platinum-based chemoradiation in Dutch daily practice LA SCCHN patients in 2008–2010. Thirty-two patients treated with RT+C were included, all ≥70 years and/or with significant

comorbidity. This study sample included patients with residual or locoregionally recurrent disease after previous surgery, as opposed to our study sample and the patients included in the "Bonner trial". Beijer et al. show worse prognostic characteristics and worse OS for patients treated with RT+C compared to patients treated with chemoradiation. In line with our conclusion, Beijer et al.[44] suggest this was "probably mainly due to patient selection and not to a treatment effect".

Our study design has several limitations. First, information was collected in only two hospitals: both large academic treatment centres. However, since the treatment of head and neck tumours in the Netherlands is centralised and both hospitals are members of the Head and Neck cancer working group, treatment in such centres is considered usual practice.[13] Our subsample of patients treated with RT+C for LA SCCHN, represents 40.4% of all patients receiving this treatment in the Netherlands within the timeframe.

Second, our data was dependent on the level of detail available in patient charts. Differences in reporting accuracy between clinicians introduce a bias, the direction of which cannot be determined. The same is true for missing data for patients who were lost to follow-up.

Obtaining more detailed information on the outcomes of cetuximab treatment is crucial, especially since there is little information about the benefit and toxicity of cetuximab in elderly and patients with comorbidity.[45,46] The most reliable way to study this would be within a randomised controlled trial.

In conclusion, RT+C seems to be chosen by clinicians in daily practice to treat those patients with relatively unfavourable prognostic characteristics, while patients with a favourable prognosis had a greater chance of receiving RT alone. This can either be the result of good clinical reasoning or undertreatment with RT+C in the favourable group of patients. Regardless, the generalisability of the trial results to Dutch daily practice seems limited.

Chapter III

Real-world cost-effectiveness of cetuximab in locally advanced squamous cell carcinoma of the head and neck

Naomi van der Linden, Chantal W.M. van Gils, Chris P. Pescott, Jan Buter, Marije R. Vergeer and Carin A. Uyl-de Groot

ABSTRACT

Clinical trial EMR 62202-006 demonstrates prolonged median locoregional control (24.4 vs. 14.9 months), progression-free survival (17.1 vs. 12.4 months) and overall survival (49.0 vs. 29.3 months) for patients who receive cetuximab added to the comparator radiotherapy for locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). In the Netherlands, hospitals receive reimbursement for cetuximab conditional on cost-effectiveness in daily practice.

To estimate the real-world incremental cost per QALY gained for RT+C over radiotherapy alone in first-line treatment of LA SCCHN, a Markov model is constructed with health states "alive without progression", "alive following progression" and "death". Transition probabilities per month are estimated from clinical trial data and retrospectively collected real-world data from two Dutch head and neck cancer treatment centres (2007–2010, n=141). Five-year, ten-year and lifetime horizons are used, without and with discounting (4% costs, 1.5% effects) to calculate incremental cost-effectiveness ratios. Two scenarios explore different assumptions on prognosis of real-world versus trial patients.

Adding cetuximab to radiotherapy results in increased costs and health gains in both scenarios and across each of the time horizons. Incremental costs per QALY gained range between €14,624 and €38,543 in the base case. For a willingness to pay of €80,000 per QALY, the acceptability curves for the different scenarios show probabilities between 0.76 and 0.87 of RT+C being cost-effective compared to radiotherapy alone.

Current results show the combined treatment of RT+C to be a cost-effective treatment option for patients with LA SCCHN.

INTRODUCTION

Treatment options for locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) include surgery and radiotherapy (RT). In case of RT, additional benefit is obtained with altered-fractionation RT, concurrent platinum-based chemoradiation, or RT combined with with cetuximab, a monoclonal antibody inhibiting the epidermal growth factor receptor.[47] Alongside the anti-tumour effect of cetuximab as a single modality, synergistic effects are demonstrated when combined with chemotherapy and/or radiation.[47-49]

Results from the pivotal randomised controlled clinical trial EMR 62202-006 (ClinicalTrials. gov number, NCT00004227) demonstrate significantly prolonged median locoregional control (24.4 vs. 14.9 months), progression-free survival (17.1 vs. 12.4 months) and overall survival (49.0 vs. 29.3 months) for patients treated with RT+C compared to RT alone.[11,38] As a result, RT+C gained a place in the therapeutic spectrum in clinical practice in the Netherlands. RT+C is prescribed to patients with a contraindication to platinum-based chemoradiation therapy. Patients who received RT+C in routine clinical practice, known as a real-world setting (RW), were found to have relatively unfavourable prognostic characteristics compared to trial subjects, or RW patients receiving RT alone (see chapter II).

In the Netherlands, expensive medicines are conditionally and temporarily reimbursed. Evidence on RW cost-effectiveness following health outcomes and pharmacoeconomic research provide information to policy makers on continuing the reimbursement status. We designed an outcomes study to generate this requested data on RW costs and effects of RT+C in the indication LA SCCHN. Data from the clinical trial[11,38] and the outcomes study (chapter II) were used to construct and populate a Markov model. The estimated incremental cost-effectiveness ratio of adding cetuximab to RT for these patients was then assessed.

METHODS

Outcomes study

RW data of LA SCCHN patients newly diagnosed between January 1st 2007 and December 31st 2010 were retrospectively analysed. Medical charts of 61 patients treated with RT+C and 80 patients treated with definitive RT alone in two specialised head and neck treatment centres in the Netherlands were reviewed. Patient and tumour characteristics, treatment and progression-free and overall survival data were captured. Resource use was collected for a subset of these patients (n=62, 31 per treatment group), matched for year of treatment start, tumour site and disease stage.

III

Real-world vs. clinical trial outcomes

As our outcomes study was not designed or powered to provide accurate, matched, survival estimates, effectiveness information was drawn from trial results. In the cost-effectiveness (CE) modelling, trial effect estimates were adapted based on RW data (see "Scenario 2"). With respect to baseline patient and tumour characteristics, RW patients differed considerably from trial subjects (Table 3.1). Higher median age and hypopharyngeal localisation of carcinomas, unfavourable prognostic characteristics, were more common in the RW RT+C population than in the trial population. Progression-free survival (PFS) and overall survival (OS) results following RT+C were worse in daily practice than in the corresponding group in the trial.[11,38]

Model Structure and transition probabilities

A Markov model was constructed using TreeAge Pro 2009 Suite (TreeAge software, Inc, Williamstown, MA) to estimate clinical and cost outcomes of first-line treatment with RT+C vs. RT for patients diagnosed with locally advanced oropharyngeal, hypopharyngeal or laryngeal SSC. The model simulates transition through the following health states: alive without progression (A), alive following progression (B) and dead (C) (Figure 3.1). Time dependent transition probabilities were derived from patient-level progression-free and overall survival results from the trial. At a cycle length of 1 month, the model simulates patients transitioning to any health state once monthly, according to changes in their clinical condition (no change, progression or death). A half-cycle correction was applied to reflect the fact that transitions between health states occur on average halfway through the cycle, rather than at the beginning or the end. Patients in the alive-without-progression state (A) may stay in that phase (tp_1), progress (tp_2), or die (tp_5). Patients in the alive-following-progression state (B) may stay in that phase (tp_3), or die (tp_4).

Incremental cost per QALY gained for RT+C over RT was the primary outcome measure. Incremental costs per life year gained (LYG) are also reported. Transition probabilities were derived from PFS and OS data of the trial, without (scenario 1) and with (scenario 2) correction for the poorer PFS and OS observed in daily practice. For both scenarios, cost-effectiveness and cost-utility estimates are reported for 5-year, 10-year and lifetime horizons, without and with discounting. Discounting is a process by which future costs and effects are assigned a lower value, thereby incorporating time preference into the model. Future costs and effects were discounted at 4 and 1.5%, respectively, consistent with current Dutch guidelines.[50] Our model was developed in collaboration with clinical experts and validated by comparing the model outputs with trial results.

Table 3.1. Comparison of the trial (EMR 62202-006) and Outcomes Research

	Trial	Outcomes Research
Study design	Phase III RCT	Retrospective observational study "Real-world (RW) patients"
Main eligibility criteria	Diagnosed LA SCC of the oropharynx, hypopharynx or larynx. Expected survival of ≥12 months. Normal renal, hepatic and hematopoietic function. No previously treated malignancy for more than 3 years. No previous chemotherapy (last 3 years), surgery (for the tumour) or RT (to head/neck).	Diagnosed LA SCC of the oropharynx, hypopharynx or larynx. First-line, definitive treatment with RT+C or RT alone.
Treatments	Patients randomized to receive: RT+C Planned dosage cetuximab: One week before start RT: 400mg/m². Followed by weekly: 250mg/m². RT alone Investigators could choose one of three RT fractionation regimens, before patient registration: 1) "once daily" (total dose 70 Gy in 35 fractions) 2) "twice daily" (total dose 72-76.8 Gy in 60-64 fractions) 3) "concomitant boost" (total dose 72 Gy in 42 fractions).	All first-line, definitive treatments with: RT+C All cetuximab dosages observed in daily practice. Protocol was dosing as in trial: 400mg/m² one week before start RT, followed by weekly 250mg/m². In 39% (n=12) planned cetuximab regimens were abandoned during the course of treatment. RT alone All RT fractionation regimens observed in daily practice. Preferred regimen was accelerated RT, total dose 70 Gy in 35 fractions, 6 fractions/week.
Number of patients	211 213	61 80

III

Table 3.1. Comparison of the trial (EMR 62202-006) and Outcomes Research (continued)

	Trial		Outcomes Research	
	RT+C	RT alone	RT+C	RT alone
Age – yr				
Median	56	58	65	62
Range	34-81	35-83	42-83	40-87
Disease stage				
III	55 (26%)	52 (24%)	16 (26%)	35 (44%)
IV	156 (74%)	161 (76%)	45 (74%)	45 (56%)
Tumour site				
Oropharynx	118 (56%)	135 (63%)	32 (53%)	20 (25%)
Larynx	57 (27%)	51 (24%)	6 (10%)	56 (70%)
Hypopharynx	36 (17%)	27 (13%)	23 (38%)	4 (5%)
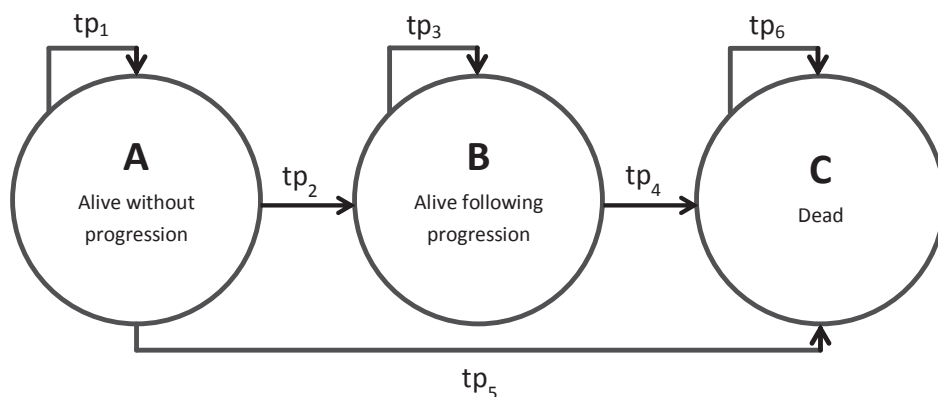
Figure 3.1. Schematic of the Markov model.

The Markov model assumes that a patient is always in one of three discrete health states: A (alive without progression), B (alive following progression) or C (dead). Events are represented as transitions from one state to another:

tp_1 = transition probability of staying in state A (alive without progression)

tp_2 = transition probability of moving from state A (alive without progression) to state B (alive following progression): estimated by subtracting tp_5 and tp_1 from 1

tp_3 = transition probability of staying in state B (alive following progression): estimated by subtracting tp_4 from 1

tp_4 = transition probability of moving from state B (alive following progression) to state C (dead)

tp_5 = transition probability of moving from state A (alive without progression) to state C (dead)

tp_6 = all patients entering state C (dead), stayed in state C (absorbing state)

Scenario 1

In scenario 1, transition probabilities were based on (1) the progression-free survival curve to estimate tp_1 and (2) the survival before progression curve to estimate tp_5, and (3) the updated survival following progression curve to estimate tp_4, supplemented with Dutch life tables for extrapolated transition probabilities after 5 years. Dutch vital statistics were combined with 25% excess mortality, since Van der Schroeff et al.[51] showed conditional long-term survival of Dutch SCCHN patients to remain poorer compared to age and sex-matched counterparts in the general population. After four years in the progression health state (B) the transition probability was assumed to equal Dutch age-matched excess-adjusted background mortality. The average life expectancy of patients without progression after 5 years was assumed to be equal for both treatment arms. Furthermore, after 5 years of follow-up the probability of progression was assumed to be negligible and equal in both treatment arms.

The cumulative survival data were converted to time dependent transition probabilities using the following formula:

$$Pt = \frac{Pt}{Pt - 1}$$

where Pt and P_{t-1} denote the cumulative probability of surviving at the end of times t and t-1, respectively; Pt denotes the transition probability for time t. After 5 years, the probability of progression (tp_2) was assumed to be zero.

Scenario 2

Scenario 2 differs from scenario 1, on the premise that all RW patients had a less favourable prognosis than patients in the clinical trial. As was shown in the outcomes research, RW patients treated with RT+C had less favourable prognostic characteristics (age, disease stage, tumour site) than the trial patients or the RW RT patients (see chapter I). For scenario 2, this was assumed to result from confounding by indication. This scenario reflects the RW costs and effects of RT+C, as compared to the RW costs and effects of RT for fictitious patients with prognostic characteristics conform the RW RT+C population. The prognosis of patients was adjusted downwards, without altering the relative effect of the two treatments.

In order to do this, patients in both arms were considered to progress and die 1.5 times earlier than patients in the same treatment arm of the trial. The factor 1.5 reflects the difference between the trial survival curve of patients treated with RT+C[11,38] and the outcomes research survival curve of RW patients treated with RT+C (chapter II). Hazard of progression and death were equally reduced for both treatment arms, combining trial outcomes on efficacy with real-world information on prognosis.[52,53]

Model input—health state utilities

Since quality of life was not measured in the trial, health utility scores for the base case were derived from a study among the nursing staff from British oncology centres (n=50), using EQ-5D.[54] Utility scores are values reflecting the preferences for different health outcomes on an interval scale from zero to one. Utilities were estimated for 11 health states, 9 of which described toxicities, based on the National Cancer Institute common toxicity criteria for adverse events. The two remaining health states correspond to treatment success and treatment failure.

For the cost-effectiveness analysis, the utility estimates for the "progression-free state" (A) and the "progressed state" (B) were assumed to correspond to the utilities of "treatment success" (0.862) and "treatment failure" (0.284), respectively. Utility experienced during treatment was assumed to be a weighted average, derived by assigning a utility score to each patient within the trial, based on experienced toxicities per person per treatment arm

and average event duration. In case of multiple simultaneous toxicities, the toxicity with the lowest utility was used to inform the quality of life analyses. Utilities associated with adverse event health states ranged from 0.101 (grade IV haematological toxicity) to 0.659 (range of grade 0–1 toxicities).

Model input—costs

For CE modelling purposes, total treatment costs were assumed to take place in the first Markov cycle. The cost analysis was conducted using a hospital perspective. Costs were obtained by multiplying the quantity of healthcare resources consumed with the unit costs. Resource consumption was based on actual use in the outcomes study and included RW patient-level cetuximab use, RT, inpatient hospital days, intensive care days, outpatient visits, daycare treatments, consultations by telephone, laboratory services, medical imaging services, medical tests and procedures and pathology. Unit costs calculations of inpatient hospital days and intensive care days, outpatient visits, daycare treatments and consultations by telephone were based on detailed microcosting studies reflecting full hospital costs, including overhead costs.[55-57] Resource use of radiotherapy, imaging services, tests, procedures and pathology was valued using tariffs issued by the NZa (Dutch Healthcare Authority). Costs for laboratory services were based on expert opinion. Costs were grouped into "treatment costs", "follow-up costs" (after treatment, before progression) and "post-progression costs". Costs were reported in 2011 Euros. Detailed cost input and results are published as a supplement to this manuscript.

Mean total treatment costs in the RT+C and in the comparator group were estimated at €24,714 (SD €9,695) and €12,862 (SD €11,713), respectively. During the First 2 years of follow-up, monthly costs of €597 were applied. This estimate was derived from our outcomes research and independent of treatment group. In subsequent cycles, from year 3 to 5, no data from outcomes research were available. Here, a monthly cost of follow-up of €57 was estimated, based on expected resource use according to current Dutch guidelines.[34-36]

Mean total post-progression costs gathered in our RW study were estimated at €18,244 (SD €30,475) per patient and assumed independent of treatment group. Mean duration of stay in health state B (alive following progression) was 6.75 months, resulting in a cost estimate of €2,703 per cycle in state B.

Sensitivity analyses

For each scenario and for each time horizon, univariate sensitivity analyses were performed to examine the impact of alternative parametric assumptions on the estimated incremental cost-effectiveness ratios (ICERs), without and with discounting. Parameters were: hazard

ratio for PFS corresponding to the lower (scenario B) and higher limit (scenario C) of the 95% confidence interval found in the pivotal trial, indirect medical costs (scenario D), drug spillage (scenario E), costs of follow-up and disease progression (scenario F) and utility scores based on outcomes study results (scenario G). Parameter inputs for all sensitivity analyses are presented in Table 3.4.

A probabilistic sensitivity analysis (PSA) explored effects of the joint uncertainty across model input parameters in a single analysis. Each model parameter was assigned a unique probability distribution based upon estimates of uncertainty (Table 3.2). Monte Carlo simulations (10,000 cycles) yielded distributions of lifetime costs and health outcomes for each scenario. PSA results are presented per scenario as incremental cost-effectiveness planes and acceptability curves.

RESULTS

Output of the Markov model matches the results of the trial (Figure 3.2) and is combined with RW data to estimate RW cost-effectiveness. Expected discounted costs and health outcomes are reported for both scenarios and three time horizons. All scenarios and time horizons show the addition of cetuximab to RT result in increased costs, while yielding additional LYs and QALYs (Table 3.3). The incremental costs gained range from €14,624 to €38,543 per QALY gained and from €11,640 to €32,405 per LYG.

Sensitivity analyses

ICERs are robust for all alternative assumptions with the exception of adaptation of the hazard ratio for PFS to the higher limit of the 95% confidence interval found in the trial (scenario C) (Table 3.4).

Scatter plots reveal outliers in the lower right quadrants of the cost-effectiveness planes, due to bootstrapping of the treatment cost input (Figure 3.3). At a willingness to pay of €80,000 per QALY gained, a threshold suggested by the Dutch council for Public Health and care (RVZ)[58], the acceptability curves (Figure 3.4) of the different scenarios show probabilities between 0.76 and 0.87 of RT+C being cost-effective when compared to RT.

III

Table 3.2. Input parameters of the model

Transitional probability parameters	Distribution	Parameters		Source
		Alpha	Beta	
Probabilities of progression, tp_2 (time-dependent, times 1.5 for scenario 2)	Beta	Derived from Kaplan-Meier PFS curves & number of patients at risk		Trial
Probabilities of moving from progressed state to dead, tp_4 (time-dependent, times 1.5 for scenario 2)	Beta	Derived from Kaplan-Meier PFS curves & number of patients at risk		Trial
Probabilities of moving from alive without progression to dead, tp_5 (time-dependent, times 1.5 for scenario 2)	Beta	Derived from Kaplan-Meier OS curves & number of patients at risk		Trial
		Mean	SD	
Logarithm of the Hazard Ratio of PFS RT+C versus RT alone HR = 0.70 (95% CI 0.54-0.9)	Normal	-3.57	0.132	Trial
Cost parameters*				
		Mean		
Treatment costs, RT alone	Bootstrapping	€12,862	€11,713	Outcomes study
Treatment costs, RT+C	Bootstrapping	€24,714	€9,695	Outcomes study
		Mean		
Costs of follow-up, first 2 years / month	Triangular (±30%)	€597.47		Outcomes study
Costs of follow-up, year 3-5 / month	Triangular (±30%)	€57.00		Oncoline
Costs of relapse / month	Triangular (±30%)	€2702.81		Outcomes study

Table 3.2. Input parameters of the model (continued)

Transitional probability parameters	Distribution	Parameters		Source
		Alpha	Beta	
Utility values		Mean		
Utility of being on RT treatment	Triangular (±30%)	0.30**		Trial + M-TAG utility study
Utility of being on RT+C treatment	Triangular (±30%)	0.28**		Trial + M-TAG utility study
		Mean	SD	
Utility of being in follow-up	Normal	0.86	0.019	M-TAG utility study
Utility of being in relapse	Normal	0.28	0.04	M-TAG utility study

*Main unit costs: radiotherapy €8,840, cetuximab €209 per 100mg, inpatient hospital day €666, intensive care day €2,107, day-care treatment €225, outpatient visit €127.

**Average of utilities for toxicity-based health states, weighted by event duration per trial subject. As derived from the M-TAG utility study [7], health states and associated utilities are: "range of effects (grade 0-1), 0.659±0.131", "mucositis (grade 3 and 4), 0.062±0.299", "mucositis (grade 2), 0.608±0.310", "nausea (grade 3 and 4), 0.108±0.350", "nausea (grade 2), 0.573±0.247", "acne/rash (grade 3 and 4), 0.226±0.404", "haematological (grade 4), 0.101±0.392", "peripheral neuropathy, 0.473±0.266" and "ototoxicity, 0.657±0.239".
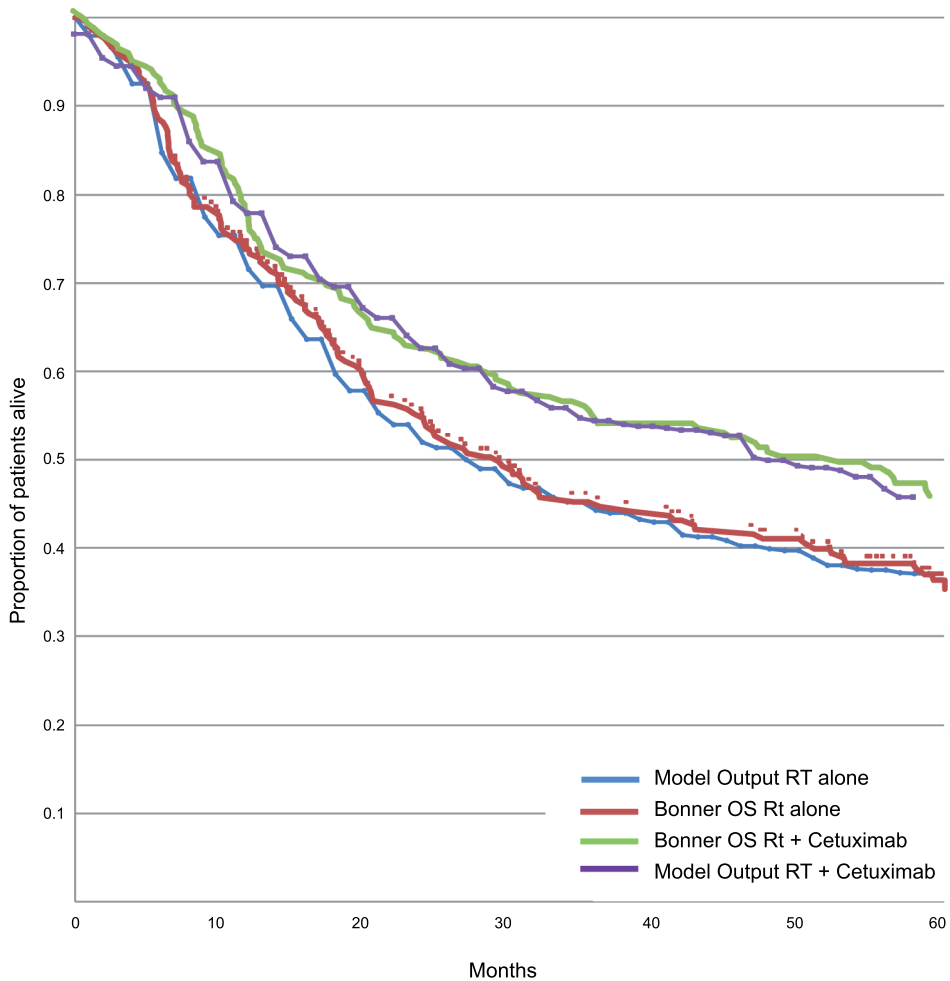
Figure 3.2. Model validation; undiscounted results from modelled OS versus trial OS, per treatment group.
To test the internal validity of the Markov model, for both treatment strategies the modeled survival results (blue and purple lines) were compared with the observed survival results from the clinical trial data (red and green lines).

Table 3.3. Summary of the cost-effectiveness results, discounted

Discounting: 4% for costs, 1.5% for effects

Time horizon	Scenario	Treatment	Mean Costs	Incremental Costs	Mean QALYs (LYs)		Incremental QALYs (LYs)		Incremental costs per QALY (LY) gained	
5 year	1	RT	€39.685	€12.131	1,962	(2,753)	0,328	(0,412)	€36.985	(€29.444)
		RT+C	€51.816		2,290	(3,165)				
	2	RT	€40.599	€13.837	1,420	(2,190)	0,359	(0,427)	€38.543	(€32.405)
		RT+C	€54.436		1,779	(2,617)				
10 year	1	RT	€46.801	€13.620	3,152	(4,331)	0,605	(0,728)	€22.512	(€18.709)
		RT+C	€60.421		3,757	(5,059)				
	2	RT	€47.617	€16.797	2,096	(3,190)	0,572	(0,744)	€29.365	(€22.577)
		RT+C	€64.414		2,668	(3,934)				
Lifetime	1	RT	€57.866	€17.914	5,737	(7,757)	1,225	(1,539)	€14.624	(€11.640)
		RT+C	€75.780		6,962	(9,296)				
	2	RT	€60.534	€21.892	3,574	(5,326)	1,140	(1,588)	€19.204	(€13.786)
		RT+C	€82.426		4,714	(6,914)				

This table shows the cost-effectiveness modelling outcomes for all time horizons and both base-case scenarios. Discounted mean costs (in €) and effects (in QALYs as well as LYs) are presented per treatment alternative. Incremental costs, incremental effects and incremental cost-effectiveness ratios are presented for RT+C as compared with RT alone.

Table 3.4: Sensitivity analyses results

Discounting: 4% for costs, 1.5% for effects									
Parameter	Base-case	Sensitivity analysis	ICER per QALY gained 5 year		ICER per QALY gained 10 year		ICER per QALY gained Lifetime		
			Scenario 1	Scenario 2	Scenario 1	Scenario 2	Scenario 1	Scenario 2	
A Base-case	–	–	€36,985	€38,543	€22,512	€29,365	€14,624	€19,203	
B Hazard ratio PFS	0.70	0.54[1]	€17,525	€18,325	€9,189	€8,799	€4,033	€5,080	
C Hazard ratio PFS	0.70	0.90[2]	€671,636	€85,016	-€347,347	-€179,459	€644,370	€107,355	
D Indirect medical costs (PAID)									
Mean costs / month	€0 (excluded)	€685	€47,015	€48,642	€33,496	€38,353	€20,288	€23,770	
Mean costs last year of life	€0 (excluded)	€29,024							
E Costs of treatment, no spillage	€24,714	€24,251	€36,577	€38,994	€22,335	€28,566	€15,676	€17,196	
F Costs									
Follow-up year 1 & 2 / month	€597	€124	€35,180	€36,089	€19,837	€22,666	€11,332	€13,026	
Follow-up year 3, 4 & 5 / month	€57	€57							
Progression / month	€2,703	€417							
G Utilities									
Utility "alive without progression"	0.86[4]	0.83[5]	€47,406	€41,224	€28,207	€23,791	€17,067	€14,651	
Utility "alive following progression"	0.28[4]	0.49[5]							

This table shows the cost-effectiveness modelling results for the base-case (A) as well as six sensitivity analyses (B to G). In the sensitivity analyses, separate model inputs were changed to the values described in column 4, to evaluate the effect on the incremental cost-effectiveness ratios (ICERs) for RT+C as compared with RT alone.

[1] = lower limit of trial PFS 95% CI [2,3]
[2] = upper limit of trial PFS 95% CI [2,3]
[3] = these costs reflect (unpublished) estimates previously submitted to the Dutch appraisal authorities
[4] = M-TAG utility study [7]
[5] = Dutch outcomes research patients, converted QLQ C30 scores
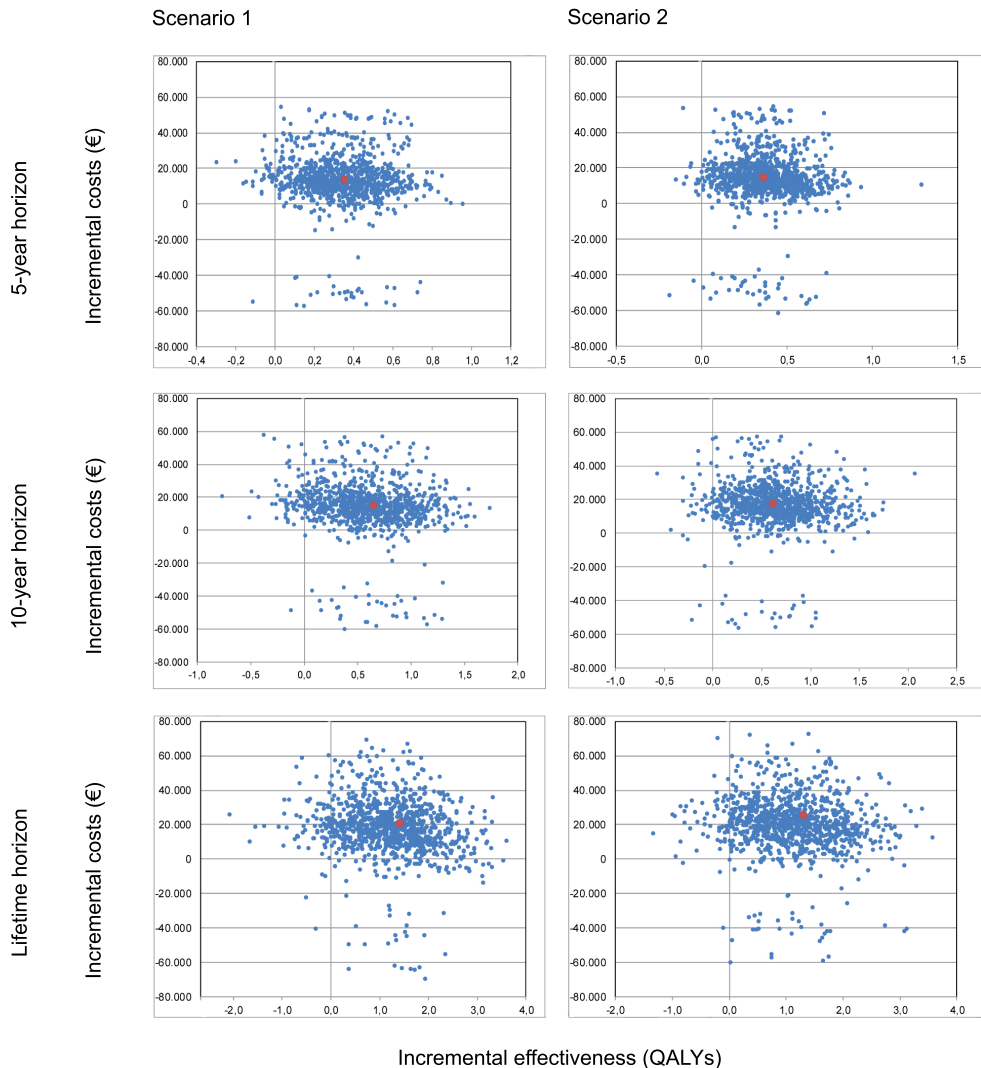
Figure 3.3. Cost-effectiveness planes for RT+C (radiotherapy+cetuximab) versus RT alone, by scenario. These cost-effectiveness planes show the incremental cost-effectiveness point estimates (red dots) as well as the bootstrapped incremental costs and effect pairs (blue dots). These scatter plots illustrate the uncertainty surrounding the estimates of expected costs and effects of RT+C compared to RT alone, for two scenarios and three time horizons.
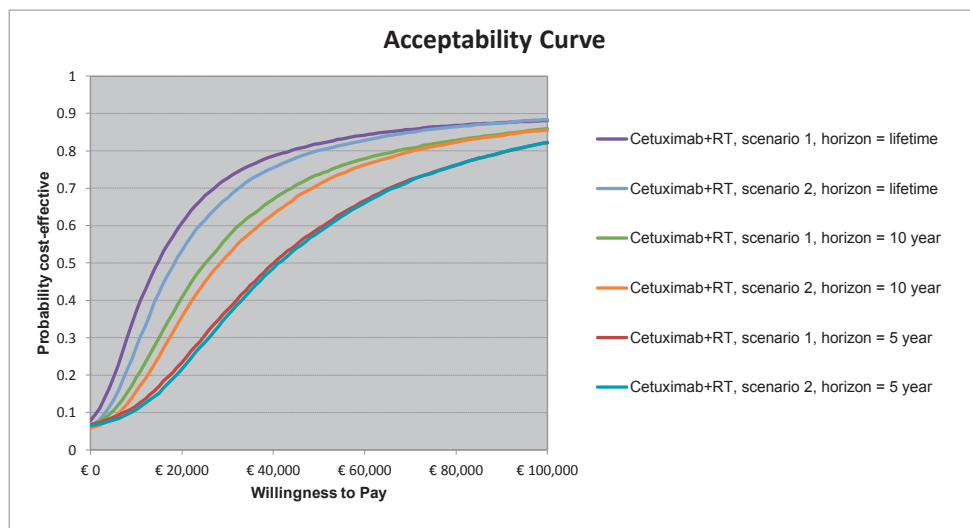
Figure 3.4. Cost-effectiveness acceptability curves for RT+C (radiotherapy+cetuximab) versus RT alone, by scenario.

These acceptability curves show the probability that RT+C is cost-effective compared with RT alone, for a range of monetary values that a decision-maker might consider the maximum acceptable cost-effectiveness ratio.

DISCUSSION

Cost-effectiveness results of both base case scenarios suggest that RT+C therapy provides good value for money when compared to RT. As cetuximab increases survival, the incremental costs per QALY gained decrease along extended time horizons. Incremental costs per QALY are higher for scenario 2 than for scenario 1. The RW study shows that patients in the RT+C group had relatively poor prognostic characteristics; it is likely the ICERs of scenario 2 better reflect cost-effectiveness of RT+C in daily practice than scenario 1.

Cost-effectiveness of RT+C has been previously reported.[59-62] Using patient data from EMR 62202-006 as a starting point for CE modelling, Brown et al. performed analyses for Belgium, France, Italy, Switzerland and England, with country-specific unit cost data.[61] Based on clinical expert opinion, medical resource use from the Bonner trial was translated to country-specific estimates. Costs were determined from the applicable health system perspective or major national payer perspective. For patients alive at the end of the trial, costs and effects were extrapolated using parametric survival models. It was assumed some patients had been cured and would therefore never experience progression or death related to SCCHN.

With a lifetime horizon and 3.5% discounting of costs and effects, estimated ICERs ranged from €7,538 (Italy) to €10,836 (France) per QALY. In our scenario 1, which best resembles that scenario (lifetime horizon, discounting 4% for costs, 1.5% for effects), we calculated an ICER of €14,624 per QALY. The difference is explained by the different model assumptions[61] and the measurement of actual Dutch RW costs vs. costs based on trial data, clinical practice norms and expert opinion.

Limitations of our outcomes study were discussed elsewhere (chapter II) and include relying on retrospective chart review to obtain RW data. Information was collected in only two large academic hospitals. As head and neck cancer care in the Netherlands is highly centralised, treatment there is considered standard practice.[13]

Furthermore, the combined use of RW and trial data was required to obtain effect estimates, due to the lack of a suitable comparator group in daily practice (chapter II). Such a synthesis approach has been taken more often to inform cost-effectiveness modelling[52,53], yet this does not solve the issues surrounding the paucity of data on RW effectiveness.

Selection and matching of patient samples for resource use estimates eliminated part of the significant differences in baseline characteristics between treatment groups in our outcomes study. However, selective allocation to treatment in daily practice limited our options for near-perfect matching. In RW, hypopharyngeal or oropharyngeal carcinomas are more often treated with RT+C, while laryngeal carcinomas are more often subject to RT treatment alone. Although laryngeal localisation of SCCHN is associated with improved clinical outcomes and prognosis, it is unlikely this resulted in a bias in resource use between groups beyond initial treatment. Next to treatment costs, costs relating to follow-up and progression were determined for the patient group as a whole.

Uncertainty around the outcome estimates, reflected in the cost-effectiveness planes was in part determined by the small patient sample size.

We chose a hospital perspective for cost estimates. While indirect costs within the health-care system are evaluated in a univariate sensitivity analysis, non-medical costs were not assessed. For RW patients receiving RT+C included in our study, inclusion of productivity costs would most likely not alter the conclusions. The mean age of these patients is 65 years; few of these patients are expected to return to work.

Since current modelling is partly based on effect estimates obtained in a clinical trial, no conclusions can be drawn directly regarding the incremental effectiveness of cetuximab

in daily clinical practice. However, current results show RT+C is a potentially cost-effective treatment option for patients with LA SSCHN, for each of the scenarios. Presented data, in addition to data on appropriate use of the drug (chapter II), informs decisions on continued reimbursement of cetuximab for locally advanced SCC of the head and neck.[63]

III

Chapter IV

Treatments and costs for recurrent and/or metastatic squamous cell carcinoma of the head and neck in the Netherlands

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ABSTRACT

For patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN), chemotherapy can prolong life and alleviate symptoms. However, expected gains may be small, not necessarily outweighing considerable toxicity and high costs. Treatment choice is to a large extent dependent on preferences of doctors and patients and data on these choices are scarce. The purpose of this study is to obtain real-world information on palliative systemic treatment and costs of R/M SCCHN in the Netherlands.

In six Dutch head and neck treatment centres, data were collected on patient and tumour characteristics, treatment patterns, disease progression, survival, adverse events, and resource use for R/M SCCHN, between 2006 and 2013.

Hundred and twenty-five (14%) out of 893 R/M SCCHN patients received palliative, non-trial first-line systemic treatment, mainly platinum+5FU+cetuximab (32%), other platinum-based combination therapy (13%), methotrexate monotherapy (27%) and capecitabine monotherapy (14%). Median progression-free survival and overall survival were 3.4 and 6.0 months, respectively. Thirty-four (27%) patients experienced severe adverse events. Mean total hospital costs ranged from €10,075 (±€9,891) (methotrexate monotherapy) to €39,459 (±€21,149) (platinum+5FU+cetuximab). Primary cost drivers were hospital stays and anti-cancer drug treatments.

Major healthcare utilisation and costs are involved in systemically treating R/M SCCHN patients with a limited survival.

INTRODUCTION

In the Netherlands, 2,970 new cases of head and neck cancer were diagnosed in 2011, approximately 1 per 6,000 inhabitants.[7] In up to 90% of cases, this concerns squamous cell carcinoma (SCCHN).[64] Approximately 17% of SCCHN patients develop local tumour recurrence, 10% of patients develop regional tumour recurrence and 11% progress to distant metastatic disease.[65] Distant metastases are present at initial diagnosis in 1.8% of patients.[65] Median survival for patients with recurrent and/or metastatic SCCHN (R/M SCCHN) is 6–9 months.[66]

For some patients with locoregional tumour recurrence, surgery or radiotherapy may still cure the disease.[67] For patients with non-curable locoregional tumour recurrence and patients with distant metastasis, palliation may be offered by surgery, radiotherapy, photodynamic therapy (PDT), or systemic treatment.

Radiotherapy may be used for locoregional recurrent tumours for radiation naïve patients or when re-irradiation is possible, typically with curative intent. Radiotherapy is also the mainstay therapy to treat symptomatic bone metastases. Systemic treatment may be used for the palliative treatment of locoregional recurrent disease and/or distantly metastasised tumours. However, this treatment is only considered in case of good performance status and symptoms related to tumour growth. The primary aim of palliative chemotherapy is to alleviate symptoms.[34-36]

Active pharmaceutical agents registered for palliative treatment in R/M SCCHN include the platinum compounds (cisplatin and carboplatin), 5-fluorouracil (5FU), methotrexate, taxanes, bleomycin, and the monoclonal antibody cetuximab.[37] They can be used as monotherapy or in various combination regimens. No new compounds have been identified in the past 5 years that demonstrate clinical benefit in late stage clinical trials.

Historically, the usual first-line treatment for incurable SCCHN has been combination chemotherapy with cisplatin and 5FU. For clinically fit patients (performance score 0–1), international guidelines[37,68] advise treatment with platinum+5FU+cetuximab. Cetuximab, an EGFR inhibitor added to platinum-5FU, increased overall survival (median 10.1 vs. 7.4 months) and progression-free survival (median 5.6 vs. 3.3 months) in a randomised controlled phase III trial.[12] In November 2009, the scientific committee (CieBOM) of the Dutch Association for Medical Oncology (NVMO) considered addition of cetuximab to platinum-5FU to provide added therapeutic benefit for clinically fit patients with R/M SCCHN.[69]

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Treatment with single agents may be offered to patients who may not tolerate combination chemotherapy. For these patients, Dutch guidelines recommend methotrexate monotherapy. Although response percentages with methotrexate are lower than with platinum-5FU, overall survival is similar.[70]

Due to possible side effects and limited clinical benefit of palliative systemic treatment in R/M SCCHN, treatment choice is, to a large extent dependent on individual preferences of doctors and their patients. In the Netherlands, a lack of data exists on daily practice treatment patterns, survival, adverse events and costs associated with management of R/M SCCHN. The aim of this study is to provide insight into these outcome measures.

METHODS

Data collection

More than 90% of SCCHN patients are treated in one of the head and neck treatment centre[13], making head and neck cancer care a highly centralised field of medicine in the Netherlands. A retrospective, observational study was conducted in six of a total of eight Dutch head and neck treatment centres. Patients were identified from hospital and pharmacy databases.

Medical charts were reviewed for patients diagnosed with recurrent and/or metastatic (M+) squamous cell carcinoma of the head and neck (ICD-O C01–C14 and C30–C32) between January 1, 2006 and July 3, 2013. Recurrence was defined as occurring within 2 cm of the original tumour or lymph node site and within 5 years after primary treatment of the initial, usually locally advanced, tumour. Data on all local and systemic treatments were recorded on case report forms. For all study patients with at least one line of palliative, non-trial systemic treatment, additional patient and tumour characteristics, treatment details, resource use and clinical outcomes were collected. Information on treatment history was collected as well, but not used for selection purposes. Patients who only received systemic treatment in a clinical trial (n=20), were excluded from this extensive data collection since we aimed to present real-world, daily practice treatment patterns and outcomes. For patients treated in trials, management and therefore resource use are usually guided by the trial protocol and, therefore, not representative of daily practice.

Comorbidity was determined from medical records, measured at baseline, using the updated Charlson comorbidity index. This index is valid for head and neck cancer patients and predicts the 1-year in-hospital mortality based on comorbidity.[71,72]

Clinical outcomes

Overall survival (OS) was defined as the duration between date of treatment start (for the first palliative, systemic, non-trial treatment) and date of death as registered in the hospital record. For none of the patients a cause of death other than head and neck cancer was registered. Progression-free survival (PFS) was defined as the time from treatment start to disease progression, defined as: (1) clinical or radiological progression of recurrent tumour and/or distant metastases; (2) start of new treatment (with the exception of treatment change due to toxicity); or (3) death, whichever occurred first. A second primary tumour was not classified as disease progression.

Adverse events (AEs) reported in the patient chart and graded by a physician were recorded using the Common Terminology Criteria for Adverse Events (case report form based on CTC version 4.03). Adverse events for which no grade was provided were recorded as severe adverse events if they resulted in hospital admission or dose reduction, postponement or change of treatment. No AE information was derived from laboratory values or administered treatments.

Economic outcomes

Resource use included inpatient hospital days, daycare hospital admissions, outpatient visits, drug usage, radiotherapy, surgery and other invasive procedures, laboratory diagnostics, imaging and pathology. Drug use other than anti-cancer drugs, including treatments for adverse events, was determined in a sub-selection of patients (n=49), for reasons of feasibility. Mean per patient treatment costs were calculated combining resource use and unit costs, derived from literature[55,56] or official tariff lists. Treatment costs were calculated from start of the respective treatment onwards and include all subsequent resource use. Costs are reported from the head and neck cancer centre perspective, in Euros. Unit costs are from 2013 or were inflated to reflect the 2013 price level.

Analyses

Descriptive analyses were performed in IBM SPSS Statistics 21. The Kaplan Meier method was used for survival estimates.

RESULTS

Treatment patterns

Eight hundred and ninety-three patients diagnosed with R/M SCCHN were identified (Figure 4.1), twenty of whom received systemic trial treatment only. If patients received trial
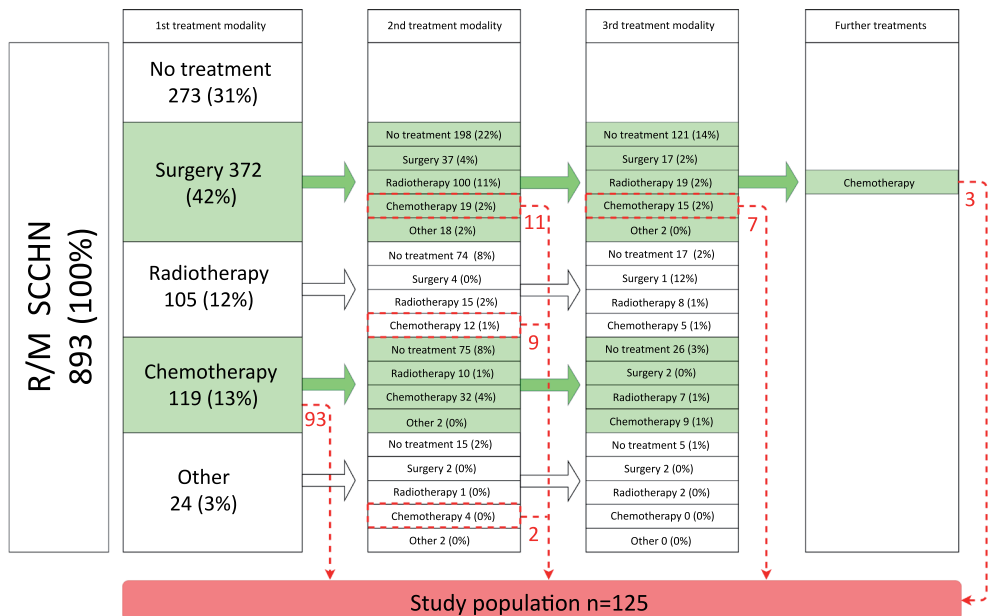
Figure 4.1. Treatment patterns for R/M SCCHN patients. The numbers with the dotted lines represent eligible patients, therefore included in the study. For the sake of readability, treatments after the third line were not further specified.

treatment at one point in time but non-trial systemic treatment at another point in time, these patients were included from start of the non-trial treatment onwards (costs for trial treatment are set to €0 from a hospital perspective). Two hundred and seventy-three patients received no antitumour treatment at all. Hundred and twenty-five patients received at least one line of palliative, non-trial systemic treatment and were included in the study. Of these 125 study patients, 7 patients had metastasised SCCHN at primary diagnosis and 118 patients had R/M SCCHN after primary treatment. Ninety-three study patients received non-trial systemic treatment as first treatment after diagnosis of R/M SCCHN and 32 study patients as second, third or fourth treatment.

Treatment characteristics

Multiple treatment modalities were administered (Figure 4.1). The most common first-line systemic treatment choices (Table 4.1) were platinum+5FU+cetuximab (n=40, 32%), other platinum-based combination therapies (n=16, 13%), methotrexate monotherapy (n=34, 27%) and capecitabine monotherapy (n=18, 14%). An example of an "other" first-line drug therapy was platinum monotherapy (n=9). Patients treated with first-line platinum-based combination therapy without cetuximab received platinum+fluorouracil (n=6), cisplatin+gemcitabine (n=4), platinum+capecitabine (n=2), and other platinum combination regimens (n=4).

Table 4.1: Drug treatment in daily practice

Treatment	First systemic treatment line (n=125)	Second systemic treatment line (n=39)
Platinum + 5FU + cetuximab	40 (32%)	4 (10%)
Other platinum-based combination therapy	16 (13%)	1 (3%)
Methotrexate monotherapy	34 (27%)	15 (38%)
Capecitabine monotherapy	18 (14%)	7 (18%)
Other	17 (14%)	12 (31%)

The percentage of patients treated with platinum+5FU+cetuximab has increased steeply since 2010 (data not presented), following a positive decision on reimbursement. In patients receiving platinum+5FU+cetuximab, 40 patients (32%) received this combination in first line, 4 (10%) in second line, and 0 (0%) in subsequent treatment lines. Other platinum-based combination therapies were administered to 16 patients (13%) as first-line therapy and to 1 (3%) in second line. This regimen was administered as subsequent treatment to 1 patient (14%).

In the second systemic treatment line, methotrexate monotherapy was the most frequently prescribed drug regimen.

Patient and tumour characteristics

Patient and tumour characteristics are depicted in Table 4.2. Seventy-four percent of patients were male and the median age was 60. Unfortunately, performance status was not routinely registered in all medical charts.

Survival measures

Table 4.3 shows PFS and OS per treatment group, from treatment start onwards, without correction for baseline characteristics. Median PFS and OS for the cohort studied were 3.4 and 6.0 months, respectively. Due to heterogeneity, possibilities for matching on baseline characteristics were limited and did not solve the issue of confounding by indication. Therefore, survival estimates should be interpreted as descriptive of the respective treatment groups rather than measures of treatment effect. Wide, overlapping confidence intervals reflect non-significance of the survival differences, due to small size of the treatment groups.

Due to heterogeneity, possibilities for matching on baseline characteristics were limited and did not solve the issue of confounding by indication. Therefore, survival estimates should be interpreted as descriptive of the respective treatment groups rather than measures of treatment effect.

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Table 4.2: Patient and tumour characteristics, stratified by first systemic treatment line group

		Total	Platinum + 5FU + cetuximab	Platinum-based combination therapy	Methotrexate monotherapy	Capecitabine monotherapy	Other
		n=125	n=40	n=16	n=34	n=18	n=17
Sex, n (%)	Male	92 (74)	28 (70)	9 (56)	27 (79)	13 (72)	15 (88)
Median age		60	58	57	62	62	60
Age n (%)	<65 yr	90 (72)	33 (83)	14 (88)	21 (62)	11 (61)	11 (65)
	≥65 yr	35 (28)	7 (18)	2 (13)	13 (38)	7 (39)	6 (35)
Tumour site n (%)	Oropharynx	38 (30)	10 (25)	6 (38)	11 (32)	6 (33)	5 (29)
	Hypopharynx	21 (17)	5 (13)	2 (13)	5 (15)	1 (6)	8 (47)
	Larynx	17 (14)	5 (13)	1 (6)	9 (27)	2 (11)	0 (0)
	Oral cavity	34 (27)	16 (40)	2 (13)	9 (27)	5 (28)	2 (12)
	Nasopharynx	10 (8)	2 (5)	5 (31)	0 (0)	1 (6)	2 (12)
	Other	5 (4)	2 (5)	0 (0)	0 (0)	3 (17)	0 (0)
Extent of disease n (%)	Locoregionally recurrent	58 (47)	20 (50)	6 (38)	18 (53)	9 (50)	5 (29)
	Metastatic with or without locoregional recurrence	67 (54)	20 (50)	10 (63)	16 (47)	9 (50)	12 (71)
Location of distant metastases n (%)	Bone(s)	18 (14)	7 (18)	5 (31)	2 (6)	2 (11)	2 (12)
	Lung	54 (43)	16 (40)	7 (44)	15 (44)	6 (33)	10 (59)
	Liver	15 (12)	5 (13)	5 (31)	1 (3)	1 (6)	3 (18)
	Lymph nodes	24 (19)	10 (25)	3 (19)	6 (18)	2 (11)	3 (18)
	Skin	13 (10)	8 (20)	1 (6)	1 (3)	2 (11)	1 (6)
	Other	10 (8)	4 (10)	1 (6)	3 (9)	2 (11)	0 (0)

Table 4.2: Patient and tumour characteristics, stratified by first systemic treatment line group (continued)

		Total	Platinum + 5FU + cetuximab	Platinum-based combination therapy	Methotrexate monotherapy	Capecitabine monotherapy	Other
		n=125	n=40	n=16	n=34	n=18	n=17
Comorbidity n (%)	0	110 (88)	35 (88)	14 (88)	31 (91)	16 (89)	14 (82)
	1	11 (9)	4 (10)	2 (13)	3 (9)	1 (6)	1 (6)
	>1	4 (3)	1 (3)	0 (0)	0 (0)	1 (6)	2 (12)
Previous treatments[a] n (%)	No previous treatments	11 (9)	6 (15)	2 (13)	2 (6)	0 (0)	1 (6)
	Surgery(s) and or radiotherapy(s) only	73 (58)	25 (63)	8 (50)	22 (65)	8 (44)	10 (59)
	Chemoradiation	37 (30)	9 (23)	6 (38)	9 (27)	8 (44)	5 (29)
	Chemotherapy	3 (2)	1 (3)	0 (0)	0 (0)	1 (6)	1 (6)
	Any cetuximab	3 (2)	0 (0)	0 (0)	1 (3)	1 (6)	1 (6)
Months between initial diagnosis SCCHN and diagnosis R/M SCCHN Mean, SD		15.6, 17.5	14.2, 16.5	20.6, 25.1	18.8, 19.9	13.2, 7.0	17.3, 14.0
Months between diagnosis R/M SCCHN and start first palliative systemic therapy Mean, SD		3.9, 6.1	4.1, 6.9	3.9, 7.6	4.0, 4.7	4.3, 8.0	2.6, 2.2

[a] Antitumour treatments for SCCHN before diagnosis of recurrence and/or metastasis. Treatment history was not a selection criterion for this study.

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Table 4.3: Overall survival and progression free survival per treatment group

First systemic treatment line	Overall survival Median (95% CI)	Progression-free survival Median (95% CI)
Platinum+5FU+cetuximab (n=40)	6.7 (4.4 – 8.9)	4.8 (3.2 – 6.4)
Other platinum-based combination therapy (n=16)	10.5 (5.8 – 15.1)	4.0 (3.5 – 4.4)
Methotrexate monotherapy (n=34)	4.8 (3.5 – 6.1)	3.1 (1.9 – 4.3)
Capecitabine monotherapy (n=18)	3.7 (1.4 – 5.9)	1.7 (1.5 – 1.9)
Other (n=17)	5.7 (1.2 – 10.3)	1.6 (0.3 – 2.9)
All (n=125)	6.0 (4.2 – 7.8)	3.4 (2.3 – 4.5)

Due to heterogeneity, possibilities for matching on baseline characteristics were limited and did not solve the issue of confounding by indication. Therefore, survival estimates should be interpreted as descriptive of the respective treatment groups rather than measures of treatment effect.

Adverse events

In the initial palliative treatment line, 34 patients (27%) experienced severe adverse events, defined as any adverse events with registered record of: CTC AE grade ≥3, treatment dose reduction(s), postponement or change of treatment, and/or hospital admission. Twenty-one hospital stays (4% of total hospital stays) resulted from AEs, for a total of 16 patients (13%). Median duration of these hospital stays was 8 days. Severe adverse events were observed more often in patients receiving combination therapy than methotrexate or capecitabine monotherapy (Table 4.4).

Costs

Table 4.5 presents mean costs per treatment group and cost category. Mean total costs per patient were €24,211 (±€22,432), ranging from €10,075 (±€9,891) (methotrexate monotherapy) to €39,459 (±€21,149) (platinum+5FU+cetuximab). Primary cost drivers are hospital stays and drug costs.

Table 4.4: Adverse events

First systemic treatment regimen	Severe adverse events N (%)	Reported severe adverse events *CTC AE grade ≥III, patient was hospitalized, and/or treatment was adapted for toxicity reasons*	Reported non-severe adverse events *CTC AE grade I and grade II[a]*
Cisplatinum +5FU + cetuximab (n=40)	19 (48%)	Anorexia, cardiac toxicity, ear and labyrinth disorder, febrile neutropenia, hand-foot syndrome, nausea, oral mucositis, thrombocytopenia, pneumonia, renal toxicity and skin and subcutaneous tissue disorders.	Acneiform rash, constipation, diarrhea, dehydration, dry skin, fatigue, erythema multiforme, hand-foot syndrome, hypokalemia, mucositis, nausea, other skin and subcutaneous tissue disorders, ototoxicity, pain, papulopustular rash, pruritus, renal disorders and vomiting.
Other platinum-based combi-nation therapy (n=16)	5 (31%)	Diarrhea, febrile neutropenia, renal disorder and vomiting.	Anorexia, dysphagia, dry skin, fatigue, hand-foot syndrome, leukopenia, nausea, pneumonia and vomiting.
Methotrexate monotherapy (n=34)	5 (15%)	Liver toxicity, malaise, neutropenia, and oral mucositis.	Dysphagia, pneumonia, pain and fatigue.
Capecitabine monotherapy (n=18)	0 (0%)	NONE REPORTED	NONE REPORTED
Other (n=17)	5 (29%)	Renal disorders, cardiac disorder, fatigue and constipation.	Alopecia and nausea.

[a] Although these adverse events were only recorded if their severity had been assessed by a physician and reported in the patient file, we could not make a clear distinction between grade I and grade II adverse events due to non-specificity in reporting habits (reading, for example, "headache grade I/II" or "low-grade headache").

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Table 4.5: Costs in 2013 € per treatment group

	Cisplatin + 5FU + cetuximab (n=40) Mean (SD)	Other platinum-based combination therapy (n=16) Mean (SD)	Methotrexate monotherapy (n=34) Mean (SD)	Capecitabine monotherapy (n=18) Mean (SD)	Other (n=17) Mean (SD)	All (n=125) Mean (SD)
In-patient hospital days, €	16,564 (11,396)	18,823 (13,267)	5,752 (7,563)	2,834 (3,874)	8,837 (8,657)	10,884 (11,173)
Intensive care unit days, €	544 (2,572)	0 (0)	58 (339)	0.00 (0.00)	0.00 (0.00)	190 (1,473)
Day-care treatment, €	1,977 (2,601)	2,143 (3,271)	709 (1,039)	1,013 (2,272)	836 (1,170)	1,359 (2,229)
Out-patient visits, €	2,186 (2,153)	4,366 (3,793)	1,260 (2,012)	1,567 (2,282)	655 (972)	1,916 (2,502)
Anticancer drug treatment[a], €	14,938 (9,085)	5,770 (7,375)	731 (1,800)	3,232 (7,468)	4,368 (7,569)	6,777 (9,094)
Concomitant medication[b], €	482 (779) n=12	346 (462) n=4	194 (279) n=14	233 (355) n=8	256 (361) n=11	297 (481) N=49
Palliative anticancer surgery, photodynamic therapy, radiotherapy, €	656 (1,442)	4,307 (6,164)	551 (1,347)	624 (1,427)	1,102 (1,760)	1,151 (2,814)
Laboratory, €	878 (475)	1,274 (1,192)	481 (452)	430 (611)	642 (678)	724 (696)
Imaging, nuclear medicine, procedure, €	1,686 (1,843)	1,849 (1,993)	511 (595)	863 (2,516)	1,039 (1,029)	1,181 (1,711)
Pathology, €	31 (58)	52 (115)	21 (44)	21 (91)	26 (64)	29 (70)
Total[c], €	39,459 (21,149)	38,584 (26,065)	10,075 (9,891)	10,585 (14,544)	17,506 (16,634)	24,211 (22,431)
Duration of period in months	7.3 (6.3)	19.2 (17.9)	6.5 (7.8)	6.0 (5.9)	7.8 (6.4)	8.5 (9.8)
Costs/month	7,537 (4,105)	3,520 (2,692)	3,013 (2,234)	2,779 (4,749)	2,525 (2,038)	4,214 (4,196)

[a] Including drug spillage.

[b] As determined in a side study among a random sample of 49 patients from VU University Medical Centre and University Medical Centre Utrecht, since these hospitals kept electronic medication records with enough detail to determine costs.

[c] Excluding concomitant medication costs, since these were determined for only 39.2% of the patient sample.

DISCUSSION

Relatively few (14%) patients in the Netherlands with R/M SCCHN received palliative systemic treatment. Patient and treatment heterogeneity as well as small sample size prevented us from statistically comparing treatment costs and outcomes. The most frequently prescribed first-line drug regimen consists of cisplatin+5FU+cetuximab, followed by methotrexate monotherapy. In the second systemic treatment line, methotrexate monotherapy is the most frequently prescribed drug regimen. Treatment with single agents is associated with fewer adverse events than combination treatments. The choice of treatment is hospital dependent (stratified data not presented for confidentiality reasons).

A multi-country survey of 256 head and neck specialists in France, Germany, Italy and Spain showed that 72% of R/M SCCHN patients were treated with first-line combination therapy: 65% of these patients were treated with cetuximab containing regimens and 35% with other platinum-based combination chemotherapy. Combination treatment with cetuximab is a common first-line choice in these countries (data published as abstract only).[73] In the Netherlands, head and neck cancer specialists seem to take a more conservative approach with respect to prescribing chemotherapy in general and platinum+5FU+cetuximab in particular (32% of all palliative, first-line, non-trial, systemic regimens). However, the difference could be explained by different study designs, recall bias and possibly a preselected patient population of the head and neck specialists in the multi-country survey. It is likely that survey results provide less reliable information on treatment allocation than medical chart review for all diagnosed R/M SCCHN patients.

For the study population as a whole, median overall survival from diagnosis was 6.0 months. Patients treated with combination platinum regimens other than platinum+5FU+cetuximab live longer, possibly due to their lower age and a higher proportion of tumours that are relatively sensitive to treatment, such as nasopharyngeal carcinomas. Nasopharyngeal carcinomas are a distinct subgroup known to respond differently to treatment than SCCHN in other localisations. They constitute a relatively favourable prognostic group.[74]

Survival of 95% CIs of patients treated with platinum+5FU+cetuximab in Dutch daily practice (median OS 6.7 months, 95% CI 4.4–8.9, median PFS 4.8, 95% CI 3.2–6.4) overlap with those from the EXTREME trial[12] (median OS 10.1 months, 95% CI 8.6–11.2, median PFS 5.6, 95% CI 5.0–6.0) and a retrospective, observational study from Portugal[75] (median OS 11 months, 95% CI 8.7–13.3, median PFS 8, 95% CI 6.1–9.9).

IV

The data presented are the only published evidence on the costs of systemically treated R/M SCCHN in the Netherlands. Hospital stays and chemotherapeutics are the main cost drivers. We report mean costs of management of systemically treated R/M SCCHN of € 24,211. These costs are considerable, yet not as high as published end-of-life healthcare consumption for various cancers in a US study population (inpatient and outpatient costs $70,956, in 2009 USD).[76] For the Netherlands, mean costs of late stage cancer management have not been explored in great detail.

Costs incurred for cancer care do not automatically result in better outcomes.[77] Policy makers, oncologists and public media increasingly express the need to curtail the rise in costs of cancer care. Suggested changes include limiting the use of chemotherapy combination regimens for metastatic cancers and limiting chemotherapy on the basis of performance status.[78] Even disregarding the costs, extensive use of chemotherapy at the end of life can be an important signal of poor quality care.[79] Our study shows relatively few R/M SCCHN patients to receive systemic palliative treatment, which might reflect careful patient selection due to the small expected gains of such treatments, considerable toxicity and high costs.

Still the presented cost estimates raise the question about the value for money that is achieved. Very little is known about this for the R/M SCCHN patient population. There is relatively little high-quality research in these patients, possibly due to rarity of the disease in western countries, heterogeneity within the patient population (amongst others in tumour localisation), lack of new treatment compounds, and difficulties associated with quality of life measurements in end stage cancer patients. To our knowledge, no pharmacoeconomic studies have been published about systemic R/M SCCHN treatments except for cost-effectiveness studies regarding platinum+5FU+cetuximab versus platinum+5FU.[80,81]

Analysis of the cost-effectiveness of systemic treatments in daily practice requires information about (changes in) health-related quality of life and a large enough patient population to compare treatment strategies while correcting for confounding by indication. Preferably these data should be collected within a population-based patient registry, including all newly diagnosed patients with head and neck SCC in the Netherlands. Such a register has the potential to boost the quality of head and neck cancer research and has a reasonable feasibility in the Netherlands due to the centralised nature of head and neck cancer care. However, several challenges exist regarding patient identification as well as patient follow-up in the terminal phase.

Limitations of the study

Squamous cell carcinoma of the head and neck patients form a relatively small and heterogeneous population. This limited possibilities to correct for confounding by indication. As a result the effect of treatment choice on outcomes could not be assessed and only descriptive results were presented.

Furthermore, the level of detail in medical records varied greatly. This prevented uniform capture of several variables, such as performance status and adverse events. For example, the lack of adverse events seen in patients receiving capecitabine monotherapy could be due to a less intensive follow-up since this treatment is self-administered at home. The lack of certain anticipated adverse events, such as hypomagnesaemia with the platinum-based treatments, results from the data managers recording AEs only when explicitly reported by clinicians, without, for example, consulting laboratory values themselves.

Notably, our research was conducted in patients identified through hospital records and focused on treatment in a specialised head and neck centre setting. Some 90% of SCCHN patients in the Netherlands visit these head and neck centres.[13] However, patients who do not seek specialised medical care were not included in this study. Therefore, the proportion of patients not receiving systemic therapy is likely to be underestimated. Furthermore, two out of eight head and neck centres did not participate in the study and might have had different treatment patterns. Also, hospital and pharmacy databases can be incomplete, especially when patients had only few hospital contacts.

Resource consumption of interventions offered outside the study hospital, i.e. for patients referred to other (outpatient) clinics for drug administration, was not recorded. Therefore, presented cost estimates reflect the costs incurred within the head and neck treatment centres. Cost utility of treatments for R/M SCCHN could not be assessed due to a lack of comprehensive outcomes reporting, specifically on quality of life.

CONCLUSION

For systemically treated patients with R/M SCCHN, healthcare utilisation and associated costs are considerable, while the survival is limited.

IV

Chapter V

Treatment and survival of non-small cell lung cancer patients in the Netherlands

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ABSTRACT

Objectives

The aims of this study are to provide insight in treatment patterns in the Netherlands and to analyse differences in survival between academic and non-academic hospitals. Current results will show the state of non-small cell lung cancer (NSCLC) care and survival in the Netherlands and will serve as foundation for future cost- and cost-effectiveness studies of treatment alternatives.

Material and Methods

Data on treatment patterns in Dutch hospitals was obtained from four, not randomly selected hospitals (two academic, two non-academic). A random sample of unselected patients diagnosed with NSCLC from 31 January 2009 until 31 January 2011 was identified through the four hospital databases. Data was obtained on patient characteristics, tumour characteristics, treatments and survival outcomes. Additionally, the Netherlands Cancer Registry provided data on survival for all Dutch hospitals. We compared overall survival for patients treated in different hospital types. We used Kaplan-Meier methods to estimate overall survival rates by hospital type and Cox proportional hazards models to estimate the relative risk of mortality (expressed as hazard ratios, HRs) and their 95% confidence intervals (95% CI) per hospital type, with all non-academic hospitals as the reference group. All statistical tests were two-sided and conducted at the 0.05 level of significance.

Results

For non-metastasised disease, patients treated in academic hospitals had superior overall survival as compared to patients treated in non-academic hospitals. Median survival was 2.66 years (95% CI 2.14-3.18) in academic versus 1.83 years (95% CI 1.73-1.93) in non-academic hospitals. For metastasised disease, median survival was 0.41 years (95% CI 0.35-0.48) in academic versus 0.39 years (95% CI 0.38-0.41) in non-academic hospitals.

Conclusion

Patients treated in academic hospitals have better median overall survival than patients treated in non-academic hospitals, mainly due to differences in overall survival for patients treated with radiotherapy, systemic treatment or combinations.

INTRODUCTION

Incidence as well as mortality from lung cancer is relatively high in the Netherlands. In 2012, lung cancer incidence was 66.1 in males and 44.5 in females per 100.000 person years (European Standardised Rates). Lung cancer mortality was 59.6 males and 35.6 females per 100.000 person years.[82]

More than 85% of lung cancers are from the non-small cell type.[7] 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 only between 45% and 50%. Unfortunately, only 20% of the patients is eligible for a tumour 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 tumour is located centrally.[20]

Alternatively, concurrent chemo-radiotherapy is the standard treatment option for inoperable non-metastatic patients. There is evidence from a meta-analysis that radiotherapy with concurrent chemotherapy reduces locally recurrent disease and mortality compared to sequential chemo-radiotherapy.[84] 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%.[85]

Within the Netherlands, differences exist between hospitals with respect to treatment and survival of patients with NSCLC. For patients diagnosed with stage I and II NSCLC in 2001-2006, the probability of tumour resection increased with the surgical experience (lung resection volume) of the hospital as well as the available expertise.[86] Therefore, minimum surgical volumes and various other conditions have been agreed upon to concentrate lung resections in specialised centres.[87]

For stage III NSCLC, probability of receiving combination treatment in the Netherlands was highly dependent on hospital as well, but no correlation was demonstrated with defined structural hospital characteristics such as teaching status or the availability of radiotherapy facilities.[86] The same was true for the probability of receiving chemotherapy for stage IV NSCLC.[88] Unfortunately, it was not reported if and how treatment variability between hospitals affected overall survival.

Apart from the minimum surgical volumes, also broader standards exist for Dutch hospitals treating patients with lung carcinoma. They include requirements regarding (multidisciplinary) staff composition and available facilities.[14] Further, a Dutch evidence-based guide-

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line for the diagnosis and treatment of NSCLC exists and (modular) revisions are performed regularly to ensure actuality.[20]

Despite efforts to standardise NSCLC treatments across the Netherlands, differences may exist in diagnostic and treatment patterns between hospitals and may result in differences in survival. The aims of this study are to provide the reader with more information regarding treatment patterns in the Netherlands and to analyse differences in survival between academic and non-academic hospitals. Current results will show the state of NSCLC care and survival in the Netherlands and will serve as foundation for future cost- and cost-effectiveness studies of treatment alternatives.

MATERIALS AND METHODS

Patients and data

Detailed data on treatment patterns in Dutch hospitals was obtained from four, not randomly selected hospitals (two academic, two non-academic). A random sample of unselected patients diagnosed with NSCLC between 31 January 2009 and 31 January 2011 was identified through the four hospital databases. This sample included patients who were referred to one of the four selected hospitals from elsewhere without receiving any NSCLC treatment before their arrival in the selected hospital. The random selection was performed by listing all NSCLC patients in Microsoft Excel, shuffling their order and including them listwise. Clinical data was manually abstracted from medical records and coded by trained data assistants, using a web-based case report form. Data was obtained on patient characteristics, tumour characteristics, treatments and survival outcomes.

Data from the Netherlands Cancer Registry (NCR) was used to validate tumour histology and disease stage collected from the hospital databases, and to update follow-up time. Patients who could not be matched reliably to NCR records were excluded from the survival analyses.

Population based NCR data was used to analyse survival differences between academic and non-academic hospitals. The NCR provided population based data on all patients diagnosed with NSCLC between January 2009 until January 2011, as identified through the automated pathological archive (PALGA) and The National Registry of Hospital Discharge Diagnoses. Clinical information was manually abstracted from medical records and coded by trained NCR data managers, using a national manual and case report form. Data was obtained on patient characteristics, tumour characteristics, primary treatment and overall survival.

Hospital type (academic versus non-academic) represents the type of hospital at diagnosis as registered in the NCR. In the four selected hospitals, patients were included only if they received treatment and/or follow-up in the study hospital.

Selected tumour histologies included ICD-O (International Classification of Diseases for Oncology) codes 8010 to 8035, 8046 to 8230, 8244 to 8246 and 8250 to 8576 (all NSCLC). Presence of distant metastasis was recorded following the NSCLC stage classification system in use at diagnosis of the tumour, being either the sixth (2009) or the seventh (2010, 2011) TNM edition. However, TNM stage can change during the diagnostic period, can differ between clinicians, and cannot always reliably be obtained from patient charts. This was a limitation of both the data we collected and the NCR data, which we used to validate our stage information. We therefore decided not to separate stages I-III, in order to minimise potential misclassification.

As our study design is not subject to the Medical Research Involving Human Subjects Act, the Medical Research Ethics Committee of VU University Medical Centre exempted the study from ethical appraisal. Informed consent was not required for chart review.

Statistical analyses
All analyses were performed in IBM SPSS Statistics 21.

We used descriptive analyses to report treatment patterns. Treatments were allocated to the categories 'aimed at non-metastasised disease' or 'aimed at metastasised disease' dependent on disease stage (M0 or M+) at treatment start. For the survival curves, disease stage was determined at diagnosis.

Treatments were classified to be either surgery, radiotherapy, systemic treatment (including chemotherapy and targeted therapies) or combinations of the above. Chemo-radiation was defined as definitive radiotherapy combined with concurrent or sequential systemic treatment.

We compared overall survival for patients in academic hospitals, non-academic hospitals and patients in the four selected hospitals, for the following groups: (1) patients with non-metastatic NSCLC, (2) patients with metastatic NSCLC, (3) patients treated with primary surgery for non-metastatic NSCLC, (4) patients treated with primary surgery for metastatic NSCLC, (5) patients treated with primary radiotherapy for non-metastatic NSCLC, (6) patients treated with primary radiotherapy for metastatic NSCLC, (7) patients treated with primary systemic treatment for non-metastatic NSCLC, (8) patients treated with primary systemic treatment for metastatic NSCLC, and (9) NSCLC patients who did not receive anti-tumour treatment.

We used Kaplan-Meier methods to estimate overall survival rates by hospital type and Cox proportional hazards models to estimate the relative risk of mortality (expressed as hazard ratios, HRs) and their 95% confidence intervals (95% CI) per hospital type, with all non-academic hospitals as the reference group, with and without adjustment for age, gender and tumour histology and stratifying for disease stage (M0 or M+). All statistical tests were two-sided and conducted at the 0.05 level of significance.

RESULTS

NCR included 13,992 patients fulfilling the selection criteria, 1,289 (9%) of whom were diagnosed in academic hospitals. In the four selected hospitals, data was collected on 1,067 patients. 58 patients (5.4%) were excluded because they came for a second opinion only. Only limited information was available about these patients, since they were treated in other hospitals than the four study hospitals. Of the remainder (n=1,009), 170 patients (17%) could not be matched reliably to NCR records and were excluded from the survival analyses. The distribution of the 1,009 patients over the four study hospitals was 195 (St. Antonius Hospital) versus 239 (University Medical Centre Groningen) versus 258 (Medical Centre Alkmaar) versus 317 (VU University Medical Centre) patients.

Table 5.1 shows baseline characteristics of both study populations. Distributions of age, gender and tumour histology in the four selected hospitals are similar to these distributions in the total NSCLC population. The total NSCLC population also includes the patients from the four selected hospitals. In the four selected hospitals, a relatively high proportion of tumours was classified as clinical stage <IV (n=616, 61% versus 6,552, 47%), mainly due to referrals from other hospitals for specialised treatments. In addition to the 363 patients diagnosed with stage IV NSCLC at baseline in the four study hospitals, 113 patients initially had other stage disease that metastasised during our study period.

WHO performance status and forced expiratory volume in 1 second (FEV1) were often not reported in the medical charts (WHO performance status 80,8% and FEV1 76% not reported).

Within the total Dutch population, 9% of patients were diagnosed in academic hospitals as opposed to non-academic hospitals. In these academic hospitals, there were less elderly patients (over 75 years of age, n=239, 19% versus n=3,275, 26% in non-academic hospitals), less squamous cell carcinomas (n=327, 25% versus n=3,734, 29%) and less large cell carcinomas (n=125, 10% versus 1,757, 14%) as opposed to adenocarcinomas (n=649, 51% versus 5,572, 44%). In the academic hospitals, relatively many patients (n=644, 50%) were diagnosed with stage <IV NSCLC, though not as many as in the four selected hospitals (n=616, 61%).

Table 5.1 Baseline characteristics

	Four selected hospitals (two academic, two non-academic) 2009-2011	Total Dutch population 2009-2011	Dutch population, patients diagnosed in academic hospitals 2009-2011	Dutch population, patients diagnosed in non-academic hospitals 2009-2011
	n (%)	n (%)	n (%)	n (%)
Total patients	1,009 (100)	13,992 (100)*	1,289 (100)	12,698 (100)
Age (years)				
<60	272 (27)	3,566 (26)	391 (30)	3,175 (25)
60-74	501 (50)	6,910 (49)	659 (51)	6,248 (49)
≥75	236 (23)	3,516 (25)	239 (19)	3,275 (26)
Gender				
Male	660 (65)**	8,841 (63)	780 (61)	8,059 (64)
Histology				
Adenocarcinoma	490 (49)	6,222 (45)	649 (51)	5,572 (44)
Squamous cell carcinoma	256 (25)	4,062 (29)	327 (25)	3,734 (29)
Large cell carcinoma	101 (10)	1,884 (14)	125 (10)	1,757 (14)
Other histology	33 (3)	407 (3)	48 (4)	358 (3)
Unknown	129 (13)	1,417 (10)	140 (11)	1,277 (10)
Clinical stage				
Stage <IV	616 (61)	6,552 (47)	644 (50)	5,904 (47)
Stage =IV	363 (36)	6,887 (49)	588 (46)	6,298 (50)
Unknown	30 (3)	553 (4)	57 (4)	496 (4)

*For five patients, hospital type was not registered.

**For one patient, gender was not registered.

Total study population, survival

For non-metastasised disease, patients treated in academic hospitals had superior overall survival as compared to patients treated in non-academic hospitals (see Figure 5.1a). Median survival was 2.66 years (95% CI 2.14-3.18) in academic versus 1.83 years (95% CI 1.73-1.93) in non-academic hospitals for non-metastasised disease. For metastasised disease(see Figure 5.1b), median survival was 0.41 years (95% CI 0.35-0.48) in academic versus 0.39 years
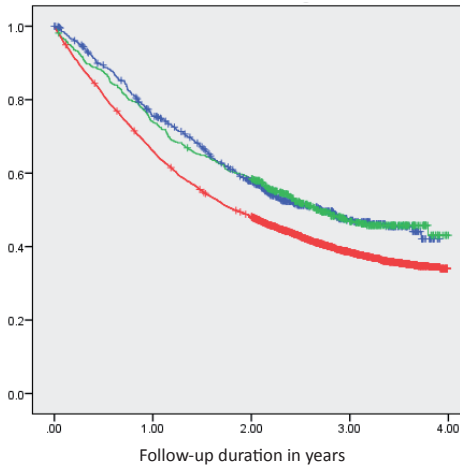
Figure 5.1a. Crude cumulative survival non-metastasized NSCLC.
Blue = four selected teaching hospitals
Green = all academic hospitals
Red = all non-academic hospitals

Figure 5.1b. Crude cumulative survival metastasized NSCLC.
Blue = four selected teaching hospitals
Green = all academic hospitals
Red = all non-academic hospitals

(95% CI 0.38-0.41) in non-academic hospitals. Overall survival for metastasised disease in the selected hospitals was 0.59 years (95% CI 0.46-0.71).

Primary surgery patients, treatment characteristics and survival

Surgery for non-metastasised disease
Out of 616 patients with non-metastasised disease, 268 patients (43.5%) were operated in the study hospitals. Including reoperations, a total of 292 surgeries for non-metastasised disease were performed during the 2-year study period. Majority of surgeries were lobectomies (66.1%, n=193), followed by wedge resections (10.3%, n=30) and pneumonectomies (7.2%, n=21). For 148 operated patients (55.2%), surgery was the only antitumour treatment received in the study hospital.

Adjuvant radiotherapy is common in case of R1 or R2 resections. In the study hospitals, 7.5% of operated patients (n=20) received adjuvant radiotherapy within two months of attempted surgery. Adjuvant systemic therapy is recommended for stage II-IIIA patients with a good performance score. Unfortunately it was not known for which proportion of patients adjuvant chemotherapy was indicated in the study hospitals, but it was prescribed within

two months of the surgery to 48 patients (17.9%). Chemo-radiation preceded surgery in 6.0% of cases (n=16).

Surgery for metastasised disease
Including patients who developed metastasis during the course of their disease (n=113), 41 patients with metastasised disease were operated (8.6%), receiving a total of 45 operations. Most of these surgeries (n=24) were non loco-regional (53.3%), mostly targeting the brain (n=9). 46.7% of surgeries (n=21) were loco-regional, most often lobectomy (n=8) or wedge resection (n=7).

Survival for surgery patients
For non-metastasised as well as metastasised disease, no significant differences were found in overall survival of operated patients (see Figure 5.2). Mean overall survival for patients operated for non-metastasised disease, was 3.16 years (95% CI 3.02-3.30) for academic hospitals, 3.05 years (95% CI 3.00-3.10) for non-academic hospitals and 2.92 years (95% CI 2.76-3.09) in the four selected hospitals (median survival unknown, >50% of patients still alive at end of follow-up). Median overall survival for patients operated for metastasised disease was 1.48 years (95% CI 0.12-2.85) for academic hospitals, 1.55 years (95% CI 0.92-2.18) for non-academic hospitals and 1.04 years (95% CI 0.48-1.60) in the four selected hospitals.

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Figure 5.2a. Crude cumulative survival non-metastasized NSCLC, primary surgery patients.
Blue = four selected teaching hospitals
Green = all academic hospitals
Red = all non-academic hospitals

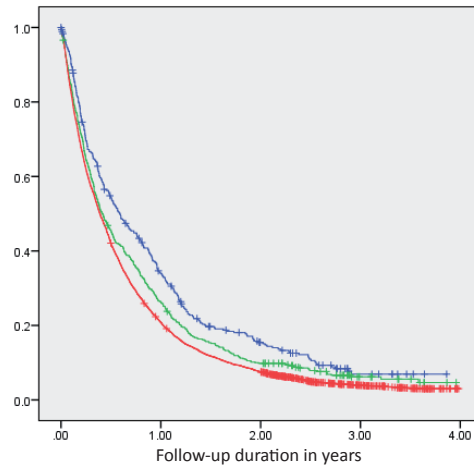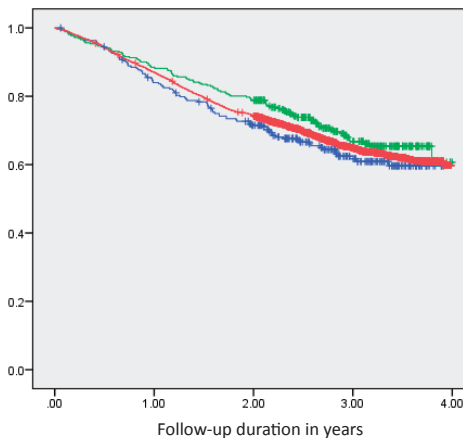**Figure 5.2b.** Crude cumulative survival metastasized NSCLC, primary surgery patients.
Blue = four selected teaching hospitals
Green = all academic hospitals
Red = all non-academic hospitals

Primary radiotherapy patients, treatment characteristics and survival

Radiotherapy for non-metastasised disease
In addition to the 268 patients operated for non-metastasised disease, 142 patients received stereotactic radiotherapy (SBRT). In total, 353 out of 616 patients with non-metastasised disease (57.3%) received any type of radiotherapy, including combined modality treatments. Twenty-five patients received locoregional radiotherapy that was classified as being of palliative intent (n=25, 7.1%).

Radiotherapy for metastasised disease
Including patients who developed metastasis during the course of their disease (n=113), 273 patients with metastasised disease were treated with (any) radiotherapy (57.4%, including combined modality treatments), 198 of whom received at least one fraction on a distant metastasis (72.5%).

Survival for radiotherapy patients
Patients treated with radiotherapy for non-metastasised disease survived significantly longer when diagnosed in an academic hospital (median 2.11 years, 95% CI 1.72-2.50) or one of the four selected study hospitals (median 2.20 years, 95% CI 1.77-2.61) as opposed

Figure 5.3a. Crude cumulative survival non-metastasized NSCLC, primary radiotherapy patients.
Blue = four selected teaching hospitals
Green = all academic hospitals
Red = all non-academic hospitals
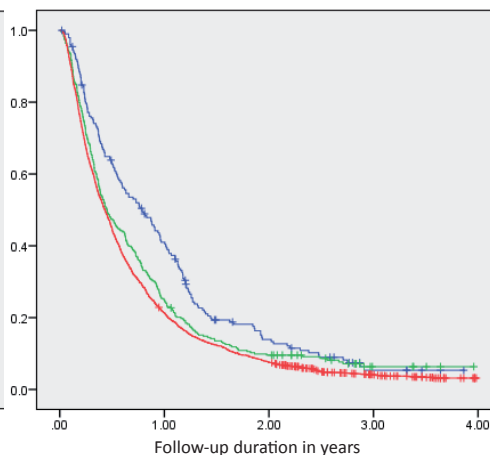
Figure 5.3b. Crude cumulative survival metastasized NSCLC, primary radiotherapy patients.
Blue = four selected teaching hospitals
Green = all academic hospitals
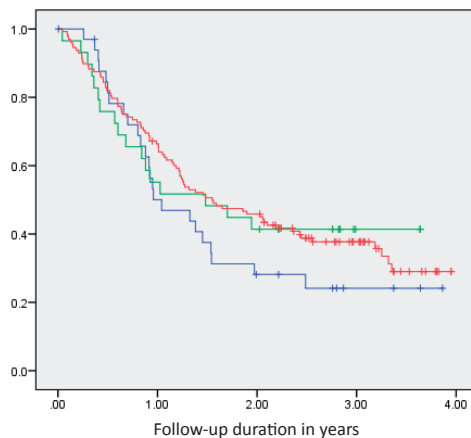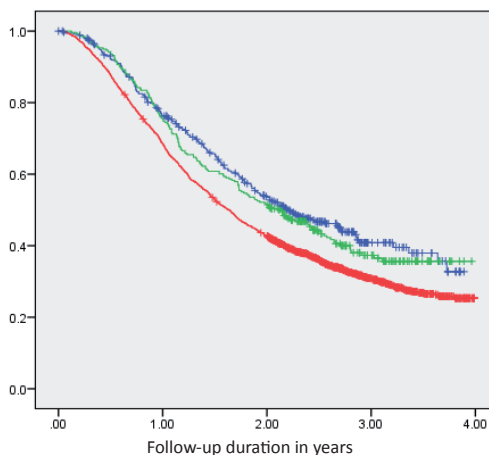Red = all non-academic hospitals

to a non-academic hospital (median 1.64 years, 95% CI 1.55-1.72). For patients treated with palliative radiotherapy for metastasised disease, median survival was longest for patients from the four selected study hospitals (0.79 years, 95% CI 0.61-0.97) as opposed to patients diagnosed in academic (0.45 years, 0.36-0.54) or non-academic (0.13, 95% CI 0.40-0.46) hospitals (see Figure 5.3).

Primary systemic treatment patients, treatment characteristics and survival

Systemic treatment for non-metastasised diseases
Two hundred and forty-two patients with non-metastasised NSCLC (39.3%) received systemic treatment in the study hospital (including combined modality treatments). The most commonly prescribed drug regimen for non-metastasised disease was gemcitabine plus cisplatin (n=70, see Table 5.2). Hundred and thirty-seven patients were registered to received chemoradiation, defined as systemic treatment with concurrent or sequential definitive, loco-regional radiotherapy.

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Table 5.2 Frequency of prescription of systemic treatment regimens for non-metastasised disease (including combined modality treatments)

Treatment	Number of patients receiving at least one administration of treatment (%)*
Gemcitabine / cisplatin	70 (28.9)
Pemetrexed / cisplatin	59 (24.4)
Vinorelbine / cisplatin	24 (9.9)
Etoposide / cisplatin	22 (9.1)
Gemcitabine / carboplatin	15 (6.2)
Gemcitabine	13 (5.4)
Pemetrexed / carboplatin	10 (4.1)
Docetaxel / carboplatin	7 (2.9)
Docetaxel	6 (2.5)
Vinorelbine / carboplatin	6 (2.5)
Other	14 (5.8)
Unknown	15 (6.2)

* Percentages do not add up to 100, since patients can receive multiple treatments.

Systemic treatment for metastasised disease

Including patients who developed metastasis during the course of their disease (n=113), 234 patients with metastasised NSCLC (49.2%) received systemic treatment in the study hospital (including combined modality treatments), see Table 5.3. For 50.8% of the patients with metastasised disease, no systemic treatment was prescribed in the study hospital. Most commonly prescribed drug regimen was pemetrexed with platinum (n=105). For patients who did not receive antitumour treatment, reasons are provided in paragraph 3.5.

Table 5.3 Frequency of prescription of systemic treatment regimens for metastasised disease

Treatment	Number of patients receiving at least one administration of treatment (%)*
Pemetrexed / cisplatin	57 (24.4)
Pemetrexed / carboplatin	48 (20.5)
Erlotinib	44 (18.8)
Gemcitabine / cisplatin	23 (9.8)
Docetaxel / carboplatin	22 (9.4)
Docetaxel	19 (8.1)
Gemcitabine / carboplatin	18 (7.7)
Pemetrexed	18 (7.7)
Paclitaxel / carboplatin	15 (6.4)
Sorafenib	10 (4.3)
Paclitaxel / carboplatin / bevacizumab	10 (4.3)
Gefitinib	7 (3.0)
Etoposide / cisplatin	6 (2.6)
Gemcitabine	5 (2.1)
GDC0941 (PI3K inhibitor, clinical trial)	5 (2.1)
Paclitaxel	5 (2.1)
Other	30 (12.8)
Unknown	11 (4.7)

* Percentages do not add up to 100, since patients can receive multiple treatments.

Survival for systemically treated patients

For systemically treated patients with non-metastasised disease, patients from academic hospitals and the four selected hospitals had better survival than patients treated in non-academic hospitals (see Figure 5.4). Median survival was 2.22 years (95% CI 1.95-2.49) in academic hospitals, 2.43 years (95% CI 1.97-2.88) in selected hospitals, and 1.66 years (95% CI 1.57-1.76) in non-academic hospitals. A similar pattern was seen for systemically treated patients with metastasised disease. Median survival was longer for patients from academic hospitals (0.81 years, 95% CI 0.74-0.89) or the four selected study hospitals (0.92 years, 95% CI 0.78-1.05) than for patients from non-academic hospitals (0.69 years, 95% CI 0.66-0.71).
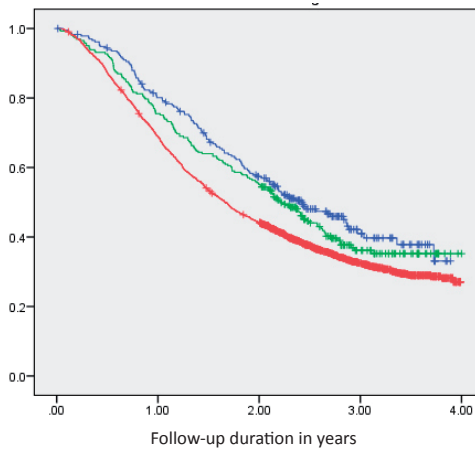
Figure 5.4a. Crude cumulative survival non-metastasized NSCLC, primary systemic treatment patients.
Blue = four selected teaching hospitals
Green = all academic hospitals
Red = all non-academic hospitals

Figure 5.4b. Crude cumulative survival metastasized NSCLC, primary systemic treatment patients.
Blue = four selected teaching hospitals
Green = all academic hospitals
Red = all non-academic hospitals

Patients who did not receive primary antitumour treatment, characteristics and survival

In the selected study hospitals, 114 patients (11.3%) did not receive any antitumour treatment. Fourteen out of 114 patients were registered to have received previous treatment in another hospital (n=5) or to be referred for treatment to another hospital during the study period (n=9). 56 (56.0%) of the remaining patients without antitumour treatment received supportive care only. An additional 18 patients did not receive antitumour treatment following their own specific wishes (18.0%). Fifteen patients died before treatment was started (15.0%), 4 patients had limited/no treatment options due to comorbidities (4.0%), in 4 cases

a wait and see policy was followed (4.0%) and for one patient, treatment for another type of cancer had priority over the symptom-free lung cancer (1.0%). For 2 patients, reason for not receiving antitumour treatment was not registered.

Patients from academic hospitals who did not receive antitumour treatment (median survival 0.10, 95% CI 0.07-0.14), did not perform better than patients from non-academic hospitals who did not receive antitumour treatment (median survival 0.15 years, 95% CI 0.14-0.16), see Figure 5.5. Median survival of patients from the four selected hospitals was longest (0.25, 95% CI 0.15-0.35).
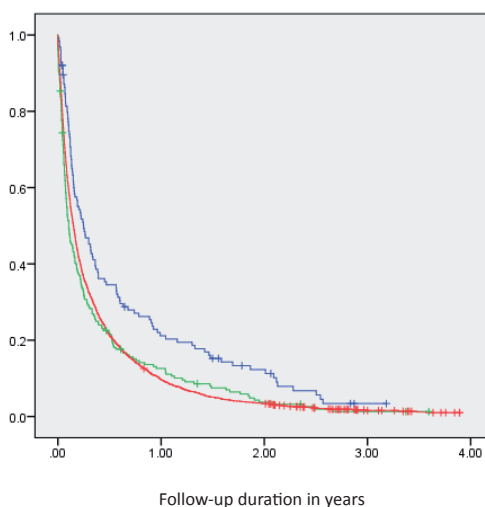
Figure 5.5. Crude cumulative survival NSCLC, patients who did not receive antitumor treatment.
Blue = four selected teaching hospitals
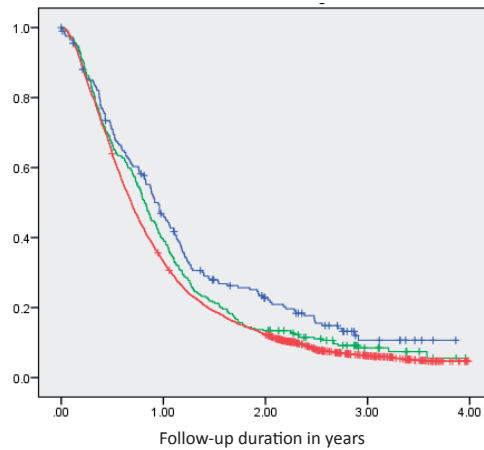Green = all academic hospitals
Red = all non-academic hospitals

Follow-up duration in years

Hospital type and mortality, adjusted for age, gender and tumour histology
Cox proportional hazard models show a significantly decreased hazard of mortality for patients from the four selected hospitals as well as for patients diagnosed in academic hospitals, as opposed to patients diagnosed in non-academic hospitals. This is specifically true for primary radiotherapy patients and patients who receive systemic treatment for non-metastasised NSCLC. For primary surgery patients and patients who receive systemic treatment for metastasised NSCLC, no significant differences in mortality existed between hospital types. For patients receiving radiotherapy for metastasised disease, the improved survival in academic hospitals was non-significant when corrected for age, gender and tumour histology (Table 5.4).

Table 5.4 Cox proportional hazards: the relationship between hospital type and mortality, adjusted hazard ratios

	Four selected hospitals* 2009-2011				Dutch population, patients diagnosed in academic hospitals 2009-2011			
	Crude HR** 95% CI	Sig	Adjusted*** HR** 95% CI	Sig	Crude HR** 95% CI	Sig	Adjusted*** HR** 95% CI	Sig
Non-metastasised NSCLC, total	0.743 (0.660-0.836)	0.000	0.805 (0.708-0.915)	0.001	0.755 (0.674-0.845)	0.000	0.775 (0.685-0.876)	0.000
Metastasised NSCLC, total	0.722 (0.645-0.809)	0.000	0.742 (0.658-0.836)	0.000	0.876 (0.802-0.956)	0.003	0.892 (0.812-0.980)	0.018
Non-metastasised NSCLC, primary surgery patients	1.103 (0.894-1.361)	0.360	1.148 (0.923-1.428)	0.215	0.875 (0.711-1.078)	0.210	0.907 (0.733-1.121)	0.364
Metastasised NSCLC, primary surgery patients	1.316 (0.834-2.076)	0.238	1.196 (0.715-2.001)	0.496	0.997 (0.591-1.682)	0.992	0.979 (0.564-1.698)	0.940
Non-metastasised NSCLC, primary radiotherapy patients	0.730 (0.627-0.850)	0.000	0.822 (0.696-0.970)	0.020	0.789 (0.673-0.926)	0.004	0.767 (0.640-0.920)	0.004
Metastasised NSCLC, primary radiotherapy patients	0.683 (0.596-0.797)	0.000	0.703 (0.598-0.827)	0.000	0.883 (0.780-0.998)	0.047	0.890 (0.778-1.018)	0.089
Non-metastasised NSCLC, primary systemic treatment patients	0.713 (0.595-0.854)	0.000	0.745 (0.617-0.901)	0.002	0.808 (0.686-0.952)	0.011	0.787 (0.656-0.942)	0.009
Metastasised NSCLC, primary systemic treatment patients	0.735 (0.628-0.859)	0.000	0.704 (0.599-0.828)	0.000	0.887 (0.785-1.003)	0.057	0.894 (0.784-1.019)	0.092
NSCLC, patients who did not receive antitumour treatment	0.673 (0.558-0.812)	0.000	0.710 (0.577-0.875)	0.001	1.046 (0.907-1.206)	0.537	0.980 (0.840-1.144)	0.800

*In the comparison between patients from the four selected hospitals and patients from the total of non-academic hospitals, samples are not completely independent since two out of four selected teaching hospitals are among the non-academic hospitals. Due to anonymisation of the NCR dataset, overlapping patients could not be removed from the analysis. However, we expect the effect of this dependency to be negligible due to the size of the total group of patients treated in non-academic hospitals (N=12,698) relative to the included number of patients from the two non-academic teaching hospitals (n=453).

**Reference category: Dutch population, patients diagnosed in non-academic hospitals 2009-2011.

***Models directly adjusted for age, gender and tumour histology.

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DISCUSSION

This article describes treatment patterns for patients treated and/or followed for NSCLC in four selected hospitals. Our study as well as other studies[89] show a multitude of treatments to be prescribed to these patients. Choice of treatment is very much patient and tumour dependent. This heterogeneity poses a challenge for cost-effectiveness studies, amongst others in selecting appropriate comparator treatment groups.

Overall survival curves are presented for patients from the selected hospitals as well as the total of NSCLC patients diagnosed in academic versus non-academic hospitals in the Netherlands. We found that patients with non-metastasised NSCLC that are treated in academic hospitals have better median overall survival than patients treated in non-academic hospitals. For metastasised disease, overall survival was best for patients diagnosed in the four selected hospitals. These differences mainly reflect differences in overall survival for patients treated with radiotherapy, systemic treatment or combinations. No significant differences in overall survival between hospital types were found for the subgroup of patients treated with surgery.

Patients who did not receive any antitumour treatment had significantly better survival in the four study hospitals compared to the total of non-academic hospitals in the Netherlands. The difference reduces when correcting for age, gender and tumour histology, but remains present. This can either result from better supportive care in the study hospitals, or from remaining confounding. We could not correct for all relevant prognostic factors since they were not registered systematically in the patient charts. For instance, WHO performance status was only registered in 19% of the cases (at baseline).

The generally improved survival of patients from academic hospitals might be explained by the higher level of experience available in (generally large) academic centres as well as their pioneer role in adopting innovations. New or improved treatment regimens are usually not uniformly implemented in all hospitals from the start. This can be a matter of (un)awareness or (lack of) available information on the new treatment and outcomes, and on current practice and outcomes. Data collection, sharing, self-reflection and communication between doctors are crucial feedback and improvement tools.[90]

Also, further centralisation of NSCLC treatments may improve treatment outcomes and reduce variability between hospitals. While literature about differences in treatments and/or survival between hospital types is mostly about surgery, recent innovation in cancer care has been mainly about combining treatment modalities.[88] Therefore, patients may benefit

from critical assessments of the minimum skills and experience in hospitals prescribing and applying these treatments for NSCLC.[14]

Obviously, "treatment in an academic hospital" does not automatically mean good quality of care, or the other way around. Academic or non-academic hospital type is probably not the main predictor of treatment or survival differences. Other important factors might be hospital- and treatment volume, infrastructure, dedication of multidisciplinary teams and adoption of innovative treatments.[88] These factors might also explain the relatively good survival of patients from the four selected study hospitals, which are relatively active in teaching and training, scientific studies, benchmarking activities and guideline development.

Selection bias may have occurred since patients referred to the study hospitals from other hospitals were included as long as they did not receive treatment before their arrival in the study hospital. Although we corrected for age, gender and tumour histology and stratified by disease stage (M0 or M+) in the Cox proportional hazard analysis, the referred patients may have better (unmeasured) prognostic characteristics. Treatment patterns were presented as such, so they include patients who were referred for specialised treatment. This reduces the generalisability of treatment patterns to other, non-specialised hospitals.

Patients who could not be matched reliably to NCR records were excluded from the survival analyses, which may bias the results in unknown direction. A reason for having no match in NCR records is the lack of NSCLC pathology or hospital admission.

The follow-up time of this study was relatively short. Since patients were included in the study as they were diagnosed within a two-year time frame, we collected relatively more data on the early phases of disease. Patients with a relatively good prognosis become censored cases as they survive end of the study follow-up. While survival was updated using NCR data, information about later treatment lines for these patients was lacking.

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. Furthermore, some patients were treated in multiple hospitals. Permission to collect and use patient chart data could only be obtained for the four study hospitals. Therefore, patients were 'lost' and considered 'censored' from the moment they were referred to a different hospital than the study hospitals. It would be more insightful to follow patients during their entire disease course, even when multiple hospitals are visited for diagnosis and treatment.

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Another challenge was the registration of disease stages. The TNM staging system has changed to the 7th edition halfway the study period, so for each patient we used the TNM edition in use at the time the clinician recorded the disease stage in the patient chart. However, TNM stage can change during the diagnostic period, can differ between clinicians, and cannot always reliably be obtained from patient charts. This was a limitation of both the data we collected and the NCR data, which we used to validate our stage information. We therefore decided not to separate stages I-III, in order to minimise potential misclassification.

The demand for real world evidence (RWE) has increased recently, as policy makers recognise its value in providing information on treatment effectiveness and cost-effectiveness. Resource use data obtained from clinical trials partly reflects resource use resulting from the trial protocols and therefore, does not reflect the resource use of clinical daily practice. With this study, we provided real world data on resource use, which can be used directly in future model-based cost-effectiveness studies.

Future outcomes research should focus on utilities as well, as this was not included in this study. However, reliable utility estimates for treatment alternatives, as well as various other aspects of real-world NSCLC management, would best be studied within a prospective population-based patient registry, including all NSCLC patients. This type of data is extremely important to evaluate the large number of new, mainly targeted, therapies that are expected to be launched in the coming years, improving not only survival but quality of life as well.

CONCLUSIONS

Differences in survival between hospital types suggest possibilities for improvement in NSCLC care in the Netherlands. However, due to limitations of the data from the current study, confirmation by other studies is advised.

Chapter VI

Real-world costs of laboratory tests

for non-small cell lung cancer

Naomi van der Linden, Egbert F. Smit and Carin A. Uyl-de Groot.

LETTER TO THE EDITOR

Cancer patients undergo a wide range of laboratory procedures, from simple blood tests to complex molecular diagnostics. These laboratory procedures involve various categories, such as clinical chemistry, pathology, microbiology, serology, hematology and pharmacology. Recent developments, amongst others in genetic biomarker testing, add complexity and costs to the range of laboratory procedures. Several new techniques reduce costs per test, but also new tests are added to an already large volume of laboratory procedures in the management of cancer in general, and non-small cell lung cancer (NSCLC) in particular.

For oncologists, policy makers, and health economists, it is difficult to determine the magnitude of the cost burden of laboratory testing. We could find no publications presenting real-world cost data for laboratory testing in NSCLC. It is reasonably easy to collect resource use and cost data for one specific test. However, in economic decision making, one would want to take all costs associated with all laboratory testing into account if these contribute significantly to the total cost burden. Especially for tests related to treatment choice, laboratory costs might impact cost-effectiveness estimates of treatment alternatives since they essentially increase the cost of the treatment. The same is true for life extending treatments when additional testing is performed during life time gained.

Recently published cost-effectiveness studies in NSCLC did not take laboratory costs into account or did not report them.[91,92] In other studies, estimates of total cost of laboratory testing was based on guidelines[93], the Summary of Product Characteristics of the drugs under evaluation[94], or expert opinion. Furthermore, several studies estimate total laboratory costs from a clinical trial database.[95] Laboratory costs within the clinical trial setting might differ significantly from real-world costs since ordering of diagnostic testing in trials is mainly guided by trial protocol and is usually limited to the duration of the trial. In studies that did take real-world laboratory costs into account, size of these costs was not reported separately from other cost categories[96], or methods of determining these costs were unclear.[97]

Here, we present recent real-world costs of laboratory procedures for NSCLC patients (inpatient as well as outpatient). We calculated these costs with the aim to inform health-economic studies and models to evaluate the cost-effectiveness of diagnostic or treatment alternatives in NSCLC. Laboratory tests were categorised in order to identify tests with the largest impact on costs associated with NSCLC.

Data was collected in an academic medical centre in the Netherlands. All hospital laboratory tests performed for stage I to IV NSCLC patients between 2009 and 2011 were recorded.

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Dates and types of the tests were registered, further clinical information (e.g., disease stage, treatment sequence, inpatient/outpatient setting and death date) could not be collected. All laboratory procedures were included, irrespective of the reason to order the test or department of the clinician who ordered it. The study was exempt from ethical review by the Medical Ethical Committee of VU University Medical Centre.

Costs per laboratory test were obtained from The Dutch Healthcare Authority (Nederlandse Zorgautoriteit) in Euros (2012). Costs were determined for the total follow-up period as well as per day. Costs per day were calculated in two ways, to serve different objectives. First, total costs per patient were divided by the number of days with at least one laboratory procedure. The outcome can be used to estimate total laboratory costs for a patient in case the number of days with laboratory testing is known. Second, total costs per patient were divided by the number of days between the first and the last laboratory test for this patient during the follow-up period. This outcome can be used when the number of actual days with laboratory testing is unknown.

Categorisation of laboratory procedures was performed by the corresponding author and critically reviewed by Prof.dr. Smit. Following classes of laboratory tests were distinguished: 1) clinical chemistry; 2) pathology (including genetic biomarkers); 3) microbiology; 4) serology, hematology, transfusion; 5) pharmacology; 6) other or unknown category (including order processing fees). Analyses were performed in IBM SPSS Statistics 22.

A total of 1015 patients were included, accounting for a total of 171,632 laboratory procedures, with a mean of 169 laboratory procedures per patient during a mean follow-up of 6.5 months. Table 6.1 shows the number of patients, number of tests and laboratory costs per category. In total, 392 different types of tests were performed. Cost of laboratory testing per patient is mean €96 (95% confidence interval (CI) 91–101) and median €51 per day with at least one laboratory procedure. Cost of laboratory testing per patient is mean €49 (95% CI 34–65) and median €10 per day between the first and last laboratory test (Table 6.1).

   Costs are driven by categories pathology (26%), other (25%, mainly order processing fees) and clinical chemistry (24%, due to high test volumes). Distribution of laboratory costs was skewed to the right (see Figure 6.1).

The previous most recent real-world cost estimate for laboratory testing in lung cancer was published by Kutikova et al. (2005).[98] Databases of claims data for the years 1998–2000 were used in order to estimate the economic burden of lung cancer, including the costs of outpatient laboratory testing. The average number of laboratory procedures per patient per month was 2.0 (SD 3.6), resulting in an average cost of €98 (SD €207) per patient per
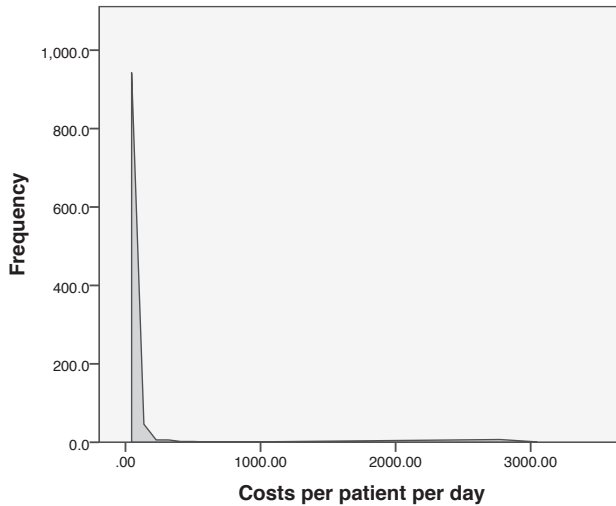
Figure 6.1. Distribution of laboratory costs was skewed to the right.
Eight patients made costs of more than €2,000 per day, since they were followed only one day, with several expensive pathology procedures.

month (using an United States dollars to euros exchange rate of 0.809). When compared to the costs of laboratory procedures for patients without lungcancer, the incremental costs attributed to lung cancer were €89 per month. Most of these costs were made in the initial treatment phase, as opposed to later in the course of the disease. Cost estimates in our study are higher, possibly due to an increase of these costs in the last decade as well as the inclusion of inpatient costs in our study.

An important limitation of this study is the use of unit costs based on tariffs instead of microcosting studies. Due to the large number of different tests (392), microcosting per test type was not feasible. It is unknown to what extent current tariffs reflect accurate estimates of the actual costs. National tariffs for molecular testing, such as the tariff for epidermal growth factor receptor (EGFR) mutation analysis (€912), might be higher than actual costs spend on performing these tests. In comparison, other studies estimate costs of EGFR testing to be €236[99] and €197.[100]

As a result of the substantial cost impact of complex molecular tests, reliable estimates are important and should be used in cost-effectiveness analyses. Such cost estimates should also take into account any efficiency gains that are reached by performing multiple tests on the same sample, as is increasingly the case in molecular testing.

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Table 6.1: Number of patients, number of tests and laboratory costs in €, per category.

Category	Number of patients with ≥1 test (% of patients)	Mean number of tests per patient	Most common test (unit cost for this test in €)	Mean cost per patient during follow-up period (% of total cost)	SD	Median
Clinical chemistry	993 (98)	104.34	Creatinine (2.05)	284.05 (24)	412.70	131.87
Pathology	107 (11)	0.33	EGFR mutation analysis (912.30)	303.80 (26)	914.74	0
Microbiology	415 (41)	5.30	Bacterial culture in more than three growth media (25.94)	105.79 (9)	269.68	0
Serology, hematology, blood transfusion	786 (77)	37.72	Hemoglobin, incl. HT, MCV, MCH, MCHC and erythrocytes (1.90)	185.84 (16)	274.59	105.83
Pharmacology	36 (4)	0.07	Tobramycin in blood, quantitative (11.84)	0.87 (0)	5.43	0
Other or unknown	1008 (99)	21.34	Order processing fee* (13.73)	294.31 (25)	568.06	123.57
Total	1015 (100)	169.10	Order processing fee* (13.73)	1174.66 (100)	1755.63	457.80

*Fee per order, independent of number of tests per order.

Furthermore, note that this study was performed in an academic hospital. Due to research activities in the academic setting, test order behavior in this setting might be different from off protocol clinical care.

This study provides oncologists, policy makers, and health economists with an initial estimate of the costs of laboratory testing in NSCLC. In economic evaluations, laboratory costs might significantly impact the results when testing practices or survival gain differs between treatment alternatives. Especially when evaluating targeted therapies, costs of associated biomarker tests should be taken into account. However, relatively simple blood tests, such as renal and liver function tests, should not be easily ignored, as they can significantly impact cost estimates due to high test volumes.

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Chapter VII

Costs of non-small cell lung cancer in the Netherlands

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ABSTRACT

Objectives

Real-world resource use and cost data on non-small cell lung cancer (NSCLC) are scarce. This data is needed to inform health-economic modelling to assess the impact of new diagnostic and/or treatment technologies. This study provides detailed insight into real-world medical resource use and costs of stage I-IV NSCLC in the Netherlands.

Materials and methods

A random sample of patients newly diagnosed with NSCLC (2009-2011) was selected from four Dutch hospitals. Data was retrospectively collected from patient charts. This data included patient characteristics, tumour characteristics, treatment details, adverse events, survival and resource use. Resource use was multiplied by Dutch unit costs expressed in EUR 2012. Total mean costs were corrected for censoring using the Bang and Tsiatis weighted complete-case estimator. Furthermore, costs of adverse events, costs per phase of NSCLC management and costs of second opinions are presented.

Results

Data was collected on 1,067 patients. Total mean costs for NSCLC diagnosis, treatment and follow-up are €28,468 during the study period and €33,143 when corrected for censoring. Adverse events were recorded in the patient charts for 369 patients (41%) and 82 patients (9%) experienced an adverse event of grade III or higher. For these patients, adverse event-related hospital admissions cost on average €2,091. Mean total costs are €1,725 for the diagnostic period, €17,296 for first treatment line, and €13,236 for each later treatment line. Costs of providing a second opinion are €2,580 per patient.

Conclusions

Total mean hospital costs per NSCLC patient are €33,143 for the total duration of the disease. Ignoring censoring in our data underestimates these costs by 14%. Main limitations of the study relate to the short follow-up time, staging difficulties and missing data. Its main strength is that it provides highly detailed, real-world data on the costs of NSCLC.

INTRODUCTION

Of new cancer cases, lung cancer has the second highest incidence. Although incidence and mortality have been reduced[101,102], due to a reduction in smoking and recent developments in diagnosis and treatment, the health burden remains considerable. In addition, the economic burden of lung cancer care on society is high; in the Netherlands, costs of lung cancer were estimated to be over 400 million euro in the year 2011. The majority of these costs involve hospital care (82%).[103]

Healthcare spending for NSCLC has increased due to the growing number of new, expensive treatments.[104] Because of the economic burden of lung cancer, it is critical to estimate the cost-effectiveness of new developments in diagnosis and treatment. Mathematical models that estimate cost-effectiveness of new strategies using available data are commonly used to support decision making.[105] Such models synthesise evidence on health effects and costs from many different sources, including data from clinical trials, claims databases, registry data and public health statistics. To inform such health-economic models with data, it is important that the best available evidence is used, and preferably data that reflects clinical practice.[106] Resulting cost-effectiveness estimates can inform hospital, industry and governmental policy makers on costs of NSCLC and impact of new diagnostic or treatment technologies.

The health effects of new interventions can generally be obtained from trial data or literature. Data from pooled clinical trials is considered the best available evidence for estimating clinical treatment efficacy of new interventions. However, health-economic trial data reflects the resource use and costs of the trial protocol and not the resource use and costs in "the real world".[107] The real-world resource use and cost data that is needed for health-economic modelling of non-small cell lung cancer (NSCLC) is scarce. In general, cost estimates in the literature are not complete enough for modelling purposes. Often, costs are not separated by phase in the treatment pathway, or different types of costs are merged into one cost.[108]

At present, two Dutch studies present NSCLC costs that can be used for health-economic modelling. One study from 2009 focused on late-stage disease[109], while the other study included a detailed analysis of the costs of radiotherapy in 2010.[110] Both studies have been used in health-economic modelling.[111,112]

The objective of this study is to provide insight into real-world medical resource use and costs of NSCLC in the Netherlands. We aimed to estimate costs for all cost items of hospital-based lung cancer care. These cost items include the full diagnostic work-up, cancer treat-

ments, concomitant medication, hospital visits, and adverse events for all phases of lung cancer care. The results can be used in a decision model of lung cancer.

MATERIALS AND METHODS

Study design

A retrospective outcomes study was conducted to capture medical resource use and costs in the management of all stages of NSCLC in the Netherlands. Patients newly diagnosed with stage I-IV NSCLC between January 31, 2009 and January 31, 2011 in participating hospitals (VU University Medical Centre, Amsterdam; University Medical Centre Groningen; Medical Centre Alkmaar; St. Antonius Hospital, Nieuwegein) were eligible. Eligible patients were identified through hospital databases and were followed until study end, transfer to another hospital, or death. Last month of data collection was July 2012.

Data was collected on 1,067 randomly selected patients and abstracted from patient charts by trained data assistants, using a web-based case report form (CRF). The CRF captured information about patient characteristics, tumour characteristics, treatment details, adverse events (AEs), survival and resource use. Adverse events were obtained from the patient charts, which noted the grade of the event according to the common terminology criteria for adverse events (CTC AE) version 4.03. In case grade was not registered by the clinician, it was derived by the data manager if the patient chart contained the necessary information. If the necessary information was not registered, the grade was considered missing.

Data from the Netherlands Cancer Registry (NCR) was used to validate tumour histology and disease stage collected from the patient charts. The NCR also provided population-based data on patient and tumour characteristics of all patients diagnosed with NSCLC in the Netherlands between January 2009 until January 2011, as identified through the automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnoses. This information was used to assess the representativeness of the study sample.

This study was performed from a hospital perspective. Direct medical costs outside the hospital (such as care by a general practitioner) and indirect medical and non-medical costs were outside the scope of the study. Oral oncolytics and other specialist drugs were considered hospital care and included in the cost.

Resource use

Information was collected on all relevant resources consumed within the hospital setting, including surgeries, radiotherapy, anticancer drug therapy, laboratory tests (including pathology, microbiology, hematology, chemistry, immunology), medical imaging services, other medical diagnostics and procedures, outpatient visits, telephone consultations, day-care visits, hospitalisations and intensive care stay.

Per patient, the number and types of resources used were counted. In the case of hospital admissions, it was specified whether admissions were needed for treatment of disease, for treatment of adverse events or other reasons.

Costs

Costs were estimated by linking resource use to Dutch unit costs, based on the Dutch costing manual[57] and NZa (Dutch Healthcare Authority) tariffs.[113] All costs were based on EUR 2012 unit cost data or were adjusted to 2012 prices using the general price index as published by Statistics Netherlands. Mean costs for drug use other than anti-cancer drugs, including treatments for adverse events, were determined for a subsample of VU University Medical Centre patients (n=107), for feasibility reasons. Mean costs for laboratory tests were obtained from a separate database, containing information on all laboratory tests performed for NSCLC patients in the VU University Medical Centre (chapter VI).

Analyses

For all analyses, costs were estimated for the two subgroups stage I-III and stage IV patients separately, as determined at diagnosis.

First, mean costs were estimated separately for relevant cost items of NSCLC, such as chemotherapy, consultations and hospitalisations. Total mean costs per patient were calculated, from the patient's first NSCLC-related hospital visit until the patient's death. Mean follow-up times are presented. Since 51% of patients were still alive at the end of the study, these patients could not be followed until the event of interest. This means that they were censored; complete follow-up information on these patients was not available for the full duration of interest. Ignoring censoring will lead to an underestimation of the total mean costs. Therefore, we corrected these costs for censoring, using the Bang and Tsiatis weighted complete-case estimator.[114] The mean total costs were estimated by:

$$\mu_{BT} = \frac{1}{n} \sum_{i=1}^{n} \frac{\Delta_i M_i}{\widehat{K}(T_i)}$$

Where Δ_i is the event indicator (0 for censored cases, 1 for complete cases), M_i is the total costs for patient i, and $\widehat{K}(T_i)$ is the Kaplan Meier estimator for the survival from censoring,

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that is, censoring is treated as the event. The basic idea of the BT estimator is that the costs of patients who die within the time frame of the study (complete cases) are weighted by the inverse of the probability of not being censored before the time of death. Thus, costs of censored patients are represented by patients with complete data.

Second, costs of adverse events (grade ≥3) were analysed. Third, mean costs per phase of NSCLC management were analysed by splitting the relevant cost items into the following phases: diagnosis, initial treatment, and second and later treatments. The diagnostic period runs from baseline (first NSCLC-related hospital visit) until the start of the first treatment/censoring/death. Treatment periods run from start of the treatment until the start of the next treatment/censoring/death (including follow-up).

Finally, we separately analysed the resource use and costs of patients in the study who came for a second opinion. Although these patients did not receive treatment in the study hospital and were referred back to their original hospital after the second opinion, they incur costs for, amongst others, diagnostic testing and hospital visits.
   All analyses were performed in IBM SPSS Statistics 21 and Microsoft Excel 2010.

RESULTS

Data was collected on 1067 patients, 102 (9.6%) of whom received previous treatment in another hospital and 58 (5.4%) of whom came for a second opinion only. The remainder of the patients (n=907) is included in Table 7.1. Table 7.1 shows baseline characteristics of the study population compared to the Dutch NSCLC population as a whole. Distributions of age, gender and tumour histology are similar, while tumours with stage <IV are overrepresented in the study population.
   Eighty-six patients (9.5%) were treated within a clinical trial.

Table 7.2 shows unit costs and their sources, per item of resource use.

Total crude mean costs for NSCLC diagnosis, treatment and follow-up, as measured during the study period, are €28,468 (see Table 7.3). Total, corrected mean costs for NSCLC diagnosis, treatment and follow-up are €33,143. Although costs per time unit are highest for patients with metastasised NSCLC, total costs are higher for non-metastasised disease due to the longer diagnosis, treatment and follow-up duration (mean 29.9 versus 12.6 months). Main cost drivers are hospital admissions, medical imaging and procedures and radiotherapy.

Table 7.1: Baseline characteristics

	Study sample, 2009-2011 n (%)	Dutch population, 2001-2006 n (%)
Total patients	907 (100)*	13,992 (100)
Age (years)		
<60	235 (26)	3,566 (26)
60-74	450 (50)	6,910 (49)
≥75	222 (25)	3,516 (25)
Gender		
Male	601 (66)*	8,841 (63)
Smoking status		
Non-smoker	60 (7)	NA
Smoker	295 (33)	
Former smoker (quit >1 month ago)	296 (33)	
Not reported	256 (28)	
Charlson comorbidity score		
0	383 (42)	NA
1	269 (30)	
2	145 (16)	
≥3	110 (12)	
Histology		
Adenocarcinoma	442 (49)	6,222 (45)
Squamous cell carcinoma	237 (26)	4,062 (29)
Large cell carcinoma	90 (10)	1,884 (14)
Other histology	29 (3)	407 (3)
Unknown	107 (12)	1,417 (10)
Clinical stage		
Stage <IV	561 (62)	6,552 (47)
Stage =IV	321 (35)	6,887 (49)
Unknown	25 (3)	553 (4)

*Initially, data was collected on 1067 patients. 1067 minus 102 (previous treatment in another hospital) minus 58 (second opinion only) = 907 patients.

**For one patient, gender was not registered.

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Table 7.2: Unit costs

	Unit costs	Source
Concomitant medication, stage I	€644.95	These are the mean concomitant medication costs per NSCLC patient per treatment line, as determined in a side study (n=107) in VU University Medical Centre. Detailed information on drug use was collected from the medical charts of a randomly selected subsample of 107 patients and multiplied by Dutch unit costs from www.medicijnkosten.nl. Main cost drivers were aprepitant, ondansetron and erytromycine.
Concomitant medication, stage II	€319.15	
Concomitant medication, stage III	€630.27	
Concomitant medication, stage IV	€254.90	
Concomitant medication, stage unknown	€528.96	
Consultations by telephone	€14.51	Dutch costing manual 2010. Inflated from €14 using Statistics Netherlands general inflation rates.
Day with laboratory testing	€71.37	Excluding pathology and genetic biomarker tests (see chapter VI).
Day care	€260.11	Dutch costing manual 2010. Inflated from €251 using Statistics Netherlands general inflation rates.
Definitive radiotherapy	€8,839.75	NZa tariff, "T4 Intensive radiotherapy excluding expensive imaging".
Drug therapies	Various	Z-index price via www.medicijnkosten.nl.
Genetic biomarker tests	€912.30	NZA tariff, "Complex molecular diagnostics – tests on isolated DNA, RNA or protein other than frequently requested tests on micro-organisms", including specialist fee.
In-patient hospital day, academic hospital	€595.87	Dutch costing manual 2010. Inflated from €575 using Statistics Netherlands general inflation rates.
In-patient hospital day, general hospital	€450.79	Dutch costing manual 2010. Inflated from €435 using Statistics Netherlands general inflation rates.
Intensive care unit day	€2262.20	€1788.61 additional to weighted average hospital day costs.
Mediastinoscopy, thoracotomy	€4,852.99	NZa tariff, "11 SURGICAL LUNG 103, declaration code 140533"
Medical imaging services & other procedures	Various	NZa tariff, 129 different types of procedures, ranging from simple pulmonary function tests to neurosurgery.

Table 7.2: Unit costs (continued)

	Unit costs	Source
Outpatient visit, academic hospital	€133.68	Dutch costing manual 2010. Inflated from €129 using Statistics Netherlands general inflation rates.
Outpatient visit, general hospital	€66.32	Dutch costing manual 2010. Inflated from €64 using Statistics Netherlands general inflation rates.
Palliative radiotherapy	€1,872.64	NZa tariff, "T1 Standard radiotherapy"
Pathology (cytology, histology)	€62.78	NZA tariff, "Anatomic pathology (histology) testing and other cytodiagnostic tests", including specialist fee.
Wedge resection, lobectomy, segmentectomy, pneumectomy, other large lung surgery	€5,956.64	NZa tariff, "11 SURGICAL LUNG 104, declaration code 140534"

Of all patients, 41% had adverse events and 9% had adverse events of grade III or higher (see Table 7.4). Grade ≥III adverse event-related hospital admissions cost on average €2,081 for stage I-III and €2,105 for stage IV NSCLC patients.

Costs for concomitant medication were not significantly associated with incidence and costs of AEs, possibly due to the preventive use of concomitant medication. For example, the preventive use of concomitant anti-emetics with chemotherapy reduces nausea and therefore decreases incidence of this adverse event.

Table 7.5 shows NSCLC costs and number of patient months per diagnostic or treatment period. Mean total costs are €1,725 for the diagnosis period, €17,296 for the first treatment line (and follow-up), and €13,236 for later treatment lines (and follow-up). Average duration of these periods is 2.4, 9.4 and 6.0 months respectively. The shorter duration of second and later treatment lines explains the lower costs compared to the first treatment line.

Note that a proportion of the patients did not receive treatment at all, or received more than two treatment lines. Therefore, mean total cost per patient (see totals in Table 7.3) is not equal to the sum of the mean costs per period.

Part of the patients (n=58) did not receive treatment in the study hospital, but came for a second opinion. Costs of providing a second opinion, per patient, including all diagnostics and hospital contacts for second opinion patients, are €2,580 (SD €4,907).

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Table 7.3: Resource use and costs NSCLC

	Ignoring censoring						Weighted cases					
	Stage I-III n=561 €		Stage IV n=321 €		Total (incl. stage = unk) n=907 €		Stage I-III n=528[1] €		Stage IV n=295[1] €		Total (incl. stage = unk) n=846[1] €	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Chemotherapy[2]	1,875	(4,293)	5,161	(9,073)	2,987	(6,569)	2,686	(825)	5,138	(894)	3,561	(617)
Concomitant medication[3]	806	(551)	477	(438)	681	(538)	779	(166)	559	(77)	713	(113)
Consultations by telephone	29	(43)	35	(49)	31	(45)	33	(10)	42	(7)	37	(7)
Day-care	442	(766)	602	(1,025)	491	(863)	555	(138)	775	(149)	645	(108)
Day with laboratory testing (excluding pathology and genetic biomarker tests)	1,334	(1,359)	1,149	(1,076)	1,263	(1,272)	1,619	(474)	1,360	(149)	1,573	(315)
Genetic biomarker tests	81	(271)	207	(416)	128	(339)	104	(31)	187	(27)	134	(21)
In-patient hospital days	9,290	(23,142)	6,541	(6,856)	8,251	(18,756)	10,689	(2,416)	7,252	(678)	9,542	(1,571)
Intensive care unit days[4]	1,074	(4,097)	245	(1,673)	759	(3,399)	1,315	(481)	225	(106)	904	(309)
Lung surgery	2,957	(3,434)	546	(1,950)	2,079	(3,208)	1,628	(324)	414	(116)	1,163	(203)
Medical imaging services & procedures	3,740	(2,837)	3,410	(2,644)	3,602	(2,775)	4,174	(1,242)	3,640	(398)	4,105	(833)
Out-patient visits	2,934	(3,437)	2,753	(3,098)	2,838	(3,303)	4,874	(2,409)	3,139	(463)	4,387	(1,584)
Pathology (cytology, histology)	187	(146)	165	(116)	178	(136)	197	(57)	171	(16)	192	(38)
Radiotherapy	5,005	(4,999)	2,371	(3,584)	4,006	(4,689)	5,032	(1,944)	2,949	(853)	4,522	(1,365)

Table 7.3: Resource use and costs NSCLC (continued)

| | Ignoring censoring | | | | | | Weighted cases | | | | | |
| | Stage I-III n=561 € | | Stage IV n=321 € | | Total (incl. stage = unk) n=907 € | | Stage I-III n=528[1] € | | Stage IV n=295[1] € | | Total (incl. stage = unk) n=846[1] € | |
	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)
Targeted therapy[2]	419	(2,841)	2,445	(10,278)	1,174	(6,707)	777	(315)	2,650	(824)	1,666	(418)
Total	30,173	(29,874)	26,109	(24,562)	28,468	(27,935)	34,241	(10,832)	28,502	(4,755)	33,143	(7,392)
Mean duration in months (95% CI)	29.9 (26.9-33.0)		12.6 (11.3-14.0)		23.6 (21.5-25.8)		n/a		n/a		n/a	
Median duration in months (95% CI)	33.3 (30.8-35.8)		8.7 (6.8-10.8)		20.7 (17.7-23.7)		n/a		n/a		n/a	
[1] Weighted cases could not be computed for patients												
With a follow-up time <1	n/a		n/a		n/a		n=16		n=20		n=37	
With follow-up time unknown	n/a		n/a		n/a		n=17		n=7		n=24	

[2] Including drug spillage.
[3] As determined in a side study among a random sample of 107 patients from VU University Medical Centre.
[4] Costs additional to the costs of a "regular" in-patient hospital day.

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Table 7.4: Costs for adverse event-related outpatient visits and hospital admissions, ignoring censoring

	Stage I-III NSCLC	Stage IV NSCLC	Total (incl. stage = unk)
Patients with registered adverse events, N (%)	233 (42)	129 (40)	369 (41)
Costs for adverse event-related hospital admissions per patient with any adverse event, Mean € (SD)	1,133 (2,865)	1,180 (2,804)	1,133 (2,816)
Patients with registered grade ≥III adverse events, N (%)	49 (9)	33 (10)	82 (9)
Costs for adverse event-related hospital admissions per patient with grade ≥III adverse events, Mean € (SD)	2,081 (3,976)	2,105 (4,275)	2,091 (4,073)

Table 7.5: Costs per phase of NSCLC management, ignoring censoring

	Stage I-III NSCLC	Stage IV NSCLC	Total (incl. stage = unk)
	Mean € (SD) [number of periods]	Mean € (SD) [number of periods]	Mean € (SD) [number of periods]
Chemotherapy*			
Diagnosis	-	-	-
1st treatment	1,104 (2,740) [523]	3,500 (7,551) [259]	1,860 (4,969) [798]
2nd and later treatments	1,706 (3,277) [278]	2,623 (4,749) [286]	2,142 (4,091) [572]
Concomitant medication**			
Diagnosis	-	-	-
1st treatment	575 (123) [523]	289 (104) [259]	481 (177) [798]
2nd and later treatments	544 (144) [278]	273 (79) [286]	409 (175) [572]
Consultations by telephone			
Diagnosis	6 (15) [561]	7 (13) [321]	6 (14) [907]
1st treatment	15 (29) [523]	16 (28) [259]	16 (29) [798]
2nd and later treatments	18 (28) [278]	17 (27) [286]	18 (28) [572]
Day-care			
Diagnosis	137 (218) [561]	155 (229) [321]	142 (221) [907]
1st treatment	187 (468) [523]	240 (569) [259]	201 (499) [798]
2nd and later treatments	265 (523) [278]	285 (744) [286]	274 (640) [572]
Day with laboratory testing (excluding pathology and genetic biomarker tests)			
Diagnosis	248 (353) [561]	280 (339) [321]	263 (352) [907]
1st treatment	819 (1,034) [523]	576 (744) [259]	740 (963) [798]
2nd and later treatments	652 (798) [278]	454 (538) [286]	552 (683) [572]
Genetic biomarker tests* **			
Diagnosis	81 (271) [561]	207 (416) [321]	128 (339) [907]
1st treatment	-	-	-
2nd and later treatments	-	-	-
In-patient hospital days			
Diagnosis	1,808 (18,840) [561]	1,706 (3,167) [321]	1,778 (14,948) [907]

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Table 7.5: Costs per phase of NSCLC management, ignoring censoring (continued)

	Stage I-III NSCLC	Stage IV NSCLC	Total (incl. stage = unk)
	Mean € (SD) [number of periods]	Mean € (SD) [number of periods]	Mean € (SD) [number of periods]
1st treatment	5,564 (10,489) [523]	3,419 (5,335) [259]	4,872 (9,152) [798]
2nd and later treatments	4,631 (12,322) [278]	2,330 (4,071) [286]	3,467 (9,145) [572]
Intensive care unit days****			
Diagnosis	41 (644) [561]	33 (446) [321]	37 (572) [907]
1st treatment	917 (3,894) [523]	159 (1,215) [259]	657 (3,249) [798]
2nd and later treatments	360 (2,052) [278]	94 (1,017) [286]	228 (1,612) [572]
Lung surgery			
Diagnosis	-	-	-
1st treatment	2,688 (2,939) [523]	359 (1,406) [259]	1,928 (2,765) [798]
2nd and later treatments	909 (2,133) [278]	288 (1,272) [286]	607 (1,793) [572]
Medical imaging services & procedures			
Diagnosis	1,680 (1,314) [561]	1,821 (1,221) [321]	1,725 (1,280) [907]
1st treatment	1,523 (1,640) [523]	902 (1,116) [259]	1,316 (1,508) [798]
2nd and later treatments	1,292 (1,487) [278]	967 (1,276) [286]	1,140 (1,396) [572]
Out-patient visits			
Diagnosis	723 (781) [561]	713 (615) [321]	719 (723) [907]
1st treatment	1,631 (2,395) [523]	1,169 (1,502) [259]	1,471 (2,140) [798]
2nd and later treatments	1,392 (1,775) [278]	1,230 (1,603) [286]	1,306 (1,683) [572]
Pathology (cytology, histology)			
Diagnosis	96 (92) [561]	122 (94) [321]	105 (94) [907]
1st treatment	73 (83) [523]	29 (63) [259]	58 (80) [798]
2nd and later treatments	47 (84) [278]	22 (52) [286]	34 (70) [572]
Radiotherapy			
Diagnosis	-	-	-
1st treatment	3,914 (4,263) [523]	1,555 (2,245) [259]	3,141 (3,884) [798]
2nd and later treatments	2,737 (3,592) [278]	1,253 (1,849) [286]	1,969 (2,928) [572]

Table 7.5: Costs per phase of NSCLC management, ignoring censoring (continued)

	Stage I-III NSCLC	Stage IV NSCLC	Total (incl. stage = unk)
	Mean € (SD) [number of periods]	Mean € (SD) [number of periods]	Mean € (SD) [number of periods]
Targeted therapy*			
Diagnosis	-	-	-
1st treatment	156 (1,974) [523]	1,230 (8,030) [259]	554 (5,068) [798]
2nd and later treatments	551 (2,374) [278]	1,630 (6,847) [286]	1,090 (5,141) [572]
Total			
Diagnosis	4,819 (19,215) [561]	5,045 (4,159) [321]	1,725 (1,280) [907]
1st treatment	19,166 (16,319) [523]	13,445 (16,757) [259]	17,296 (16,665) [798]
2nd and later treatments	15,104 (15,905) [278]	11,466 (11,886) [286]	13,236 (13,940) [572]
Duration in months			
Diagnosis: median, mean (SD)	1.4, 2.4 (3.9)	1.2, 2.3 (4.0)	1.4, 2.4 (4.0)
1st treatment: median, mean (SD)	11.0, 11.9 (9.7)	2.4, 4.6 (5.1)	5.9, 9.4 (9.1)
2nd and later treatments: median, mean (SD)	5.0, 7.9 (8.2)	3.1, 4.2 (3.4)	3.9, 6.0 (6.9)

*Including drug spillage.

**As determined in a side study among a random sample of 107 patients from VU University Medical Centre.

***For genetic biomarker tests, data was not registered so all were allocated to the diagnosis period.

****Costs additional to the costs of a "regular" in-patient hospital day.

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Table 7.6: Summary of lung cancer costs from various studies, ordered by year of publication

Study	Country	N	Indication	Main cost findings	Year and currency of costing	Cost per patient in euros 2012*	Other interesting findings
Davis et al. (2015)[117]	US Medicare beneficiaries	17,133	Metastatic squamous NSCLC	Mean NSCLC-related costs: $50,701 per patient.	2012, US$	€44,868	The period between completion of systemic treatment and death/study completion was the costliest period, with a mean cost of $30,951 per patient.
Buck et al. (2014)[118]	Southern and Midwestern US (network of community oncology practices)	609	NSCLC stage IB-IIIA after surgery.	Mean overall cost of care during the entire duration of adjuvant treatment: $49,132. Mean overall cost from diagnosis until the end of the initial systemic therapy regimen following recurrence or end of medical record: $62,986 per patient.	2013, US$	€54,380	During adjuvant treatment, monthly median cost per patient was $17,390. Monthly cost from diagnosis until the end of the initial systemic therapy regimen following recurrence or end of medical record: $1,185.

Table 7.6: Summary of lung cancer costs from various studies, ordered by year of publication (continued)

Study	Country	N	Indication	Main cost findings	Year and currency of costing	Cost per patient in euros 2012*	Other interesting findings
Dinan et al. (2014)[119]	US Medicare beneficiaries	51,374	NSCLC	Total costs in the post-PET (positron emission tomography) cohort: $52,209 per patient ($26,944 inpatient).	2008, US$	€49,666	Adoption of PET between 1998 and 2005 was accompanied by decreases in rates of surgery and radiotherapy and in short-term inpatient costs among Medicare beneficiaries with NSCLC, although there was an increase in chemotherapy and overall costs.
Zeng et al. (2012)[105]	China (one hospital)	253	Advanced NSCLC	Mean cost of treatment over one year, progression-free state: $11,566. Mean cost of treatment over one year, disease-progression state: $14,519.	2010, US$	Unknown	Medical care costs in the three successive months prior to death were US$3,754, US$5,829 and US$7,372, respectively. The monthly costs are higher initially than in subsequent months.
Kang et al. (2012)[115]	South Western Sydney, Australia (one cancer therapy centre)	210	Lung cancer (86.2% NSCLC)	Mean costs for managing NSCLC: $13,659.	2005, AUD	€10,578	Hospitalisation and cancer treatment, particularly chemotherapy, accounted for the major components of direct medical costs.

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Table 7.6: Summary of lung cancer costs from various studies, ordered by year of publication (continued)

Study	Country	N	Indication	Main cost findings	Year and currency of costing	Cost per patient in euros 2012*	Other interesting findings
Cipriano et al. (2011)[108]	US Medicare beneficiaries	60,231	Lung cancer	Monthly treatment costs for a 72-year-old patient, diagnosed with lung cancer in 2000, in the first 6 months ranged from $2,687 (no active treatment) to $9,360 (chemotherapy).	2006, US$	Unknown	Patient liability represented up to 21.6% of care costs and increased over the period 1992-2003 for most stage and treatment categories, even when care costs decreased or remained unchanged.
Neubauer et al. (2010)[120]	US (eight practices in the US Oncology network)	1,409	NSCLC	Mean outpatient cost per patient per year: $18,042 (patients treated on-pathway) and $27,737 (patients treated off-pathway).	2007, US$	Unknown	Costs remained significantly less for patients treated on-pathway versus off-pathway in the adjuvant and first-line settings, whereas no difference in overall cost was observed in patients in the second-line setting.

Table 7.6: Summary of lung cancer costs from various studies, ordered by year of publication (continued)

Study	Country	N	Indication	Main cost findings	Year and currency of costing	Cost per patient in euros 2012*	Other interesting findings
Pompen et al. (2009)[109]	Netherlands (five hospitals)	102	Advanced NSCLC	Mean total treatment cost per patient per year: €32,840 (patients receiving best supportive care after first-line chemotherapy) and €31,187 (patients receiving second-line chemotherapy after first-line chemotherapy).	2005, €	Unknown	In spite of the difference in numbers of treatment lines provided to patients in groups A and B, the total mean costs per patient per year were similar. Hospitalisation was the main cost driver (55% in group A, 44% in group B).
Lang et al. (2009)[116]	US Medicare beneficiaries	31,158	Advanced NSCLC treated with commonly used two-drug chemotherapy	Medical-care costs: approximately $70,000. On-treatment costs for first-line chemotherapy: approximately $30,000.	2005, US$	€69,562	Although doublet therapy with platinum and a taxane was the most frequently utilized regimen, it was associated with the highest lifetime and on-treatment costs.

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Table 7.6: Summary of lung cancer costs from various studies, ordered by year of publication (continued)

Study	Country	N	Indication	Main cost findings	Year and currency of costing	Cost per patient in euros 2012*	Other interesting findings
Fleming et al. (2008)[121]	Northern Ireland (Northern Ireland Cancer Registry patients (NICR))	724	Lung cancer (62% NSCLC)	Mean hospital costs: £5,956 per patient with NSCLC, for 12 months since presentation.	2004, £	Unknown	The main component of cost was inpatient stay, representing between 62 and 84% of costs depending on cell type. Total annual hospital costs were 13 times as high as the estimated enforcement cost of the smoke-free legislation in Northern Ireland.
Demeter et al. (2007)[122]	Canada (Alberta Cancer Registry)	611	Lung cancer (81% NSCLC)	Mean NSCLC costs: $15,023.	2000-2001, US$	€16,604	The vast majority of overall costs occurred just before, or within, three months of diagnosis.
Kutikova et al. (2005)[123]	US (employees, dependents and retirees of multiple large employers)	2,040	Lung cancer	Regression-adjusted mean monthly costs: $6,520 for patients versus $339 for controls. Overall costs across the study period: $45,897 for patients and $2,907 for controls.	2000, US$	€48,606	The main cost drivers were hospitalisation (49.0% of costs) and outpatient office visits (35.2% of costs). Failure of initial treatment was associated with markedly increased costs.

Table 7.6: Summary of lung cancer costs from various studies, ordered by year of publication (continued)

Study	Country	N	Indication	Main cost findings	Year and currency of costing	Cost per patient in euros 2012*	Other interesting findings
Dedes et al. (2004)[124]	Switzerland (one hospital)	118	Lung cancer (89% NSCLC)	Mean cost per NSCLC patient: €19,212.	1999, €	€25,086	71% of the costs were due to hospitalisation. Patients with advanced stages of lung cancer show the highest cost, mainly due to the costs of chemotherapy.
Braud et al. (2003)[125]	France (four hospitals)	100	Lung cancer after diagnosis of a first recurrence (78% NSCLC)	Mean cost per NSCLC patient: €13,969.	2001, €	€17,446	51% of the total NSCLC cost corresponded to terminal care, with up to seven lines of chemotherapy.

*Using 15/06/2015 exchange rates (€1 = US$1.13 / AUD1.45) and Consumer Price Index rates from Statistics Netherlands (statline.cbs.nl).

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DISCUSSION

Crude mean hospital costs per NSCLC patient in the Netherlands were €28,468 during our study period and €33,143 for the total disease duration, corrected for censoring. The largest component of these costs (29%) is costs for inpatient hospital days. The Dutch National Institute of Public Health and the Environment (RIVM) reported the total costs for lung cancer in the Netherlands to be 401 million euro in 2011. With an estimated prevalence of 20,500 patients in that same year, costs of lung cancer are expected to be less than €20,000 per patient per year; 82% (±€16,000 per patient per year) is spent on hospital care.[103] Given the mean duration (23.6 months) and mean hospital costs (€28,468) in the present study, costs amount to €14,475 per patient per year. In the present study, costs were calculated bottom-up; resource use per patient was multiplied by prices and summed over all patients. The RIVM calculated costs top-down: total national healthcare expenditures were divided over the diseases. Both outcomes are fairly similar, especially given the uncertainties associated with costing studies. The difference of ±€1,500 might be due to patients generating costs at hospitals other than those in the study.

Table 7.6 shows a summary of lung cancer costs reported in other studies published from 2003 onwards. These studies were obtained from a non-systematic review of the literature, selecting cost studies with any estimate of the general (not specific for one therapy) costs of lung cancer from a hospital or oncology practice perspective. Reported costs range from €10,578 to €69,562 per NSCLC patient, compared to €33,143 per patient (corrected for censoring) in our study. Variations are partly due to differences in healthcare systems, unit costs and research methodology.

The smallest cost estimate is from an Australian study by Kang et al. This study was carried out for 210 NSCLC and small-cell lung cancer (SCLC) patients.[115] By subtracting data retrospectively from clinical records, they calculated mean costs of €10,578 (A$ 13,659) per NSCLC patient. Patient inclusion criteria were not reported, except that patients with recurrent disease were excluded from the analyses. There was a larger proportion of stage IV patients than in the present study (51% versus 35%), relatively more patients with large cell carcinoma (37% versus 10%) and fewer patients with adeno (36% versus 49%) and squamous cell carcinoma (21% versus 26%). The inclusion of cost components was similar to the current study, except that the Australian cost study did not include routine blood tests. However, it is not likely that these differences in patient case mix and cost components explain the lower mean costs in their study. One possible explanation may be that several unit costs in Australia are significantly lower than they are in the Netherlands, for example for hospitalisation (approximately €202 compared to €451 per hospital admission day in the

Netherlands[57]). Furthermore, the median follow-up time was 16.6 months for both NSCLC and SCLC patients, which is lower than in the present study (20.2 months).

The largest cost estimate is from an American study by Lang et al.[116] All patients included in this study were aged 65 years or older, had stage IIIB or stage IV NSCLC and were treated with two-drug chemotherapy. Since two-drug chemotherapy is a relatively expensive treatment and our study included patients irrespective of treatment (including patients receiving supportive care only), this selection criterion may be the most important reason for the large cost difference. Furthermore, the study by Lang et al. also included home healthcare, hospice and physician service costs, while these were excluded from our study.

Only one other NSCLC cost study was performed in the Netherlands. Dutch data from 2005[109] showed annual costs of hospital treatment of patients with unresectable advanced NSCLC to be on average €32,840 (group A: first-line chemotherapy, second-"line" best supportive care) and €31,187 (group B: first and second-line chemotherapy). In our study, yearly costs for stage IV NSCLC were mean €24,866 (€26,109/12.6*12) (2012 prices). As Pompen et al. followed patients for almost four years after diagnosis, relatively more complete information was available (18 out of 102 patients were still alive at the end of follow-up). Mean follow-up time was similar to our study (12.2 and 14.4 months in the two study groups). Their sample size was very small (n=106) compared to our sample size (n=907 total, n=321 stage IV). Patient selection was more restricted than in our study, as they selected patients who received first-line chemotherapy followed by either best supportive care or second-line chemotherapy. This selection based on treatment may explain the higher costs in the study by Pompen et al. Both in our study and in the study of Pompen et al., hospital admissions were the major cost driver.

Limitations of this study

Hospital care and (the fees of) medical specialists account for 82% (330 million euro) of lung cancer costs. By taking a hospital perspective, we limited our analyses to hospital care and medical specialists, thereby excluding the other 18% of medical costs incurred by lung cancer patients.[103] These costs arise from, amongst others, visits to the general practitioner, other healthcare providers (such as a physiotherapist), other institutions (such as a hospice), and extramural drugs not prescribed by a clinician from the hospital. Moreover, non-medical and indirect costs for lung cancer patients, which can be considerable, were excluded from our study.

Furthermore, this study did not assess the cost-effectiveness of NSCLC management or the cost-effectiveness of alternative treatment choices. Unfortunately, increased spending on

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cancer care does not necessarily result in better outcomes[77]. Since this study did not evaluate diagnostic or treatment (cost-)effectiveness, it does not provide information on how to decrease NSCLC spending or improve cost-effective allocation of resources.

Additionally, this study included only four out of eighty-four Dutch hospitals. Although the results represent real-world costs, these costs are not necessarily representative for other hospitals in the Netherlands and elsewhere. In order to promote generalisability, two academic as well as two non-academic hospitals were included. However, all participating hospitals are teaching hospitals, are relatively large, and they employ some of the key opinion leaders in the Dutch field of lung oncology. Innovative practices may therefore be more common in our study sample than elsewhere in the Netherlands.

Limitations of the data

We aimed to present the costs of the complete disease course of NSCLC patients. However, the follow-up time of this study was relatively short. Furthermore, since patients were included in the study as they were diagnosed within a two-year time frame, we collected relatively more data on the early phases of disease. By using the Bang and Tsiatis estimator we corrected for the fact that cost data was censored.

When censoring was ignored, total mean costs were underestimated by 14%. For surgery the Bang and Tsiatis correction resulted in lower cost estimates than the original estimates. This is due to the fact that a surgery is usually the first treatment choice, and costs are therefore high at the beginning of the disease course. These patients have a relatively good prognosis and become censored cases as they survive past the end of the study follow-up. The B&T estimator only includes costs of complete cases, that is, patients who have died within the study follow-up. In the case of surgery, these are patients who have died during or shortly after surgery. As they have died shortly after the start of follow-up, the Kaplan Meier estimator weights these costs less than it weights other cost items, where the death is more equally distributed over the follow-up time.

Next, selection bias may have occurred, as we had information on the full course of disease only for those patients who were diagnosed and who had died within these two years. These patients may be more expensive patients, requiring more intensive treatment than patients who died after the two-year follow-up period.

Furthermore, some patients were treated in multiple hospitals. Permission to collect and use patient chart data could only be obtained for the four study hospitals. Therefore, patients

were "lost" and considered "censored" from the moment they were referred to a hospital that was not one of the study hospitals.

Another challenge was the registration of disease stages. The TNM staging system changed to the 7th edition halfway through the study period, so for each patient we used the TNM edition that was in use at the time the clinician recorded the disease stage in the patient chart. However, TNM stage can change during the diagnostic period, can differ between clinicians, and cannot always reliably be obtained from patient charts. This was a limitation of both the data we collected and the NCR data, which we used to validate our stage information. We therefore decided not to separate stages I-III, in order to minimise potential misclassification.

Finally, we found that many relevant prognostic factors were not registered systematically. For instance, WHO performance status was only registered in 19% of the cases (at baseline). The same was true for important disease-related events over time, such as a local or locoregional recurrence and a metastasis. However, we were able to register if patients moved to metastatic disease within the follow-up time of the study.

Future perspective

The demand for real-world evidence (RWE) has increased recently, as policy makers recognise its value in providing information on treatment effectiveness and cost-effectiveness.[126] Such RWE cannot be obtained from clinical trials, since the resource use in clinical trials does not reflect the resource use in daily practice. In clinical trials, resource use is partly determined by the trial protocol. In the current study, we provided actual real-world data on resource use and costs. The results can be used in future model-based cost-effectiveness studies.

Future outcomes research should focus on utilities as well, as this was not included in this study. However, reliable utility estimates for treatment alternatives, as well as various other aspects of real-world NSCLC management, would best be studied within a prospective population-based patient registry that included all newly diagnosed NSCLC patients. This type of data is extremely important for evaluating the large number of new, mainly targeted, therapies that are expected to be launched in the coming years, which aim to improve not only survival but quality of life as well.[127]

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CONCLUSIONS

The current study provides real-world data on the costs of NSCLC, per cost category, from a hospital perspective. This data can be used to inform health-economic models and decision making by hospital, industry and governmental stakeholders. Total mean hospital costs per NSCLC patient are €33,366 for the total duration of the disease.

Chapter VIII

Balancing the optimal and the feasible

A practical guide for setting up patient registries for the

collection of real-world data for healthcare decision making

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ABSTRACT

Objective

The aim of this paper is to provide practical guidance in setting up patient registries to facilitate real-world data collection for healthcare decision making.

Methods

This guidance was based on our experiences and involvement in setting up patient registries in The Netherlands. All aspects were structured according to i) "the Why" (mission and goals), ii) "the Who" (stakeholders and funding), iii) "the What" (type and content), and iv) "the How" (identification and recruitment of patients, data handling and pharmacovigilance).

Results

The mission of most patient registries is improving patient health by improving patient care; monitoring patient care is often the primary goal ("the Why"). It is important to align the objectives of the registry and agree on a clear and functional governance structure with all stakeholders ("the Who"). Expertise is essential on both clinical and real-world data to select appropriate data elements. There is often a trade-off between reliability, validity and specificity of data elements and feasibility of data collection ("the What"). Patient privacy should be carefully protected including training in Good Clinical Practice and addressing (inter-)national and local regulations. Patient registries can reveal unique safety information but it can be challenging to comply with pharmacovigilance regulations ("the How").

Conclusion

It is crucial to set up an efficient patient registry that serves its aims by collecting the right data of the right real-world patient in the right way. It can be expected that patient registries become the new standard alongside RCTs considering their unique value.

INTRODUCTION

Globally, there is an increasing trend to use real-world data to inform decision making in health care. Real-world data is often collected using a patient registry. A patient registry can be defined as "an organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes".[128]

The United States Food and Drug Administration (FDA) can require a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. A REMS could involve a registry. Similarly, a registry could be part of a risk management plan which can be required by the European Medicines Agency (EMA).[129] Besides regulatory authorities, local reimbursement agencies can use real-world data in reimbursement decisions. Furthermore, countries as Denmark, Finland, Iceland, Norway and Sweden have extensive experience with patient registries. These countries implemented national databases to track prescription drugs in ambulatory care[130] that are linked to other data sources (e.g., cancer registries and health surveys). With these databases drug use can be studied, just as beneficial or adverse outcomes of drug use in real-world clinical practice.[130]

As consequence of a coverage with evidence development policy implemented in 2006, the number of patient registries is rapidly increasing in The Netherlands. This policy guarantees early access to expensive drugs, but requires in return the collection of additional data regarding appropriate drug use, effectiveness and cost-effectiveness in real-world clinical practice. These data are used to evaluate a drug's real-world value after four years of initial reimbursement.

In this paper, we provide practical guidance in setting up patient registries for the collection of real-world data on behalf of health care decision making. This paper is based on our experiences and involvement in setting up patient registries in The Netherlands for various types of cancer such as melanoma (e.g., DMTR), lung (e.g., POSEIDON), prostate (CAPRI and PRO-CAPRI), renal cell (PERCEPTION), haematological (PHAROS 1)[131,132], colorectal and head and neck cancer (chapter I-III). This paper first discusses the mission and goals ("the Why") of patient registries and highlights issues related to the involvement of diverse stakeholders and the funding of registries ("the Who"). After that, challenges and solutions will be discussed regarding the type and content of a patient registry and data collection ("the What") and the identification and recruitment of patients, data handling, and pharmacovigilance

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("the How"). Lastly, we discuss the main challenges in balancing the optimal and the feasible in setting up patient registries.

MISSION AND GOALS ("THE WHY")

Why use a patient registry, and how to guarantee valorisation of outcomes to real-world clinical practice?
The mission of most registries is improving patient health by improving patient care. Therefore, monitoring patient care is often the primary goal of a registry. But patient registries can serve many additional goals. For example, patient registries are one of EMA's tools to gain more insight into known and potential risks of a certain product in real-world clinical practice.[129] In addition, patient registries can provide information on appropriate drug use (which indicates whether a drug is used in the right way in the right patients), effectiveness (as opposed to efficacy in a clinical trial), costs, and cost-effectiveness in real-world clinical practice.[133,134] Besides effectiveness in terms of progression-free survival, overall survival or response rates, registries can provide essential information on patient reported outcomes in case data is prospectively collected (Table 8.1). This gives important insight into patient's experiences and health-related quality of life, and enables the estimation of quality adjusted life years for economic evaluations. These outcomes are important in reimbursement decision making. Furthermore, data from patient registries can inform public health planning, for example by detecting common causes of a disease illustrating the need for a prevention program.[135]

It should be noted that gathering all these data will not immediately improve patient health. It is essential to frequently discuss the findings with clinicians and ensure a quality-of-care feedback loop. In this way clinicians are able to improve their patient care. Furthermore, outcomes can be used in the development of clinical guidelines to improve the (efficiency of) delivery of care. Although all registries in which we are involved ensure transparency to the public through presentations and publications, the DMTR is the only registry that uses clinical auditing and fortnightly provides clinicians with online feedback regarding a predefined set of quality indicators developed by the professional organisation (see Table 8.1). This benchmarking facilitates insights in clinician and hospital performance. Creating a feedback loop (with or without a benchmark) will not immediately improve patient care or impact the health of current patients, but could improve the health of future patients.

Table 8.1: Mission and goals ("the Why")

Name of registry	PHAROS 1	CAPRI and PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON	Locally advanced Head & Neck	Recurrent and/or metastatic Head & Neck
The Why										
Disease	CLL, MM, NHL	CRPC	Melanoma (stage IIIc/IV)	Melanoma	mCRC	mRCC	NSCLC	NSCLC	(LA) SCCHN	(RM) SCCHN
Aim: Providing insights into patient and disease characteristics and treatment patterns	x	x	x	x	x	x	x	x	x	x
Providing insights into clinical outcomes and economic outcomes	x	x	x	x	x	x	x	x	x	x
Providing insights into patient reported outcomes*	x	x	x			x				
Providing online benchmarked feedback to clinicians, hospitals and manufacturers			x							
Identifying prognostic groups based on classical and non-classical parameters						x				

* Patient reported outcomes in these registries at least include health-related quality of life.

Abbreviations: CLL, chronic lymphocytic leukemia; MM, multiple myeloma; NHL, Non Hodgkin lymphoma; CRPC, castration-resistant prostate cancer; mCRC, metastatic colorectal carcinoma; mRCC, metastatic renal cell carcinoma; NSCLC, Non-small-cell lung carcinoma; LA SCCHN, locally advanced Squamous Cell Carcinoma of the Head and Neck; RM SCCHN, recurrent and/or metastatic Squamous Cell Carcinoma of the Head and Neck.

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STAKEHOLDERS AND FUNDING ("THE WHO")

Who are involved in the registry?

Broad support for the registry and its goals is needed to maximise the benefits. Stakeholders can include clinicians, researchers, patients, governmental parties, healthcare insurers and manufacturers. Involvement from clinical experts (including key opinion leaders) improves the valorisation of the research results. Involvement of patient representatives secures patient participation and may help to ensure that the aims of the registry are pursued with minimal burden to patients. Participation of manufacturers may financially support the registry. Note that the term "manufacturers" is used in this article to refer to all companies involved in manufacturing, marketing or selling pharmaceuticals or medical devices.

Stakeholder can, however, have conflicting interests, for example with respect to aims, (level of) data access and data ownership (including publishing rights). Table 8.2 shows the different involvement of stakeholders in the registries we are familiar with. An essential and possibly time-consuming step in setting up a registry, is to align the main aim(s) of the registry. It is important to discuss primary and secondary objectives with key stakeholders at an early stage of drafting the plans for a new registry. It is also important to establish a clear and functional governance structure with all stakeholders, to define tasks and responsibilities and agree on the decision-making processes.

Furthermore, data sharing might be an issue. For example when multiple manufacturers fund the registry, they may not be willing to share access to product-specific data with their competitors. In this case, detailed product-specific data can be shared with the manufacturer of the respective product, while sharing only aggregated data on products owned by other companies. By allowing variation in the level of data sharing[136], even competing parties can participate and may benefit from collaboration within the same registry.

Technical solutions are available to many practical challenges, but agreeing on the objectives and governance structure is crucial before moving on to technical matters. Identifying and engaging relevant stakeholders is, therefore, key to the success of a patient registry.

Who funds the registry?

It is crucial to secure sufficient funding for designing and running a registry to ensure viability and sustainability. Funding can be a challenge, especially when a large amount of money is needed, for example, due to extensive data collection or long-term follow-up. Funding must be sufficient to secure commitment from competent staff and experts. Long-term funding arrangements (e.g., four years or longer) are essential for the sustainability of a registry.

Table 8.2: Stakeholders and funding ("the Who")

	The Who?	PHAROS 1	CAPRI & PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON	Locally advanced Head&Neck	Recurrent and/or metastatic Head&Neck
Funding	Clinicians and/or hospitals	×									
	Governmental party		×	×			×				×
	Manufacturer(s)		×	×	×	×	×	×	×	×	×
Consultation*	Clinicians and/or hospitals	×	×	×	×	×	×	×	×	×	×
	Governmental party			×							
	Manufacturer(s)	×	×	×	×	×	×	×	×	×	×
	Patients		×	×					×		
	Researchers / academia	×	×	×	×	×	×	×	×	×	×
Decision making / governance**	Clinicians and/or hospitals	×	×	×					×		
	Governmental party			×							
	Manufacturer(s)	×		×							
	Patients			×							
	Researchers / academia	×	×	×	×	×	×	×	×	×	×

*Stakeholders involved with the registry initiative and/or design.

**Stakeholders who have a formal say in decisions regarding the project when it is running.

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Registries can be funded from one or more sources including public and private sources (see Table 8.2). Potential funding sources are manufacturers, healthcare insurers, governmental organisations, patient organisations, professional societies, private foundations and advocacy groups. Dependent on the healthcare system, a more structural way to fund disease registries could be the inclusion of registry's expenses in the cost of treating the disease (e.g., by increasing the price of a Diagnosis Treatment Combination or Diagnosis Related Group).

We are involved in various registries that have been funded by multiple manufacturers. These registries were largely motivated by the need to collect real-world data on the performance of drugs for the Dutch reimbursement authority. Multi-sponsor registries have the advantage of decreasing the financial burden for each party and securing wider support for the registry. On the other hand, however, funders may have competing interests and ideas about the planning and design of the registry. In cases where multiple parties are involved, reaching consensus can be difficult and may require a long time. For example, multiple manufacturers were involved in PHAROS-1 and had products for various haematological indications in various treatment lines. Since the optimal approach for data collection differs per treatment (e.g., dependent on treatment line), priorities need to be set and need to be acceptable for all parties involved.

Another example is the POSEIDON lung cancer registry. The set-up of this registry started three years ago, but we still do not know whether or not data collection will actually commence. During the design of this registry, more and more stakeholders became involved and objectives became broader. While this increases the potential benefits of the registry, it also complicates decision making. Time-consuming processes include agreeing on the study protocol, governance structure and funding. It is important not only to secure funding for the design and running of the registry, but also for all other activities needed prior to the start of data collection (e.g., stakeholder meetings, writing/revising the study protocol, ethical approval, defining data sets).

TYPE, CONTENT, AND DATA COLLECTION ("THE WHAT")

What is a suitable type and content of the registry?
A patient registry can either be disease-based or intervention-based.[128] An intervention-based registry can answer questions regarding appropriate use, effectiveness, cost-effectiveness and safety. Disease-based registries provide additional information; for example, the number of untreated patients and whether these patients would have been eligible

Table 8.3: Type and content of the registry ("the What")

Name of Registry	PHAROS 1	CAPRI and PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON	Locally advanced Head & Neck	Recurrent and/or metastatic Head & Neck
The What										
Type: Disease-based	×	×	×	×		×	×	×		
Intervention-based					×				×	×
Scope: Population-based			×							
Sample-based	×	×		×	×	×	×	×	×	×
Content: Clinical outcomes	×	×	×	×	×	×	×	×	×	×
Economic outcomes	×	×	×	×	×	×	×	×	×	×
Patient reported outcomes	×	×	×			×		×		
Quality of care indicators*			×							
Patient material			To be decided			×		To be decided		

*Quality of care indicators can be derived from all registries (e.g., length of a stay in a hospital). However, the DMTR is the only registry providing online benchmarked feedback to clinicians, hospitals and manufacturers.

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for treatment (appropriate use). Moreover, it is possible to study the full disease course. In contrast to intervention-based registries, disease-based registries can provide complete information on (sequential) treatment pathways (Table 8.3). However, it should be noted that this adds to complexity, time and costs of a registry.

Both disease-based and intervention-based registries can include all patients that meet the inclusion criteria of the registry or can only include a sample of the population of interest (Table 8.3). Including all patients adds to time and costs, whereas selecting a sample could be more efficient but can have pitfalls as well. In particular, the representativeness of the total patient population (external validity) may be hampered. A random sample or a cluster sample can be taken to prevent selection bias. In a cluster sample, some or all patients in a certain cluster, for example a region or a hospital are included, assuming that this cluster is comparable to the clusters not included in the registry.

To increase efficiency, it may be an option to use multiple-phase sampling. For example, in a two-phase design, limited data is first collected in a large sample, then a subsample is selected consisting of patients fulfilling a certain defined set of criteria. In this manner, minimal data can be collected on all patients and more comprehensive data can be collected from a smaller sample. The DMTR uses such an approach. Minimal data is collected on patients who are not treated in a melanoma centre (due to a worse prognosis), whereas full data (clinical, economic, PROMs) are collected for all patients who were treated in one of the fourteen Dutch melanoma centres (Table 8.3). Furthermore, detailed data (additional health care resource use, productivity losses and informal care) are only collected in a selection of four of the fourteen melanoma centres.

What data elements should be included?
After determining the type and content, the actual data elements for the registry need to be carefully selected. Preferably, this selection is based on clinical data standards (e.g., from the Clinical Data Interchange Standards Consortium, CDISC), current data sets (e.g., national disease registry), and/or on standard terminology (e.g., Systematised Nomenclature of Medicine, SNOMED). This facilitates comparison of registry data to other studies and creates the possibility to link different data sets using the same data definitions.

An expert advisory board can be consulted to ensure the selection of appropriate data elements.[137] It is important to involve clinical experts as well as experts in real-world data handling. Clinical experts who are not experienced with outcomes research may advise on the inclusion of data elements that are difficult to collect in a real-world setting. It is advisable to always test the availability of data elements, for example in a pilot study. If there

is a lack of reliable data about certain variables (e.g., progression-free survival) it may be possible to substitute them with other variables (e.g., time to next treatment as a proxy for progression-free survival).

Using real-world data implies that there is always a trade-off between reliability, validity and specificity of data elements on the one hand, and the feasibility of data collection (affordability and completeness) on the other hand. The available data sources will set boundaries to what can be collected and will influence the way of data collection.

For example, in clinical trials data on adverse event is commonly reported by using the Common Terminology Criteria for Adverse Events (CTC AE) and the grade of the adverse event is scored by the clinician. This is, however, often not feasible in a registry, unless the CTC AE are consistently used and concisely reported in patients' medical charts in clinical practice. In our lung cancer study, data were retrospectively collected from medical charts. Only 81 out of 956 adverse events (8.5%) were graded by a clinician using a standardised grading system and subsequently reported in the medical chart. Only 491 adverse events (51.4%) were reported with sufficient information to retrospectively derive a grade, as judged by data managers. Therefore, a tension may exist between optimising reliability (only register an adverse event grade if recorded by the treating clinician) and optimising other properties of the registry such as data completeness.

To improve data quality, clinicians can be requested to register or verify registry data. However, this is often not feasible, especially when clinicians lack time to do so. Furthermore, in cases where registry data is used for the evaluation of the quality of care, using external data managers may increase objectivity and may enable the collection of data in multiple hospitals in a uniform way.

In the DMTR, all data that is recorded by data managers needs to be validated by the treating clinician. However, the validation process lags behind; clinicians clearly indicated that the validation process was too time consuming. Another way of improving the quality of the DMTR data was that 10% of all patients have been recorded by two data managers (one external) and all of these records were compared in order to increase uniformity of data recording.

To conclude, it is crucial to be aware of the quality and efficiency trade-offs, involve experts, extensively test the data elements, and perform preliminary analyses as early as possible.

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IDENTIFICATION AND RECRUITMENT OF PATIENTS, DATA HANDLING, AND PHARMACOVIGILANCE ("THE HOW")

How to identify patients?

Any type of registry may bring practical hurdles in identifying patients. In population-based patient registries, it is essential to identify all patients with the diagnosis of interest or treated with the intervention of interest. When selecting a sample of the target population, it is crucial to ensure the sample's representativeness.

In the retrospective part of PERCEPTION, patients were identified through the Netherlands Cancer Registry, which includes basic information on 95% of all cancer patients (see Table 8.4). A cluster sample, i.e. all patients with metastatic renal cell carcinoma within 42 from 51 hospitals in four regions, was selected from this registry. A practical hurdle may arise in case there is no sufficient information available on the target population. For the prospective part of PERCEPTION, the Netherlands Cancer Registry did not fulfil the prerequisite of containing a timely and complete list of eligible patients given the mission and goals of PERCEPTION. Therefore, lists of patients with metastatic renal cell carcinoma were fortnightly derived from hospitals' financing systems. As such, we ensured a complete overview of all patients eligible for PERCEPTION.

Alternative ways for patient identification can be the involvement of treating clinicians and patient associations.

How to recruit patients?

The next step is recruiting patients for participation in the registry. This can be a serious challenge. Participation in a patient registry by patients and clinicians can be voluntary or compulsory. To increase participation, it could be made compulsory for patients to gain access to a health care product, for example an expensive drug or it could be made compulsory for a provider in order to be eligible for payment of this health care service. This was the case in the DMTR, the Dutch minister made the financing of a melanoma drug conditional on the set-up of a population-based registry and centralisation of melanoma care in fourteen specialist centres.

However, participation in most registries is voluntary. Patients can have multiple incentives for participating in a registry. Because a registry most likely does not change a patient's current treatment, improving future patients' health may be the most important incentive. Clinicians or hospitals may be incentivised by a particular research interest or the ability to achieve other goals through the registry (e.g., transparency, reimbursement and improvement of quality of care).[128] Furthermore, a (financial) compensation for time invested by

Table 8.4: Handling data, identification and recruitment of patients, and pharmacovigilance ("the How")

The How?	PHAROS 1	CAPRI & PRO-CAPRI	DMTR	Melanoma	Metastatic colorectal carcinoma	PERCEPTION	Non-small cell lung carcinoma	POSEIDON	Locally advanced Head&Neck	Recurrent and/or metastatic Head&Neck
Data collection: prospective or retrospective?	Retrospective	Both	Both	Retrospective	Retrospective	Both	Retrospective	Prospective	Retrospective	Retrospective
Identification of patients	National database	Hospital databases	Clinicians	National database	Hospital databases	National database and hospital databases	Hospital databases	Clinicians	Clinician databases	Hospital databases
(S)AE collection	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(S)AE reporting	No	Yes, (S)AE level	No	No	No	No	No	To be decided	No	No

(S)AE = (serious) adverse event.

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either clinicians or patients, may help to increase participation, but may induce selection bias.

How to handle the data?

Paper or electronic case report forms (CRFs) can be used to record patient and treatment information. Electronic CRFs offer the advantage of automatic validation checks and do not require transferring data from paper to an electronic database. The database needs to be suitable for the specific registry, including the level of detail that is collected with the CRF. The process of data collection, data management and data analysis should be organised in such a way that it protects patient privacy and maximises data quality.

It is crucial to ensure patients' privacy in a registry, in particularly for patient identifiers. Training in Good Clinical Practice (GCP) and awareness of local rules and regulations will help designing the registry in such a way that patient privacy will be fully protected. This includes anonymisation or pseudonymisation of the data to ensure that information cannot be traced back to the patient. Anonymisation may not be an option when patient identifiers are needed for specific registry functionalities (e.g., to combine data from different sources). Pseudonymisation is a procedure by which identifying fields in a dataset are replaced by artificial identifiers, or pseudonyms. Pseudonymisation can be performed using a Trusted Third Party (TTP), guarding the encryption to the procedure while enabling re-identification when necessary. However, even in cases where a TTP is used, the inclusion of identifiable information in the CRF should be carefully scrutinised and only allowed in cases where this is absolutely necessary. Approval by a medical-ethical authority is required.

Furthermore, it is essential to ensure adequate and ongoing training for data managers including a detailed and up-to-date manual. This also includes guidance on when to record a value as missing, unknown, or as negative. For example, there is a difference between a patient who had no test for locating metastases and a patient who had a test but no metastases were found. Inconsistencies in data recording hamper a valid interpretation of the results.

Training of data managers and preliminary analyses allow identifying and sharing information on common mistakes in order to continuously improve the quality of data in the registry.

How should pharmacovigilance be incorporated in the registry?

In most patient registries, information is collected on safety outcomes. This is, for example, important to attribute resource use to an adverse event in order to facilitate economic evaluations. However, such information is often not sufficient for pharmacovigilance. European

and national legislation and sponsor policies increasingly require that pharmacovigilance is a formal part of a patient registry and requirements on pharmacovigilance increase as well. Patient registries have the potential to reveal unique pharmacovigilance information since the follow up allows for the identification of long term toxicity, and real world toxicity may differ from toxicity profiles in clinical trials because of differential populations, treatment patterns, adverse event handling and clinician experience.[138] However, it can be a difficult challenge to comprehensively collect safety data within a registry, especially in case data is collected retrospectively. While adverse events may have occurred weeks, months or even years prior to the data collection, pharmacovigilance regulations may require serious adverse events reporting within 24 hours of recording them in the registry database. Such a timeframe allows manufacturers and authorities to take immediate action when needed to prevent that these serious adverse events occur in other patients. However, this requires a clear workflow and infrastructure. Another challenge is preventing double registration of adverse events in case the event has been reported at time of occurrence (e.g., to a national Pharmacovigilance Centre), which should usually be the case with serious adverse events.

Furthermore, dependent on the data sources of the registry, it may be difficult to comprehensively collect safety information. It may, for example, not be possible to determine causality. Another complicating factor is that safety reporting requires medical expertise of the study team and short communication lines with the treating clinicians. Furthermore, safety reporting can be extremely time consuming for clinicians and data managers.

Interim analyses in CAPRI revealed that 50% of patients had a recorded hospitalisation or death during treatment with chemotherapy. Although this percentage includes both related and unrelated adverse events, all needed to be reported. This illustrates that SAEs are common and may significantly add to data management time and thus costs of running a registry. However, it also emphasises that pharmacovigilance may be an important aspect in improving patient health.

   Therefore, a plan for pharmacovigilance can be part of setting up a patient registry. This needs to be consistent with national and international guidelines, and agreed upon by all involved stakeholders. Ideally, however, all safety information should already be registered and reported by the clinician at the moment of occurrence of the adverse event.

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LESSONS LEARNED

Patient registries provide valuable information on real-world patients, real-world practice, real-world costs, real-world effects, and real-world cost-effectiveness. If designed and

executed properly, registries can support decision-making at different levels. Regulatory authorities and local reimbursement agencies can use real-world data in market access and reimbursement decisions. Furthermore, sharing real-world outcomes can improve decision making at the individual patient level, and, ultimately, improve patient health.

Since patient registries can serve multiple goals and inform decision making at different levels, practical guidance in setting up a registry is important to ensure a proper design and execution. This paper provides a practical guidance on the Why, Who, What and How in setting up a patient registry, which is based on experiences from multiple registries in The Netherlands. It is essential to cooperate with all relevant stakeholders and collect the right data from the right patients in the right way. The "right" is not always the most extensive approach. It is crucial that the registry is designed in such a way that it serves its aims and it as efficient as possible. In registries, it is, therefore, particularly important to balance the optimal and the feasible in order to maximise the gains within the constraints of the available resources.

Although our experiences in setting up patient registries are based on registries in cancer, we believe that our recommendations are applicable to patient registries in all other disease areas. We also believe that our experiences in The Netherlands will benefit researchers in other countries.

Future prospects of registries
The number of patient registries will continue to rise in the near future.[139] Their importance was shown in many areas including general practice[140], neurology[141,142], orthopedics[143,144], and oncology.[145,146]

Various initiatives exist to facilitate designing high quality registries, such as the High-Value Health Care Project[147] and the PARENT project (cross-border PAtient REgistries iNiTiative) for European member states (2012-2015). The PARENT project recommended tools for implementation of interoperable and cross-border patient registries. They also created a registry of registries which is online available.[148]

Several trends may influence the design of patient registries in the near future. First of all, there will be a further evolution of data standards and an improvement of interoperability of registries with electronic health records.[149] Moreover, there is an increasing trend in setting up multi-institution and multi-country registries.[150] Especially in rare diseases, multi-country registries are needed to include a sufficient number of comparable patients. Finally, the content of registries will reflect important clinical developments (e.g., biobanking).[151]

Considering the unique value of and increasing demand for real-world evidence, we expect that patient registries will become the new standard alongside RCTs.

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Chapter IX

General discussion

Clinical studies, including randomised controlled clinical trials (RCTs), provide indispensable evidence about the efficacy and safety of new oncology drugs. This evidence is needed for a drug to be approved for marketing. However, after marketing approval, important questions still remain to be answered. These questions concern the real-world (RW) efficacy and safety of the drug as well as additional information on (appropriate) use, patient-reported outcomes, costs, budget impact and/or cost-effectiveness.

WHAT ARE THE DIFFERENCES BETWEEN RW EVIDENCE AND EVIDENCE OBTAINED IN RCTS?

In modern medicine, high-quality RCTs are considered the golden standard for judging treatment efficacy. Due to the randomisation procedure, observed differences in clinical outcomes between treatment groups in RCTs are likely caused by the treatment alone, rather than other differences between the treatment groups. However, this is not the case in observational studies. Differences between treatment groups in observational studies can either be caused by pre-existing differences between the treatment groups or by the treatment itself.

Pre-existing differences between treatment groups are common. Clinicians usually have a reason to prescribe treatment one to person A and treatment two to person B. If this reason/indication (e.g.: age) is also related to a patients' prognosis, differences between groups A and B can be due to the treatment as well as the treatment indication. This is called "confounding by indication". Various techniques exist to handle this problem, such as propensity score matching.[152] However, unobserved differences cannot be matched or corrected for and may therefore continue to confound the results of observational studies. RCTs prevent this problem through randomisation and – all other things being equal – are therefore better able to attribute effects to treatments than non-randomised studies. However, this does not mean that randomised studies are always best suited to answer the type of research question(s) at hand.[153]

RCTs may suffer from other sources of bias[154] as well as significant generalisability issues. "Randomly subjecting a person to a milieu of hidden exposures and then spotlighting him or her with relentless observation does not nurture normalcy".[154] The generalisability of RCT results to the real world can be limited due to differences in patient characteristics, clinicians, procedures and any other factors influencing treatment results.

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Considering the differences in patients, Stuart et al. stated that "participants in […] trials are rarely representative of the target population of interest and effects often vary for different types of people and in different contexts."[155] This is called "heterogeneity of treatment effect". If the treatment effect was homogeneous, it would be applicable to everyone with an indication for treatment. However, often we expect a treatment's effect to differ depending on the patient, provider or situation.[156] In these cases, trial evidence is not necessarily applicable to the real world when RW patients differ from trial patients.

In this thesis, differences between RW and trial patients were demonstrated for patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). Chapter II shows RW patients treated with radiotherapy plus cetuximab (RT+C) for LA SCCHN to have unfavourable baseline characteristics compared to the pivotal trial patients. Median age of the RW patients was higher and RW tumour characteristics at baseline were also indicative of poor prognosis compared to trial patients. This was reflected in survival outcomes since, beyond one year after treatment start, the patients treated with RT+C in daily practice died earlier than patients treated with RT+C in the trial.

Unfortunately, such a difference between the RW and RCT outcomes is not exceptional. In 2011, Al-Refaie et al. published a study which identified predictors of enrolment in cancer trials by using RW data from the California Cancer Registry. They found, amongst others, that older patients (>65 years) and early stage cancer patients were less likely to be enrolled in cancer trials.[157] RCTs commonly have an extensive list of eligibility criteria, selecting patients on, for example, age, comorbidities and performance status. However, outcomes in these patients may differ from outcomes in the general population. For example, in laryngeal cancer it was shown that elderly patients do not demonstrate similar treatment outcomes to those reported in clinical trials.[158] This decreases the generalisability of trials to the real world. As a solution, the authors appeal to physicians, payers, the National Cancer Institute and other stakeholders to develop broader cancer trials.[157]

A relatively "broad" type of cancer trial would be a practical clinical trial, also called pragmatic clinical trial. While "regular" ("explanatory") clinical trials evaluate if a treatment works under ideal conditions, the aim of a practical clinical trial is to study risks and benefits of a treatment under clinical conditions. Therefore, in a practical clinical trial, the study setting(s) as well as study population and outcomes are chosen to be representative of the real world.[159,160] Since pragmatic trials are designed to study RW practice and therefore represent less-perfect experiments than "regular"/explanatory/efficacy trials, they sacrifice some internal validity to achieve more generalisability.[161]

Practical clinical trials provide a valuable addition to explanatory trials, since they can evaluate treatment effect under clinical conditions. Furthermore, their randomised setting allows for direct comparison between treatment groups. However, they often require relatively large sample sizes and, while having higher external validity, can have lower internal validity than explanatory trials.[162] Therefore, explanatory trials remain the most efficient way to demonstrate treatment efficacy, especially initially, when rapid market access is pursued.

Furthermore, although practical clinical trials approximate the real world as closely as possible in the trial setting, they are still protocol-guided and therefore unable to answer research questions about the actual real world. In order to study RW treatment patterns, RW clinical outcomes and RW costs, observational outcome studies are needed. These studies solely observe what happens in daily practice, without prescribing diagnostic or treatment protocols.

RCTs and observational outcome studies have complementary roles. Both can answer a different type of important questions. The choice of study should match the questions at hand. In general, RCTs are best suited to further scientific knowledge, while outcome studies are best suited to study the translation of this knowledge to clinical practice. Both study designs can be relevant for treatment decisions and can be combined in decision-analytic modelling.

HOW CAN THE ADDITION OF RW EVIDENCE TO RCT EVIDENCE SUPPORT DECISION MAKING?

In decision-analytical modelling, costs and consequences of treatment alternatives can be compared by synthesising information from multiple sources, including RCTs as well as observational studies.[163] The aim is to provide the best available evidence to reach a decision, for example on whether or not to approve a drug for reimbursement. Many different types of modelling approaches exist to answer various types of questions. In chapter III of this thesis we used a Markov model to evaluate the cost-effectiveness of cetuximab in LA SCCHN, to inform a decision on drug reimbursement.

Since the aim was to estimate Dutch, RW cost-effectiveness of RT+C, RW information was used as much as possible to inform the model. However, effectiveness information was not available from the real world due to limited possibilities to correct for confounding by indication. Therefore, the relative effect of the treatments was taken from the pivotal trial (efficacy).[11] The prognoses of patients in both treatment groups were adjusted downwards in one of the two model scenarios, to match RW survival estimates without altering the relative treatment effect. Thereby information from the trial and the outcome study were

combined to approach the question at hand (chapter III). Unfortunately, the actual RW cost-effectiveness could not be calculated, since we had to rely on trial efficacy outcomes instead of RW effectiveness evidence. However, RW cost data were used, since resource use could be collected in RW clinical practice.

It is not exceptional that valid effectiveness outcomes cannot be obtained from observational data, for example due to limited possibilities to correct for confounding by indication.[53,164] Van Gils et al. also experienced this problem in their study on the RW cost-effectiveness of oxaliplatin. Similarly, they decided to inform their decision-analytic model with trial evidence in addition to RW data. Based on the trial selection criteria, they were able to determine which part of the RW patients would have been eligible for the RCT. They therefore included four scenarios in their modelling: (1) cost-effectiveness analyses based on trial patients only; (2) cost-effectiveness analyses using trial patients and trial-eligible RW patients; (3) cost-effectiveness analyses using trial patients and both trial-eligible and trial-ineligible RW patients, assuming oxaliplatin had an equal effect in ineligible and eligible patients; and (4) cost-effectiveness analyses using trial patients and both trial-eligible and trial-ineligible RW patients, assuming oxaliplatin had no effect amongst ineligibles.[52] This approach provided the decision maker with a good idea about the range of probable values given various alternative assumptions on Dutch, RW treatment effectiveness. Costs were based on actual RW resource use as obtained in the observational study.

In the Netherlands, RW evidence is required within the context of conditional drug reimbursement. At the time the studies in this thesis were performed, hospitals could receive additional reimbursement for expensive drugs, given that an initial (T=0) value dossier showed that the drug would cost Dutch hospitals more than 2.5 million euro per year. Furthermore, pharmacotherapeutic evidence, pharmacoeconomic evidence and a study plan for outcomes research had to be submitted. After four years (T=4), approved drugs were re-evaluated and cost-effectiveness had to be substantiated with RW data.[30,165] Chapter III and IV of this thesis were based on studies performed within the context of such re-evaluations.

For both indications, LA SCCHN and recurrent/metastatic squamous cell carcinoma of the head and neck (RM SCCHN), cetuximab was approved for continuation of reimbursement. Cost-effectiveness of treatment with cetuximab was reasonable for patients with LA SCCHN and was not evaluated for patients with RM SCCHN, due to limitations of the data. However, the budget impact of the drug was small for both indications and therefore the financial risk and opportunity costs involved with a positive reimbursement decision were small as well.

Recently Cerri et al. published a study about multivariate analyses to evaluate which variables were determining CVZ reimbursement decisions (in 2004-2009). One of the outcomes was that budget impact estimates had a significant influence on these decisions. As opposed to budget impact, cost-effectiveness estimates did not seem to impact reimbursement decisions.[166] With respect to the practical use of RW cost-effectiveness estimates and other health-economic evidence, much work still remains to be done in the Netherlands and elsewhere. One important issue is the apparent failure of evidence from economic evaluations to influence governmental decision making as much as expected.[167]

In the United Kingdom, cost-effectiveness requirements are applied more strictly. From a British health perspective, cetuximab was not recommended for patients with RM SCCHN. It was concluded that patients "were not shown to receive a significant survival benefit from cetuximab plus [chemotherapy] compared with [chemotherapy] alone and that even setting a lower price for cetuximab would not strengthen the manufacturer's case for cost-effectiveness".[80] Meanwhile, "it is the preferred regimen in commonly used guidelines in the US, where economic evaluations are not incorporated in the drug approval process."[40]

A negative decision regarding reimbursement has commonly caused criticism by patients and clinicians. Patients may worry that they are being denied a potentially effective treatment and clinicians may share this worry and feel their professional freedom is being restricted for the sake of money. However, since the volume as well as the prices of new drugs keep rising[28], choices need to be made. Since 2011, expenditure on expensive drugs in the Netherlands increased with 80% to €675 million per year, paid from hospital budgets. For 2016 an extra increase of €300 million is foreseen, €75 million of which will be spend on immunotherapy for non-small cell lung cancer (NSCLC).[168]

When reimbursement of non-cost-effective drugs is denied, this allows the available resources to be spent in a more cost-effective way, on care that provides more value to the patients in need. Another option is not to deny reimbursement of these drugs, but to negotiate a more favourable price. Moreover, various countries have experimented with the use of risk-sharing agreements between healthcare payers and product manufacturers, for example by relating the price of a product to its actual RW performance in clinical practice.[169]

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In clinical practice, RW evidence is considered by clinicians, including oncologists. Narayanan (2013) performed a multi-country survey to assess the perception of oncologists about their country-specific healthcare reforms and the consideration of RW evidence when prescribing medications. The study was performed in five European countries (United Kingdom, Germany, Spain, France and Italy), the United States, Brazil and China. Twenty-three percent

of the oncologists indicated that healthcare reforms in their country did not have enough focus on the need for RW evidence and evidence on cost-effectiveness of medications. Between one-third and half of the oncologists reported considering RW data while prescribing medicines. RW evidence on patient quality of life was used more often than RW evidence on product effectiveness, safety or costs.[170] Unfortunately, for many clinical decisions, impact on patient quality of life is unknown.

HOW CAN RW COST DATA IMPROVE LUNG AND HEAD AND NECK CANCER CARE?

Clearly, medical spending on cancer care can improve patient quality of life and survival.[77,171] However, this relation is not linear at all[77]. In this thesis, chapters III, IV, VI and VII present RW cost estimates of cancer diagnostics and treatments. Of these four chapters, chapter III is the only one addressing the cost-effectiveness of treatments. Since the other chapters in this thesis do not provide information about value for money, they do not inform decisions on cost reductions. They do, however, provide insight into the most important cost drivers and the financial burden associated with these aspects of cancer care.

It is important for clinicians to be aware of these costs in order to curtail the current escalation of healthcare spending.[172] In 2009, Howard Brody (MD, PhD) called upon the medical community to identify, per specialty, "five diagnostic tests or treatments that are very commonly ordered by members of that specialty, that are among the most expensive services provided, and that have been shown by the currently available evidence not to provide any meaningful benefit to at least some major categories of patients for whom they are commonly ordered.[173] In oncology, many responded to his call.

In response to Brody's call, Smith and Hillner[78] created a list of five suggested changes in oncologists' behaviour and five suggested changes in oncologists' attitudes and practices. Their suggestions include adaptations of various diagnostic as well as treatment practices, including a more sparing use of chemotherapy. For example, they suggest clinicians "limit second-line and third-line treatment for metastatic cancer to sequential monotherapies for most solid tumours", "limit chemotherapy to patients with good performance status, with an exception for highly responsive disease" and "for patients who are not responding to three consecutive regimens, limit further chemotherapy to clinical trials". Furthermore, they stress the need for cost-effectiveness analyses.[78] Stemming from within the professional society, these suggestions are very helpful in order to find possibilities to reduce costs while causing the least harm to patients.

The American Society of Clinical Oncology (ASCO) also responded to Brody's call with a top five list of diagnostic, surveillance and therapeutic interventions that may better be discontinued. Among them is the advice not to "use cancer-directed therapy for solid tumour patients with the following characteristics: low performance status (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and no strong evidence supporting the clinical value of further anti-cancer treatment."[174] Given the results presented in chapter IV and VII of this thesis, these suggestions may be useful to decrease medical spending in RM SCCHN and NSCLC. However, a lack of evidence on the clinical value of treatments for certain patient groups, does not automatically mean these treatments should be discontinued. It emphasises the importance of RW evidence, especially about those patient groups excluded from clinical trials.

In the study presented in chapter IV, the study population consisted of patients with a poor prognosis. Kelly and Smith[175] identify end-of-life care as one of three areas in which total cancer care costs could be reduced while causing the least harm. Since care at the end of life is expensive and sometimes ineffective, Kelly and Smith suggest that changes could actually improve quality and reduce costs. Possible approaches to achieve this, in general, are to provide clinicians with feedback on their centre's use of end-of-life chemotherapy and discuss palliative care and dying with patients at a relatively early stage.[175] Much may be gained with open communication between clinicians and patients on the expected costs and gains of treatments, on an individual as well as on a national basis. Shared decision making between patients and clinicians may favour less extensive hospital treatment and therefore lower costs.[77,176]

However, treatments that are initially considered to be end-of-life treatments may prove to have additional benefits. New drugs starting out as end-of-life treatments can move to other treatment lines over time. While their cost-effectiveness may be limited in the palliative phase, the indication of new treatments may expand over time, when more RCT results become available regarding their safety and efficacy in earlier treatment lines. Strictly denying access to drugs that initially seem non-cost-effective may deny clinicians the opportunity to gain experience with the drug and find out its optimal, possibly cost-effective, use and indication.

Chapter VI of this thesis presented the costs of laboratory testing for NSCLC patients. It shows that the costs associated with biomarker tests are substantial. However, results of such tests also have the potential to reduce costs in the longer run and improve clinical outcomes. When cancer biomarkers provide information about disease progression or

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treatment response, they can be used to guide treatment and confer both clinical and economic benefits.[172]

In economic evaluations costs of both the targeted therapies and their companion diagnostics (such as biomarker tests) should be taken into account. Note that the number of patients receiving the test (and therefore inducing costs) may be considerably higher than the number of patients who will benefit from the targeted treatment; this ratio depends on the prevalence of the target that is tested for.[177] However, in the future, "Next Generation Sequencing" (NGS) techniques may allow for simultaneous testing of multiple targets at once, and subsequently prescribing the optimal targeted therapy.

Cancer drugs are not the only treatments impacting costs and health outcomes in oncology. While other treatments and interventions may impact clinical and economic outcomes at least as much, in the Netherlands their cost-effectiveness does not need to be shown in order to obtain reimbursement. As was shown in chapter III, IV and VII, radiotherapy also has an important share of the costs of cancer management. Furthermore, radiotherapy is an innovative field of medicine as well, and "obtaining reliable and extensive local assessments on budget impact and costs of radiotherapy will be highly relevant for policy and planning in many world regions."[178] Recent technical advances in radiotherapy for NSCLC include the more widespread use of stereotactic body radiation for stage I NSCLC, concurrent chemoradiation for stage III NSCLC, the implementation of 4-dimensional computed tomography and positron emission tomography and adaptive radiation therapy strategies.[179]

Advances in treatments may also reduce the costs of adverse events, such as surgical complications. Research has shown that improvements in treatment-related patient safety are highly likely to reduce costs.[180] However, while it is usually the costs of treatments in general and drugs specifically that get the most attention, other areas may be just as important for controlling cancer costs.

One of these other areas is prevention. The relatively high costs of cancer care underline the value of investing in effective cancer prevention. One effective type of cancer prevention is the prevention of smoking.[181,182] In an article about lung cancer costs in Northern Ireland, Fleming et al. showed annual lung cancer related hospital costs to be 13 times as high as the estimated enforcement cost of the smoke-free legislation in Northern Ireland.[121]

Another area to consider is diagnostics. In the recent past, the adoption of the PET (positron emission tomography) and PET-CT (positron emission tomography-computed tomography) scan significantly reduced inpatient costs by reducing the number of patients undergoing

surgery or radiation therapy. Unfortunately however, this did not result in cost reductions: "[…] during the same period, the use of chemotherapy and non-inpatient expenditures increased rapidly, more than offsetting potential savings in inpatient expenditures."[119]

HOW CAN RW DATA ON TREATMENT PATTERNS IMPROVE LUNG AND HEAD AND NECK CANCER CARE?

Previous chapters discuss treatment patterns (chapters IV and V) as well as differences in overall survival between academic and non-academic hospitals (chapter V). Apparent differences between hospital types can be caused by various factors, including clinician expertise, differences in case mix that could not be corrected for, or even differences in documentation.[185] If differences are caused by differences in clinician experience or expertise – indicating that clinicians in some hospitals treat their patients better than clinicians in other hospitals – this is reason for action.

One of the most efficient ways to allow hospitals to find opportunities for improving their practice is benchmarking. Comparing practices and outcomes between hospitals also allows them to monitor progress after corrective action is taken.[186] Real-world data is needed to inform this process. For example, some important variables from patient registries can be fed back to participating hospitals in a way that shows them how they are performing compared to other treatment centres (see chapter VIII).

Another important factor in reducing treatment heterogeneity between hospitals is the use of clear, evidence-based guidelines. Uptake of clinical guidelines can be hampered by concerns about evidence quality, medical culture, delay in process, and evolving treatment options not addressed in the guideline.[187] This last concern may be especially relevant for chapter IV, since head and neck cancer guidelines were relatively old and did not include all available evidence regarding new treatment options. However, new guidelines will be published shortly.

Hall et al. advise frequently monitoring adherence to guidelines, especially when the guideline is controversial. Furthermore, a more fluid guideline format may be needed when the evidence is evolving rapidly.[187] For the Dutch NSCLC guideline this is realised by undertaking modular revisions in addition to complete revisions.

Reames et al. evaluated US oncology guidelines and concluded they are not as "trustworthy" and complete as they should be.[188] To our knowledge, such an evaluation of Dutch oncology guidelines has not been performed.

As was discussed in chapter V, treatment volumes per hospital may also have an effect on the quality of care and on survival outcomes. Potential reasons for this in the case of surgery include patient selection, preoperative evaluation and preparation, surgical judgment, skill, and postoperative care, which require a multidisciplinary team approach in the perioperative period and beyond.[158] Studies on the influence of treatment volume on non-surgical treatments in oncology are scarce.

Centralisation of treatment within a limited number of hospitals, such as the head and neck cancer centres, may improve quality of care since it increases the number of patients per centre and therefore the treatment volumes. Furthermore, it may speed up the uptake of innovations, especially since these treatment centres are also heavily involved in clinical trials:

> "It is well known that doctors who have participated in clinical trials are more eager to adopt an innovation than colleagues who did not. The "trial" doctors and "trial" centres already have experience with the innovation, thus when there is a proven clinical benefit they are inclined to administer the innovation to their patients."[77]

However, rapid uptake of innovations is not necessarily a gain. Key opinion leaders can be too enthusiastic about an innovation, for example focusing on a gain in progression-free survival, rather than in overall survival, side effects or cost. However, in the case of cetuximab for the treatment of head and neck cancer, we did not find any indication of overtreatment. In fact, chapter IV shows that the prescription of cetuximab to R/M SCCHN patients in the Netherlands is highly selective. It would be interesting to compare the Dutch treatment decisions and outcomes for R/M SCCHN to the treatment decisions and outcomes in other countries as well as the clinical guidelines. Possibly more patients may benefit from treatment with cetuximab than currently receive this drug.

HOW CAN PATIENT REGISTRIES BE USED TO COLLECT HIGH-QUALITY RW DATA?

Chapter VIII discusses patient registries as one of the possible sources of real-world data. Proper design and monitoring of patient registries can minimise some of the limitations commonly associated with real-world data.[53,189] Furthermore, registries can be used for "studying heterogeneity of diseases, examining treatment patterns, measuring patient-reported outcomes, examining economic outcomes, and performing comparative effectiveness research".[190] Herewith, they can expand on clinical trial evidence and bring the real-world foundation needed to inform the daily practice of clinical cancer management.

In order to impact the daily practice of cancer management, clinicians should be closely involved with the registry. An effective feedback loop should be created, informing the profession about its performance and about important study findings relevant to clinical practice. Furthermore, the profession should be open to feedback and willing to implement changes in their practice in order to improve results. This requires an open and self-critical culture as well as profound trust in the quality and relevance of the registry data.

Supportive IT infrastructure can improve the quality of RW data by facilitating the collection, storage, integration, analysis, and archiving of information. Continued improvement of clinical data standards as well as communication between and integration of medical information systems increases the potential for automation of RW data collection for research purposes. However, many hurdles are still to be overcome, such as the use of different types of hospital information systems in different hospitals and the large amount of clinical information registered in non-standardised ways.

LIMITATIONS

The limitations of the studies in this thesis have been presented per study, in chapters II-VIII. Most limitations were related to the use of real-world data that was retrospectively collected. Although real-world data has important advantages compared to clinical trial evidence – alleviating generalisability issues – it has important drawbacks as well. These drawbacks were discussed in the respective chapters and some will be repeated here.

First of all, availability of good-quality data was often a problem. Since we were dependent on the completeness and level of detail available in patient charts, important data on some prognostic factors and treatment outcomes could not be collected reliably. The most troublesome in this respect were missing data on disease stage, WHO performance status and locoregional recurrences.

Furthermore, the data did often not cover the complete disease courses of HN SCCHN and NSCLC patients. For example, when patients were referred to other hospitals not participating in our studies, they were considered lost to follow-up. Our conclusions were therefore limited to the timeframe we were able to observe and we had to use statistical techniques (such as Kaplan Meier survival curves and the Bang and Tsiatis estimator for costs) to correct for censoring.

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Data availability also limited our information on resource use and costs. In all studies presented in this thesis, costs were calculated from a hospital perspective. This excludes important cost categories, such as the costs of visits to the general practitioner, other healthcare providers and institutions (such as a hospice), and extramural drugs not prescribed by a clinician from the hospital. Additionally, non-medical and indirect costs can be considerable and were excluded from our studies, for feasibility reasons. Furthermore, some resource use had to be valued using tariffs instead of costs obtained from detailed costing studies. Although these tariffs were the best approximation we could find, they do not necessarily represent the actual cost prices and can be either higher or lower. However, for the most important items of resource use (cost drivers), reliable cost prices and/or reference prices were available and used.

An important area of concern in observational studies is the internal validity of the data and therefore the need to correct for confounding by indication when groups are being compared. Since the nature of our data did not allow for sufficient correction, some of our questions (regarding RW treatment effectiveness) could not be answered. All researchers working with RW data should be aware of the limitations of this type of data and refrain from analyses and conclusions they cannot substantiate with reliable and valid observational evidence.

CONCLUDING REMARKS

The development of large, high-quality, disease-wide patient registries, may be the answer to RW data needs in Dutch outcomes research and cost-effectiveness analysis. These registries should not only include clinical variables and quality of care indicators, but also information on resource use and quality of life. This information in crucial in order to evaluate the costs and benefits associated with new diagnostic and treatment interventions.

The collection of detailed information on resource use may be time-consuming. It is therefore advisable to collect only the most important items of resource use (such as hospital admissions) for all patients, and to collect less important items (such as the use of over-the-counter medication) only for a subset of patients. Based on patient, tumour or treatment characteristics, the costs for less important items of resource use can than be extrapolated to the rest of the population. However, the need for such extrapolations may reduce over time. Interconnectivity of IT systems, such as hospital information systems and registry databases, may bring important advances in the efficiency of data collection.

The comprehensive collection of quality of life data may be more challenging. Especially in the case of end-of-life care it may be burdensome for patients to complete quality of life questionnaires. However, improving quality of life is often an important treatment objective. Help of healthcare professionals (e.g. nurses) or family members as well as improvement of the instruments (questionaires) and tools (e.g. apps) to measure quality of life may relief some of the burden and increase response, in order for researchers to assess the value of new interventions.

However, importantly, the patient should always remain in the centre of all data collection efforts. IT advances may allow future patients to have more insight in and influence on the data collected about them. For example, advanced electronic medical files may allow patients to view their medical information online, give or deny permission for the use of certain data elements by researchers and provide and share additional information (e.g. on quality of life).

In the near future, advances in medical data collection will shape clinical as well as health economic research. If carefully designed, carefully analysed and carefully used to improve the quality and cost-effectiveness of diagnosis and treatment strategies, registries will prove invaluable to Dutch healthcare as a whole and oncology in particular.

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Summary

GENERAL INTRODUCTION

New oncology drugs have been studied extensively before they enter the market. In clinical trials, their safety and efficacy is evaluated. However, after they enter the market, important questions still remain to be answered. These include questions about real-world effectiveness and safety, but also questions about appropriate use, patient-reported outcomes, budget impact and/or cost-effectiveness.

Information about real-world effectiveness and safety of new drugs is needed to evaluate if the harms and benefits of drugs in daily practice are acceptable and similar to what was expected based on clinical trial results. Data on treatment patterns can be used to evaluate how a certain drug is being prescribed and, for example, if this is according to guidelines. The budget impact of a new drug informs the payer about the extent to which it will take up available resources. Moreover, the value for money of a drug is represented by its cost-effectiveness. Given the limited national healthcare budgets, information about budget impact and cost-effectiveness is increasingly important to ensure rational allocation of scarce resources.

This thesis discusses real-world evidence obtained from observational outcome studies in two clinical areas: head and neck cancer and lung cancer. It shows the use of real-world data in addition to clinical trial evidence. Furthermore, it discusses the design of patient registries to collect real-world data.

HEAD AND NECK CANCER

Chapter II and chapter III discuss the use and cost-effectiveness of cetuximab for patients with locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). In a randomised controlled trial in patients with LA SCCHN, treatment with radiotherapy plus cetuximab (RT+C) resulted in prolonged median locoregional control (24.4 vs. 14.9 months),

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progression-free survival (17.1 vs. 12.4 months) and overall survival (49.0 vs. 29.3 months) compared to treatment with RT alone. However, uncertainty existed about the generalisability of these trial results for the Dutch healthcare setting and the value for money of cetuximab in daily practice. A retrospective study was designed to provide this information.

In this study 141 patients were included, diagnosed between 2007 and 2010 in two head and neck treatment centres. Patients were treated with first-line RT+C or RT alone. Patient characteristics, treatment characteristics and treatment outcomes were compared between trial patients and patients from daily practice. The resulting information was used in chapter II and III.

Chapter II shows that, in line with Dutch guidelines, RT+C was prescribed in patients who were unfit to receive traditional platinum-based chemotherapeutics. These patients had unfavourable baseline characteristics, due to selection on—amongst others—high age of the patients. Patients treated with RT+C in daily practice died earlier than patients treated with RT+C in the trial. It seems like selective treatment allocation in daily practice limits generalisability of the trial results. Evidence is needed about the effectiveness of RT+C for patients with unfavourable clinical baseline characteristics, in addition to the evidence obtained in the pivotal clinical trial.

Chapter III of this thesis was based on the same study. We estimated the real-world incremental cost per quality-adjusted life year gained for RT+C over RT alone in first-line treatment of LA SCCHN. A Markov model was constructed with health states "alive without progression", "alive following progression" and "death". Transition probabilities per month were estimated from clinical trial data and the real-world data discussed in chapter II. Five-year, ten-year and lifetime horizons were used, without and with discounting (4% costs, 1.5% effects) to calculate incremental cost-effectiveness ratios.

Two scenarios explored different assumptions on the prognosis of real-world versus trial patients. In scenario 1, transition probabilities were fully based on efficacy results from the clinical trial. In scenario 2, RW patients were assumed to have a less favourable prognosis than patients in the clinical trial, consistent with the results described in chapter II. Adding cetuximab to radiotherapy resulted in increased costs and health gains in both scenarios and across each of the time horizons.

Incremental costs per QALY gained ranged between €14,624 and €38,543 in the base-case. For a willingness to pay of €80,000 per QALY, the acceptability curves for the different scenarios showed probabilities between 76% and 87% of RT+C being cost-effective compared

to RT alone. In conclusion, current results show the combined treatment of RT+C to be a cost-effective treatment option for patients with LA SCCHN, when adopting clinical trial efficacy estimates.

Chapter IV, also about head and neck cancer, discusses real-world information on palliative systemic treatment and costs of recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) in the Netherlands. For patients with R/M SCCHN, chemo-therapy can prolong life and alleviate symptoms. However, expected gains may be small, not necessarily outweighing considerable toxicity and high costs. Treatment choice is to a large extent dependent on preferences of doctors and patients and data on these choices is scarce. In this study, data were collected on patient and tumour characteristics, treatment patterns, disease progression, survival, adverse events, and resource use for R/M SCCHN.

The study was conducted in six Dutch head and neck treatment centres, for patients diagnosed between 2006 and 2013. Hundred and twenty-five (14%) out of 893 R/M SCCHN patients received palliative, non-trial first-line systemic treatment, mainly platinum+5FU+cetuximab (32%), other platinum-based combination therapy (13%), methotrexate monotherapy (27%) and capecitabine monotherapy (14%). Median progression-free survival and overall survival were 3.4 and 6.0 months, respectively. 34 (27%) patients experienced severe adverse events. Mean total hospital costs ranged from €10,075 (±€9,891) (methotrexate monotherapy) to €39,459 (±€21,149) (platinum+5FU+cetuximab). Primary cost drivers were hospital stays and anticancer drug treatments.

NON-SMALL CELL LUNG CANCER

Chapter V-VII discuss survival, treatment patterns and costs of non-small cell lung cancer (NSCLC).

The aim of chapter V was to analyse differences in NSCLC survival between academic and non-academic hospitals and to provide insight in NSCLC treatment patterns. Population-based information about NSCLC patients was obtained from the Netherlands Comprehen-sive Cancer Organisation. Overall survival for patients in academic hospitals and patients in non-academic hospitals were compared. We used Kaplan Meier methods to estimate overall survival rates by hospital type and Cox proportional hazards models to estimate the relative risk of mortality (expressed as hazard ratios, adjusted for case mix) and their 95% confidence intervals (95% CI) per hospital type, with all non-academic hospitals as the reference group. Data on treatment patterns in Dutch hospitals was obtained from four,

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not randomly selected hospitals (two academic, two non-academic). A random sample of unselected patients newly diagnosed with NSCLC from 31 January 2009 until 31 January 2011 was identified through the four hospital databases.

In NSCLC, choice of treatment is very much patient and tumour dependent. For non-metastasised disease, patients treated in academic hospitals had superior overall survival as compared to patients treated in non-academic hospitals, even when adjusting for case mix. Median survival was 2.66 years (95% CI 2.14-3.18) in academic versus 1.83 years (95% CI 1.73-1.93) in non-academic hospitals. For metastasised disease, median survival was 0.41 years (95% CI 0.35-0.48) in academic versus 0.39 years (95% CI 0.38-0.41) in non-academic hospitals.

Chapter VI reports the costs of laboratory tests for NSCLC management. Cancer patients undergo a wide range of laboratory procedures, from simple blood tests to complex molecular diagnostics. In cost-effectiveness analyses, costs of laboratory testing are often ignored or estimated inappropriately. We present real-world costs of laboratory procedures for NSCLC patients, per category of laboratory testing. In a Dutch academic hospital, all laboratory tests performed for NSCLC patients between 2009 and 2011 were recorded and categorised in clinical chemistry; pathology; microbiology; serology, hematology, transfusion; pharmacology; and other or unknown. Number of tests per type were multiplied with unit costs per test obtained from The Dutch Healthcare Authority.

A total of 1,015 patients was included, with 171,632 laboratory procedures. The number of different types of tests was 392. Mean cost of laboratory testing per patient was €96 (95%CI 91-101) per day with at least one laboratory procedure. This price can be used to value laboratory testing when the number of days with laboratory testing is known. A price of €49 per day between the first and the last laboratory test can be used when the number of days with laboratory testing is unknown, but the number of days between the first and the last laboratory test is known.

Relatively simple blood tests contributed significantly to the laboratory costs due to high test volumes. Main cost driver however was molecular testing by the pathologist, for the use of targeted therapies. In pharmacoeconomic evaluations, taking laboratory costs into account significantly impacts results, especially when testing practices differ between treatment alternatives.

Chapter VII uses data from the studies presented in chapter V and VI to present resource use and cost data on all aspects of hospital care for NSCLC patients. Data was retrospectively col-

lected from patient charts and included detailed information on resource use. Resource use was multiplied by Dutch unit costs expressed in EUR 2012. Total mean costs were corrected for censoring using the Bang and Tsiatis weighted complete-case estimator.

Total mean costs for NSCLC diagnosis, treatment and follow-up were €28,468 during the study period and €33,143 when corrected for censoring. Adverse events were recorded in the patient charts for 369 patients (41%) and 82 patients (9%) experienced an adverse event of grade III or higher. For these patients, adverse event-related hospital admissions costed on average €2,091. Mean total costs were €1,725 for the diagnostic period, €17,296 for the first treatment line, and €13,236 for each later treatment line. Costs of providing a second opinion were €2,580 per patient. Although the study had important limitations related to the short follow-up time, staging difficulties and missing data, it provided highly detailed, real-world information on the costs of NSCLC.

PATIENT REGISTRIES

In chapter VIII we focused on the collection of real-world data instead of actual real-world outcomes. With this chapter we aimed to provide guidance in setting up patient registries for the collection of real-world data for healthcare decision making. We discuss the mission and goals of patient registries, stakeholders and funding, type of registry, content, data collection, identification and recruitment of patients, data handling and pharmacovigilance.

The mission of most registries is improving patient health by improving patient care. Therefore, monitoring patient care is often the primary goal of registries. In order to reach this goal, registry objectives need to be aligned and stakeholders need to agree on a clear and functional governance structure. For the selection of data elements, help from clinical experts as well as experts in outcomes research can be valuable. In data collection there is a trade-off between reliability, validity and specificity of data elements on the one hand, and feasibility on the other hand. In order to design the registry in a way that protects patient privacy, training in Good Clinical Practice and awareness of local regulations is important. Moreover, since patient registries have the potential to provide unique safety information, a solid pharmacovigilance plan is needed.

Considering the unique value of real-world evidence, we expect patient registries to become the new standard in medical data collection, alongside RCTs. RCTs and observational outcome studies have complementary roles and the choice of study should match the questions at hand. In decision-analytical modelling, expected costs and consequences of

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treatment alternatives can be compared by synthesising information from multiple sources, including RCTs as well as observational studies. Decision-analytic models can be used to calculate the cost-effectiveness of treatment alternatives in order to promote the rational use of healthcare resources.

Real-world data can also be used for other purposes, including benchmarking and comparison with guidelines in order to inform quality improvement processes. In the Netherlands, various initiatives now exist to collect real-world evidence within disease registries on a national level. If carefully designed, carefully analysed and carefully used to improve the quality and cost-effectiveness of diagnosis and treatment strategies, these registries will prove invaluable to Dutch healthcare.

Samenvatting

ALGEMENE INTRODUCTIE

Voordat nieuwe oncologische medicijnen op de markt komen, zijn zij al uitgebreid onderzocht. In klinische *trials* is hun veiligheid en doeltreffendheid bepaald. Hierna blijven er echter nog belangrijke vragen onbeantwoord. Dit zijn vragen over de effectiviteit en veiligheid in de dagelijkse praktijk, maar ook vragen over gepast gebruik, patiënt-gerapporteerde uitkomsten, budget impact en kosteneffectiviteit.

Informatie over de effectiviteit en veiligheid van nieuwe medicijnen in de dagelijkse praktijk is nodig om te evalueren of de kosten en baten van medicijnen acceptabel zijn en vergelijkbaar met de verwachtingen op basis van klinische *trial(s)*. Gegevens over behandelpatronen kunnen gebruikt worden om te evalueren hoe een medicijn wordt voorgeschreven en bijvoorbeeld of dit volgens de richtlijnen is. De budget impact van een nieuw medicijn informeert de betalende partij over de mate waarin het medicijn beslag legt op de beschikbare middelen. De mate waarin een medicijn waar voor zijn geld oplevert, wordt de kosteneffectiviteit genoemd. Gegeven dat de nationale budgetten voor gezondheidszorg beperkt zijn, is informatie over budget impact en kosteneffectiviteit steeds belangrijker om rationele keuzes te maken over de inzet van schaarse middelen.

Dit proefschrift presenteert de resultaten van observationele uitkomstenstudies in de dagelijkse behandelpraktijk van twee ziektebeelden: hoofd-halskanker en longkanker. Het toont de toegevoegde waarde van data uit de dagelijkse praktijk in aanvulling op klinische *trials*. Bovendien wordt in dit proefschrift het opzetten van patiëntregisters besproken, ter verzameling van data uit de dagelijkse praktijk.

HOOFD-HALSKANKER

Hoofdstuk II en hoofdstuk III tonen het gebruik en de kosteneffectiviteit van cetuximab voor patiënten met lokaal gevorderd plaveiselcelcarcinoom van het hoofd-hals gebied (LG

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HHPCC). Uit een gerandomiseerde, gecontroleerde *trial* onder patiënten met LG HHPCC bleek dat behandeling met radiotherapie plus cetuximab (RT+C) leidt tot langere mediane locoregionale controle (24,4 vs. 14,9 maanden), progressievrije overleving (17,1 vs. 12,4 months) en totale overleving (49,0 vs. 29,3 maanden) vergeleken met behandeling met alleen RT. Het was echter niet duidelijk in hoeverre deze studieresultaten generaliseerbaar waren naar de Nederlandse situatie en wat de kosteneffectiviteit van cetuximab was in de dagelijkse praktijk. Er is een retrospectieve uitkomstenstudie opgezet om in deze informatie te voorzien.

In deze studie werden 141 patiënten geïncludeerd, gediagnosticeerd tussen 2007 en 2010 in twee gespecialiseerde hoofd-hals centra. Patiënten werden behandeld met ofwel eerstelijns RT+C ofwel alleen RT. Patiëntkarakteristieken, behandelkarakteristieken en behandeluit-komsten werden vergeleken tussen de *trial* en de uitkomstenstudie.

Hoofdstuk II laat zien dat, in overeenstemming met de Nederlandse richtlijnen, RT+C wordt voorgeschreven aan patiënten die combinatietherapie nodig hebben maar platinumhou-dende chemotherapie niet kunnen verdragen. Deze patiënten hebben ongunstige *baseline* karakteristieken door selectie op onder andere hoge leeftijd. Vanaf een jaar na start van de behandeling stierven patiënten behandeld met RT+C in de dagelijkse praktijk sneller dan patiënten behandeld met RT+C in de *trial*. Het lijkt erop dat selectieve behandelkeuzes in de dagelijkse praktijk de generaliseerbaarheid van de *trial* verminderen. Er is meer informatie nodig over de effectiviteit van RT+C voor patiënten met ongunstige klinische *baseline* karak-teristieken, in aanvulling op de resultaten van de klinische *trial*.

Hoofdstuk III van dit proefschrift is gebaseerd op dezelfde studie als hoofdstuk II. Met behulp van een Markov model hebben we de incrementele kosten per gewonnen QALY geschat voor RT+C ten opzichte van alleen RT als eerstelijns behandeling van LG HHPCC. Het Markov model bestond uit drie gezondheidstoestanden: "levend zonder progressie", "levend na progressie" en "overleden". Overgangskansen per maand werden geschat vanuit de klinische *trial* data en de uitkomstendata besproken in hoofdstuk II. De tijdshorizonnen waren 5 jaar, 10 jaar en levenslang en de incrementele kosteneffectiviteit is bepaald met en zonder *discounting* (4% voor kosten, 1,5% voor effecten).

Met behulp van twee scenario-analyses hebben we verschillende aannames getest wat betreft de prognose van patiënten uit de dagelijkse praktijk ten opzichte van patiënten uit de klinische *trial*. Het toevoegen van cetuximab aan RT resulteerde in hogere kosten en gezondheidswinsten in beide scenarios en voor alle tijdshorizonnen. De incrementele kosten per gewonnen QALY liggen tussen de €14.624 en €38.543 in de base case. Hiermee

lag, bij een *willingness to pay* van €80.000 per QALY, de kans dat RT+C kosteneffectief is ten opzichte van alleen radiotherapie tussen de 76% en 87%. De resultaten van hoofdstuk III laten zien dat RT+C een kosteneffectieve behandeloptie is voor patiënten met LG HHPCC als we uitgaan van de resultaten uit de klinische *trial*.

Hoofdstuk IV, ook over hoofd-halskanker, bespreekt dagelijkse praktijk data over palliatieve, systemische behandeling en kosten voor teruggekeerd/gemetastaseerd plaveiselcelcarcinoom van het hoofd-hals gebied (T/G HHPCC) in Nederland. Voor patiënten met T/G HHPCC kan chemotherapie het leven verlengen en symptomen verlichten. De verwachte baten zijn echter beperkt en wegen niet altijd op tegen de toxiciteit en hoge kosten. Hierdoor is de behandelkeuze sterk afhankelijk van de voorkeur van artsen en patiënten. Data over de behandelkeuzes die gemaakt worden, is beperkt. In deze studie werden gegevens verzameld over patiënt- en tumorkarakteristieken, behandelpatronen, ziekteprogressie, overleving, bijwerkingen en zorggebruik voor T/G HHPCC.

De studie is uitgevoerd in zes Nederlandse hoofd-hals centra, bij patiënten die gediagnosticeerd zijn tussen 2006 en 2013. 125 (14%) van de 893 T/G HHPCC patiënten ontvingen palliatieve, eerstelijns systemische therapie buiten studieverband. De meest voorgeschreven behandelingen waren: platinum+5FU+cetuximab (32%), andere platinumhoudende combinatietherapie (13%), methotrexaat monotherapie (27%) en capecitabine monotherapie (14%). De mediane progressievrije- en totale overleving waren respectievelijk 3,4 en 6,0 maanden. 34 (27%) patiënten hadden ernstige bijwerkingen. De gemiddelde totale ziekenhuiskosten liepen van €10.075 (±€9.891) (methotrexaat monotherapie) tot €39.459 (±€21.149) (platinum+5FU+cetuximab). De grootste kostenposten waren ziekenhuisopnames en medicatie tegen kanker.

NIET-KLEINCELLIG LONGKANKER

Hoofdstuk V-VII bespreken overleving, behandelpaden en kosten van niet-kleincellig longkanker (NKLK). Het doel van hoofdstuk V is om verschillen in overleving tussen academische en perifere ziekenhuizen in Nederland te analyseren en om inzicht te geven in NKLK behandelpatronen. Landelijke informatie over de overleving van NKLK patiënten werd verkregen via Integraal Kankercentrum Nederland. Data over behandelpaden is verkregen in vier, niet-*random* geselecteerde ziekenhuizen (twee academisch, twee perifeer). Een *random sample* van patiënten, gediagnosticeerd met NKLK tussen 31 januari 2009 en 31 januari 2011, werd geïdentificeerd via vier ziekenhuisdatabases.

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De overleving van NKLK patiënten werd vergeleken tussen academische en de perifere ziekenhuizen. Met behulp van Kaplan Meier methoden werd de totale overleving geplot per ziekenhuistype en met behulp van een *Cox proportional hazards* analyse werd het relatieve risico op mortaliteit geschat (uitgedrukt in *hazard ratios*, gecorrigeerd voor *case mix*), met alle perifere ziekenhuizen als referentiecategorie.

Deze studie laat zien hoe NKLK patiënten behandeld worden. Behandelkeuze verschilt sterk tussen patiënten en type tumoren. Patiënten met niet-gemetastaseerde ziekte die behandeld werden in academische ziekenhuizen hadden een betere overleving dan patiënten met niet-gemetastaseerde ziekte in perifere ziekenhuizen, zelfs wanneer gecorrigeerd werd voor *case mix*. De mediane overleving was 2,66 jaar (95% BI 2,14-3,18) in academische versus 1,83 jaar (95% BI 1,73-1,93) in perifere ziekenhuizen. Bij gemetastaseerde ziekte was de mediane overleving 0,41 jaar (95% BI 0,35-0,48) in academische versus 0,39 jaar (95% BI 0,38-0,41) in perifere ziekenhuizen.

Hoofdstuk VI rapporteert de kosten van laboratoriumonderzoeken voor NKLK. Kankerpatiënten ondergaan een breed spectrum aan laboratoriumonderzoeken, van simpele bloedtesten tot complexe moleculaire diagnostiek. In kosteneffectiviteitsanalyses worden de kosten van laboratoriumtesten vaak achterwege gelaten of op een verkeerde manier geschat. Wij presenteren de daadwerkelijke kosten van laboratoriumonderzoek voor NKLK patiënten in de dagelijkse praktijk, per categorie testen. In een Nederlands, academisch ziekenhuis werden alle laboratoriumonderzoeken die uitgevoerd waren tussen 2009 en 2011 geregistreerd en gecategoriseerd in klinische chemie; pathologie; microbiologie; serologie, hematologie en transfusie; farmacologie; en overig of onbekend. Het aantal testen per type werd vermenigvuldigd met de eenheidskosten per test zoals verkregen van de Nederlandse Zorgautoriteit.

Een totaal van 1.015 patiënten werd geïncludeerd, met 171.632 laboratoriumonderzoeken. Het aantal verschillende soorten testen was 392. De gemiddelde kosten van laboratoriumonderzoeken per patiënt was €96 (95%BI 91-101) per dag met minimaal één laboratoriumonderzoek en €49 per dag tussen de eerste en de laatste laboratoriumtest. Een groot deel van de kosten kwam ten goede aan relatief simpele bloedtesten, omdat deze veel werden uitgevoerd. De voornaamste kostenpost was echter moleculair onderzoek door de patholoog, ten behoeve van het gebruik van doelgerichte therapieën. In farmaco-economische evaluaties kunnen de kosten van laboratoriumonderzoek de resultaten significant beinvloeden, met name wanneer het laboratoriumonderzoek verschilt tussen de behandelalternatieven.

Hoofdstuk VII gebruikt data uit de studies uit hoofdstuk V en VI om een schatting te geven van het totale zorggebruik en kosten van alle onderdelen van ziekenhuiszorg voor NKLK

patiënten. Data werd retrospectief verzameld uit patientenstatussen en bestond onder andere uit gedetailleerde informatie over zorggebruik. Zorggebruik werd vermenigvuldigd met Nederlandse eenheidskosten in euro's uit 2012. De totale gemiddelde kosten werden gecorrigeerd voor censoring met behulp van de "Bang and Tsiatis weighted complete-case estimator".

De totale gemiddelde kosten voor NKLK diagnose, behandeling en follow-up waren €28.468 gedurende de studieperiode en €33.143 gecorrigeerd voor censoring. Bijwerkingen werden geregistreerd voor 369 patiënten (41%) en 82 patiënten (9%) hadden een bijwerking van graad III of hoger. Voor deze patiënten kostten bijwerking-gerelateerde ziekenhuisopnamen gemiddeld €2.091. De gemiddelde kosten van NKLK waren €1.725 voor de diagnostische periode, €17.296 voor de eerste behandellijn, en €13.236 voor iedere latere behandellijn. De kosten voor het uitvoeren van een *second opinion* waren €2.580 per patiënt. Hoewel de studie belangrijke beperkingen heeft met betrekking tot de korte *follow-up* duur, stadiëring en ontbrekende gegevens, levert deze zeer gedetailleerde data over de kosten van NKLK in de dagelijkse praktijk.

PATIËNTENREGISTERS

In hoofdstuk VIII hebben we ons gericht op de dataverzameling van dagelijkse praktijkgegevens in plaats van het daadwerkelijke gebruik van deze gegevens. Met dit hoofdstuk hebben we geprobeerd om onze ervaringen te delen wat betreft het opzetten van patiëntenregisters voor de verzameling van dagelijkse praktijk gegevens ten behoeve van besluitvorming. We bespreken de missie en doelen van patiëntenregisters, stakeholders en financiering, type register, inhoud, dataverzameling, identificatie en rekrutering van patiënten, manier van omgaan met de data en geneesmiddelenbewaking.

De missie die met de meeste patiëntenregisters wordt nagestreefd is het verbeteren van de gezondheid van patiënten door het verbeteren van de zorg. Het voornaamste doel is hiermee om de zorg van patiënten te monitoren. Om dit doel te bereiken moeten de belangen van *stakeholders* in lijn met elkaar zijn en moet men het eens zijn over de manier waarop het register bestuurd wordt. Voor de selectie van data elementen is het waardevol om de hulp in te schakelen van zowel klinische experts als experts in het doen van uitkomstenonderzoek. Bij dataverzameling moeten er altijd afwegingen worden gemaakt tussen enerzijds het maximaliseren van betrouwbaarheid, validiteit en specificiteit van data elementen en anderzijds de haalbaarheid. Om het register dusdanig op te zetten dat de privacy van patiënten gewaarborgd blijft, dienen de onderzoekers bekend te zijn met *Good Clinical Practice* en

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zich bewust te zijn van lokale regelgeving. Bovendien kunnen registers een goede bron zijn van informatie over de veiligheid van geneesmiddelen en mag een plan voor de geneesmiddelbewaking niet ontbreken.

Gegeven de unieke waarde van uitkomsten uit de dagelijkse praktijk, verwachten we dat patiëntenregisters de nieuwe standaard zullen worden in medische dataverzameling, naast gerandomiseerde klinische studies. Gerandomiseerde studies en observationele studies zijn complementair en de keuze voor het type studie moet afhankelijk zijn van het type vraag. Met behulp van beslismodellen kunnen de verwachte kosten en effecten van behandelalternatieven worden vergeleken door het combineren van informatie uit verschillende bronnen waaronder zowel gerandomiseerde studies als observationele studies. Deze modellen kunnen gebruikt worden voor het berekenen van de kosteneffectiviteit van behandelalternatieven ter bevordering van de rationele inzet van schaarse middelen.

Gegevens uit de dagelijkse praktijk kunnen gebruikt worden voor meerdere doelen, inclusief *benchmarking* en vergelijking met de richtlijnen ten behoeve van kwaliteitsverbetering. In Nederland bestaan er momenteel verschillende initiatieven om belangrijke dagelijkse praktijk uitkomsten te verzamelen op nationaal niveau. Wanneer dit gebeurt op een zorgvuldige manier, met het doel om de kwaliteit en kosteneffectiviteit van zorg te verbeteren, zullen deze registers ontzettend waardevol worden voor de Nederlandse gezondheidszorg.

Dankwoord

Eind 2010 belde mijn promotor Carin mij met de vraag wat ik van promoveren zou vinden. Een paar maanden later lag mijn kersverse bureau vol met *case report forms*, hoofdhalskanker *trials* en aantekeningen voor wat mijn eerste studierapport zou worden. Carin, ontzettend bedankt voor het vertrouwen dat je me altijd hebt gegeven, jouw passie voor onze onderzoeken en jouw vakkundige begeleiding. Ik heb ongelofelijk veel van je geleerd en een heerlijke tijd gehad bij het iMTA.

Die heerlijke tijd heeft mede vorm gekregen door een geweldige groep collega's. In het bijzonder door mijn kamergenootjes Parida en Remziye en na de verhuizing Maartje en Ellen. Bedankt voor de gezelligheid, de discussies, de thee, en al die successen en frustraties die we gedeeld hebben.

Chantal, ook jij was heel even mijn kamergenootje, in mijn tijd als student-assistent. Bedankt voor jouw enthousiaste begeleiding tijdens het eerste jaar van mijn promotie en jouw hulp bij het modelleren. Het heeft mijn onderzoek een vliegende start gegeven.

Ook na die vliegende start heb ik een hoop hulp van collega's gekregen. Gezien er meerdere collega's aan de slag waren met ziekteregisters, kwamen we regelmatig samen om ervaringen en ideeën uit te wisselen (bedankt Hans!). Binnen deze groep hebben we onder andere gewerkt aan een workshop en een artikel over het opzetten van ziekteregisters (hoofdstuk VIII van mijn proefschrift). Saskia, Margreet, Hans, Hedwig, Brenda en Ellen, ik heb ervan genoten om met jullie te brainstormen, te presenteren, te schrijven en te reflecteren op onze onderzoeken.

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patiënten. Bedankt voor al jullie inzet en bijdragen die dit proefschrift mogelijk hebben gemaakt. Belangrijke bijdragen zijn ook geleverd door de Nederlandse Kankerregistratie, ZonMW, Merck (mede in de persoon van Chris Pescott) en GSK (mede in de persoon van Hans Tamminga). Bedankt voor jullie betrokkenheid, financiering en het beschikbaar stellen van de nodige data. Verder zijn de illustraties in dit proefschrift te danken aan Akha Hulzebos (omslag en boekenlegger) en Terese Winslow (anatomische illustraties): wat een mooi eindresultaat!

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PhD portfolio

PhD student: Naomi van der Linden
Instiute: Institute of Health Policy and Management, Erasmus University Rotterdam, the Netherlands
PhD period: 2011-2015
Promotor: Prof.dr. Carin A. Uyl-de Groot

PhD TRAINING

Master Clinical Epidemiology, Netherlands Institute for Health Sciences, Rotterdam, 2012–2014.

Academic writing in English for PhD students, Erasmus University Rotterdam, Language and Training Centre, Rotterdam, 2013.

Propensity Scores and Observational Studies of Treatment Effect, International Society for Pharmacoeconomics and Outcomes Research, Berlin, 2012.

Elements of Pharmaceutical/Biotech Pricing, International Society for Pharmacoeconomics and Outcomes Research, Berlin, 2012.

Discrete Event Simulation for Economic Analyses – Concepts, International Society for Pharmacoeconomics and Outcomes Research, Berlin, 2012.

Discrete Event Simulation for Economic Analyses – Applications, International Society for Pharmacoeconomics and Outcomes Research, Berlin, 2012.

Didactics (group dynamics, feedback, examination), Erasmus University Rotterdam, Risbo Research-Training-Consultancy, Rotterdam, 2012.

European Head and Neck course, Amsterdam, 2011.

Advanced Modeling Methods for Economic Evaluation, University of Glasgow, Centre for Health Economics, Glasgow, 2011.

Ready in four years, Hertz training for scientists, Rotterdam, 2011.

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(INTER)NATIONAL CONFERENCES AND MEETINGS

Podium presentations

"Treatments and costs for recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) in the Netherlands", 5th International Federation of Head and Neck Oncologic Societies World Congress, July 2014, New York.

"Economic evaluation of SNB, USgFNAC and/or END to evaluate the clinically N0 neck", 5th International symposium on sentinel node biopsy in head and neck cancer, May 2012, Amsterdam.

"Technology as creator of proximity", Symposium "The strength of professionalism", Hogeschool Rotterdam, Institute for Healthcare, 2009, Rotterdam.

Workshop

"As real as it gets: challenges in setting up patient registries for the collection of real-world data on behalf of policymaking", International Society for Pharmacoeconomics and Outcomes Research 16th Annual European Congress, November 2014, Amsterdam.

Poster presentations

"Real-world Costs of Laboratory Tests for Non-Small Cell Lung Cancer", International Society for Pharmacoeconomics and Outcomes Research 16th Annual European Congress, November 2014, Amsterdam.

"Real-world data to calculate cost-effectiveness of monoclonal antibodies: problems and solutions", International Society for Pharmacoeconomics and Outcomes Research 15th Annual European Congress, November 2012, Berlin.

"Return Visits to the Emergency Department: Avoidable?" (presented by co-author), Emergency Nurses Association Annual Conference, September 2012, San Diego.

"Walk-out Patients in the Emergency Department" (presented by co-author), Emergency Nurses Association Annual Conference, September 2011, Tampa.

"A Virtual Acute Admission Unit: Nurses' Perceived Effects" (presented by co-author), Emergency Nurses Association Annual Conference, 2010, San Antonio.

Visits

International Society for Pharmacoeconomics and Outcomes Research 14th Annual European Congress, November 2011, Madrid.

Low Lands Health Economists' Study Group, May 2011, Soesterberg.

Nederlandse Vereniging voor Technology Assessment in de Gezondheidszorg Lustrum Symposium "Back to the Future", April 2011, Rotterdam.

Lustrum symposium Nederlandse Kankerregistratie, March 2011, Utrecht.

Fourth International Erasmus Master Class on Anaesthesia and Perioperative Care, focussing on the Obese Patient, March 2010, Rotterdam.

TEACHING ACTIVITIES

Distribution problems, February-March 2013, 2014 and 2015, bachelor Healthcare Policy and Management, year 2, Erasmus University Rotterdam.

Supervision and coevaluation of bachelor and master thesis students, 2011-2015, institute for Healthcare Policy and Management, Erasmus University Rotterdam.

Writing and research skills, 2013-2014, premaster Healthcare Policy and Management, Erasmus University Rotterdam.

Introduction in Healthcare, September-November 2011 and 2013, bachelor Healthcare Policy and Management, year 1, Erasmus University Rotterdam.

SCIENTIFIC PUBLICATIONS NOT INCLUDED IN THIS THESIS

Van der Linden N, Van der Linden MC, Richards JR, Derlet RW, Grootendorst DC, Van den Brand CL. Effects of emergency department crowding on the delivery of timely care in an inner-city hospital in the Netherlands. *European Journal of Emergency Medicine*. 2015.

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