MAARTEN CHRISTIAAN DORR

UNLOCKING VALUE

Towards outcome-based decision making in Head and Neck Cancer

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M.C. Dorr

The cover reflects the following statement:
Although time is finite, outcome data from individual patients can unlock limitless opportunities for healthcare improvement, benefiting every future patient

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Unlocking Value

Towards outcome-based decision making in head and neck cancer

Het ontsluiten van waarde

Op weg naar uitkomstgerichte besluitvorming bij hoofd-halskanker

Proefschrift

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Erasmus Universiteit Rotterdam
op gezag van de
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Het leven (thuis) vieren

Het is een vroege maandagochtend.

Onderweg naar mijn werk, maar eigenlijk naar jou.

Vier dagen voor je verjaardag ben je helaas weer opgenomen.

Juist nu de kanker terug is, is het duidelijk:
de wens is om thuis te zijn.

Op die vroege ochtend neem jij de volledige regie.
Jij bepaalt hoe het verder gaat.

De arts komt naast je zitten, een menselijk gesprek volgt.

Je verjaardag, die wordt thuis gevierd.

Lieve papa, de ervaringen in deze fase van jouw leven hebben mij een meer empathisch mens en dokter gemaakt.

Ook heeft het mijn proefschrift persoonlijker en beter gemaakt.

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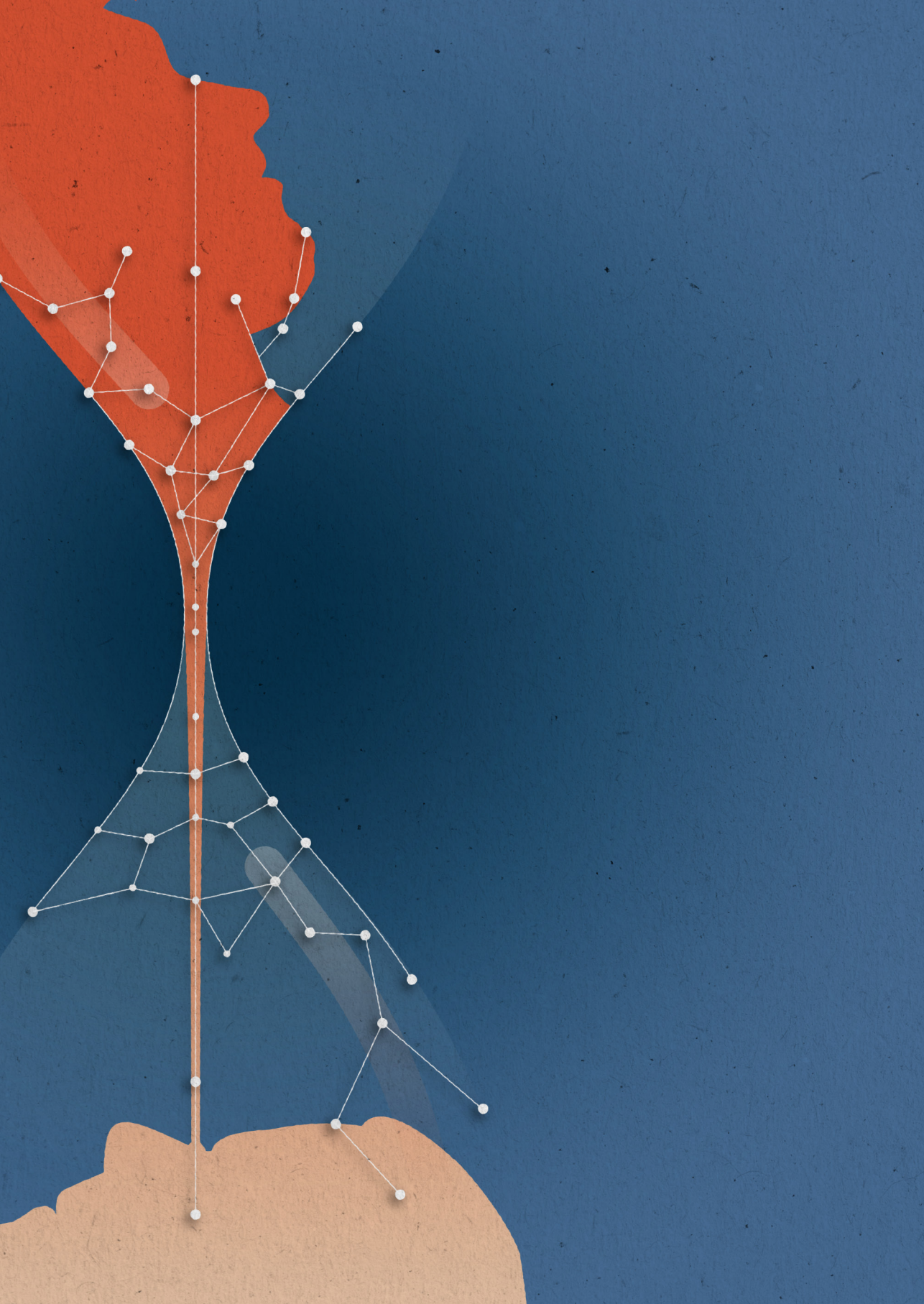

Chapter 1

General introduction and aims of this thesis

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Head and Neck squamous cell cancer (HNSCC) is a malignant disease that has a significant impact on the life and well-being of patients and their caregivers. When patients are diagnosed with cancer, they are confronted with difficult treatment decisions comprising a trade-off between survival and quality of life (QoL). During the decision-making process, healthcare professionals have a significant role and bear responsibility for adequate counseling and managing patients' expectations regarding long-term functioning and QoL. In recent years, there is a growing awareness for individualized counseling and shared decision-making. Routinely measurement of quantitative and qualitative outcome information within the healthcare process is pivotal as basis for optimizing healthcare. This outcome data can be used for both individual counseling and quality improvement strategies. This thesis provides new scientific insights into the use of outcome information for individual decision-making and quality improvement in HNSCC care.

Head and neck cancer

HNSCC is a malignant disease of the upper respiratory tract, which is diagnosed in 3000 patients in the Netherlands annually and is considered the sixth most common cancer worldwide[2,3]. The most common risk factors for HNSCC are tobacco use, alcohol consumption and infection with human papillomavirus[4,5]. Once diagnosed with HNSCC, patients are confronted with the enormous negative impact on both quantity of life in terms of survival, and quality of life in terms of an individual's physical, emotional and psychosocial well-being[6]. HNSCC has an overall five-year survival of 50%-60%, local recurrences occur in 30%-60%, and approximately 25-30% of the patients with HNSCC will at a certain moment reach the palliative phase[7,8]. The disease and all types of treatment are associated with high morbidity, sometimes comprising vital functions like swallowing and speech. HNSCC is also associated with psychosocial problems and high rates of depressive disorders[9,10]. Adequate communication with patients, including informed counseling and expectation management, is therefore important.

Value in healthcare

Achieving the highest value of care for individual HNSCC patients and populations is the day-to-day objective for healthcare professionals. Value is the improvement in

a person's health outcomes in relation to the cost of achieving that improvement[11]. The concept value comprises a multi-pillar framework. According to an expert panel on effective ways of investing in health, value in healthcare can be obtained by providing appropriate care to achieve patients' personal goals (personal value), achievement of best possible outcomes with available resources (technical value), equitable resource distribution across all patient groups (allocative value), and contribution of healthcare to social participation and connectedness (societal value)[12]. In this thesis, the main focus will be on the first pillar, personal value, and how personal value can be improved by the use of outcome information on an individual level and population level.

When looking at personal value, within the last decades, there was a shift from a disease-centered and paternalistic view to a more patient- and person-centered approach[13-15]. Both approaches have similarities, however interesting differences. Patient-centered care is considered a key element in high-quality healthcare. In literature, it is described as the experience of transparency, individualization, recognition, respect, dignity, and choice (to the extent the informed, individual patient desires it) in all matters, without exception, related to one's person, circumstances, and relationships in healthcare[16]. The focus in patient-centered care is on improving outcomes that matter most to individual patients, and therefore creating the most individual value.
A person-centered approach emphasizes the need to know the person behind the illness, in order to engage the person in his/her own care. This approach puts the person in the center with their context, their history, their family, and individual strengths and weaknesses[17].

A philosophy in which patient- and person-centeredness are considered main priority, is Value-Based Healthcare (VBHC). Since 2006, this approach is adopted and implemented with the goal of quality improvement in healthcare. The VBHC approach aims to improve outcomes that matter most to patients, relative to the costs, and therefore creates the highest value of care[13,18]. This relatively new, however by now worldwide adhered approach was proposed by Michael Porter and Elizabeth Teisberg, who aimed for the paradigm shift from volume-based healthcare delivery to value-based healthcare delivery[19]. Consequently, this would improve affordability of healthcare and improve equal quality among healthcare providers

and payers. A key element in VHBC is the transition to outcome-based healthcare. It consists of measuring and understanding outcome information in order to improve care on both individual and aggregated population level. In addition to clinical and process outcomes, specifically the patient perspective, in the form of patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs), fulfills an important role in VBHC.

Outcome-based healthcare

The focus on continuous outcome measurement in healthcare has become a corner stone in healthcare delivery and quality improvement strategies. There is a growing awareness of the importance of measuring and understanding the impact of the disease and treatments, as well as the increasing availability of data and analytics to support this goal. The Dutch Ministry of Health, Welfare and Sport stimulates the use of outcome-based healthcare since 2018[20]. In the recent published healthcare agreement from the Ministry, outcome-based healthcare is one of the pillars of the concept 'appropriate care', 'passende zorg' in Dutch[21]. Outcome measurement allows for the tracking of individual patient outcomes during treatment and follow-up, the evaluation of efficacy and limitation of new treatments or techniques, identification and addressing gaps in healthcare, and for benchmarking and comparison between healthcare providers and systems.

Historically, the best known example of outcome measurement is Florence Nightingale, whose practices significantly improved the conditions within hospitals and care worldwide[22]. During the Crimean War (1853-1856), she systematically measured outcomes and concluded that the high death rate among soldiers was largely due to poor sanitation and inadequate medical care. Upon her return to England, here data caused a revolutionary reform in healthcare and a shift in the use of data in healthcare. As in Nightingales case, first outcomes used in healthcare analysis were vital outcomes, such as birth and death rates. Later, these were complemented with more specific outcomes, like process, patient, tumor and treatment related outcomes. Driven by the increasing availability of new medical technologies in the 20th century, as well as the growing awareness of the need to demonstrate their effectiveness, there was more focus directed to the evaluation of treatments and interventions.

Outcome information can be divided into: 1) clinical outcomes, 2) patient-reported outcomes, like QoL, physical and psychosocial functioning, and 3) process outcomes, like waiting times and length of stay. Consequently, these types of outcome information can be used at three levels: the micro, meso and macro level (figure 1). At a micro level, in this thesis called the individual patient level, outcome data can facilitate informed and shared decision-making, and the delivery of patient-centered care[23-26]. At a meso level, the organizational level, data can be used for analytical and organizational purposes in order to improve and regulate health in specific populations as a result of enhanced understanding, self-reflection, benchmarking and comparison between healthcare professionals and practices[27-29]. At a macro level, outcomes can be used for overall population surveillance and policy[30,31]. For better understanding and alignment within this thesis, meso and macro level are named 'population level'. It should be emphasized that these levels are not separate silos, however interrelated processes that contribute to continue quality improvement in healthcare. Micro-level measurements enable professionals to analyze and benchmark their data on an aggregated meso or macro level. Consequently, conclusions and insights obtained can be used for defining quality improvement strategies and implementation at the micro level again. This interrelated process is also used within the outline of this thesis.

Figure 1. different levels of using PROMs within value-based healthcare.

Patient-reported outcomes

Nowadays, the importance of qualitative outcome information like PROMs in the decision-making and research process cannot be overlooked[32,33]. Initially, PROMs were used in clinical trials. However, since the introduction of value-based healthcare by Porter in 2006, an increase in PROMs is observed for individual decision-making and patient expectation management. PROMs capture a person's perception of their own health status or well-being through standardized and validated questionnaires[34,35]. They are so called self-reported, and are able to quantify subjective and for patients important outcomes. A variety of validated PROMs is available in HNSCC. Every PROM measures different subjective constructs, for example symptoms (e.g. pain and fatigue), physical outcomes (e.g. swallowing function or voice quality) or psychosocial outcome (e.g. anxiety and depression). PROMs can be subdivided into disease- or domain-specific and generic questionnaires. Disease-specific PROMs evaluate an individual's perception within domains that are specifically related to the disease or treatment. This in contrast to domain-specific PROMs, which provide important information on one specific domain. For example, the hospital anxiety and depression scale (HADS). Domain-specific PROMs can be used beyond the scope of one specific disease. Generic PROMs are applicable for different disease populations and can be used to make comparisons across diseases and conditions. Specific measures are often more responsive to change than generic measures but may not capture the effects of comorbidities and do not allow for comparisons across conditions. In HNSSC, disease-specific measures provide better opportunities for identification of symptoms and problems.

PROMs are hot and happening in healthcare nowadays and used for a variety of purposes. Besides their original purpose in scientific research, they are increasingly used for local and national quality registrations, and provide opportunities for individual or institutional comparison[27-31,36]. At an individual level, continuous PROM measurements are used as screening- and monitoring tools in order to facilitate informed and shared decision-making, and provision of patient-centered care[25,26,37-39]. Within our institute, PROMs for QoL, physical and psychosocial functioning are structurally assessed and used as guidance for individual patient contacts in the consultation room using the Healthcare Monitor (figure 2)[1,40]. Electronic PROMs are filled in by the patient prior to each consultation with the healthcare professional.

In this way, patients can be more actively involved in their own care and enables professionals' structural screening of PROMs and therefore improve patient management by detecting issues earlier. When patients are vulnerable or lack digital skills, they are supported by a volunteer or specialized oncology nurse.

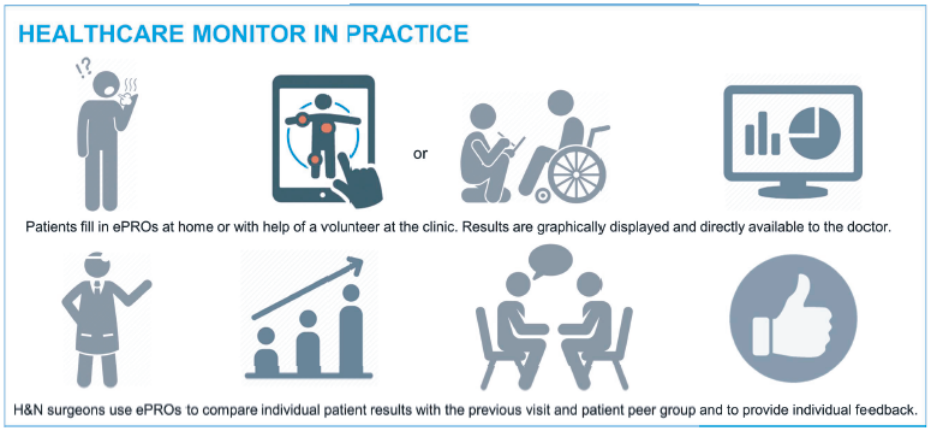

Figure 2. infographic Healthcare monitor[1]

Individualized counseling

Decision making in HNSCC comprises a trade-off between quantitative outcome information, like prolonging survival, and qualitative outcome information, such as QoL. Decision-making in the context of a life-threatening disease such as HNSCC is complex and often associated with uncertainty and potential decisional conflict[41,42]. During the oncological work-up, prior to the treatment decision consultation, patients are discussed within the multidisciplinary consultation meeting (MCM). The MCM has a pivotal role within the oncological work-up by ensuring that tumors are accurately staged, and treatment recommendations are reached by consensus[43-46]. Based on the recommendations from the MCM, patients are able to make a well-informed and shared decision together with their treating healthcare professional [13,14,47].

Shared-decision making (SDM) is a concept which should be applied in HNSCC with nuances[48]. It is presented as a collaborative process in which patients and their healthcare professionals work together to make healthcare decisions that align with their values, preferences, and goals[49-52]. It is described as a balanced approach

between a paternalistic model, in which the healthcare professional makes all therapeutic decisions for the patient, and the informed decision model, where the healthcare professional acts as a source of information and the patient solely makes the final decision[53]. It allows patients to take an active role in their care process, rather than simply following the recommendations of their healthcare professional. Within this process, healthcare professionals use their scientific expertise and medical experience for adequate counseling. However, the view of the patients' values is key in this shared process, and can only be clarified by the patient himself. Benefits of SDM are improved patient satisfaction, better treatment outcomes, increased trust in healthcare provider, increased efficiency and improved patient-empowerment during initial treatment decision[50,51,54], and follow-up[55].

It is advocated that SDM can be particularly helpful when patients are faced with a treatment decision that has multiple options with potential benefits and risks, a so-called preference sensitive decision. However, as the multidisciplinary work-up in HNSCC follows a protocolized approach[56,57], there is usually one best treatment available. However, in the absence of choice, or only the alternative of no treatment at all, SDM can still be applicable. Nevertheless, it is not evidently how specifically the elements of SDM can best be applied in HNSCC[48].

Individualized prognosis

Individual prognosis is an important factor within the decision-making process[58-62]. Obviously, a diagnose is important during the work-up, but, a prognosis is needed for patients in order to have perspective on the impact of the disease and treatment[63]. Patients are interested in what the likely course of the disease and treatment will be, both for quantity of life and QoL[33]. It is advocated that prognostic information enables well-informed decision-making and that the question whether a patients wants to know their prognosis should be standard procedure[64-66]. Clinical prediction models may provide the evidence-based input for shared decision-making, by providing estimates of the individual probabilities of risks, benefits and outcomes[58]. Other terms for prediction models are prognostic models or nomograms. They include statistical tools used to predict the likelihood of a future outcome based on certain predictor variables.

Prognostic information can be disclosed quantitatively and qualitatively. Quantitative prognostic information comprises numbers, such as percentages and five-year survival estimates. Healthcare professionals disclosing qualitative prognostic information, use phrases as 'the cancer is curable' and 'the disease has a good prospect'. Previous research in HNSCC has found that in only 6% of the consultations doctors provided quantitative prognostic information, by discussing numbers, such as percentages[67]. This is caused by the lack of reliable predictions and knowledge about patient preferences. A focus group study by Hoesseini et al. among patients highlights the necessity for receiving prognostic information, however through a tailor-made approach which fits the patients thoughts and needs[33]. It was advocated that quantitative estimates of survival should be provided within the framework of expected QoL. In HNSCC literature, pre-treatment QoL, physical functioning and psychological coping abilities have been found to be predictors for survival and recurrence of disease[68-71]. Nevertheless, no clinically available prediction models have been developed in HNSCC for longitudinal QoL.

In HNSCC, prognostic models are mainly developed for prediction of overall survival or chances for recurrent disease[33,72-81]. Overall, prognostic models can be a useful tool in healthcare for predicting future health outcomes and informed clinical decision-making. However, it is important to note that prognostic models are only as accurate as the data used to develop them, and they should only be used as one piece of information among many when making clinical decisions[59]. To support prognostication and decision-making in HNSCC, an internally and externally validated prognostic model named 'OncologIQ' has been developed by the head and neck department of the Erasmus MC. This model estimates the 1- to 10-year overall survival (OS) chances of patients with primary HNSCC, based on the average treatment effect[33,72-77]. It can be found at www.oncologIQ.com. Apart from tumor data, it includes other patient-specific factors, such as age, comorbidity, performance status, and socioeconomic status. Despite the advantages of prognostication for patient-centered care, and the increase in prognostic model development in literature, there is a lack of studies evaluating these models in clinical practice[58-60].

Standing on the shoulders of giants

Most evidently, this thesis continues the broad experience and line of research into prognostic counseling, shared decision making, palliative care and doctor-patient communication from the Department of Otorhinolaryngology and Head and Neck Surgery of Erasmus MC Cancer Institute in Rotterdam.

Research on prognostic modeling in HNSCC was first introduced in 2001 by Baatenburg de Jong[74]. He introduced a 7-variable prognostic Cox regression model for individual patient prognosis. Van der Schroeff (2011) and Datema (2012) later extended and improved the model[73]. Predictors were added and the clinical applicability was improved by external validation within a dataset from the United States. Van der Schroeff introduced time as a new prognostic factor enabling dynamic predictions over time[76]. The updated models were included in OncologIQ, a dedicated software package with a user-friendly interface. Hoesseini (2023) continued this research by updating the model OncologIQ[75]. In her research she also showed that healthcare professionals face difficulties in making accurate individual survival predictions[82]. Moreover, she conducted qualitative research into patients' and healthcare professionals' preferences for using prognostic information[33]. Research into laryngeal cancer was conducted by Sewnaik (2006), who also investigated the relation between surgical techniques and QoL.

Valuable insights into the impact of Head and Neck Cancer on psychosocial well-being and QoL were obtained by the dissertations from de Boer, van den Brink, Mehanna, and Offerman[9,39,68,83,84]. This line of research was initiated by de Boer (1998), finding that HNSCC patients experienced persistent psychosocial distress, diminished self-esteem, and body image issues long after treatment[68]. Van den Brink (2006) focused on the improvement of QoL of HNSCC patients through telemedicine[85]. In 2005, the expert center of palliative care was established[8,86]. Offerman's dissertation (2013) focused on research within the palliative phase of HNSCC and understanding the impact of HNSCC on psychosocial functioning for patients in all disease stages and their spouses[9,87,88]. Mehanna (2010) investigated patients' perspectives on routine QoL measurements during consultations, finding that questionnaires aided patients in describing their health status[84]. This was the start of the value-based approach at our department in 2013. However, routine QoL measurements remained underutilized in general practice due to time, resource, and

manpower constraints. Therefore, Dronkers (2020) continued this line of research by implementing an electronic patient-reported outcome system (ePROs), showing real-time outcome information during patient-doctor consultation. This so called "Healthcare Monitor" empowered patients, enabled shared decision making and enhanced patient-physician communication[40].

This thesis will build on this broad line of research. As there is an increasing demand for active patient participation within the decision-making process, we first focused on the lack of knowledge on how patients experience the decision-making process and their degree of active participation. Next, we will address the knowledge gap in literature on how individual outcome information from a prognostic model can be used in clinical practice and can improve the decision-making process. In addition to the use of a prognostic model for the clinical outcome survival, we will expand our research by investigating the use of PROMs for individualized predictions and counseling. Finally, the use of outcome information, both clinical and PROMs in order to improve healthcare quality on a population level is explored.

Thesis aim and objectives

The research in this thesis focuses on the use of outcome information for empowering individual decision-making and quality improvement in HNSCC care. The objectives of the studies in this thesis are:

1. Understanding the individual decision-making process in HNSCC from the perspective of the patient.
2. To assess the effect of using quantitative outcome information for empowering decision-making in HNSCC.
3. To assess feasibility of using longitudinal qualitative outcome information for the development of a prediction model.
4. Investigating to what extent routinely obtained outcome information on a population level can be used for healthcare quality improvement

Outline

This thesis is written in two parts. It follows the use of outcome information within the healthcare process: from the individual patient level for empowering individual decision making based on quantitative and qualitative outcome information (part I) to the aggregated population level for healthcare quality control and improvement (part II).

Part I: Outcome-based individual decision-making

In healthcare, everything starts with the individual patient. In order to empower individual decision making in HNSSC, studies in part I are conducted. This part is divided in three sub-parts:

Informed and shared decision making.

In order to understand how patients experience the decision-making process for the treatment of head and neck cancer, we conducted the research in ***chapter 2***. Within this chapter, the personal perception of patients regarding their (un) certainty of the decision-making process and decision made is assessed. In addition, the degree of shared decision making experienced during that decision-making process is measured.

The use of quantitative outcome information

Studies into the use of quantitative outcome information with a prognostic model are conducted. In ***chapter 3***, we conducted a clinical trial in which implementation of the prognostic model OncologIQ within a head and neck cancer multidisciplinary consultation meeting is assessed. During the decision-making process for individual patients, 1- to 10-year overall survival estimates chances from OncologIQ were used as supplementary information. User value of OncologIQ and its impact on the decision-making process were assessed by quantitative and qualitative outcome measures. We continued with a large prospective clinical trial in ***chapter 4***. In this trial we assessed the impact of individualized prognosis from OncologIQ during treatment decision consultations between patients and their healthcare provider.

The use of qualitative outcome information

When patients are counselled, they want to know what to expect from their disease and treatment in terms of daily functioning and quality of life. We investigated how routinely obtained PROMs could be used for empowering individual decision-making. In ***chapter 5***, the impact of early-stage glottic cancer is assessed by longitudinal analysis of routinely obtained patient-reported outcomes. This chapter focusses specifically on the longitudinal trajectories of patient-reported voice quality for three different treatment modalities used in early-stage glottic cancer. Consequently, the results of this chapter are used in ***chapter 6,*** the development and validation of an individualized prediction model.

Part II: Outcome-based healthcare quality control and improvement

In part II, we use routinely obtained outcome information from the individual patient level for healthcare quality control and improvement on a population level. A systematic review of the literature on the use and effect of quality improvement methods based on aggregated patient-reported outcomes is conducted in ***chapter 7***. In this chapter, elaboration on the barriers, facilitators and lessons learned in literature when using patient-reported outcome measures for quality improvement of the healthcare trajectories is also provided. In ***chapter 8,*** insight is obtained into the impact of different patterns of distant metastasis on longitudinal quality of life for palliative head and neck cancer patients. Part three of this thesis is finished with ***chapter 9***, in which we obtained learnings from longitudinal patient-reported and clinical outcomes in palliative head and neck cancer care.

Finally, this thesis is completed by a general discussion in **chapter 10**, in which the results of this thesis are discussed and future directions for research and clinical implementation are provided. An elaboration is provided on the actions that need to be taken to continue and improve the use of clinical and patient-reported outcome information for individual decision-making and healthcare quality improvement.

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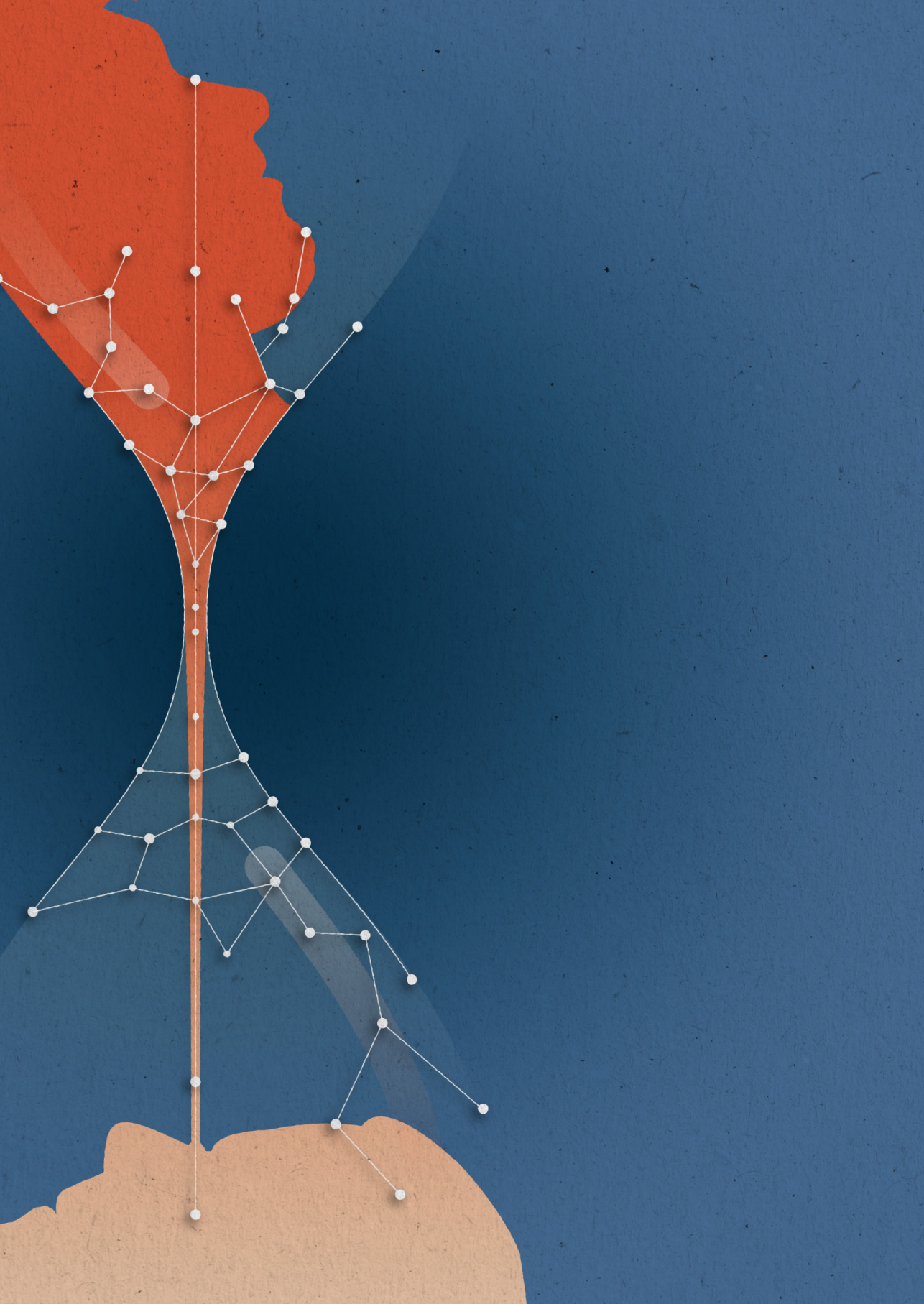

Chapter 2

Decisional Conflict in Patients With Head and Neck Cancer

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ABSTRACT

Importance: Patients who experience less decisional conflict (DC) are more engaged in treatment, and less prone to decisional regret, nervousness, and fretting.

Objectives: To assess DC among patients with head and neck squamous cell carcinoma (HNSCC) after the treatment decision consultation and the association between DC and quality of life as well as the degree of control patients experience in the decision-making process using the control preference scale and the association with DC.

Design, setting and participants: This prospective cohort study with 2 separate cohorts was conducted at a tertiary cancer center and included patients who were eligible for curative treatment of a primary squamous cell carcinoma between January 2014 and August 2018. The 2 cohorts comprised 102 patients with small laryngeal squamous cell carcinoma (SLSCC) and 161 patients with other HNSCC.

Main outcomes and measures: Decisional Conflict Scale (DCS) score, which was scored within 2 weeks after the treatment decision consultation. Other measures included patient characteristics, tumor characteristics, and Control Preference Scale, EuroQol-5D, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, Hospital Anxiety and Depression Scale (HADS), Eating Assessment Tool, Voice Handicap Index (VHI) scores.

Results: Of 263 patients, 50 (19%) were women; the mean (SD) age was 66.1 (11.4) years in the SLSCC group and 64.9 (9.8) years in the other HNSCC group. In the SLSCC group, 51 patients (50%) experienced clinically significant DC (total score ≥25) compared with 74 patients (46%) in the other HNSCC group. In the SLSCC group, there was a large difference in the median EuroQoL-5D, Global Health status, HADS anxiety, HADS depression, and VHI scores between the patients with a total DCS score of less than 25 and total DCS score of 25 or greater, whereas in the other HNSCC group, this only applied to the VHI. Forty-four patients (43.1%) in the SLSCC group felt their treatment choice was a shared decision, and 39 (38.2%) made the decision themselves. In the other HNSCC group, 62 (38.5%) felt that the

physician decided, and 56 (34.8%) felt it was a shared decision. In both groups there was a weak association between control preference scale scores and DC.

Conclusions and relevance: The results of this cohort study found that almost half of patients (48%) experienced clinically significant DC. Several quality-of-life measures associated with clinically significant DC were identified. These results suggest that there is room for improvement in aiming to reduce decision delay and decision-related distress.

INTRODUCTION

Decision-making in oncology is often a complex process[1]. Physicians and patients must carefully weigh the risk of treatment and their association with quality of life (QoL) on one hand and the potential benefit for survival chances on the other. In the case of head and neck squamous cell carcinoma (HNSCC), this trade-off is delicate, as treatment is often mutilating and affects some of the most basic functions like speech, eating, and breathing[2,3]. Therefore, informing and actively involving patients in the decision-making process is important. However, while the shared decision-making (SDM) approach is gradually becoming part of standard care, this approach is not always convenient for patients with HNSCC. Previous qualitative research, including 22 semistructured interviews, suggests that decision-making among patients with HNSCC with serious illness, considerable pain, and discomfort does not adhere to the conventional SDM model as they focus on a decision to do something more than choosing a specific treatment[3]. In addition, these patients heavily relied on a trusted relationship with their physicians and considered this as the most important factor in decision-making instead of the type or amount of information received[3].

One of the ways to measure the personal perception of patients regarding their (un)certainty of the decision-making process and the decision made is by assessing decisional conflict using the Decisional Conflict Scale (DCS)[4]. The DCS is used to access patients' uncertainty in the decision-making process, the factors contributing to the uncertainty, and the perceived effectiveness of their decision-making[4,5]. Patients in different clinical contexts (i.e., oncology, primary care and cardiology)

who experience less DC are often more engaged in treatment and experience less decisional regret, nervousness, and fretting[6-8]. The degree of control patients experience in the decision-making process can be assessed by using the Control Preference Scale (CPS)[9]. The CPS comprises 5 options regarding patients' role in the treatment decision-making process, which range from the individual making the treatment decisions to a shared decision to the physician making the decision.

In contrast to other cancer types, such as prostate cancer and breast cancer, to our knowledge relatively little research has been done on decision-making in HNSCC[3,10,11]. Although there are patients with fragility who are not covered by the standard treatment protocols, treatment advise is generally based on these protocols, which is often associated with 1 best treatment option. An exception is small laryngeal squamous cell carcinoma (SLSCC), as there are often 2 similar treatment options, (laser) surgery or radiotherapy, which both aim to cure the cancer and improve survival while preserving laryngeal function and a good voice quality[12]. Subsequently, often a preference-sensitive decision can be made after weighing the advantages and disadvantages of both treatments. For this reason, this group was described separately.

The aim of this study was to assess DC shortly after the treatment decision consultation among patients with HNSCC. The association between clinically significant DC and QoL was explored. Finally, the degree of control patients experience in the decision-making process and its association with DC was assessed.

METHODS

Design, setting, and participants

This prospective cohort study was approved by the ethics committee of the Erasmus Medical Center. Written informed consent was obtained from study participants. Patients with a diagnosis of primary HNSCC (n = 2013) or carcinoma in situ (n = 50) of the glottic larynx, supraglottic larynx, oropharynx, oral cavity, hypopharynx, nasopharynx, and parotid gland who were eligible to receive curative treatment at the Erasmus MC Cancer Institute between January 2014 and August 2018 were approached for inclusion during their first consultation at the outpatient clinic. Five

patients had a parotid gland squamous cell carcinoma. In 2 cases, this was a primary gland tumor, and in 3 cases a metastasis without any sign of the primary tumor. Of the 50 patients who had a carcinoma in situ, 3 were located supraglottic, 1 in the oral cavity, and the remaining 46 glottic. Exclusion criteria were: younger than 18 years, simultaneous or synchronic multiple primary HNSCC, illiteracy, and patients who were mentally unable to consider their own treatment choice due to dementia or other cognitive disease. A total of 263 patients were included. Patients with SLSCC were described in a separate cohort as, in contrast to other HNSCC, there are often 2 similar treatment options, (laser) surgery or radiotherapy, to choose from, which enables a preference-sensitive decision. The SLSCC cohort comprised 102 patients with Tcis (carcinoma in situ) to T2a laryngeal squamous cell carcinoma, and the other types of HNSCC cohort comprised 161 patients. The flowchart of the study inclusion is presented in the Figure.

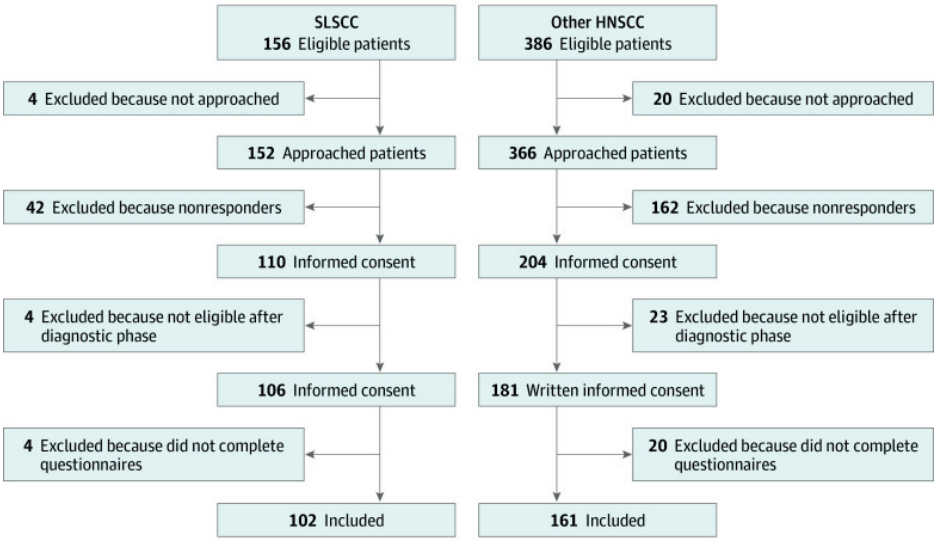

Figure 1. Flowchart of inclusion. HNSCC indicates head and neck squamous cell carcinoma; SLSCC, small laryngeal squamous cell carcinoma.

Main outcomes and measures

Patient and tumor characteristics were collected at the time of diagnosis. The DCS and CPS were scored within 2 weeks after the treatment decision consultation before the initiation of treatment. This implied that patients received the questionnaires after the consultation(s) with the treating physician(s): all patients were seen by a head and neck surgeon and, if relevant, subsequently by a radiotherapist and/or oncologist. The DCS is a validated 16-item 5-point Likert scale measurement for assessing patients' uncertainty regarding their medical decisions[13]. It comprises 5 subscales that measure: (1) uncertainty, (2) feeling uninformed, (3) feeling unclear about values, (4) feeling unsupported, and (5) ineffective decision-making[13]. The overall score of the DCS ranged from 0 to 100. Higher scores indicated higher decision-related distress. Scores less than 25 were associated with implementing decisions, while scores greater than 37.5 were associated with decision delay or feeling unsure about implementation[13]. Several studies suggest a total score of 25 or more as a cutoff for clinically significant decisional conflict[14,15]. The CPS scale measures the degree of control an individual experiences during the decision-making process[9], and consists of the following subscales: (1) I made the decision myself (active), (2) I made the decision after considering the physician's opinion (active), (3) it was a shared decision (collaborative), (4) the physician made the decision after considering my opinion (passive), and (5) the physician made the decision (passive). All other questionnaires were scored at the intake (first consultation) with the head and neck surgeon. The functional domain of QoL was measured by the Eating Assessment Tool (EAT-10) and the Voice Handicap Index (VHI). The EAT-10 is a validated 10-item dysphagia instrument for assessing symptom severity, QoL and treatment efficacy[16]. A score of 3 or greater is considered as abnormal [16]. The VHI comprises 30 items that are equally distributed over 3 domains: functional, physical, and emotional aspects of voice disorders, with a score range from 0 to 120[17]. The Hospital Anxiety and Depression Scale (HADS) was used to assess levels of anxiety and depression. The HADS comprises 14 items, with 7 associated with anxiety and 7 with depression, with a score range from 0 to 21 for anxiety and depression[18]. Scores of 8 or greater indicate a possible anxiety disorder or depression[18,19]. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30) was also assessed.

The EORTC-QLQ-C30 is a 30-item Likert scale questionnaire that incorporates 9 multiitem scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and QoL scale plus several single-item symptom measures[20]. In this study, we analyzed the global health status scale and the five functional scales. Finally, the EuroQol-5D (EQ-5D) was assessed. The EQ-5D is a 5-item non-disease-specific instrument for describing and valuing health-related QoL[21,22].

Statistical analyses

Statistical analyses were performed using the SPSS, version 28 (IBM). As the frequency of missing data was very low (see Table 2), multiple imputation of missing values was not applied. A univariable binary logistic regression analysis for total DCS scores was conducted (DCS <25 or ≥25) (Table 2). The absolute difference between median values for QoL measures was reported as the effect size metric and the 95% CI as a measure of the precision of the estimate using bootstrapping in R studio (Table 3). The correlation between DCS and CPS was calculated using η squared, including the 95% CI.

RESULTS

Decisional Conflict Scale

Table 1 shows the total DCS scores, including the 5 subscales. A total of 125 patients (48%) experienced clinically significant DC. In the SLSCC group, 51 patients (50.0%) experienced clinically significant DC (DCS ≥25). The highest median scores were found in the values clarity (median, 33.3; quartile 1 [Q1] to quartile 3 [Q3], 16.7-41.7) (i.e. "I am clear about which risks and side effects matter most") and the uncertainty subscale (median, 33.3; Q1-Q3, 8.3-41.7), (i.e. "I am clear about the best choice for me"). In the other HNSCC group, 74 patients (45.9%) experienced clinically significant DC (DCS ≥25). The highest median scores were also found in the values clarity subscale (median, 33.3; Q1-Q3, 16.7-50.0) and, in contrast to the SLSCC group, in the informed subscale (median, 33.3; Q1-Q3, 16.7-41.7) (i.e. "I know which options are available to me"). In both groups, the lowest score was found in the effective decision subscale (SLSCC median, 0; Q1-Q3, 0-25.0, other HNSCC, median, 6.3; Q1-Q3, 0-25.0) (i.e. "I am satisfied with my decision").

Table 1. Decisional Conflict Scale, Including the 5 subscales, Score of Patients With SLSCC and other HNSCC.

Decisional Conflict Scale	Total	Informed	Values clarity	Support	Uncertainty	Effective decision
SLSCC (n = 102)						
Median (Q1-Q3)	24.2 (12.1 - 31.3)	25.0 (0 - 41.7)	33.3 (16.7 - 41.7)	16.7 (0 - 33.3)	33.3 (8.3 - 41.7)	0 (0 - 25.0)
Categories, No. (%)						
Low <25	51 (50.0)	40 (39.2)	31 (30.4)	58 (56.9)	36 (35.3)	62 (60.8)
Medium 25 - 37.5	38 (37.3)	32 (31.4)	35 (34.3)	26 (25.5)	35 (34.3)	34 (33.3)
High >37.5	13 (12.7)	30 (29.4)	36 (35.3)	18 (17.6)	31 (30.4)	6 (5.9)
Other HNSCC (n = 161)						
Median (Q1-Q3)	21.9 (12.5 - 33.6)	33.3 (16.7 - 41.7)	33.3 (16.7 - 50.0)	16.7 (4.2 - 33.3)	25.0 (0 - 41.7)	6.3 (0 - 25.0)
Categories, No. (%)						
Low <25	87 (54.0)	64 (39.8)	50 (31.1)	81 (50.3)	78 (48.4)	111 (68.9)
Medium 25 - 37.5	49 (30.4)	37 (23.0)	46 (28.6)	44 (27.3)	40 (24.8)	34 (21.1)
High >37.5	25 (15.5)	60 (37.3)	65 (40.4)	36 (22.4)	43 (26.7)	16 (9.9)

Abbreviations: HNSCC, head and neck squamous cell carcinoma; SLSCC, small laryngeal squamous cell carcinoma.

Baseline characteristics and univariable analysis

Baseline characteristics, missing data, and the odds ratios of the univariable binary logistic regression analysis on clinically significant decisional conflict for both groups are summarized in Table 2. Missing data were limited (0%-8.8%). In both groups, none of the candidate predictors showed a univariable significant association with the odds of experiencing clinically significant DC. One patient in this group rejected curative treatment. In the other HNSCC group 4 patients rejected curative treatment.

DCS and QoL

The QoL questionnaires were scored at the first consultation with the head and neck surgeon. The median time between filling in the questionnaires and the treatment decision consultation was 7.0 days (quarter 1 to quarter 3, 7.0-17.0). Table 3 shows the association between various QoL measures and clinically significant decisional conflict. In the SLSCC group, there was a large difference in the EQ-5D, Global Health status, HADS anxiety, HADS depression, and VHI scores between the patients with a total DCS score of less than 25 and total DCS score of 25 or greater. Among patients with other HNSCC, there was a large difference in the VHI score between those with clinically significant DC and those without.

Table 2. Baseline Characteristics, Missing Data, and Binary Logistic Regression of Clinically Significant DCS Scores of Patients With SLSCC and Other HNSCC.

Characteristics	SLSCC			Other HNSCC		
	Frequency (%)	Missing (%)	Univariable OR on DCS ≥25 (95 CI)	Frequency (%)	Missing (%)	Univariable OR on DCS ≥25 (95 CI)
No. of patients	102	NA	NA	161	NA	NA
Mean age, years (SD)	66.1 (11.4)	NA	0.995 (0.961-1.030)	64.9 (9.8)	NA	0.997 (0.967-1.029)
Sex						
Men	87 (85.3)	NA	1 [Reference]	126 (78.3)	NA	1 [Reference]
Women	15 (14.7)	NA	0.855 (0.285-2.564)	35 (21.7)		1.324 (0.625-2.803)
Tumor localization						
Glottic	93 (91.2)	NA	1 [Reference]	30 (18.6)	NA	1 [Reference]
Supraglottic	9 (8.8)	NA	0.783 (0.198-3.100)	32 (19.9)	NA	1.000 (0.369-2.708)
Oropharynx	NA	NA	NA	51 (31.7)	NA	0.821 (0.333-2.028)
Oral cavity	NA	NA	NA	23 (14.3)	NA	0.533 (0.174-1.630)
Hypopharynx	NA	NA	NA	18 (11.2)	NA	1.571 (0.479- 5.153)
Nasopharynx	NA	NA	NA	2 (1.2)	NA	NA
Parotid gland	NA	NA	NA	5 (3.1)	NA	NA
Tumor stage						
I	82 (80.4)	NA	1 [Reference]	7 (4.3)	NA	0.294 (0.053-1.641)
II	20 (19.6)	NA	1.283 (0.481-3.425)	33 (20.5)	NA	0.420 (0.175-1.010)
III	NA	NA	NA	62 (38.5)	NA	0.531 (0.258-1.093)
IV	NA	NA	NA	59 (36.6)	NA	1 [Reference]

Table 2. Baseline Characteristics, Missing Data, and Binary Logistic Regression of Clinically Significant DCS Scores of Patients With SLSCC and Other HNSCC. (*Continued*)

Characteristics	SLSCC			Other HNSCC		
	Frequency (%)	Missing (%)	Univariable OR on DCS ≥25 (95 CI)	Frequency (%)	Missing (%)	Univariable OR on DCS ≥25 (95 CI)
ACE-27						
0 (none)	30 (29.4)	NA	1 [Reference]	54 (33.5)	NA	1 [Reference]
1 (mild)	49 (48.0)	NA	0.960 (0.387-2.382)	77 (47.8)	NA	0.870 (0.432-1.752)
2 (moderate)	17 (16.7)	NA	1.125 (0.342-3.703)	23 (14.3)	NA	1.063 (0.400-2.826)
3 (severe)	6 (5.9)	NA	1.000 (0.173-5.772)	7 (4.3)	NA	2.900 (0.517-16.274)
Smoking						
Current/former	97 (95.1)	NA	1 [Reference]	142 (88.2)	NA	1 [Reference]
No	5 (4.9)	NA	0.235 (0.025-2.179)	19 (11.8)	NA	1.066 (0.409-2.782)
Median (Q1– Q3), y[a]	40.0 (28.0 – 45.5)	9 (8.8)	0.978 (0.949-1.007)	40.0 (25.0 – 46.5)	16 (9.9)	0.995 (0.973-1.017)
Alcohol						
Yes	69 (67.6)	NA	1 [Reference]	108 (67.1)	NA	1 [Reference]
No	33 (32.4)	NA	0.637 (0.276-1.472)	53 (32.9)	NA	1.692 (0.872-3.281)
No. of units alcohol/d (Q1-Q3)[a]	2.0 (1.0 – 3.0)	1 (1.0)	1.165 (0.908-1.496)	1.0 (0 – 3.0)	NA	0.885 (0.769-1.019)
Prior cancer						
No	89 (87.3)	NA	1 [Reference]	141 (87.6)	NA	1 [Reference]
Yes	13 (12.7)	NA	0.584 (0.177-1.925)	20 (12.4)	NA	0.348 (0.120-1.009)
Education Level	NA	6 (5.9)	NA	NA	5 (3.1)	NA

Table 2. Baseline Characteristics, Missing Data, and Binary Logistic Regression of Clinically Significant DCS Scores of Patients With SLSCC and Other HNSCC. (*Continued*)

Characteristics	SLSCC			Other HNSCC		
	Frequency (%)	Missing (%)	Univariable OR on DCS ≥25 (95 CI)	Frequency (%)	Missing (%)	Univariable OR on DCS ≥25 (95 CI)
Lower	45 (46.9)	NA	1 [Reference]	66 (42.3)	NA	1 [Reference]
Intermediate	39 (40.6)	NA	1.829 (0.765-4.370)	62 (39.7)	NA	1.047 (0.520-2.109)
Tertiary	12 (12.5)	NA	0.571 (0.150-2.172)	28 (17.9)	NA	1.357 (0.559-3.295)
Employment	NA	7 (6.8)	NA	NA	9 (5.6)	NA
Retired	57 (60.0)	NA	1 [Reference]	81 (53.3)	NA	1 [Reference]
Yes	22 (23.2)	NA	1.036 (0.387-2.770)	42 (27.6)	NA	0.982 (0.465-2.077)
No	16 (16.8)	NA	1.036 (0.342-3.140)	29 (19.1)	NA	0.839 (0.356-1.981)
Marital status	NA	2 (0.2)	NA	NA	1 (0.6)	NA
Partner or married	73 (73.0)	NA	1 [Reference]	124 (77.5)	NA	1 [Reference]
Alone	27 (27.0)	NA	1.950 (0.788-4.827)	36 (22.5)	NA	0.813 (0.384-1.722)
Treatment proposal[b]						
Radiotherapy	37 (36.3)	NA	1.176 (0.456-3.035)	50 (31.1)	NA	1 [Reference]
Surgery or Radiotherapy	32 (31.4)	NA	1 [Reference]	2 (1.2)	NA	0.587 (0.156-2.203)
Surgery	31 (30.4)	NA	0.824 (0.306-2.217)	12 (7.5)	NA	1.048 (0.483-2.274)
Surgery and Radiotherapy	-	NA	NA	44 (27.3)	NA	1.072 (0.476-2.414)
Chemotherapy or bioradiation	1 (1.0)	NA	NA	53 (32.9)	NA	1.174 (0.069-19.834)

Table 2. Baseline Characteristics, Missing Data, and Binary Logistic Regression of Clinically Significant DCS Scores of Patients With SLSCC and Other HNSCC. (*Continued*)

Characteristics	SLSCC			Other HNSCC		
	Frequency (%)	Missing (%)	Univariable OR on DCS ≥25 (95 CI)	Frequency (%)	Missing (%)	Univariable OR on DCS ≥25 (95 CI)
Wait and see	1 (1.0)	NA	NA	0	NA	NA
Acceptance of treatment proposal?						
Yes	101(99.0)	NA	NA	157 (97.5)	NA	NA
No	1 (1.0)	NA	NA	4 (2.5)	NA	NA

Abbreviations: ACE-27, Adult Comorbidity Evaluation-27; DCS, Decisional Conflict Scale; HNSCC, head and neck squamous cell carcinoma; NA, not applicable; Q, quartile; SLSCC, small laryngeal squamous cell carcinoma.

[a] In the total group.

[b] Treatment proposal suggested by the multidisciplinary tumor board.

Table 3. Clinically Significant Decisional Conflict vs Quality of Life Measures of Patients With SLSCC and Other HNSCC.

		Total DCS, median (Q1-Q3)		
Variable	**Clinical cutoff[a]**	**< 25**	**≥ 25**	**Effect size (95% CI)**
SLSCC (n = 102)				
No. of patients (%)	NA	51 (50.0)	51 (50.0)	NA
EQ-5D	0 to 1	1.00 (0.8 -1.00)	0.81 (0.72-1.00)	0.19 (0.04-0.23)
EORTC-QLQ-C30 score				
Global health status	> 66.7	83.3 (66.7-91.7)	66.7 (66.7-83.3)	16.6 (0.00-16.66)
Physical functioning	> 86.7	100.0 (86.7-100.0)	93.3 (80.0-100.0)	6.7 (-6.67-13.33)
Role functioning	= 100	100.0 (83.3-100.0)	100.0 (83.3-100.0)	0 (0-0)
Emotional functioning	> 75	83.3 (66.7-91.7)	75.0 (58.3-83.3)	8.3 (-8.33-16.66)
Cognitive functioning	= 100	100.0 (83.3-100.0)	100.0 (83.3-100.0)	0 (0.00-16.67)
Social functioning	= 100	100.0 (83.3-100.0)	100.0 (83.3-100.0)	0 (0-0)
HADS score				
Anxiety	<8	4.0 (1.0-7.0)	5.0 (2.0-7.0)	-1.0 (-3-1)
Depression	<8	1.0 (0.0-4.0)	3.0 (1.0-5.0)	-2.0 (-3-0)
EAT-10 score	<3	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0 (0.00-0.03)
VHI score	≤30	21.0 (14.0-40.0)	31.0 (16.0-47.0)	-10 (-18-4)
Other HNSCC (n = 161)				
No. of patients (%)	NA	87 (54.0)	74 (46.0)	NA
EQ-5D	0 to 1	0.81 (0.72-1.0)	0.81 (0.72-1.0)	0. (-0.04-0.04)
EORTC-QLQ-C30 score				
Global health status	> 66.7	75.0 (58.3-83.3)	75.0 (50.0-83.3)	0 (-16.66-16.66)
Physical functioning	> 86.7	93.3 (73.3-100.0)	93.3 (80.0-100.0)	0 (-6.67-13.33)
Role functioning	= 100	100.0 (83.3-100.0)	100.0 (66.7-100.0)	0 (0-0)
Emotional functioning	> 75	83.3 (50.0-83.3)	75.0 (58.3-85.4)	8.3 (0-16.66)
Cognitive functioning	= 100	100.0 (83.3-100.0)	100.0 (83.3-100.0)	0 (0-0)
Social functioning	= 100	100.0 (100.0-100.0)	100.0 (83.3-100.0)	0 (0-0)
HADS score				
Anxiety	<8	5.0 (2.0-9.0)	5.0 (3.0-9.0)	0 (-2-1)
Depression	<8	2.0 (1.0-5.0)	2.0 (0.8-6.0)	0 (-2-1)
EAT-10 score	<3	2.0 (0.0-8.0)	1.5 (0.0-15.0)	0.5 (-3-3)
VHI score	<30	3.0 (0.0-30.0)	11.5 (0.0-40.3)	-8.5 (-24-4)

Abbreviations: DCS, Decisional Conflict Scale; EAT-10, Eating Assessment Tool; EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D, EuroQol-5D; HADS, Hospital Anxiety and Depression Scale; HNSCC, head and neck squamous cell carcinoma; NA, not applicable; Q, quartile; SLSCC, small laryngeal squamous cell carcinoma; VHI, Voice Handicap Index.

[a]Score that is considered as normal/mild.

Control Preference Scale

Table 4 shows the CPS, which measures the degree of control patients experience in the decision-making process. A total of 44 patients (43.1%) in the SLSCC group felt their treatment choice was a shared decision (collaborative role), followed by an active role (39 [38.2%]) and passive role (19 [18.6%]). In the other HNSCC group, 62 (38.5%) felt their physician decided (passive role), followed by a collaborative role (56 [34.8%]) and active role (43 [26.7%]).

DCS and CPS

In both groups there was a weak association between CPS and DC [(η squared: SLSCC, 0.011 [95% CI, 0.008-0.151]; other HNSCC, 0.048 [95% CI, 0.018-0.154]). In the other HNSCC group, 32 patients (43.2%) experiencing clinically significant DC felt the physician decided, while 36 patients (41.4%) experiencing low DC felt it was a shared decision.

Table 4. The Control Preference Scale,[a] Including the 5 Subscales in Both Groups.

		No. (%)				
Control preference scale	**No.**	**1: Active, patient decides**	**2: Active**	**3: Collaborative, shared decision**	**4: Passive**	**5: Passive, physician decides**
SLSCC	102	14 (13.7)	25 (24.5)	44 (43.1)	10 (9.8)	9 (8.8)
Other HNSCC	161	16 (9.9)	27 (16.8)	56 (34.8)	24 (14.9)	38 (23.6)

Abbreviations: HNSCC, head and neck squamous cell carcinoma; SLSCC, small laryngeal squamous cell carcinoma.

The control preference scale measures the degree of control an individual experiences in the decision-making process and comprises the following subscales: (1) I made the decision myself (active), (2) I made the decision after considering the doctor's opinion (active), (3) it was a shared decision (collaborative), (4) the physician made the decision after considering my opinion (passive), (5) the physician made the decision (passive).

DISCUSSION

This study assessed decisional conflict before treatment in different subtypes of HNSCC. In the SLSCC group, 50% experienced clinically significant total DC, while in the other HNSCC group this was 46%, leaving room for improvement. The effective decision subscale had the lowest score in both groups, which means patients often felt that they had made an informed choice that reflected what was important for them, felt satisfied by the decision, and expected to stick with it[13]. The total DCS scores were comparable with DCS scores in a study among patients with stage I to IV laryngeal tumors, although in that study DCS was scored after treatment[10].

Decisional Conflict and QoL in SLSCC

In the SLSCC group, the highest DCS scores were found in the values clarity and uncertainty subscale. This implies that patients are not clear about the best choice, feel uncertain which option to choose, and find it a hard decision to make. This could be due to the fact that almost one-third of these patients was given a choice between radiotherapy and laser surgery (Table 2). Patients experiencing clinically significant DC had worse median EQ-5D, Global Health status, HADS anxiety, HADS depression, and VHI scores. These QoL estimates could be used to identify patients at risk of decisional conflict. In a previous study by Köther et al,[23] emotional distress, defined as clinically relevant HADS scores, significantly predicted a higher degree of decisional conflict.

CPS in SLSCC

Fourty-four patients (43.1%) had a collaborative role in the process, meaning that they felt they had made a shared decision together with their physician. Thirty-nine patients (38.2%) had an active role, as they felt they had made the decision themselves (with or without considering a physician's opinion). The fact that in almost one-third of cases the decision-making process was based on a preference-sensitive decision could be a reason why most patients in this group felt it was a shared decision or that they made the decision by themselves.

Decisional conflict and QoL in other HNSCC

In the other HNSCC group, the highest DCS scores were seen in the values clarity and informed subscales. This implies that patients did not know which options were

available to them, as well as the benefits, risks, and adverse effects of each option. An explanation for this could be that most of these patients did not have comparable treatment options to choose from, as there was often only 1 best treatment option according to the treatment protocols. Patients who experienced clinically significant DC had worse median VHI scores.

CPS in other HNSCC

Control preference scale scores showed that more than one third of patients (38.5%) had a passive role. During a recently published focus group study[24], we also talked with patients with HNSCC about SDM as a warm-up topic (this topic was not included in the article). Several patients addressed the feeling of having no choice: "Doing nothing versus treatment is not a choice. (...) It is accepting treatment or death." This was also mentioned several times by patients who were included in the present study. In that light, it can potentially be argued whether the DCS is an appropriate tool for this group. Although these patients have a high informative score, this does not necessarily mean that they would like to have more information, since they scored favorable on the support subscale ("I have enough advice to make a choice") and the effective decision subscale ("I feel I have made an informed choice"). Patients with low DC felt they made a shared decision, while patients experiencing clinically significant DC more often felt that the physician made the decision.

Clinical Implications and Future Research

The DCS subscales with a high score could be targeted by improving patient information and counseling on the potential risks and benefits of treatment. However, the high score on the uninformed subscale in the other HNSCC group could be due to the fact that there was only 1 best treatment option according to the treatment protocols, resulting in "not having a choice", as well as a passive role in the decision process, as they felt that the physician made the decision.

Several QoL measures associated with clinically significant DC were identified. These measures could be used to identify patients at risk for DC. For example, the HADS depression score can be used to identify patients who are at risk of high decisional conflict. Consequently, DC should be assessed in these patients. Another option could be to assess DC in all patients after their treatment decision consultation and offer patients with a high score an additional consultation that

aims to reduce uncertainty regarding the treatment decision and empower patients through being better prepared on what is to come. Reducing decisional conflict could be associated with less decisional regret and increased engagement in the treatment process[6-8]. A updated Cochrane review on published randomized clinical trials comparing patient decision aids with usual care and/or alternative interventions showed that patient decision aids were associated with improved knowledge among patients about the treatment options and reduced decisional conflict[11]. Although SDM is increasingly becoming a part of standard care, not all patients would like to be fully informed and participate actively in the decision-making process and would rather leave the decision up to the physician.

This study is part of a clinical trial with sequential cohorts. While the main aim of this first study phase was to measure the status quo, in the second phase of this study, we measured the same outcomes after individualized prognostic counseling with the prognostic model OncologIQ. This internally and externally validated model calculates the 1-year to 10-year overall survival probability of patients with primary HNSCC who are eligible to receive curative treatment[25-28]. While survival rates are typically solely based on the TNM-classification of the specific tumor, OncologIQ also includes other factors, like age, sex, body mass index, and pack years, as prognostic factors, therefore enabling personalized prognostic counseling[25-27]. Like many other studies in cancer care[29], we will evaluate the effect of the intervention using the DCS.

Strengths and limitations

The strengths of this study are the population size and the timing of the data collection. In a published review of the use of the DCS over its initial 20 years[29], most studies failed to report when decisional conflict was measured during the decision-making process, making it difficult to interpret the results. We scored DCS and CPS within 2 weeks after the treatment decision consultation and before the initiation of treatment. In addition, QoL measures were all scored at the first consultation. A limitation of this study is that there could have been some selection bias, as informed consent was necessary before participating in this study. Also, there is no clear consensus in literature on which cutoff point decisional conflict is clinically relevant. While the user manual states that scores less than 25 are associated with implementing decisions, and scores greater than 37.5 are associated with decision delay or feeling unsure about implementation[13], several studies suggest a total score

of 25 or more as a cutoff for clinically significant decisional conflict[14,15]. When a patient has the worst score for 4 out of 16 questions, the total score will be 25. In our opinion these patients should not be ignored or regarded as clinically irrelevant cases. We therefore applied 25 or greater as the cutoff.

CONCLUSIONS

In this cohort study of patients with SLSCC and other HNSCC, almost half of all patients (48%) experienced clinically significant DC. Several QoL measures associated with clinically significant DC were identified. These results suggest that there is room for improvement in aiming to reduce decision delay and decision-related distress.

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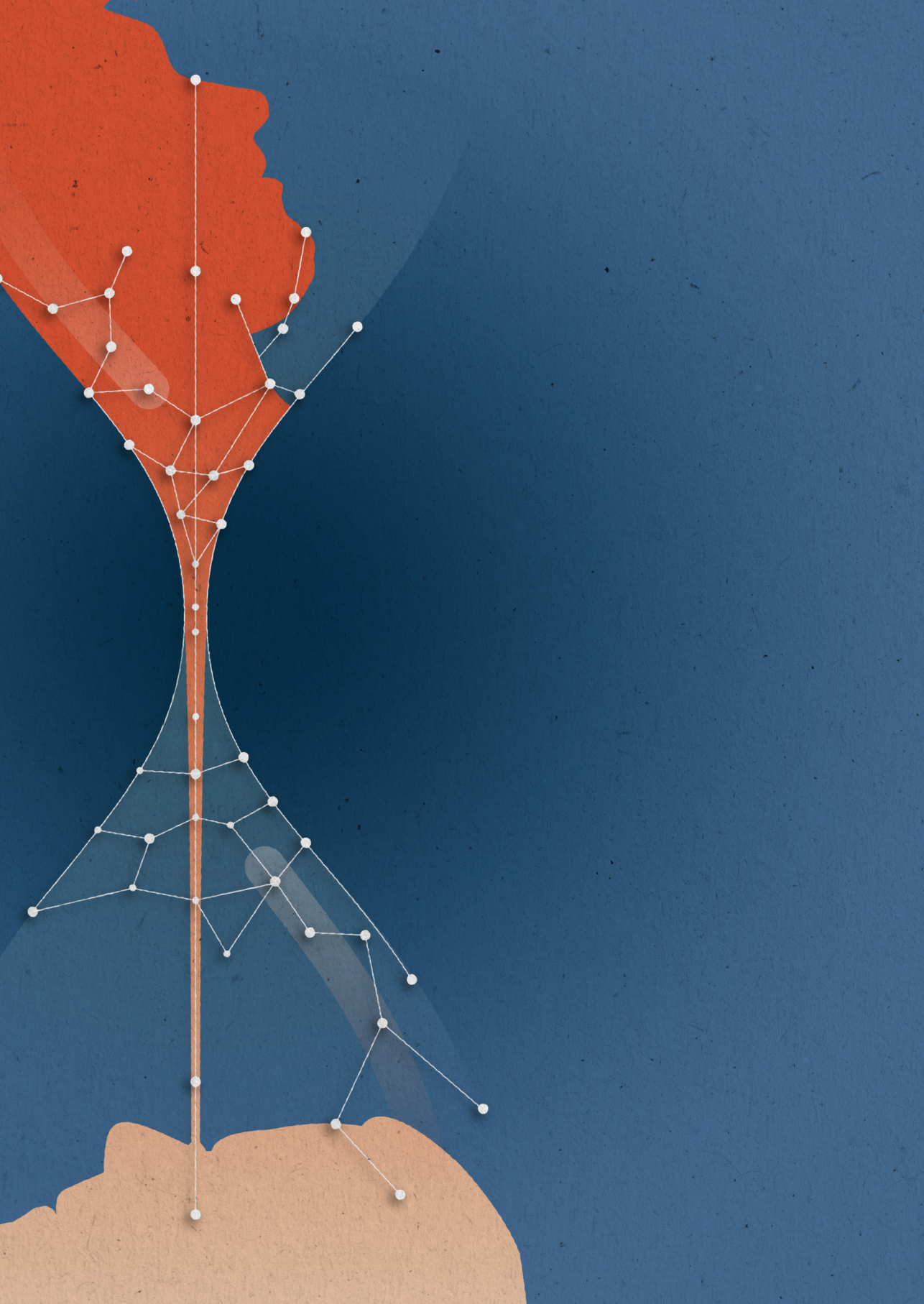

Chapter 3

Impact of a prognostic model for overall survival on the decision-making process in a head and neck cancer multidisciplinary consultation meeting

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Abstract

Background: Multidisciplinary decision-making in head and neck cancer care is complex and requires a tradeoff between prolonging survival and optimizing quality of life. To support prognostication and decision-making in head and neck cancer care, an individualized prognostic model for overall survival (OncologIQ) is available.

Methods: By quantitative and qualitative research we have studied user value of OncologIQ and its impact on the decision-making process in a multidisciplinary consultation meeting.

Results: Healthcare professionals experienced added value upon using prognostic estimates of survival from OncologIQ in half (47.5%) of the measurements. Significant impact on the decision making process was seen when OncologIQ was used for older patients, patients having a WHO performance score ≥ 2, or high tumor stage.

Conclusions: The prognostic model OncologIQ enables patient-centered decision-making in a multidisciplinary consultation meeting and was mostly valued in complex patients.

Introduction

Decision-making in head and neck cancer care requires a tradeoff between prolonging survival and optimizing quality of life (QoL). The multidisciplinary consultation meeting (MCM) is therefore pivotal in the oncological workup. The MCM ensures that tumors are accurately staged, and treatment plans are evidence-based and reached by consensus[1-4]. However, making well-informed and patient-centered treatment plans remains challenging[5-13]. All patient and tumor-related variables should be available and considered structurally by the MCM[5-7]. Weighing all these variables is complex, and healthcare professionals may face difficulty in making accurate individual survival predictions[14,15].

To support prognostication and decision-making in head and neck cancer (HNC), an internally and externally validated prognostic model named OncologIQ has been developed by the head and neck department of the Erasmus MC. This model estimates the 1- to 10-year overall survival (OS) chances of patients with primary HNC, based on the average treatment effect[16-22]. Apart from tumor data, it includes other patient-specific factors, such as age, comorbidity, performance status, and socioeconomic status. Prognostic models are increasingly developed and it is advocated that prognostic models could support and individualize the decision-making process, for example, during MCMs and doctor-patient consultations. However, more research is necessary for evaluating the impact in clinical practice[23-25].

The overall aim of this study was to explore user value of the prognostic model OncologIQ and its impact on the decision-making process in a head and neck cancer multidisciplinary consultation meeting . This was done by measuring: 1) perceived added value of the use of OncologIQ; 2) therapeutic doubt in the multidisciplinary treatment plan; and 3) adjustments in the multidisciplinary treatment plan due to OncologIQ. User value was assessed by qualitative interviews with healthcare professionals from the MCM.

Materials and methods

We conducted a mixed method study to explore user value and impact of the prognostic model OncologIQ in the Erasmus MC head and neck cancer MCM. For this study, the explanatory design was used. This comprises qualitative data collection during a second phase as follow-up to the quantitative data. This design enables us to use qualitative outcome data to better understand quantitative outcomes[26].

OncologIQ

OncologIQ is an internally and externally validated prognostic model which supports shared decision-making for patients with primary HNC[16-22]. This model estimates the 1- to 10-year overall survival chances (OS) of patients with primary HNC, based on the average treatment effect. It combines TNM-classification with the following patient-specific predictors: age, sex, comorbidity, tumor location, smoking, BMI, weight loss, WHO performance, and socioeconomic status. OncologIQ includes the following tumor locations: lip, oral cavity, oropharynx, nasopharynx, hypopharynx and larynx. The current model is however only developed for patients with a primary curative tumor and does not apply to secondary primary tumors, recurrent or non-curative disease. The model can be found at www.oncologIQ.com. An example can be seen in figure 1.

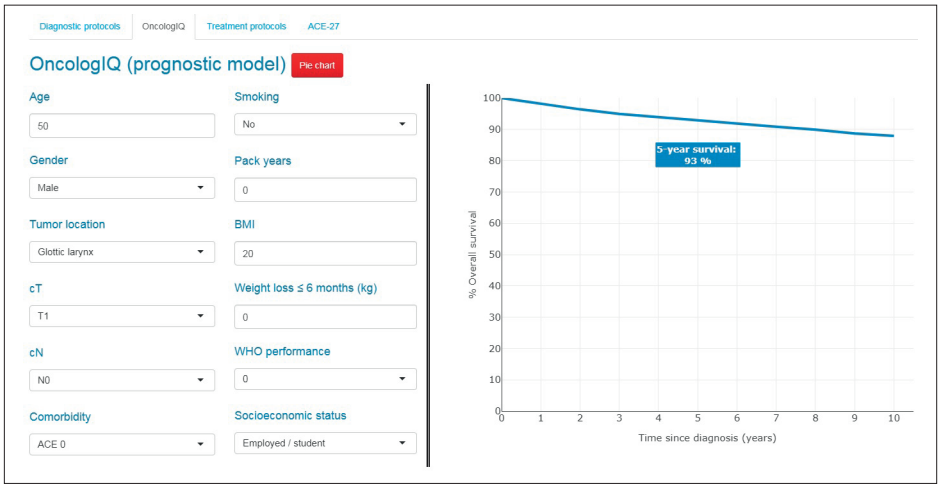

Figure 1. An example of OncologIQ, as used in the multidisciplinary disciplinary team

Institutional routine

All newly diagnosed patients from the department of head and neck surgery and oral and maxillofacial surgery of the Erasmus MC were discussed during the weekly MCM. The attending medical specialties were head and neck surgery, radiation oncology, oral and maxillofacial surgery, medical oncology, radiology, and geriatrics. Patients were presented by their own treating specialist and discussed according to local and national guidelines[1,27].

Setting and participants

Six meetings were attended by the research team. The decision for six meetings was made in agreement with the healthcare professionals, based on feasibility for this study, and to avoid bias due to a learning effect after more meetings. All healthcare professionals involved in the decision-making participated in this study. Patients were included if diagnosed with a primary head and neck squamous cell carcinoma (HNSCC) of the lip, oral cavity, larynx, oropharynx, nasopharynx, or hypopharynx, and eligible for curative treatment. Exclusion criteria were synchronous primary or recurrent HNSCC. This study is part of a prospective cohort study, which was approved by the ethics committee of the Erasmus MC (MEC number: MEC-2013-052). All participants provided written informed consent.

Research team

The research team consisted of three main investigators. M.P.J. Offerman (MO), PhD and psychologist; A. Hoesseini (AH), MD, PhD-candidate, and clinical epidemiologist; M. Dorr (MD), MD and PhD-candidate. Both MO and AH have experience with conducting qualitative research[19,28,29]. The researchers were not members of the MCM. A work relationship exists between the participating healthcare professionals and the research team. MO and AH are co-developers of the prognostic model OncologIQ.

Quantitative research

Main outcomes and design
During the MCM a six-step design was used. Main outcomes and measures were:

1. Perceived added value of the use of OncologIQ.
2. Therapeutic doubt in the multidisciplinary treatment plan.
3. Adjustments in the multidisciplinary treatment plan with respect to the use of OncologIQ.

Patients were discussed in the MCM according to the standard way of working (*step 1*). After formulating a treatment plan for the individual patient, all healthcare professionals were asked to rate their individual *therapeutic doubt* in making a well-founded multidisciplinary treatment plan with the available information 'as normal' on a 10-point visual analogue scale (VAS) scale for this specific patient (*step 2*). Thereafter, the personalized prognostic information from OncologIQ was displayed on a screen (*step 3*). Again, the professionals rated their *therapeutic doubt* on a 10-point VAS scale (*step 4*) for this specific patient. The healthcare professionals were asked if they would reconsider the treatment plan given the supplementary prognostic information (*step 5*). The research team (MD, AH) noted any adjustments. Finally, the professionals scored their perceived *added value* of the use OncologIQ for the specific patient on a 4-point Likert scale (*step 6*). These steps were repeated for every patient.

Analyses
Statistical analyses were performed using SPSS version 25.0[30]. There were no missing data. Descriptive statistics were used to calculate frequencies and proportions. Added value was scored on a 4-point Likert scale, but converted to a binomial variable for further analyses. For therapeutic doubt, a delta value was calculated and categorized as more doubt, less doubt, or no change. These are used as categorical data for further analysis. For categorical data, the Pearson Chi-squared test and Fisher's exact test were used when appropriate to assess heterogeneity between groups. For continuous data, the student's t-test and the analysis of variance (ANOVA) model were used. Statistical significance was established at $p<0.05$.

Qualitative research

Main outcomes and design

After six MCMs, structured interviews with the healthcare professionals were conducted. The interviews were held by a male researcher (MD). Questions were prepared via a structured interview guide and discussed previously by the research team (MD, AH, MO). The healthcare professionals were asked about whether they did or did not experienced the use of OncologIQ as added value. Questions from the interviews can be found in Appendix I. All participating healthcare professionals who attended at least two MCMs were approached by email to participate in these structured interviews after finishing the quantitative study. A minimum of two meetings attended was chosen because experience with the use of OncologIQ within the MCM is needed. The interviews were held at the hospital and took 20 minutes each. Interviews were not repeated. The interviews were audio recorded and transcribed (MD) in Microsoft Excel. No field notes were available. As part of the interviews, suggestions for future use were explored. In addition, the Net Promoter Score was measured. This score measures the likelihood for recommending OncologIQ to other colleagues. This is measured on a Likert scale from 0 (do not recommend) to 10 (will definitely recommend).

Analyses

The theoretical framework of phenomenology was used to analyze the data and determine healthcare professionals experience with OncologIQ. Three researchers (MD, AH, MO) coded all transcripts. After individual analysis of the data, inductive categories were derived during three intensive sessions. Consensus was reached by discussion. When a given answer needed more elaboration, the healthcare professional was asked for more details. Participants did not provide feedback on the findings. As all available healthcare professionals were interviewed, we did not consider data saturation. Qualitative results are described using the consolidated criteria for reporting qualitative research (COREQ)[31].

Results

Quantitative results

In six MCMs, the supplementary prognostic information for 38 patients was included during the decision-making process. A total of 419 measurements were retrieved from 18 healthcare professionals. Participating healthcare professionals consisted of seven head and neck surgeons, five radiation oncologists, two medical oncologists, two physician assistants, one otorhinolaryngology, and one maxillofacial surgery resident. Not every healthcare professional attended every meeting. Baseline patient characteristics are summarized in Table 1.

Added value

Table 2 displays the added value according to the healthcare professionals. In nearly half (47.5%) of the measurements, the healthcare professionals experienced added value in using OncologIQ during the MCM: 125 times (29.8%) as low added value, 71 times (16.9%) as moderate and, 3 times (0.7%) as high added value. Patients for whom the prognostic information was considered to be of added value were significantly older ($p=0.02$), had a WHO performance score of ≥ 2 ($p=0.001$), and tumor stage IV ($p\leq0.001$). The median 2- and 5-year survival chances were significantly lower in the added value group ($p<0.001$).

Table 1. Baseline characteristics

No. of patients	38
No. of measurements	419
Mean age, years (SD)	65.6 (11.4)
Sex	
men	30 (78.9%)
women	8 (21.1%)
ACE-27	
0 (none)	13 (34.2%)
1 (mild)	15 (39.5%)
2 (moderate)	6 (15.8%)
3 (severe)	4 (10.5%)
WHO	
0	29 (76.3%)
1	4 (10.5%)
2	4 (10.5%)
3	1 (2.6%)
Smoking	
No	3 (10.5%)
Yes	21 (55.3%)
Former	13 (34.2%)
Mean PY (SD)	26.0 (15.7)
Mean weight loss (SD)	1.3 (2.4)
Mean BMI (SD)	24.2 (4.2)
Employment	
Retired	22 (57.9%)
Yes	11 (28.9%)
No	5 (13.2%)
Tumor localization	
larynx	9 (23.7%)
oral cavity	12 (31.6%)
oropharynx	11 (28.9%)
HPV-positive	2 (18.2%)
HPV-negative	9 (81.8%)
hypopharynx	6 (15.8%)

Table 1. Baseline characteristics (*Continued*)

No. of patients	38
Tumor stage	
I	12 (31.6)
II	4 (10.5%)
III	8 (21.1%)
IV	14 (36.8%)
Treatment plan	
surgery	9 (23.7%)
radiotherapy	11 (28.9%)
surgery AND radiotherapy	6 (15.8%)
surgery OR radiotherapy	4 (10.5%)
chemo radiation	7 (18.4%)
curative OR palliative radiotherapy	1 (2.6%)

Table 2. Added value of OncologIQ score according to healthcare providers

	No added value	**Added value**	**Sig***
No. of measurements	220 (52.5%)	199 (47.5%)	
Mean age, years (SD)	64.6 (10.6)	67.1 (11.3) *	*0.02*
Sex			
men	179 (81.4%)	151 (75.9%)	0.17
women	41 (18.6%)	48 (24.1%)	
ACE-27			
0	78 (35.5%)	59 (29.6%)	0.24
1	91 (41.4%)	78 (39.2%)	
2	33 (15.0%)	36 (18.1%)	
3	18 (8.2%)	26 (13.1%)	
WHO			
0	177 (80.5%)	138 (69.3%)	*0.009*
1	23 (10.4%)	23 (11.6%)	
≥2	20 (9.1%)	38 (19.1%) *	
Smoking			
No	19 (8.6%)	24 (12.1%)	0.16
Yes	118 (53.6%)	116 (58.3%)	
Former	83 (37.7%)	59 (29.6%)	

Table 2. Added value of OncologIQ score according to healthcare providers (*Continued*)

	No added value	Added value	Sig*
Mean PY (SD)	24.9 (16.3)	23.1 (17.1)	0.39
Mean weight loss, kg (SD)	1.4 (2.3)	1.5 (2.4)	0.64
Mean BMI (SD)	24.4 (4.3)	25.0 (5.1)	0.13
Employment			
Retired	115 (52.3%)*	131 (65.8%)	*0.007*
Yes	77 (35.0%)	43 (21.6%)	
No	28 (12.7%)	25 (12.6%)*	
Tumor stage			
I	96 (43.6%) *	40 (20.1%)	*<0.001*
II	11 (5.0%)	30 (15.1%)	
III	45 (20.5%)	44 (22.1%)	
IV	68 (30.9%)	85 (42.7%) *	
2-year median survival (Q1 – Q3)	86.0% (72.0 – 90.0)	73.0% (56.0 – 86.0)	*<0.001*
5-year median survival (Q1 – Q3)	73.0% (51.0 – 80.0)	53.0% (31.0 – 73.0)	*<0.001*

*Significance based on residuals

Therapeutic doubt

Mean therapeutic doubt in the multidisciplinary treatment plan before and after seeing OncologIQ was 1.0 (± 1.5) and 1.1 (± 1.7) in the total group, respectively. Table 3 displays the change in therapeutic doubt after seeing OncologIQ's estimates of the individuals' survival chances. In 100 (23.8%) measurements, the personalized prognostic information caused a change in therapeutic doubt. In 47 (11.2%) measurements, healthcare professionals expressed less doubt with a mean delta of 1 (±1), and in 53 (12.6%) measurements, they expressed more doubt with a mean delta of 3 (±2) related to the initial treatment plan. Patients for whom the prognostic information caused more therapeutic doubt were significantly older ($p<0.001$), had moderate or severe comorbidity ($p=0.03$), a WHO performance score of ≥ 2 ($p<0.001$), and tumor stage IV ($p<0.001$). Less therapeutic doubt was experienced regarding patients who were significantly younger ($p<0.001$), had no or less comorbidity ($p=0.003$), and with low WHO performance status ($p<0.001$). Estimated median survival chances differed significantly between the groups ($p<0.001$).

Table 3. Change in therapeutic doubt after using OncologIQ

	Less doubt	No change	More doubt	Sig*
No. of measurements	47 (11.2%)	319 (76.1%)	53 (12.6%)	
Mean Age (SD)	66.2 (10.8)	64.6 (11.1)	72.8 (6.8) *	*<0.001*
Sex				
men	37 (78.7%)	256 (80.3%)	37 (69.8%)	0.23
women	10 (21.3%)	63 (19.7%)	16 (30.2%)	
ACE-27	13 (27.7%)	110 (34.5%)	14 (26.4%)	
0	25 (53.2%) *	129 (40.4%)	15 (28.3%)	*0.03*
1	4 (8.5%)	50 (15.7%)	15 (28.3%) *	
2	5 (10.6%)	30 (9.4%)	9 (17.0%) *	
3				
WHO				
0	40 (85.1%)*	252 (79.0%)	23 (43.4%)	*<0.001*
1	6 (12.8%)	37 (11.6%)	3 (5.7%)	
2 + 3	1 (2.1%)	30 (9.4%)	27 (50.9%) *	
Smoking				
No	7 (14.9%)	34 (10.7%)	2 (3.8%)	0.25
Yes	27 (57.4%)	172 (53.9%)	35 (66.0%)	
Former	13 (27.7%)	113 (35.4%)	16 (30.2%)	
Mean PY (SD)	23.7 (17.5)	23.9 (16.7)	25.8 (16.1)	0.74
Mean weight loss, kg (SD)	1.7 (2.4)	1.5 (2.4)	0.9 (1.6)	0.16
Mean BMI (SD)	24.9 (5.3)	24.6 (2.7)	24.9 (4.3)	0.84
Employment				
Retired	29 (61.7%)	168 (52.7%)	49 (92.5%)*	*<0.001*
Yes	11 (23.4%)	107 (33.5%)	2 (3.8%)	
No	7 (14.9%)	44 (13.8%)	2 (3.8%)	
Tumor stage				
I	14 (29.8%)	119 (37.3%)	3 (5.7%)	*<0.001*
II	1 (2.1%)	24 (7.5%)	16 (30.2%)	
III	16 (34.0%)	65 (20.4%)	8 (15.1%)	
IV	16 (34.0%)	111 (34.8%)	26 (49.1%) *	
2-year median survival (Q1 – Q3)	76.0% (72.0 – 86.0)	83.0% (72.0 -90.0)	47.0% (44.0 – 58.0)	*<0.001*
5-year median survival (Q1 – Q3)	58.0% (52.0 – 74.0)	68.0% (51.0 – 80.0)	22.0% (19.0 – 33.0)	*<0.001*

*Significance based on residuals

Change of multidisciplinary treatment plan

For one patient, the supplementary individual prognostic information led to an adjustment in the treatment plan. Before displaying the estimated survival chances from OncologIQ, there was a consensus for curative treatment with radiotherapy. The displayed 5-year overall survival chance of 31% led to a discussion about the treatment plan. The multidisciplinary team decided that both curative and palliative radiotherapy should be discussed with the patient. For this patient, the prognostic information provided by OncologIQ was valued moderate to high.

Qualitative results

A total of 15 healthcare professionals participated in the structured interviews about the use of OncologIQ in the MCM. Participants included seven professionals from the head and neck department, five from radiation oncology, two from oral and maxillofacial surgery, and one medical oncologist. One healthcare professional did not participate because he worked elsewhere during the interviews; two only joined the MCM once.

User value

From the structured interviews, we derived six themes: complex patients, patient-centered care, holistic awareness, individual patient counseling, protocol-based care and concerns. These main themes are divided in 'added value' or 'no added value', which is in line with the overall construct of our study and research question. These themes and verbatim examples can be found in Table 4.

Feedback for further use

Suggestions for future use included the integration of the prognostic information into the standard application form used by the multidisciplinary tumor board. Furthermore, these suggestions included the addition of parameters such as prediction of disease-free survival, quality of life, and toxicity.

Net Promoter score

Healthcare professionals would recommend OncologIQ to other healthcare providers on a Likert scale from 0-10, with an average of 7.6.

Table 4. (Sub)themes and quotations, derived from the structured interviews exploring user value

	Theme	Quotation
ADDED VALUE	**Complex patients:** OncologIQ provides useful predictions when the MCM is confronted with therapeutic dilemmas in patients with advanced tumors, higher age, more comorbidity and higher WHO performance score.	*'The information is of added value for complex patients where extensive treatment is the only option and doubt about curative intention could arise'* (*3.14*) *'In complex patients, where the prognosis is important but more difficult to predict due to age and comorbidity'* (*3.2*) *'When there is a poor 2-year prognosis, there is more substantiation for waiving impactful treatment'* (*2.12*)
	Patient centered care: The information from OncologIQ enables a more tailor-made approach in the decision making process.	*'OncologIQ ensures more individualized patient care'* (*2.2*) *'Protocols are often used under the guise 'we always do it this way', exact outcomes provide a more tailored approach'* (*2.10*)
	Holistic awareness: Understanding of the individual prognosis and the underlying factors enables a more realistic view of the patients health status.	*'It enables a better view on the health status of the patient. Normally, we only look at the tumor and the protocol without incorporating other important patient factors in the decision making.'* (*2.15*) *'It provides short- and long term predictions and could therefore support the decision making process'* (*2.13*) *'It provides a different view on the prognosis, which could be taken into account by the MCM.'* (*2.5*)

Table 4. (Sub)themes and quotations, derived from the structured interviews exploring user value (*Continued*)

	Theme	Quotation
	Individual patient counseling: Awareness of the predicted prognosis is useful at the outpatient clinic in supporting patient counseling.	*'Awareness of the predicted outcome could influence patient counseling. In patients where there is a low prognosis, more emphasis could be given on waiving treatment.'* (*2.3*) *'Due to different views of doctors within the MCM, I think OncologIQ will be of most value in patient counseling. Within the MCM, the more aggressive doctors' opinion - we have to try everything - conflicts with the opinion of the more conservative doctor – not everything that is possible should be done. The outcome from the MCM will be that both options should be discussed with the patient.'* (*2.6 & 3.6*)
NO ADDED VALUE	**Protocol-based care:** OncologIQ is less informative for patients with straightforward protocol based treatment.	*'For patients with curable disease that fit protocol well, OncologIQ will be less contributive to the decision making process.'* (*2.16*)
	Concerns: Concerns could arise about the consequences of using OncologIQ in situations where it is used for waiving treatment.	*'Based on a bad predicted prognosis, sometimes it could be dangerous to decide for no curative treatment intention.'* (*2.7*) *'It could be confusing when we want to treat the patient, but there is a poor predicted prognosis and no other treatment options.'* (*2.8*)

Discussion

Our overall aim was to explore user value of the prognostic model OncologIQ and its impact on the decision-making process in a head and neck cancer multidisciplinary consultation meeting (MCM).

Our quantitative results showed that healthcare professionals experienced added value in the use of OncologIQ within the MCM in nearly half (47.5%) of the measurements. This was associated with a higher age of patients, high WHO performance status, higher tumor stage, and therefore lower estimated survival chances. No added value was associated with lower age, low WHO performance status, tumor stage I, and therefore higher estimated survival chances. Our qualitative results are in line with these results: healthcare professionals mentioned to value OncologIQ most in complex patients when confronted with therapeutic dilemmas. Patients were considered complex when they were older, had advanced tumors, more comorbidity, or higher WHO performance score. Other themes that showed the added value of OncologIQ were the ability to improve patient-centered care, holistic awareness and provide the foundation on which patient and treating healthcare professional are able to make a well-informed and shared decision. Previous elaboration on the development and benefit of prediction models for clinical practice are in line with our qualitative results[25].

By measuring therapeutic doubt before and after the use of OncologIQ, we tried to quantify the extent to which healthcare professionals would feel less or more doubtful about making a well-founded multidisciplinary treatment plan after receiving supplementary prognostic information. Overall therapeutic doubt was low, which we believe can be attributed to our protocolled approach[12,32]. This is also mentioned in our qualitative outcome. Surprisingly, we found that the cases in which healthcare professionals experience more or less therapeutic doubt after the use of OncologIQ were equally distributed. Moreover, more and less doubt was associated with respectively a lower and higher estimated median survival chance. We would argue that both the experience of less and more doubt would impact the decision making process. A good – maybe expected – prognosis could empower the MCM in their decision-making and decreases doubt. On the other hand, a low prognosis – maybe unexpected – could increase doubt. This would suggest

the patient is more complex and it would create more awareness regarding the underlying prognostic factors. This phenomena corresponds with the qualitatively obtained theme 'holistic awareness', which mentions the realistic view of a patients' health status by understanding the individual prognosis from OncologIQ.

In our study, the estimated prognosis led to a change in the multidisciplinary treatment plan once. Consequently, the use of OncologIQ was valued by all healthcare professionals in this specific patient.

Strengths and limitations

This study can be considered unique, as this evaluation step is often left out in prognostic research. The results of this study can guide further implementation of OncologIQ in clinical practices. A major strength of this study was the use of the prognostic model OncologIQ, which has been internally and externally validated[16-22]. This prognostic model is a practical web-based tool that is easily accessible during the MCM. The current model is however only developed for patients with a primary curative tumor and does not apply to secondary primary tumors, recurrent or non-curative disease. Other strengths were the participation of many healthcare professionals every meeting and the obtained qualitative data on user value during interviews with the healthcare professionals. A limitation can be found in the fact that this was a single-center study and it is unclear whether our conclusions can be generalized to other oncological centers as well. Another limitation is that we were not able to investigate the effect of human papillomavirus (HPV) status on therapeutic doubt and added value due to a small number of HPV positive tumors. We do however acknowledge the possible impact of HPV status and corresponding prognosis on the multidisciplinary decision making, especially when more evidence is available for de-escalation therapies[33]. Furthermore, we believe our outcomes can be susceptible for confirmation bias which can be a reason for the little amount of change in treatment plan.

Future perspectives

There is an ongoing paradigm shift in the field of medical decision making and the use of prognostic models. There is an increase in the development of prognostic models, which is accelerated by improved techniques and algorithms for analyzing more complex and larger datasets. However the use of prognostic models in clinical

practice is still limited. It is considered important that models are validated and clinically tested[25]. For OncologIQ, consecutive steps have been taken towards developing a valued and clinically useful prognostic model that is tailored to patients' and physicians' needs[19,29]. This study is the first step in the implementation of OncologIQ in clinical HNC practice. A current trial with sequential cohorts in the Erasmus MC evaluates the impact of the individualized prognosis from the model OncologIQ during the treatment decision consultations. Currently, a prognostic model for palliative HNC patients is being developed. As suggested by the healthcare professionals and patients as well, including QoL in prediction models would benefit the decision-making process[19]. This will be a future objective for our department.

Conclusion

This study showed that in the case of complex patients, healthcare professionals find estimates of survival chances from the prognostic model OncologIQ of added value during the multidisciplinary decision making process. OncologIQ improves patient-centered care and provides healthcare professionals with a more realistic view on the patients' prospects in term of survival chances. OncologIQ is ready for use as standard of care in multidisciplinary decision-making.

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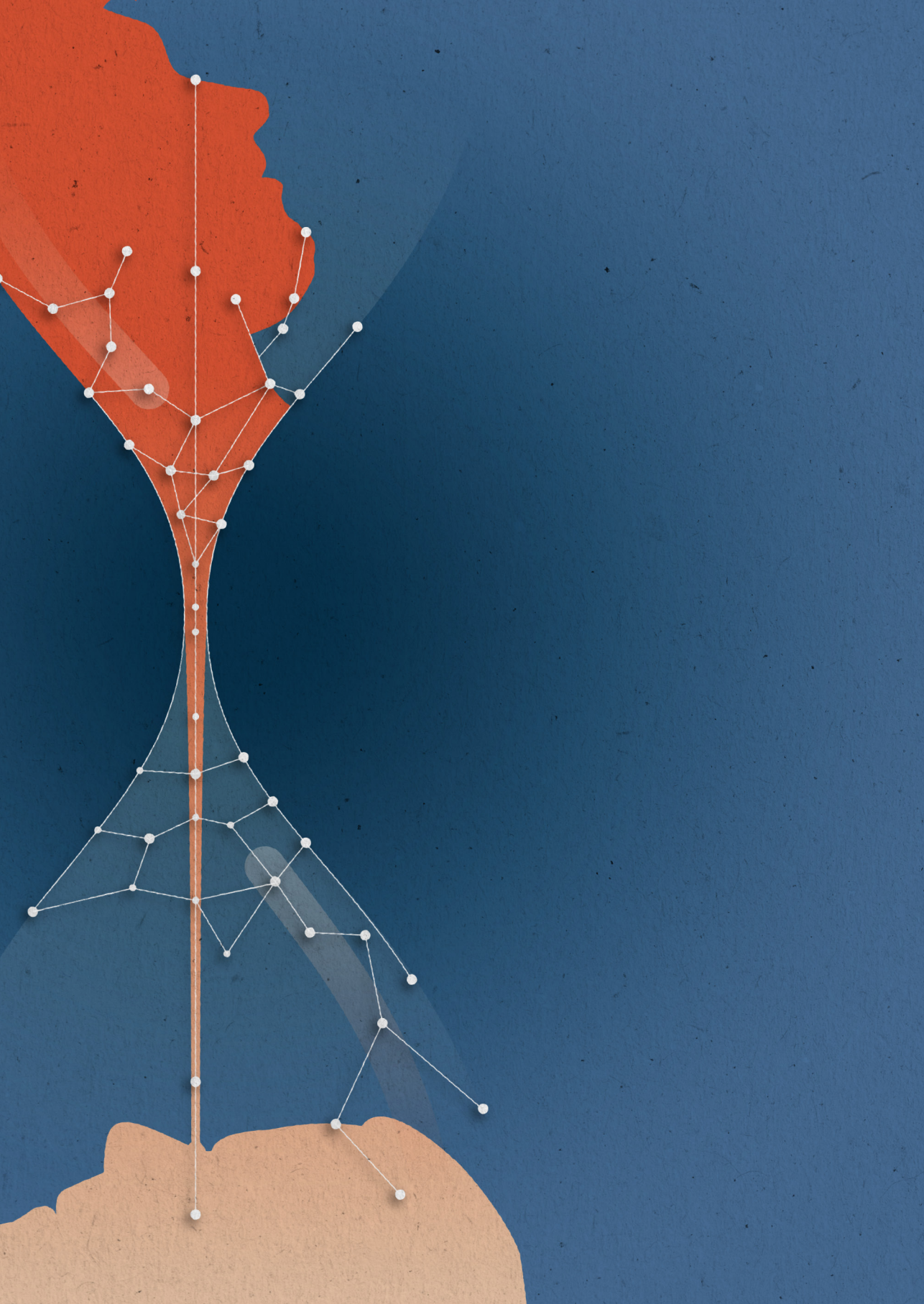
Appendix I. Structured interview

1. What is your personal experience with OncologIQ?
2. Why is or isn't the personalized prognostic information of added value in the decision-making process?
3. In case you find OncologIQ of added value in the decision making process, for which patients is this the case?
4. Have you changed your opinion about the use of OncologIQ during the pilot study?
5. Do you see areas of improvement for the use of OncologIQ within the MCM?
6. To what degree would you recommend the use of OncologIQ to other colleagues? (rating from 0= not recommended at all. 10= absolutely recommended



Chapter 4

The effect of individualized prognostic counselling on the decision-making process in head and neck cancer

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Abstract

Objective: Treatment for head and neck squamous cell carcinoma (HNSCC) is associated with high morbidity and sometimes compromising vital functions. Therefore, accurate counselling for treatment options, survival rates and quality of life is important. To support prognostication and decision-making in head and neck cancer, an individualized prognostic model named OncologIQ has been developed. This model estimates the 1- to 10-year overall survival (OS) chances of patients with primary HNSCC, based on the average treatment effect. Apart from tumor data, it includes other patient-specific factors, such as age, comorbidity, performance status, and socioeconomic status. The aim of this study is to evaluate the effect of individualized counseling with OncologIQ on the decision-making process by measuring decisional conflict.

Materials and Methods: A prospective clinical trial with sequential cohorts was performed. Newly diagnosed patients, eligible for curative treatment of a primary HNSCC were included. Patients in cohort I received standard counseling from their treating physician. Patients in the second cohort received additional individualized prognostic counselling with OncologIQ. Both cohorts were divided in Small laryngeal squamous cell carcinoma (SLSCC) and other Head and Neck squamous cell carcinoma (HNSCC). Study parameters were: decisional conflict, the perceived role in the decision-making process (control preference scale), decisional regret, treatment choice and quality of life.

Results: At baseline, mean age was 66.1 (SD 8.8). We included a total of 258 patients in cohort I, and 200 patients in cohort II. Median total decisional conflict scores were significantly lower in cohort II for both SLSCC (24.2 vs. 14.8, p=0.004) and other HNSCC (22.7 vs. 14.1, p=0.001). In the SLSCC group, significant lower decisional conflict was found in the informed decision making subscale. For other HNSCC, significant lower decisional conflict was found in the subscales informed decision making, values clarity, support and effective decision making. For SLSCC, no significant differences in the perceived role in the decision-making process were found. In the other HNSCC group, patients experienced significantly more often a shared or active role in the decision making process after individualized counseling with OncologIQ (p=0.02). Decisional regret was significant lower at T1 (3-6 months

after finishing treatment) for both groups in the second cohort. This significance was lost at T=2 (12 months after finishing treatment). In the other HNSCC group, eight patients in cohort II declined the treatment proposal after individual counseling with OncologIQ vs. four patients in cohort I. No significant differences in quality of life were found.

Conclusion: Patients who received individualized prognostic counseling with OncologIQ experienced less decisional conflict and less decisional regret 3-6 months after treatment. After individual counseling with OncologIQ for patients within the group of other HNSCC, patients were able to make treatment decisions more actively and during a process of shared decision making with their healthcare professional.

Introduction

Decision making in Head and Neck Squamous Cell Carcinoma (HNSSC) management can be a complex process as it often requires a tradeoff between optimizing prognosis whilst retaining quality of life (QoL). Patients heavily rely on a trusted relationship with their physicians[1]. Therefore, involving patients in the decision-making process is an important step[1,2]. When patients are able to make well-informed treatment decisions, there is less decisional conflict and uncertainty[2-6].

In addition to practical aspects concerning treatment, individualized prognostic information is considered a valuable factor within the decision-making process[7-11]. However, communicating prognosis is difficult and individualized estimations of survival seem to be unreliable[12-15]. The current strategies in prognostic counselling are usually led by the patient explicitly asking. When prognostic information is provided by physicians, this can range from qualitative estimates (e.g. good or moderate prognosis) to quantitative survival rates (e.g. 5-year survival rates from literature) [15,16]. To support prognostication and decision-making, in the past decades several HNSCC specific prognostic models have been developed as an extra evidence-based tool[8,11,14,17,18]. However, the availability and applicability of externally validated models in clinical practice is still limited[7-9].

In the past 20 years, our clinical research group at Erasmus Medical Center in Rotterdam, the Netherlands (Erasmus MC), has taken consecutive steps towards developing, validating and implementing a valuable and clinically useful prognostic model for HNSCCC, OncologIQ, that is tailored to patients' and physicians' needs[14-16]. It is online available via open access[19], and estimates the 1- to 10-year overall survival (OS) chances of patients with curative primary HNSCC, based on the average treatment effect[12,15,20-24]. Apart from tumor data, it includes other patient-specific factors, such as age, comorbidity, performance status, and socioeconomic status. After updating the model[23], based on patients'[15] and physicians' needs, OncologIQ was implemented in a multidisciplinary team (MDT) showing its benefit for discussing patient cases with a poorer prognosis[11]. The aim of the current study was to evaluate the effect of personalized prognostic counseling with OncologIQ in the consultation room. Primary outcome was the difference in decisional conflict between patients that were counseled with and without OncologIQ. Secondary outcome parameters were the perceived role in the decision-making process (control preference scale), decisional regret, treatment choices and quality of life. Our hypothesis was that individualized prognostic counseling leads to less decisional conflict and a more active role in the decision-making process.

Material and Methods

Ethical considerations

This project was approved by the review board and ethics committee from the Erasmus MC (MEC number: MEC-2013-052) and follows the principles of the declaration of Helsinki. It was registered in the international clinical trial registry platform (NTR4106) and complies with recommendations from the International Committee of Medical Journal Editors. All participating patients provided electronic written informed consent.

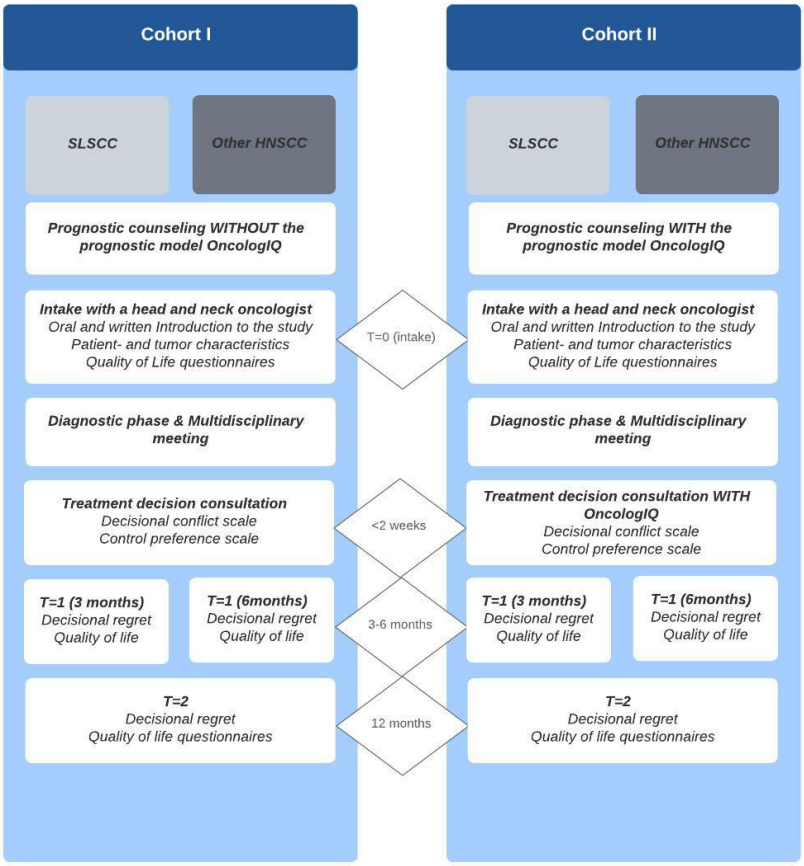

Figure 1. baseline characteristics

Setting

The study setting is a prospective sequential trial with two cohorts with a one year follow-up period after treatment conducted in the Erasmus Medical Center (figure 1). Patients included in cohort I were counseled by their physician following current practice (without the use of an online prognostic model)[16]. Patients included in the second cohort received individualized prognostic counseling with OncologIQ. The setting of sequential cohorts was chosen to limit performance bias, as we expect physicians experience a learning curve from using the model which can impacts counseling in the group in which OncologIQ is not used.

For cohort I, patients were included between January 2014 and August 2018; for cohort II, between October 2019 and January 2022. Both cohorts were divided in two groups of patients: small laryngeal squamous cell carcinoma (SLSCC) and other HNSCC, leading to four different groups of patients for analysis (figure 1). In contrast to other HNSCC, patients with SLSCC often have two relatively comparable treatment options in terms of survival: laser surgery or radiotherapy. These treatment options differ in duration, side effects, laryngeal preservation, and functional outcomes[25-31], which offers patients a preference-sensitive decision. A part of the data of cohort I has been previously published. For the current study, patients with a parotic gland tumor were not included.

Participants

Patients diagnosed with a primary HNSCC or carcinoma in situ of the larynx, oropharynx, oral cavity, hypopharynx and nasopharynx and eligible for curative treatment at the Erasmus MC Cancer Institute were approached for inclusion during their first consultation at the outpatient clinic. Exclusion criteria were: age < 18 years, simultaneous or synchronic multiple primary HNSCC, illiteracy, insufficient knowledge of Dutch language, and patients who were incompetent to consider their own treatment choice due to dementia or other cognitive disease. Patients were individually informed on the study by the research team and received written information during their first consultation at the outpatient clinic. A week after receiving information on the study and prior to the treatment decision consultation, patients were called to confirm their willingness to participate.

OncologIQ

OncologIQ is an internally and externally validated prognostic model which supports shared decision-making for patients with primary HNSCC[12,15,20-24]. This model estimates the 1- to 10-year overall survival chances (OS) of patients with primary HNSCC, based on the average treatment effect. It combines TNM-classification with the following patient-specific predictors: age, sex, comorbidity, tumor location, smoking, BMI, weight loss, WHO performance, and socioeconomic status. OncologIQ includes the following tumor locations: lip, oral cavity, oropharynx, nasopharynx, hypopharynx and larynx. The model is via open access online available can be found at www.oncologIQ.com[19]. An example can be seen in figure 1.

Main outcomes and measures

At baseline, the following patient and tumor characteristics were collected: age, sex, tumor localization, tumor stage, smoking behavior, education level, employment, treatment proposal from the MDT. The flowchart for this study can be found in figure 1. In both cohorts, T1 is three months after finishing treatment for the SLSCC group and six months for the other HNSCC. T2 is 12 months after finishing treatment for both groups in both cohorts. To evaluate the difference in decisional conflict and experienced shared decision making between both cohorts, the Decisional Conflict Scale (DCS) and the Control Preference Scale (CPS) were scored within two weeks after the treatment decision consultation, and before the start of treatment. When patients spoke to more healthcare professionals prior to starting treatment (i.e. surgeon, radiotherapist, oncologist), these outcome measures were taken within two weeks after the last consultation. The DCS is a validated 16-item 5-point Likert-scale measurement for assessing patients' uncertainty regarding their medical decision[32]. It consists of five subscales measuring: 1) uncertainty, 2) feeling uninformed, 3) feeling unclear about values, 4) feeling unsupported and 5) ineffective decision making. [32] The overall score of the DCS ranges from 0-100. Higher scores indicate higher decision-related distress. Scores <25 are associated with implementing decisions, while scores >37.5 are associated with decision delay or feeling unsure about implementation. [32] Several studies suggest a total score of ≥25 as a cut-off for clinically significant decisional conflict. [33,34] The CPS measures the degree of control an individual experiences in the decision making process, [35] and consists of the subscales: 1) I made the decision myself (active), 2) I made the decision after considering the doctor's opinion (active), 3) It was a shared decision (collaborative), 4) The doctor made the decision after considering my opinion (passive), 5) The doctor made the decision (passive). Decisional regret was measured through the decisional regret scale (DRS). This is a validated 5-item tool to assess regret regarding therapy decisions[36]. The difference in proposed treatments by the MDT and definite chosen treatment by the patient during the treatment decision consultation was noted. For measuring quality of life and daily functioning, patient-reported questionnaires were used. The functional domain of QoL was measured by the Eating Assessment Tool (EAT-10), and the Voice Handicap Index (VHI). [37,38] The Hospital Anxiety and Depression Scale (HADS) was used to assess levels of anxiety and depression[39,40] The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30)

was also assessed. In this study we analyzed the global health status scale and the five functional scales(physical, role, cognitive, emotional, and social).[41] Finally the EuroQol-5D (EQ-5D) was assessed. The EQ-5D is a 5-item non-disease-specific instrument for describing and valuing health-related QoL.[42,43] Differences in survival are not a parameter in this study.

Statistical analyses

A sample size calculation on the primary outcome decisional conflict showed that 79 patients per group are needed to find a statistical significant difference (α: 0.05; power: 0.80).[44] Taken into account non response, at least 200 patients were needed in both cohorts. Statistical analyses were performed using SPSS, version 28 (IBM) [45]. There was no missing data at baseline. During follow-up, the frequency of missing data was low (<2%). Multiple imputation of missing values was not applied. Cohort I was compared to cohort II for the SLSCC group and other HNSCC separately. The aim of the study was not to compare the SLSCC group with the other HNSCC. Descriptive statistics were used to calculate frequencies and proportions for every group for both cohorts. For categorical data, the Pearson Chi-squared test and Fisher's exact test were used when appropriate to assess heterogeneity between groups. For continuous data, the Student's t test and the analysis of variance (ANOVA) model were used. Statistical significance was established at $p<0.05$. For all patient-reported outcomes, clinical relevance was taken into account according to the user manuals[32,36,46].

Results

In total, 919 patients were eligible for this study and were approached and informed. Finally, 458 patients (49.8%) were included in this study (Cohort I: 258; Cohort II: 200). Patients were not obliged to give a reason for non-partition. However, within cohort II, it was recorded whether patients were willing to receive prognostic information. From the non-participating patients in cohort II, 161 patients (42,1%) expressed explicitly that they didn't want to receive prognostic information.

In total, 258 patients were included in cohort I, with 102 in the SLSCC group and 156 in the Other HNSCC group. A total of 200 patients were included in cohort

II, with 80 in the SLSCC group and 120 in the other HNSCC group. In cohort I and II, respectively 2 and 1 patients were lost to follow-up. In total, 55 patients died during follow-up, respectively 31 and 25 in cohort I and II. In both the SLSCC and other HNSCC group, most baseline variables were not significantly different between cohorts. There were significantly (p=0.002) more none-smokers in cohort II within the SLSCC group, compared to cohort I. Further baseline characteristics can be found in Table 1.

Table 1. Baseline characteristics for Cohort I (N=258) and II (N=200), divided by two groups: 1) Small Laryngeal Squamous Cell Carcinoma (SLSCC) and 2) Other Head and Neck Squamous Cell Carcinoma.

	SLSCC		Sig.	**Other HNSCC**		Sig.
	Cohort I	Cohort II		Cohort I	Cohort II	
No. of patients (%)	102 (39.5)	80 (40.0)		156 (60.5)	120 (60.0)	
Mean age, years (SD)	66.1 (11.4)	68.4 (10.4)		64.9 (9.8)	65.9 (8.4)	
Sex			0.9			0.3
Men	87 (85.3)	68 (85.0)		121 (77.6)	86 (71.7)	
Women	15 (14.7)	12 (15.0)		35 (22.4)	34 (28.3)	
Tumor localization			0.3			0.3
Glottic	93 (91.2)	76 (95.0)		30 (19.2)	21 (17.5)	
Supraglottic	9 (8.8)	4 (5.0)		32 (20.5)	14 (11.7)	
Oropharynx	-	-		15 (32.7)	40 (33.3)	
Oral cavity	-	-		23 (14.7)	26 (21.7)	
Hypopharynx	-	-		18 (11.5)	15 (12.5)	
Nasopharynx	-	-		2 (1.3)	4 (3.3)	
Tumorstage			0.3			<0.001
I	82 (80.4)	69 (86.3)		6 (3.8)	24 (20.0)	
II	20 (19.6)	11 (13.8)		31 (19.9)	29 (24.2)	
III	-	-		61 (39.1)	23 (19.2)	
IV	-	-		58 (37.2)	44 (36.7)	
Smoking			0.002			0.2
Current/former	97 (95.1)	66 (50.0)		138 (88.5)	98 (81.7)	
No	5 (4.9)	18 (22.5)		18 (11.5)	22 (18.3)	

Table 1. Baseline characteristics for Cohort I (N=258) and II (N=200), divided by two groups: 1) Small Laryngeal Squamous Cell Carcinoma (SLSCC) and 2) Other Head and Neck Squamous Cell Carcinoma. (*Continued*)

	SLSCC		Sig.	**Other HNSCC**		Sig.
	Cohort I	Cohort II		Cohort I	Cohort II	
Education Level			0.3			0.4
Lower	45 (44.1)	32 (40.0)		64 (42.4)	38 (31.7)	
Intermediate	39 (38.2)	34 (42.5)		61 (39.1)	54 (45.0)	
Tertiary	12 (11.8)	13 (16.3)		26 (16.7)	22 (18.3)	
Unknown	6 (5.9)	1 (1.3)		5 (3.2)	6 (5.0)	
Employment			0.5			0.07
Retired	57 (55.9)	49 (61.3)		76 (48.7)	63 (52.5)	
Yes	22 (21.6)	23 (28.7)		42 (26.9)	34 (28.3)	
No	16 (15.7)	8 (10.0)		29 (18.6)	23 (19.2)	
Unknown	7 (6.9%)	-		9 (5.8)	-	
Treatment proposal[c]			0.4			0.002
Radiotherapy	37 (36.3)	38 (47.5)		50 (32.1)	42 (35.0)	
Surgery OR Radiotherapy	32 (31.4)	22 (27.5)		2 (1.3)	6 (5.0)	
Surgery	31 (30.4)	18 (22.5)		12 (7.7)	20 (16.7)	
Surgery AND Radiotherapy	-	-		39 (25.0)	11 (9.2)	
Chemo- or Bioradiation	1 (1.0)	-		53 (34.0)	41 (34.2)	
Wait-and-see	1 (1.0)	2 (2.5)		-	-	
Acceptance of treatment proposal			0.4			0.09
Yes	101(99.0)	80 (100)		152 (97.4)	112 (93.3)	
No	1 (1.0)	-		4 (2.6)	8 (6.7)	

[a]ACE-27: Adult Comorbidity Evaluation-27. [b]In the total group. [c]Treatment proposal suggested by the multidisciplinary tumor board.

Table 2. The decisional conflict scale including the five subscales in both cohorts and subgroups.

Decisional Conflict Scale	Total	Informed	Values clarity	Support	Uncertainty	Effective decision
SLSCC Median(Q1-Q3)						
Cohort I n=102	24.2 (12.1 – 31.3)	25.0 (0.0 – 41.7)	33.3 (16.7 – 41.7)	16.7 (0.0 – 33.3)	33.3 (8.3 – 41.7)	0.0 (0.0 -25.0)
Cohort II n=80	14.8 (9.4 – 26.6)	16.7 (2.1 – 33.3)	25.0 (8.3 – 41.7)	16.7 (0.0 – 33.3)	33.3 (8.3 – 41.7)	0.0 (0.0 – 12.5)
Significance	0.04	0.03	0.24	0.71	0.83	0.11
Other HNSCC Median(Q1-Q3)						
Cohort I n=156	22.7 (14.1 – 34.0)	33.3 (16.7 – 41.7)	33.3 (16.7 – 50.0)	25.0 (8.3 – 33.3)	25.0 (0.0 – 41.7)	6.3 (0.0 – 25.0)
Cohort II n=120	14.1 (5.1 – 29.7)	16.7 (0.0 – 33.3)	16.7 (0.0 – 41.7)	16.7 (0.0 – 25.0)	16.7 (0.0 – 50.0)	0.0 (0.0 – 18.8)
Significance	0.001	<0.001	<0.001	0.002	0.85	0.03

The CPS scale measures the degree of control an individual experiences in the decision making process, and consists of the subscales: 1) I made the decision myself (active), 2) I made the decision after considering the doctor's opinion (active), 3) It was a shared decision (collaborative), 4) The doctor made the decision after considering my opinion (passive), 5) The doctor made the decision (passive).

Decisional conflict and decisional regret

In both groups there was a significant decline in median DCS after individualized counseling with OncologIQ. Median decisional conflict for the SLSCC group was 24.2 vs. 14.8, p=0.004 for cohort I and II respectively. For other HNSCC the median scores were 22.7 vs. 14.1, p=0.001 (Table 2). This decline indicates less decision-related distress among patients after counselling with OncologIQ. Analyses of subscales of the DCS showed significant lower decisional conflict in the 'informed decision making' subscale in both groups. In addition, in the other HNSCC group significant lower scores were also found in the group values clarity (p<0.001), support (p=0.002) and effective decision making (p=0.03). Decisional regret was significantly lower in cohort II for both groups at T1. This significance was lost at T2 for both groups (Table 3).

Table 3. The decisional regret scale in both cohorts and subgroups.

Decisional Regret Scale	T1	T2
No. of patients (%)	n=362 (79.0)	N=282 (61.6)
SLSCC Median(Q1-Q3)		
Cohort I	20.0 (1.25 – 28.8)	0.0 (0.0 – 27.5)
Cohort II	5.0 (0.0 – 20.0)	5.0 (0.0 – 20.0)
Significance	0.05	0.76
Other HNSCC Median(Q1-Q3)		
Cohort I	20.0 (10.0 – 25.0)	15.0 (5.0 – 30.0)
Cohort II	10.0 (0.0 – 20.0)	10.0 (0.0 -20.0)
Significance	<0.001	0.19

Control preference scale

For the SLSCC group, no significant differences in the perceived role during the decision-making process measured by the CPS were found (Table 4). For the group other HNSCC, patients experienced a more active role in the decision making process after individualized counseling with OncologIQ. A significantly lower proportion of patients in cohort II in the other HNSCC group expressed that the doctor made the decision (23.7% vs. 8.4%, p=0.02). In addition, a higher proportion of patients in cohort II felt that they made a shared decision (34.6% vs 40.3%).

Table 4. The control preferences scale in both cohorts and subgroups.

Control preference Scale No. (%)	1 patient decides (active)	2 (active)	3 shared decision (collaborative)	4 (passive)	5 doctor decides (passive)	*Significance*
SLSCC						p=0.496
Cohort I n=102	14 (13.7)	25 (24.5)	44 (43.1)	10 (9.8)	9 (8.8)	
Cohort II n=80	10 (12.5)	18 (22.5)	29 (36.3)	9 (11.3)	14 (17.5)	
Other HNSCC						p=0.02
Cohort I n=156	16 (10.3)	26 (16.7)	54 (34.6)	23 (14.7)	37 (23.7)	
Cohort II n=120	13 (10.9)	28 (23.5)	48 (40.3)	20 (16.8)	10 (8.4)	

Table 5 Quality of life in both cohorts and subgroups.

	clinical cut-off[a]	**Cohort I**	**Cohort II**	
Time		**Intake**		
1) SLSCC				
No. of patients (%)		n=102 (100)	n=80 (100)	
EQ-5D[b]	0 - 1	0.84 (0.75 – 1.00)	0.89 (0.81 – 1.00)	0.9
EORTC-QLQ-C30[c]				
Global health status	> 66.7	83.3 (66.7 – 83.3)	83.3 (66.7 – 83.3)	0.6
Physical functioning	> 86.7	100 (86.7 – 100)	100 (80.0 – 100)	0.3
Role functioning	= 100	100 (83.3 – 100)	100 (100 – 100)	0.2
Emotional functioning	> 75	75.0 (58.3 – 91.7)	75.0 (62.5 – 87.5)	0.6
Cognitive functioning	= 100	100 (83.3 – 100)	100 (83.3 – 100)	0.6
Social functioning	= 100	100 (83.3 – 100)	100 (100 – 100)	0.5
HADS[d] Anxiety	<8	5.0 (2.0 – 6.5)	4.0 (2.0 – 7.0)	0.8
HADS[d] Depression	<8	2.0 (0.5 – 4.0)	2.0 (0.8 – 5.0)	0.7
EAT-10[e]	<3	0.0 (0.0 – 2.0)	0.0 (0.0 – 2.0)	0.6
VHI[f]	≤30	25.0 (13.5 – 43.0)	30.5 (15. – 51.3)	0.04
2) Other HNSCC				
No. of patients		n=156 (100)	n=120 (100)	
EQ-5D[b]	0 - 1	0.83 (0.72 – 1.0)	0.84 (0.77 – 1.00)	0.2
EORTC-QLQ-C30[c]				
Global health status	> 66.7	75.0 (66.7 – 83.3)	70.8 (50.0 – 91.7)	0.8
Physical functioning	> 86.7	100 (80.0 – 100)	93.3 (86.7 – 100)	0.4
Role functioning	= 100	100 (83.3 – 100)	100 (100 – 100)	0.3
Emotional functioning	> 75	75.0 (58.3 – 91.7)	66.7 (52.0 – 83.3)	0.5
Cognitive functioning	= 100	100 (83.3 – 100)	100 (83.3 – 100)	0.1
Social functioning	= 100	100 (100 – 100)	100 (83.3 – 100)	0.6
HADS[d] Anxiety	<8	4.0 (2.3 – 7.0)	5.0 (2.0 – 7.3)	0.3
HADS[d] Depression	<8	2.0 (0.0 – 4.0)	2.0 (1.0 – 6.0)	0.9
EAT-10[e]	<3	1.0 (0.0 – 5.0)	0.5 (0.0 – 4.0)	0.01
VHI[f]	<30	0.0 (0.0 – 6.8)	1.0 (0.0 – 10.0)	0.02

[a] Score that is considered as normal / mild.

[b] EQ-5D: EuroQol-5D

[c] EORTC-QLQ-C30: The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30

[d] HADS: Hospital Anxiety and Depression Scale

[e] EAT-10: Eating Assessment Tool

[f] VHI: Voice Handicap Index

Cohort I	Cohort II		Cohort I	Cohort II	
T=1			T=2		
N=85 (83.3)	N=73 (91.3)		N=49 (48.0)	N=66 (82.5)	
0.84 (0.75 – 1.00)	0.89 (0.76 – 1.00)	0.3	0.86 (0.79 – 1.00)	0.95 (0.81 – 1.00)	0.6
75.0 (66.7 – 83.3)	75.0 (66.7 – 83.3)	0.9	83.3 (62.5 – 87.5)	83.3 (70.8 – 100)	0.5
100 (73.3 – 100)	93.3 (80.0 – 100)	0.2	93.3 (76.7 – 100)	93.3 (76.7 – 100)	0.4
100 (66.7 – 100)	100 (66.7 – 100)	0.2	100 (66.7 – 100)	100 (66.7 – 100)	0.8
83.3 (66.7 – 100)	91.7 (66.7 – 100)	0.1	91.7 (75.0 – 100)	91.7 (70.8 – 100)	0.5
100 (83.3 – 100)	83.3 (83.3 – 100)	0.5	100 (66.7 – 100)	100 (83.3 – 100)	0.4
100 (66.7 – 100)	100 (83.3 – 100)	0.2	100 (91.7 – 100)	83.3 (66.7 – 100)	0.06
4.0 (1.0 – 6.0)	3.0 (1.0 – 6.3)	0.9	3.0 (1.0 – 5.5)	3.0 (1.0 – 5.0)	0.9
2.0 (0.0 – 5.5)	1.5 (0.0 – 4.0)	0.2	2. (0.0 – 4.0)	1.0 (0.0 – 5.0)	0.7
0.0 (0.0 – 3.5)	0.0 (0.0 – 1.0)	0.004	0.0 (0.0 – 1.0)	0.0 (0.0 – 0.0)	0.3
15.0 (2.0 – 37.5)	17.5 (8.0 – 33.8)	0.1	11.0 (0.0 – 27.5)	11.5 (3.8 – 35.0)	0.3
N=115 (73.7)	N=87 (72.5)		N=91 (58.3)	N=70 (58.3)	
0.86 (0.81 – 1.0)	0.84 (0.78 – 1.0)	0.2	0.84 (0.78 – 1.0)	0.89 (0.81 – 1.0)	0.3
75.0 (66.7 – 83.3)	83.3 (60.4 – 83.3)	0.5	83.3 (66.7 – 91.7)	83.3 (60.4 – 100)	1.0
86.7 (73.3 – 100)	90.0 (75.0 – 100)	0.9	93.3 (73.3 – 100)	86.7 (80.0 – 100)	0.6
83.3 (66.7 – 100)	100 (66.7 – 100)	1.0	100 (66.7 – 100)	100 (66.7 – 100)	0.8
91.7 (66.7 -100)	91.7 (75.0 – 100)	0.8	91.7 (83.3 – 100)	91.7 (68.8 – 100)	0.8
83.3 (83.3 – 100)	91.7 (66.7 – 100)	0.5	100 (83.3 – 100)	100 (83.3 – 100)	0.6
100 (66.7 – 100)	100 (70.8 – 100)	0.8	100 (83.3 – 100)	100 (83.3 – 100)	0.4
2.0 (0.3 – 4.0)	3.0 (1.0 – 5.0)	0.2	2.0 (0.0 – 5.0)	2.0 (1.0 – 5.0)	0.6
2.0 (0.3 – 4.8)	2.0 (0.8 – 6.0)	0.7	2.0 (1.0 – 4.0)	1.5 (0.0 – 6.0)	1.0
3.5 (0.0 – 15.8)	1.5 (0.0 – 8.3)	0.02	5.0 (0.0 – 12.0)	0.0 (0.0 – 4.3)	<0.001
13.0 (0.0 – 30.8)	6.5 (0.0 – 23.8)	0.03	10.5 (1.0 – 37.0	2.0 (0.0 – 24.5)	<0.001

Treatment choice

In total, 13 patients declined the treatment proposal, one in the SLSCC group and 12 in the other HNSCC. Within the other HNSCC group, 4 (2.6%) patients in cohort I declined and 8 (6.7%) in cohort II declined. These twelve patients chose for palliative care without further interventions instead of the proposed treatment. In both cohorts, 75% were patients with stage IV disease. No trend could be found in type of treatments that were declined. One patient (cohort I) chose for watchful waiting instead of transoral laser surgery. Median scores on the DCS for patients declining a treatment proposal were 10.9 for cohort I and 12.5 for cohort II, both lower than total scores in table 2. According to the CPS, all patients expressed that they had made the treatment decision themselves.

Quality of life

A few significant, however not clinically relevant, differences in quality of life and daily functioning were found between cohorts (table 5).

Discussion

This unique study assessed the effect of individualized prognostic counseling on the patient perception of the decision-making process for treatment of Head and Neck Cancer (HNSCC). Our results show a benefit of using our prognostic model during the treatment decision consultation for patients in need of prognostic information. Patients who received individualized prognostic counseling with OncologIQ experienced less decisional conflict and less decisional regret 3-6 months after treatment. Patients within the other HNSCC group experienced significantly more often a shared or active role in the decision making process after individualized counseling with OncologIQ. These results offer opportunities for improved counseling and decision making for patients and HNSCC surgeons, -radiologists and –oncologist. The results of this study are unique within this field of research as many models are developed, however their impact in clinical practice are never tested.

Decisional conflict appeared significantly lower in the second cohort for both treatment groups. A median improvement of 10.6 points (SLSCC) and 8.6 points (other HNSCC) was found, which are significant improvements considering the

proposed meaningful differences (0.3 - 0.4 points) by O'Connor at al[32]. Previous research found that improving individual decisional conflict is associated with less treatment changes, less treatment delay, improved knowledge on proposed treatment and less decisional regret[47]. Gattelari and Ward also found that when DCS is increased by one unit, patients were 19% more likely to blame their doctor for bad outcomes[48]. The latter was also related to decisional regret, which in our study was significant better in cohort II. This, however, was only at T1. We believe that this can be attributed to time passing on and therefore patients forget or downplay the harm experienced.

A significant difference in experienced shared decision making between cohorts was only found for the other HNSCC group. We would argue that the use of OncologIQ enables a more in-depth conversation on prognosis, and that this is a more relevant topic within the other HNSCC group, comprising more advanced disease with lower prognostic estimates. This aligns with our clinical experience during the study that OncologIQ enables a more in-depth conversation and therefore understanding of the impact of the disease and treatment. In addition, the finding of this study that more patients choose for a less invasive palliative treatment shows the importance of discussing prognosis. Despite this is not significant, we do find this outcome very relevant as it could be possible that patients are more aware of the predicted survival and make other decisions, which also includes the choice for early palliative care. However, this would require an impossible sample size. The effects of early palliative care are studied among patients with metastatic non-small-cell lung cancer. The results in this group showed that early palliative care led to less aggressive care at the end of life but longer survival[49]. Reasons for non-acceptance were difficult to extract. Especially, whether OncologIQ was a reason for declining the proposed treatment from the MDT. We have not included this as a question afterwards.

Within our study, no clinical relevant differences in QoL were found. No clinical relevant differences in QoL were expected as this is a multifactorial variable and the use of a prognostic model won't change such outcomes after treatment. The hypothesis that QoL may be improved in patients with a poor prognosis by choosing for a less aggressive, non-protocol based treatment is not supported by this study.

Strength and limitations

For this study, the method of a prospective sequential trial was chosen. By choosing this, a fair comparison between cohorts could be made because healthcare professionals in cohort I were not biased by knowledge from the use of OncologIQ. Prior to the start of Cohort II, all healthcare professionals were trained in using OncologIQ according to a standard format. In both cohorts, the same healthcare professionals participated in the study. During the period of the study, there was an international increase in attention to adequate counseling and shared decision making. This could have caused improved counseling as well. Differences at baseline in smoking behavior can be attributed to the fact that the amount of patients actively smoking declined over time, and that there is more awareness and prevention strategies on smoking. Also, there could be a Hawthorne effect in this study: patients modify behavior in response to their awareness of being observed[50].

Future perspectives

Considering the results of this study, we believe that OncologIQ can facilitate an important role within the decision-making process. We recommend that patients should be offered the opportunity to hear more on their individual prognostic estimates. Asking patients "How much do you want to know about prognosis?" enables a more patient-centered approach[15,51]. Therefore, a clinical practice guideline was developed to support professionals in sharing prognostic information[14,15]. OncologIQ is made electronically available in het electronic patient record.

During the development and clinical use of OncologIQ, we noticed that we could not meet the need of palliative HNSCC patients in providing individual estimates of survival. From experience and literature, we know that cancer patients in the palliative phase have a higher prognostic information need than curative patients[15]. Therefore, a prognostic model has recently been developed by our research team and will be clinically tested[52].

Conclusion

Patients who received individualized prognostic counseling with OncologIQ experienced less decisional conflict and less decisional regret 3-6 months after treatment. After individual counseling with OncologIQ for patients within the group

of other HNSCC, patients were able to make treatment decisions more actively and during a process of shared decision making with their healthcare professional.

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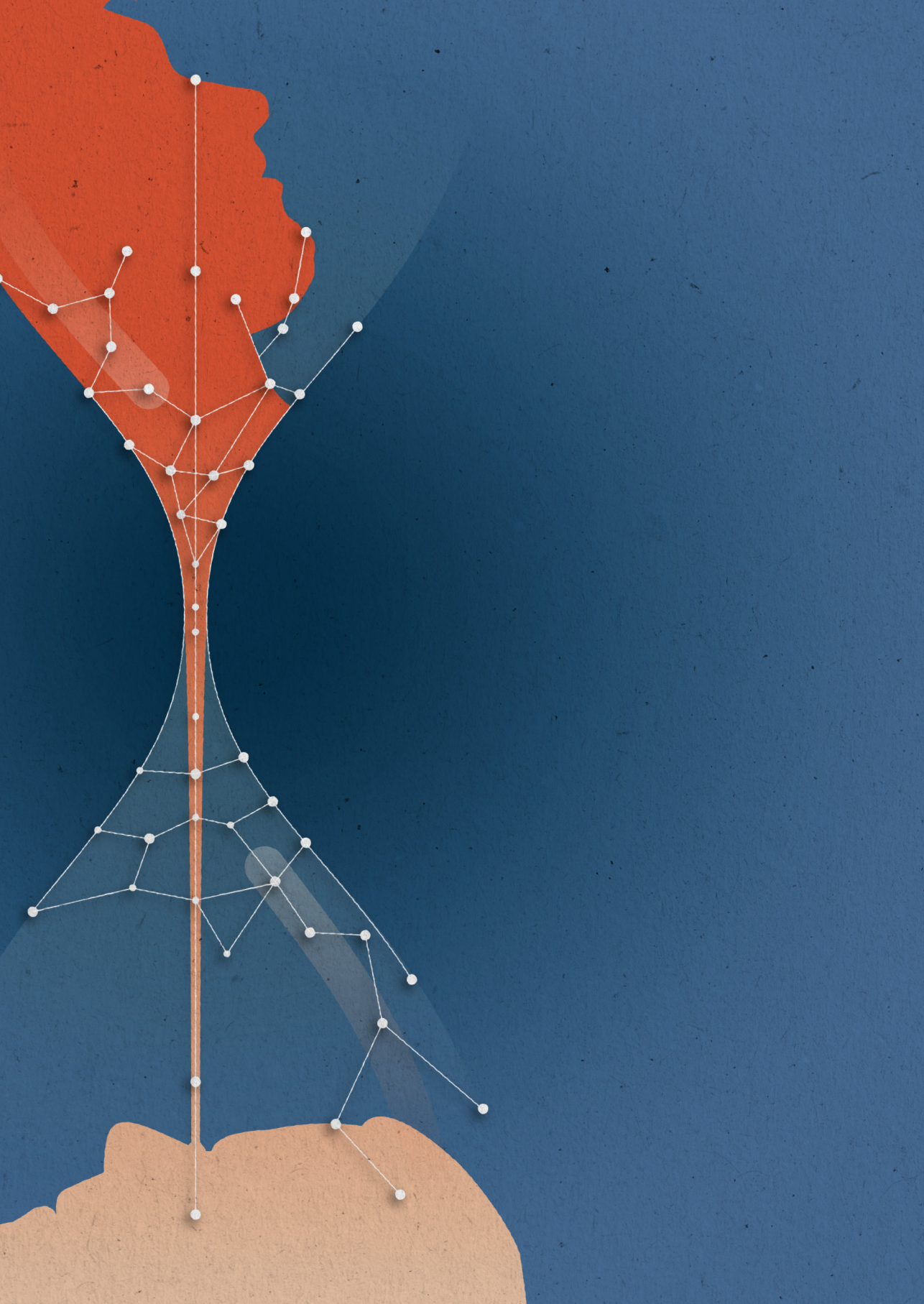

Chapter 5

Longitudinal Patient-Reported Voice Quality in Early-Stage Glottic Cancer

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Abstract

Objective: Patient-reported voice quality is an important outcome during counseling in early-stage glottic cancer. However, there is a paucity of adequate longitudinal studies concerning voice outcomes. This study aimed to investigate longitudinal trajectories for patient-reported voice quality and associated risk factors for treatment modalities such as transoral CO2 laser microsurgery, single vocal cord irradiation, and local radiotherapy.

Study Design: A longitudinal observational cohort study

Setting: Tertiary cancer center.

Methods: Patients treated for Tcis-T1b, N0M0 glottic cancer were included in this study (N = 294). The Voice Handicap Index was obtained at baseline and during follow-up (N = 1944). Mixed-effects models were used for investigating the different trajectories for patient-reported voice quality.

Results: The mean follow-up duration was 43.4 (SD, 21.5) months. Patients received transoral CO2 laser microsurgery (57.8%), single vocal cord irradiation (24.5%), or local radiotherapy (17.5%). A steeper improvement during the first year after treatment for single vocal cord irradiation (-15.7) and local radiotherapy (-12.4) compared with laser surgery (-6.1) showed a more stable trajectory. All treatment modalities showed equivalent outcomes during long-term follow-up. Associated risk factors for different longitudinal trajectories were age, tumor stage, and comorbidity.

Conclusion: Longitudinal patient-reported voice quality after treatment for early-stage glottic cancer is heterogeneous and non-linear. Most improvement is seen during the first year of follow-up and differs between treatment modalities. No clinically significant differences in long-term trajectories were found. Insight into longitudinal trajectories can enhance individual patient counseling and provide the foundation for an individualized dynamic prediction model.

Introduction

Early-stage glottic cancer (ESGC) is a common malignancy of the head and neck area and is mostly found in an early stage due to functional complaints like dysphonia[1,2]. ESGC can be treated with transoral CO2 laser microsurgery (TLM), local radiotherapy (LRT), or single vocal cord irradiation (SVCI)[3]. The choice for the best treatment differs per patient and should be made during a shared decision-making process. Although all treatment modalities have comparable and good five-year survival rates[4-9], they differ in duration, side effects, laryngeal preservation, and functional outcomes[4-7,10-16]. TLM is performed in one session and enables targeted resection and preservation of tissue. However, it requires special equipment and trained professionals. On the other hand, radiotherapy is a widely available therapy and does not require anesthesia. But it takes multiple sessions and comes with sequelae like xerostomia. Moreover, in the case of recurrent disease, the need for partial laryngectomy is less when treated with TLM[11]. SVCI is a new technique, developed in our institution, that uses a mild hypofractionated scheme with limited volumes and highly conformal target coverage. This resulted in a significant reduction of the radiation dose to the adjacent organs[17-19]. In the case of ESGC, it was found to be non-inferior to LRT[18,20,21].

Patient-reported voice quality is considered an important outcome during counseling in ESGC. It is compromised by the disease and its treatment, which impact social communication and interaction and, as a result, the psychological and social well-being of the patient. Within our institute, patient-reported voice quality is structurally assessed and used as guidance for individual patient contacts in the consultation room using a Healthcare Monitor[22].

Despite the increasing literature concerning patient-reported voice outcomes in ESGC, it is considered a limitation that many studies are not able to provide insight into longitudinal dynamic evolution because these studies are based on non-randomized, cross-sectional data with varying time frames or short-term data comprising small sample sizes[4-9,23,24]. There is a need for long-term longitudinal patient-reported outcome data with a large sample size, as this type of data can improve our understanding of the dynamic trajectories of voice quality. In addition to survival and practical information, this data can be pivotal in empowering both

patients and healthcare professionals for improved counseling[25,26]. Furthermore, when systematically collected, these data can be used for individualized prediction modeling[27], quality monitoring and improvement[28-30].

Our structurally collected outcome data can be used to obtain longitudinal insight into patient-reported voice quality. So, this study aimed to investigate longitudinal dynamic trajectories for the three different treatment modalities, such as TLM, LRT, and SVCI, as well as associated risk factors for patient-reported voice quality in patients treated for ESGC.

Methods

Setting and participants

All patients treated for ESGC (Tcis – T1b, N0M0) with TLM, LRT, and SVCI at the Erasmus Medical Center between 2013 and 2018 and participating in the Healthcare Monitor were included in this non-randomized, longitudinal outcome study. The Healthcare Monitor is our electronic patient-reported outcome-based clinical support syste[22]. The questionnaires were completed by all the patients before every outpatient clinic visit. This was done either at home or in the clinic with an iPad before the appointment. When patients (1) had low-grade dysplasia and were appointed to strict follow-up, (2) had synchronous tumors, (3) had a prior head and neck malignancy, (4) had no patient-reported outcome measures (PROM) data available, or (5) did not provide informed consent on using data for research purposes, they were excluded from the study.

Ethical considerations

This project was approved by the institutional review board and ethics committee (MEC-2020-0314) from the Erasmus Medical Center Cancer Institute and follows the principles of the Declaration of Helsinki. All participating patients provided electronic, written informed consent.

Main outcomes and measures

In this study, we used the prospectively obtained Dutch version of the Voice Handicap Index (VHI),[31,32] which is a validated 30-item questionnaire that measures

the perceived psychosocial voice impairment in daily life[33]. Each item is scored on a 5-point Likert scale (0 = never, 5 = always). The VHI was measured at baseline and during follow-up, starting two to four months after the completion of the treatment. During the first, second, third, fourth, and fifth years, the VHI was obtained every two, three, four, six, and 12 months, respectively. The total score is the sum of all scores and ranges from 0 to 120. A higher outcome indicates greater voice impairment. A difference of ten points on the VHI was used as the cutoff point for clinical relevance[34].

The treatment modalities in this study are TLM[35] and radiotherapy. The latter can be divided into LRT with 66Gy and SVCI.

The tumor-specific and patient-specific data were retrospectively obtained from Erasmus Medical Center patient records. The variables were treatment, age (in years), gender, adult comorbidity evaluation 27 (ACE-27) score (0–3), World Health Organization (WHO) performance score (0–4), smoking status (yes, no, or former), tumor stage (Tcis, T1a, or T1b), and involvement of the anterior commissure (yes or no). The performance score includes a score for the physical ability of the patient to function in daily life. Comorbidity was scored at the time of diagnosis by the ACE-27, which varies between 0 (no comorbidity) and 3 (severe comorbidity), and was developed specifically for head and neck cancer[36,37].

Statistical analyses

Statistical analyses were performed using R version 4.0.2[38]. Descriptive statistics were used to summarize the characteristics of patients, tumors, and treatment modalities. Means (standard deviation [SD]) and medians (quartiles [Q]1–Q3) were used for continuous variables, and numbers (%) for categorical variables. The VHI measurements taken shortly before and after the development of a recurrence were excluded from the analysis. Starting points for longitudinal analysis after treatment were calibrated for all treatment modalities. Mixed-effects models were used to investigate different longitudinal trajectories of voice quality over time, which uses all available measurements and accounts for unbalanced data, meaning that time points of questionnaires differ between patients and should be assessed accordingly. Moreover, these models account for the correlation between measurements from the same patients. Above mentioned tumor-specific and

patient-specific data were used during the model development. During development, we first checked whether different time structures (linear or nonlinear) for the fixed and random effects improved the model's fit, assuming all the aforementioned variables and their interaction with time. Then, it was investigated whether different interactions and main effects could be removed. Natural cubic splines were used for nonlinear structures[39]. The Akaike information criterion (AIC) and likelihood ratio test were used for observing the final model. The AIC criteria is an estimator of prediction error and, thus, the relative quality of statistical models. From the final model, coefficients, standard errors [SE], and p-values are obtained. Effect plots are used for the interpretation of interactions and nonlinear terms.

Results

Between January 1, 2013, and December 31, 2018, 344 patients treated for ESGC were identified. Fifty patients were excluded, as 24 (48.0%) were assigned to strict follow-up with smoking cessation advice if applicable, 11 (22.0%) had synchronous tumors, seven (14.0%) had a prior head and neck malignancy, and eight (16.0%) did not want the data to be used for research purposes. In total, 294 patients were included in this study for further analysis.

Baseline characteristics

The mean follow-up duration was 43.4 (SD, 21.5) months, and a total of 1944 VHI measurements were retrieved. The mean age at diagnosis was 67.2 (SD, 10.6) years, with 81.3% of patients being male. Patients were treated with TLM (57.8%), SVCI (24.5%), and LRT (17.7%). Patients endured Tcis (35.0%), T1a (52.7%), and T1b (12.2%) malignancies. In total, 37 patients (12.6%) had recurrent disease, with a mean time to recurrence of 26 (SD, 18.8) months. Per treatment group, the recurrent disease was observed in six (8.5%) patients for SVCI, 26 (15.3%) for TLM, and five (9.4%) for LRT. No significant differences between treatment modalities were observed ($p = 0.26$).

At baseline, the mean VHI was 31.1 (SD, 22.8). At baseline, 38.8% of patients scored below 20, 30.2% between 20 and 40, 19.4% between 40 and 60, and 11.6% above 60. No significant differences between the predicted mean VHI scores at baseline

were observed: TLM (32.0, SE: 2.8), SVCI (30.6, SE: 3.3), and LRT (33.3, SE: 4.7). Table 1 shows all baseline characteristics.

Table 1: Baseline characteristics

Variable	TLM	SVCI	LRT	Overall
Patients	170 (57.8%)	72 (24,5%)	52 (17.7%)	294 (100%)
Mean age (SD)	66.2 (10.7)	68.5 (9.5)	68.9 (11.4)	67.4 (10.6)
Gender				
Male	127 (74.7%)	64 (88.9%)	48 (92.3%)	239 (81.3%)
Female	43 (25.3%)	8 (11.1%)	4 (7.7%)	55 (18.7%)
T-stage				
Cis	74 (43.5%)	16 (22.5%)	14 (26.4%)	103 (35.4%)
1a	92 (54.1%)	55 (77.5%)	12 (22.6%)	155 (54.1%)
1b	4 (2.4%)	0 (0.0%)	27 (50.9%)	36 (12.2%)
Comorbidity (ACE-27)				
0	40 (23.5%)	22 (30.6%)	16 (30.8%)	78 (26.5%)
1	78 (45.9%)	31 (43.1%)	20 (38.5%)	129 (43.9%)
2	37 (21.8%)	10 (13.9%)	13 (25.0%)	60 (20.4%)
3	15 (8.8%)	9 (12.5%)	3 (5.8%)	27 (9.2%)
ECOG Performance Status				
0	132 (77.6%)	56 (77.8%)	41 (78.8%)	229 (77.9%)
1	27 (15.9%)	11 (15.3%)	10 (19.2%)	48 (16.3%)
2 + 3	11 (6.5%)	5 (6.9%)	1 (1.9%)	17 (5.8%)
Anterior commissure				
Yes	46 (27.1%)	29 (40.3%)	33 (63.5%)	108 (36.7%)
No	124 (72.9%)	43 (59.7%)	19 (36.5%)	186 (63.3%)
Smoking				
Yes	83 (48.8%)	26 (36.1%)	29 (55.8%)	138 (46.9%)
No	6 (3.5%)	8 (11.1%)	2 (3.8%)	16 (5.4%)
Former	81 (47.6%)	38 (52.8%)	21 (40.4%)	140 (47.6%)
Mean pack years (SD)	35.1 (17.2)	31.4 (19.9)	36.5 (18.2)	34.4 (18.1)
Alcohol				
Yes	99 (58.2%)	45 (62.5%)	39 (75.0%)	183 (62.2%)
No	55 (32.4%)	21 (29.2%)	10 (19.2%)	86 (29.3%)
Unknown	16 (9.4%)	6 (8.3%)	3 (5.8%)	25 (8.5%)
Weight loss				

Table 1: Baseline characteristics *(Continued)*

Variable	TLM	SVCI	LRT	Overall
Yes	17 (10.0%)	13 (18.1%)	5 (9.6%)	35 (11.9%)
No	142 (83.5%)	56 (77.8%)	44 (84.6%)	242 (82.3%)
Unknown	11 (6.5%)	3 (4.2%)	3 (5.8%)	17 (5.8%)
Marital status				
Married / Living together	113 (66.5%)	51 (70.8%)	35 (67.3%)	199 (67.7%)
Alone	51 (30.0%)	21 (29.2%)	16 (30.8%)	88 (29.9%)
Unknown	6 (3.5%)	0 (0.0%)	1 (1.9%)	7 (2.4%)
Education				
Low	69 (40.6%)	25 (34.7%)	20 (38.5%)	114 (38.8%)
Intermediate	58 (34.1%)	24 (33.3%)	18 (34.6%)	100 (34.0%)
Tertiary	17 (10.0%)	15 (20.8%)	3 (5.8%)	35 (11.9%)
Missing	26 (15.3%)	8 (11.1%)	11 (21.2%)	45 (15.3%)
Work				
Employed	38 (22.4%)	15 (20.8%)	11 (21.2%)	64 (21.8%)
Not employed	25 (14.7%)	10 (13.9%)	8 (15.4%)	43 (14.6%)
Retired	92 (54.1%)	45 (62.5%)	31 (59.6%)	168 (57.1%)
Missing	15 (8.8%)	2 (2.8%)	2 (3.8%)	19 (6.5%)
VHI at baseline (SE)	32.0 (2.8)	30.6 (3.3)	33.3 (4.7)	31.1

Model development

Figure 1 depicts all the VHI trajectories for the different treatment modalities as well as highlights individual patients with varying trajectories. This figure illustrates both the heterogeneity and non-linearity of the VHI over time. Most patients start with a relatively high VHI score before treatment (t = 0), with a gradual decline over time. Other patients start with lower scores and show a more variable course after treatment.

After visual inspection of the individual VHI profiles and using the AIC criteria, we observed that the nonlinear structure for time assuming natural cubic splines with three and six degrees of freedom (two and five internal knots) provided us with the best fit, and we decided to use this time structure for further interpretation. A diagonal matrix for the variance-covariance of the random effects was assumed. The following five models with different fixed effects structures were tested: Voice

outcome as a function of the interaction of time with (1) only treatment as well as the main effects of age, gender, comorbidity, performance score, smoking status, tumor stage, involvement of the vocal cord (VC); (2) treatment, comorbidity, smoking status, tumor stage and involvement of VC as well as the main effects of age, gender and performance score; (3) treatment, tumor stage and involvement of VC as well as the main effects of comorbidity, smoking status, age, gender and performance score; (4) treatment, age, gender, tumor stage and involvement of VC as well as the main effects of smoking status, comorbidity and performance score; (5) all variables. Corresponding formulas can be found in Appendix I. Using the likelihood ratio test, we observed that the more complicated models did not improve the fit; therefore, we decided to continue with the simplified model 1. A sub-analysis, in which patients with recurrent disease were excluded, showed no differences in longitudinal trajectories.

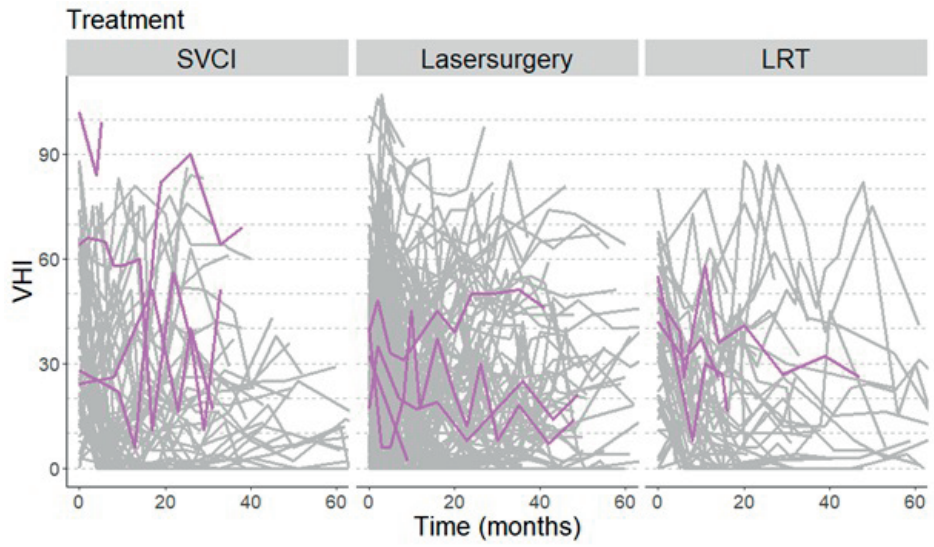

Figure 1. Voice Handicap Index (VHI) profiles for all 294 patients, highlighting five individual patients. This figure shows the variability between patients in longitudinal outcomes.

Longitudinal dynamic trajectory

Figure 2 shows the average predicted longitudinal trajectory with confidence intervals of the VHI for the different treatments, based on Model 1. No clinically significant differences in longitudinal trajectories between treatment modalities

were found. Predicted values after 12 months were 15.9 (SE: 3.4), 25.8 (SE: 2.8), and 20.9 (SE: 4.8) for SVCI, TLM, and LRT, respectively. During the first year of follow-up, a steeper clinically significant improvement was seen for SVCI (-15.7) and LRT (-12.4), which was followed by a non-clinically significant deterioration. Patients treated with TLM show a clinically non-significant improvement during the first 12 months (-6.1). All treatment modalities show equivalent outcomes during longitudinal follow-up. Two-, three-, and four-year follow-up VHI outcomes were 20.2, 23.6, and 22.9 for SVCI, 24.1, 23.5, and 23.4 for TLM, and 23.5, 24.6, and 21.7 for LRT, respectively.

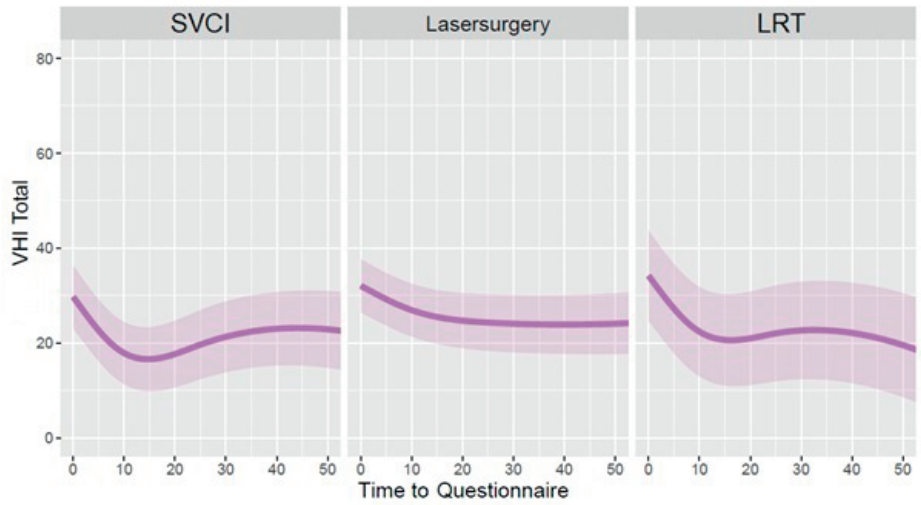

Figure 2. The predicted longitudinal dynamic trajectory for the Voice Handicap Index (VHI) from baseline to 50 months post-treatment for single vocal cord irradiation (SVCI), transoral carbon dioxide laser microsurgery (TLM), and local radiotherapy (LRT).

Associated risk factors

Table 2 presents the results of the final mixed-effects model. In particular, the coefficients, SE, and p-values are presented. Older age, increased tumor stage, and severe comorbidity were found to be associated with the longitudinal VHI profiles in the final model. A one-year increase in age comes with an overall lower VHI of 0.3 points (SE: 0.1) at baseline, after correcting for the other covariates. The clinical significance of this difference is low. This also applies to patients with T1a tumors, who show an overall higher VHI of 6.2 points (SE: 2.6) at baseline compared

to patients with Tcis. However, patients with severe comorbidity (ACE 3) score overall 13.6 points (SE: 4.8) higher on the VHI than patients with no comorbidity ($p = 0.005$) at baseline (correcting for the other covariates), which is considered clinically significant. Other variables, such as T1b and ACE 2 and 3, had no impact on the longitudinal VHI.

Table 2: results of the final mixed-effects model

Variable	Estimates (B)	Standard Error	P-value
Age	-0.3	0.1	**0.02**
Gender (ref: male)			
Female	-0.1	3.0	0.97
Comorbidity ACE27 (ref: ACE 0)			
ACE 1	0.3	2.9	0.92
ACE 2	1.1	3.7	0.76
ACE 3	13.6	4.8	**0.005**
WHO Performance score (ref: WHO 0)			
WHO 1	2.3	3.2	0.49
WHO 2 + 3	2.3	5.5	0.67
Smoking (ref: no)			
Yes	-9.8	5.37	0.07
Former	-9.7	5.2	0.07
T-stage (ref: Tcis)			
T1a	6.2	2.6	**0.02**
T1b	8.7	4.9	0.08
Anterior commissure (ref: no)			
Yes	-0.2	2.6	0.94

Discussion

Patient-reported voice outcome has extensively been studied in ESGC with cross-sectional data. However, to our knowledge, this current large cohort study is the first to provide insight into longitudinal dynamic trajectories and associated risk factors for all three treatment modalities. Our outcomes are important as they enhance knowledge of the longitudinal dynamics of voice quality, which can be used during counseling in addition to oncological and practical considerations. At the same time, this data will provide the foundation for the development of an individualized prediction tool.

Longitudinal patient-reported voice quality

No clinically significant differences in longitudinal trajectories between treatment modalities were found. However, during the first year of follow-up, patients treated with both radiotherapy modalities showed a steeper and clinically significant improvement compared to a more stable and clinically insignificant improvement over time with TLM. The non-linear stable trajectory for TLM has been described previously by Lane et al[40]. It is in accordance with the belief that full remodeling of the glottic tissue takes 12 to 24 months. However, because the first follow-up measurement is taken at two to four months, short deteriorations after surgery may go undetected. In our analysis, we found a "rebound" effect within the longitudinal trajectories for both radiotherapy modalities. This is, however, not clinically significant (<10 points on the VHI). The longitudinal outcomes of all treatment modalities are equivalent, which is in line with previous systematic reviews and meta-analyses[5,6]. Additionally, the longitudinal improvement in patient-reported voice quality was clinically significant for SVCI and LRT. This corresponds with a previous study that investigated two-year follow-up data for TLM[23].

Associated risk factors

By using all available patient- and tumor-specific variables, we were able to shed light on the risk factors associated with different longitudinal trajectories. Previous cross-sectional studies reported that associated risk factors can be divided into patient, tumor, and treatment factors[41-43]. The associated risk factors, such as age and tumor stage, from our findings are in alignment with these studies. However, comorbidity by means of ACE 27 has not previously been associated with patient-

reported voice quality. It is worth noting that comorbidity was not considered in previous studies[41-43]. We would argue that this association is due to the fact that many patients with ACE 3 in our cohort had severe pulmonary comorbidity, which can also affect the VHI. There was no impact of the involvement of the anterior commissure, which was surprising because we believe these are more difficult to treat, especially with TLM, and thus have a lower patient-reported voice quality[44]. Due to missing data, we were unable to include the depth of the cordectomy and smoking cessation behavior, but both of them were found to be important factors for functional outcomes in ESGC[41,45].

Strengths and limitations

A strength of our study is the use of statistical techniques for repeated measurement data. Mixed-effects models are relatively new and have been shown to be superior to older methods such as linear regression, repeated measurements of analysis of variance, or paired t-tests for concluding repeated measurements data[27,46-48]. Another strength is the large number of patients included in this study and the corresponding number of measurements. The latter can be attributed to the fact that these PROMs are embedded in our routine care. A limitation of this study is that the VHI is not a multidimensional voice assessment and only provides limited subjective information. In our cohort, 60% underwent TLM, which could cause treatment bias. It is important to mention that no comparison between treatment modalities can be made due to confounding by indication[49,50]. This is caused by differences in the tumor or patient characteristics like tumor stage, anatomical difficulties, etc. Also, differences between healthcare professions in counseling cause bias. A randomized controlled trial would provide the opportunity to make a fair comparison. It should be noted that we did not exclude patients with recurrent disease prior to this study. We acknowledge the impact of recurrent disease in ESGC on patient-reported outcomes, especially due to a second treatment. By excluding measurements before and after the recurrence, we think the remaining measurements are valuable for further analysis. However, it would be more equitable and statistically correct to use joint modeling to account for and predict these events alongside longitudinal patient-reported voice quality[27].

Impact on clinical practice

Our findings can be used for individual counseling and shared decision-making in addition to oncological and practical considerations. Our results can be used to help patients manage their treatment expectations. This data, however, cannot be used as a decision-making tool because it is susceptible to confounding by indications[49,50]. However, when counseling patients for whom TLM and radiotherapy are equivalent treatment options, insights into expected voice quality after treatment can be used in addition to oncological and practical considerations[51,52]. We believe PROMs, like the VHI, provide unique opportunities to provide patient-centered counseling by means of individualized dynamic prognostic models. In our institution, we have experience with developing prognostic models for overall survival,[53-56] and the next step is to do this for patient-reported outcomes as well. By doing this, we will be able to provide patients with individualized predictions on both quantity and quality of life aspects prior to their treatment and during follow-up. For patients, this can give a full perspective on what to expect from certain treatment modalities. This study will form the basis for a second study concerning the development of an individualized dynamic prediction model for longitudinal patient-reported voice outcome and recurrent disease in ESGC. We also would like to investigate whether longitudinal PROMs are helpful in predicting recurrent disease.

Conclusion

Longitudinal patient-reported voice quality after treatment of ESGC is heterogeneous and non-linear. Most improvement is seen during the first year of follow-up and differs between treatment modalities. No clinically significant differences in long-term longitudinal trajectories over time for patient-reported voice quality were observed. Associated risk factors for different longitudinal trajectories for voice quality were older age, increased tumor stage, and severe comorbidity. These longitudinal dynamic trajectories can enhance individual patient counseling and provide the foundation for an individualized dynamic prediction model.

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Appendix 1: Tested models during model development

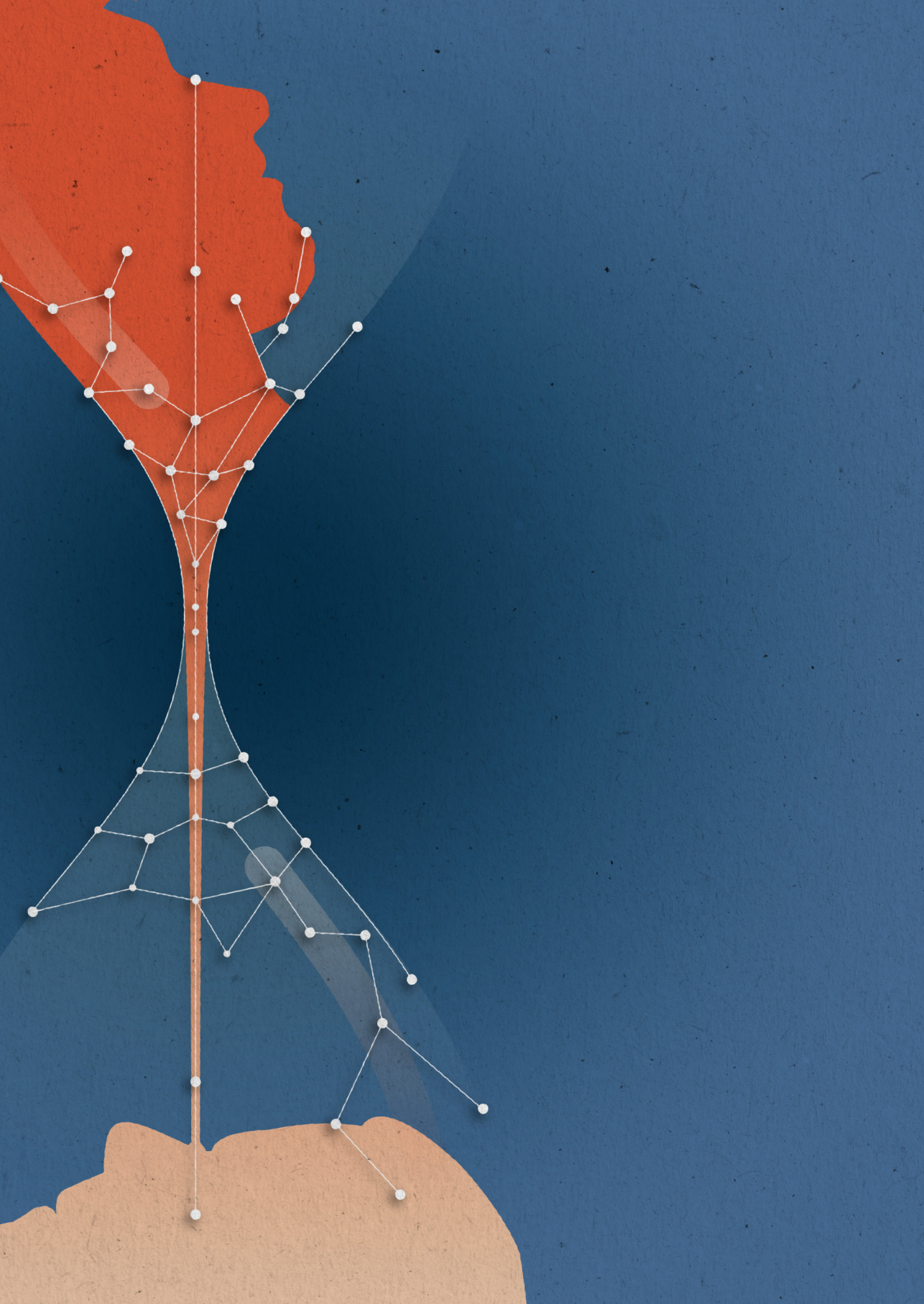
*Model 1: VHI = nonlinear Time * Treatment + Age + Gender + Comorbidity + Performance score + Smoking + T stage + VC involvement.*

*Model 2: VHI = nonlinear Time * (Treatment + Comorbidity + Smoking + T stage + VC involvement) + Age + Gender + Performance status.*

*Model 3: VHI = nonlinear Time * (Treatment + T stage + VC involvement) + Comorbidity + Smoking + Age + Gender + Performance status.*

*Model 4: VHI = nonlinear Time * (Treatment + Age + Gender + T stage + VC involvement) + Smoking + Comorbidity + Performance status.*

*Model 5: VHI = nonlinear Time * (Treatment + Age + Gender + Comorbidity + Performance status + T stage + VC involvement).*



Chapter 6

Individualized Dynamic Prediction Model for Patient-Reported Voice Quality in Early-Stage Glottic Cancer

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Abstract

Objectives: Early-stage glottic cancer is a malignancy of the head and neck. Besides disease control, preservation and improvement of voice quality are essential. To enable expectation management and well-informed decision making, patients should be sufficiently counselled with individualized information on expected voice quality. This study aims to develop an individualized dynamic prediction model for patient-reported voice quality. This model should be able to provide individualized predictions at every time point from intake to the end of follow-up.

Study Design: Longitudinal cohort study

Setting: Tertiary cancer center.

Methods: Patients treated for early-stage glottic cancer were included in this study (N=294). The Voice Handicap Index was obtained prospectively. The framework of mixed and joint models were used. Prognostic factors used are treatment, age, gender, comorbidity, performance score, smoking, T-stage and involvement of the anterior commissure. Overall performance of these models was assessed during an internal cross-validation procedure and presentation of absolute errors using box-plots.

Results: Mean age in this cohort was 67 years and 81.3% are male. Patients were treated with transoral CO2 laser microsurgery (57.8%), single vocal cord irradiation up to (24.5) or local radiotherapy (17.5%). Mean follow-up was 43.4 months (SD 21.5). Including more measurements during prediction improves predictive performance. Including more clinical and demographic variables did not provide better predictions. Little differences in predictive performance between models were found.

Conclusion: We developed a dynamic individualized prediction model for patient-reported voice quality. This model has the potential to empower patients and professionals in making well-informed decisions and enables tailor-made counseling.

Introduction

Early-stage glottic cancer (ESGC) is a common malignancy of the head and neck area with a good overall clinical outcome in terms of survival and recurrent disease. However, the tumor and its treatment have a significant impact on patient-reported quality of voice[1-11]. Voice and speech are crucial aspects in social communication and interaction, and therefore can impact a patient's psychosocial well-being as well. Therefore, providing patients with individualized information on expected voice quality after treatments is important and enables optimal decision-making. Prognostic modelling can be supportive in this process. For survival, prediction models have been developed and used in clinical practice. However, prediction modelling for patient-reported outcomes is new and more difficult as structural collected longitudinal data is scarce, and specific statistical techniques for repeated measurements data are required[12]. Within our institute, a few models for patient-reported outcomes have been developed in urology[13,14] and neurology[15,16].

Most prediction models in medicine provide static predictions as they have been developed with classic linear, logistic or cox regression models[17-19]. During follow-up however, additional information will become available that might change prognostic estimations of clinical and patient-reported outcomes. Conventional static prediction models are not able to use this updated information to provide new and more adequate predictions. Developing prediction models that are able to combine all available (changing) variables over time requires extension of the available prediction statistical methods. This could be done by methodological innovations based upon mixed-effects models and joint models for longitudinal and time-to-event data, which have enjoyed a renaissance in recent years in the statistics and biostatistics literature[12,20,21]. Mixed-effect models enable longitudinal analysis by using all available data and account for unbalanced data and correlation between measurements from the same patients[22]. Joint-models combines mixed-effect modelling with a time-to-event cox regression model.

Within our institute, structural collection of patient-reported outcome measurements (PROMs) is embedded in our routine care since 2013 with the Healthcare Monitor[23]. Alongside the use of these PROMs during patient-doctor consultations for improving patient-centered care, this data is used on an aggregated

level for obtaining longitudinal insights and developing individualized prediction models.

To our knowledge, no prediction models for longitudinal PROMs and recurrent disease in head and neck cancer are available. With this study, we continue our previous research describing longitudinal trajectories and associated risk factors of patient-reported voice quality in ESGC[24]. In this study we showed that patient-reported voice quality is heterogeneous and non-linear, improved most in the first year of follow-up. Associated risk factors were older age, increased tumor stage, and severe comorbidity. Hence, the goal of our study is to develop a web-based and clinically useful individualized dynamic prediction model for patient-reported voice quality. This model will be dynamic, which means that it can provide new predictions during follow-up at every new consultation, as soon as new information becomes available. By doing this we will empower patients and professionals to make well-informed decisions and enable tailor-made counseling and customized solutions prior to treatment and during the long period of follow-up.

Methods

Setting and participants

All patients treated for ESGC (Tcis – T1b, N0M0) with transoral laser microsurgery, local radiotherapy, single vocal cord irradiation at the Erasmus Medical Center between 2013 – 2018 and participating in the Healthcare Monitor were included in this longitudinal outcome study. The Healthcare Monitor has 95% patient compliance at intake and over 80% during follow-up up to five years. All patients complete questionnaires before every outpatient clinic visit at home or with a tablet at the clinic. The first year, questionnaires are filled in every two months, the second year every three months, the third year every four months, and every six months in year four. Patients were excluded from this study when they had low grade dysplasia and were appointed to strict follow-up, had synchronic tumors, a prior head and neck malignancy, had no PROM-data available due to insufficient knowledge of the Dutch language or suffering disorders affecting cognitive abilities, or did not provide informed consent on using data for research purposes.

Ethical considerations

This project was approved by the institutional review board and ethics committee (MEC-2020-0314) from the Erasmus MC. Our study follows the principles of the declaration of Helsinki. All participating patients provided electronic written informed consent.

Main outcomes and measures

In this study, we used the prospectively obtained Dutch version of the Voice Handicap Index (VHI) at previous mentioned time points[25,26]. This is a validated, 30-item, questionnaire that measures the perceived psychosocial voice impairment in daily life[27]. Each item is scored on a 5-point Likert scale (0 = never, 5 = always). The total score is the sum of all scores and ranges from 0 to 120. A higher outcome indicates higher voice impairment.

Treatment modalities in this study are transoral laser microsurgery and radiotherapy[28-31]. The latter can be divided in local radiotherapy with irradiation of the larynx in a total dose of 60-66Gy in 25 to 33 fractions, and single vocal cord irradiation with a mild hypofractioned scheme up to 58.08Gy in 16 fractions. This resulted in significant reduction of the radiation dose to the adjacent organs[29-31]. For early-stage glottic cancer it showed is noninferiority compared to local radiotherapy[30,32,33]. Tumor-specific and patient-specific data were retrospectively obtained from Erasmus Medical Center patient records. These variables included: treatment, age (years), gender, ACE-27 comorbidity (0 – 3), WHO performance score (0 – 4), smoking (yes/no/former), T-stage (Tcis/T1a/T1b), involvement of the anterior commissure (yes/no). WHO performance score comprises a score for a patients' physical capability of functioning in daily life. Comorbidity was scored at the time of diagnosis by the ACE-27 which is developed specifically for Head and Neck Cancer[34,35]. Time to recurrence was the calculated time from initial treatment up to the occurrence of recurrent disease.

Statistical analysis

Statistical analyses were performed using R version 4.1.0 (28). Packages that were used are: JMbayes2: version 0.3.0 (to apply the joint models)[36]; splines: version 4.2.1 (to assume non-linear time structure)[37]; lattice: version 0.20.45 (to visualize the data and results)[38]. Descriptive statistics were used to summarize patient-,

tumor- and treatment characteristics. Means (SD) and medians (Q1-Q3) were used for continuous variables and n (%) for categorical variables. The framework of joint models of longitudinal and time-to-event data was used to obtain dynamic predictions for patient-reported voice quality and recurrent disease. A joint longitudinal model consists of a mixed-effects and a time-to-event submodel. These models can be used when focusing either on the longitudinal outcome (patient-reported outcomes), and we want to correct for non-random dropout (due to recurrence), or on the time-to-event outcome (time-to-recurrence) when we want to account for the effect of an endogenous time-dependent covariate (patient-reported outcomes)[12]. An advantage of these models is that the predictions can be updated as more information becomes available.

For the longitudinal submodel, we assumed similar model structures as previously presented. In particular, in previous research, the associations between the outcome and several demographic and clinical variables were investigated[24]. We assumed natural cubic splines (with different degrees of freedom) to capture the non-linear profiles of the outcome and previous mentioned demographic and clinical variables. By assuming different non-linear time structures and variations in demographic and clinical variables, we can test whether more included variables also provide better predictions. For the time-to-event submodel, we assume a relative risk submodel with P-splines approximation for the baseline hazard and treatment and age as covariates. The optimal model was selected by means of comparing the predictive performance of the different models. This was done by comparing the predicted and the observed VHI measurement of the testing data set. The overall performance of the longitudinal submodel was assessed by calculating the absolute difference between the predicted and the observed VHI measurement (absolute error). Also root mean square error (RMSE) per model was calculated. Overfitting-corrected estimates of the predictive performance measures described above were obtained using a cross-validation procedure (internal validation). For long-term clinical relevance, the cross-validation procedure was focused on predictions between 22 and 26 months. The dataset was split into five subsets, of which four were used to fit the model and one for obtaining predictions. In smaller datasets, the heterogeneity between these different subsets can be considerable. Hence, to stabilize the results, we have repeated the splitting of the original dataset into five subsets 100 times. Due to the small number of events it was not possible to evaluate the risk predictions for

the time-to-recurrence event. However, incorporation of the time-to-event model does correct for non-random dropout due to recurrent disease. This means that patients with recurrent disease were included, however it was corrected for in the longitudinal prediction analysis. The distribution of the absolute errors is presented using box-plots (figure 2). Finally, we illustrate the dynamic longitudinal predictions and the 95% prediction interval for a randomly selected patient.

Results

This prospectively obtained data set consisted of 294 patients treated for ESGC, of which 81.3% patients are male. Patients endured Tcis (35.0%), T1a (52.7%) and T1b (12.2%) malignancies. 37 patients (12.6%) had recurrent disease with a mean time to recurrence of 26 months (SD 18.8). Mean follow-up was 43.4 months (SD 21.5) and a total of 2266 measurements were retrieved, with a mean of 8 per patient. The amount of patients during follow-up were: intake (n=294, 100%), 12 months (n=273, 92.9%), 24 months (n=244, 83.0%), 36 months (n=189, 64.3%), 48 months (n=131, 44.6%), 60 months (n=82, 27.9%). For all baseline characteristics, see Table 1.

Table 1: Baseline characteristics

Variable	Overall
Patients	294 (100%)
Mean age (SD)	
Gender	
Male	239 (81.3%)
Female	55 (18.7%)
T-stage	
Cis	103 (35.4%)
1a	155 (54.1%)
1b	36 (12.2%)

Table 1: Baseline characteristics *(Continued)*

Variable	Overall
Comorbidity (ACE-27)	
0	78 (26.5%)
1	129 (43.9%)
2	60 (20.4%)
3	27 (9.2%)
WHO Performance Status	
0	229 (77.9%)
1	48 (16.3%)
2 + 3	17 (5.8%)
Anterior commissure	
Yes	108 (36.7%)
No	186 (63.3%)
Smoking	
Yes	138 (46.9%)
No	16 (5.4%)
Former	140 (47.6%)
Mean pack years (SD)	34.4 (18.1)

Joint model development

Figure 1 depicts all the VHI trajectories and highlights individual patients with varying trajectories. During model development we used natural cubic splines with 4, 5, and 6 degrees of freedom and variations of the following demographic and clinical variables. These models can be found in table 2. Consequently, the prediction overall performance of these models was validated.

Cross-validation of prediction performance and model selection

For the nine different prediction models, the absolute errors per number of measurements used in the prediction models are plotted in figure 2. All corresponding absolute errors with 25th and 75th percentiles (IQR) can be found in appendix 1. As shown in figure 2, increasing the amount of longitudinal VHI measurements decreases the absolute error and provides more trustworthy predictions.

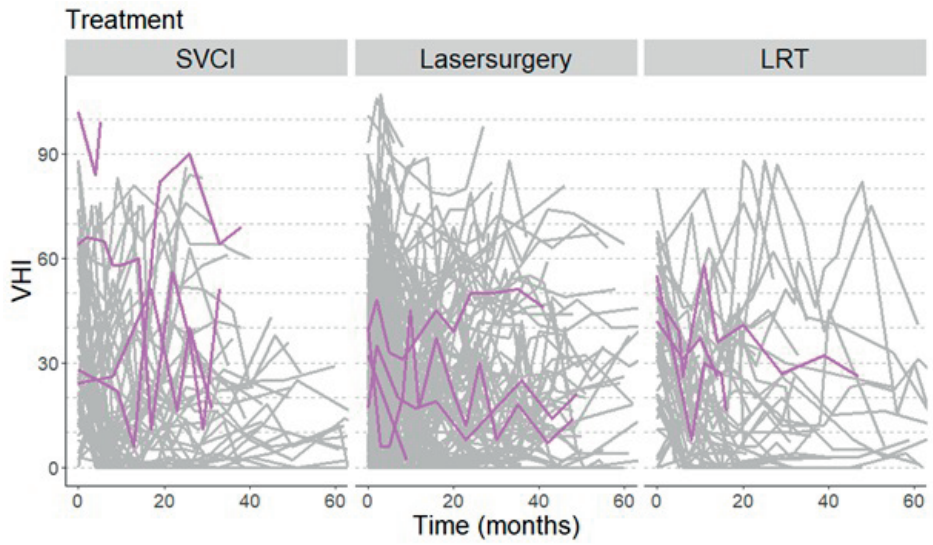

Figure 1. VHI profiles for all 294 patients and highlighting 5 individual patients. This figure shows the variability between patients in longitudinal outcomes.

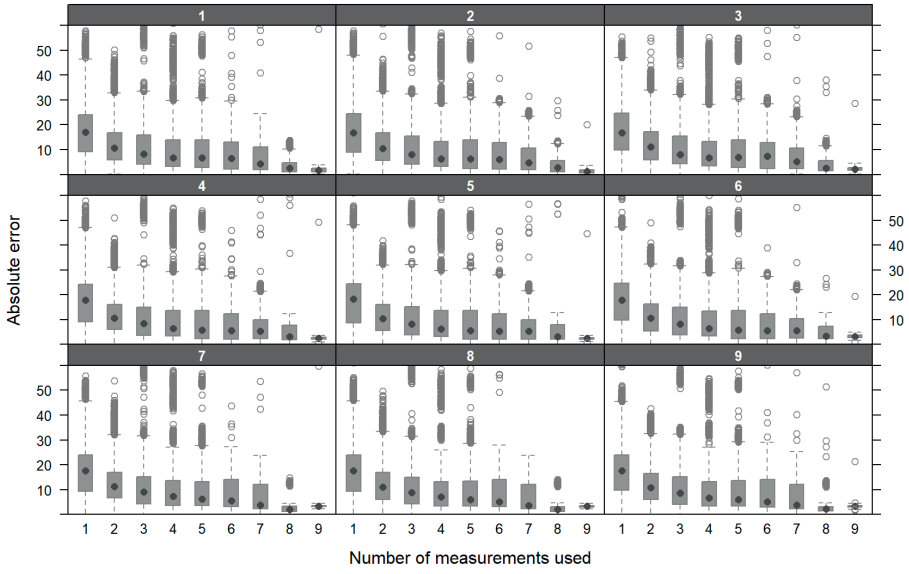

Figure 2. For the nine different prediction models, the absolute errors per number of measurements used to obtain the predictions. Each panel represents a different model assuming different fixed effects structure.

Table 2. Created joint models assuming different non-linear time structures and variations of demographic and clinical variables. Every mixed-effects submodel (1-9) were combined with the time-to-event submodel to create a joint model.

Mixed-effects submodel 1: interaction between time (natural cubic splines with **6 degrees of freedom**) and treatment; *main effects of time, treatment, age, sex, ACE-27 comorbidity, WHO performance score, smoking, T-stage and involvement of anterior commissure.*
Mixed-effects submodel 2: interaction between time (natural cubic splines with **6 degrees of freedom**) and treatment; *main effects of time, treatment, age, sex, ACE-27 comorbidity, smoking and T-stage.*
Mixed-effects submodel 3: interaction between time (natural cubic splines with **6 degrees of freedom**) and treatment
Mixed-effects submodel 4: interaction between time (natural cubic splines with **5 degrees of freedom**) and treatment; *main effects of time, treatment, age, sex, ACE-27 comorbidity, WHO performance score, smoking, T-stage and involvement of anterior commissure.*
Mixed-effects submodel 5: interaction between time (natural cubic splines with **5 degrees of freedom**) and treatment; *main effects of time, treatment, age, sex, ACE-27 comorbidity, smoking and T-stage.*
Mixed-effects submodel 6: interaction between time (natural cubic splines with **5 degrees of freedom**) and treatment
Mixed-effects submodel 7: interaction between time (natural cubic splines with **4 degrees of freedom**) and treatment; *main effects of time, treatment, age, sex, ACE-27 comorbidity, WHO performance score, smoking, T-stage and involvement of anterior commissure.*
Mixed-effects submodel 8: interaction between time (natural cubic splines with **4 degrees of freedom**) and treatment; *main effects of time, treatment, age, sex, ACE-27 comorbidity, smoking and T-stage.*
Mixed-effects submodel 9: interaction between time (natural cubic splines with **4 degrees of freedom**) and treatment
Time-to-event submodel: main effects of treatment and age

For example, the median absolute error for model one incorporating only one VHI-measurement is 16.9 (IQR 9.0 - 24.1), compared to an error of 1.7 (IQR 1.0 - 2.5) when nine previous measurements are used. When comparing the overall performance of the different models between 22 and 26 months, no clinically significant differences were found in median absolute errors between the models. Including more clinical and demographic variables within these models did not provide better predictions. Furthermore, the time structure did not seem to affect the predictive performance of the models. In addition, the simpler non-linear structure (4 cubic splines and three degrees of freedom) performed similarly to more complex structures. The RMSE measures are 18.6 (1), 17.9 (2), 17.8 (3), 17.6 (4), 18.3 (5), 18.8 (6), 18.1 (7), 18.2 (8), 17.6 (9).

Overall, the simpler model (model 9) with only treatment can be selected for further analysis and patient-specific prediction visualization. Median absolute errors for this model varies between 17.6 (IQR 9.7 – 24.0) when incorporating one VHI-measurement, and 3.3 (IQR 2.0-3.6) for nine incorporated measurements.

Patient-specific prediction visualization

Figure 3 shows an example of a patient-specific longitudinal dynamic prediction trajectory for a randomly chosen patient. This prediction model is able to update predictions at every time point (e.g. visit to the outpatient clinic during follow-up) when new information on perceived voice quality becomes available. In this figure, 95% prediction intervals are visualized in blue. They become narrower and predictions become more accurate when additional measurement are used.

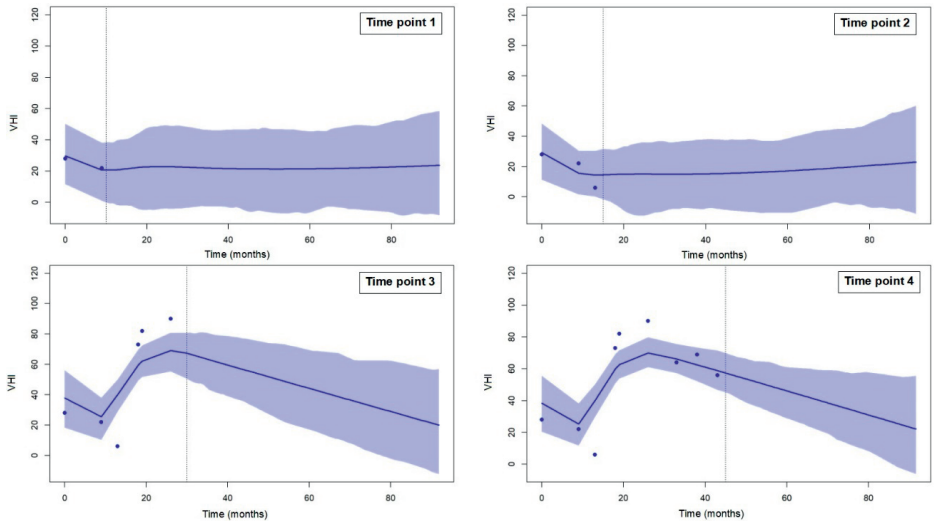

Figure 3. An example of the graphical output of a dynamic prediction model for one specific patient. VHI is plotted on the Y-axis, time on the X-axis. Every frame is a following point in time. This prediction model is able to update predictions at every time point (e.g. visit to the outpatient clinic during follow-up).

Discussion

In this study, a unique individualized, dynamic predictions model for patient-reported voice quality was developed by using the framework of joint modelling. To our knowledge, this is the first model in head and neck oncology that dynamically predicts longitudinal patient-reported voice quality, which means that individualized predictions can be provided at every time point from intake to the end of follow-up. We propose a clinical applicable model which provides new predictions during follow-up as soon as new information on the Voice Handicap Index (VHI) becomes available. With this study, we showed the feasibility of an individualized longitudinal prediction model and corresponding graphical outcome.

Prognostication is considered an important aspect of clinical decision-making. The use of individualized prognostic models in clinical practice enables expectation management and, therefore, more personalized counseling and care. Within head and neck oncology, most prediction models focus on clinical binomial outcomes like survival and recurrent disease and use classic linear, logistic, or Cox regression analysis. In contrast to these conventional models, the prediction of longitudinal PROMs requires a different approach. The collection and use of PROMs on an individual level in clinical practice is expanding in all specialties[39-42]. Therefore, we believe that this study is a major step forward within the field of prognostic research and an excellent showcase for the use of PROMs within individualized prediction models.

Both mixed and joint modelling have enjoyed a renaissance in recent years in the statistics and biostatistics literature, which improved the current status quo in prognostic research as it provides more opportunities for longitudinal data than the aforementioned conventional methods[12,43]. These models have shown similar and interesting results and clinically useful models in urology[13,14] and neurology[15,16].

Unfortunately, we were not able to combine our longitudinal dynamic predictions with the prediction of time-to-event data (recurrent disease) predictions. This was due to the small number of recurrent events, which caused the inability to investigate the predictive performance using a cross-validation procedure. Using

a larger, maybe multicenter dataset would be beneficial to optimize our prediction model.

During cross-validation, we found that a model with only treatment and non-linear time assuming no more than 4 degrees of freedom performed just as good as models including more clinical and demographic variables. This is in line with the results of our previous study, in which we identified longitudinal trajectories for patient-reported voice quality for transoral laser microsurgery, local radiotherapy, single vocal cord irradiation[24]. In that study we showed that there were few predictive factors for longitudinal patient-reported voice quality, each with a small or negligible effect.

The use of the prediction model that we have developed is able to provide insight into the outcome VHI, which can be used to better inform patients and healthcare experts on the expectation for a specific patient. However, the used data is not based on a randomized controlled trial and is therefore prone to confounding by indication[44,45]. The current model broadens our possibilities, however it should not be used as decision tool. When treatment options are equivalent in ESGC, insights from this model can also be used prior to treatment during shared decision making in addition to oncological and practical considerations[46,47].

Clinical application and future perspectives

The dynamic model with treatment and non-linear time will be integrated in our current PROM based clinical support system, Healthcare Monitor[23]. By doing this, healthcare professionals can obtain real-time individualized graphical predictions for patient-reported voice quality at any given moment during follow-up. At our department, a prognostic model for overall survival (OncologIQ) is already integrated in our electronic health record via Healthcare Monitor[19,48]. By combining quantitative with qualitative prognostic information, we hope to empower patients and professionals to make well-informed and shared decisions and enable tailor-made counseling and customized solutions during follow-up. Based on the methodology of this study, we will continue developing individualized prediction models for other PROMs. For example, we can use domains from other validated and internally used QoL questionnaires (EORTC-QLQ-C30, EORTC-QLQ-HN35, Hospital Anxiety Depression Scale, and Eating Assessment Tool-10). We will also focus on

investigating appropriate predictive performance measures using bootstrapping in joint models, while assuming different scenarios for the longitudinal and the survival outcomes[43]. Furthermore, we will focus on dashboard development and evaluation together with healthcare professionals and patients.

Strengths and limitations

A major strength of our study is the use of relatively new, but appropriate statistical techniques for prediction of repeated measurements and time-to-event data. We would argue that dynamic prediction modelling should be standard in this field of research as it provides a solution to the need for updated and more precise predictions during follow-up due to changing medical and patient-reported outcomes. Another strength is the amount of included measurements which can be attributed to our institutional routine with the Healthcare Monitor[23]. However, we acknowledge the subjectivity of the VHI and therefore a need for as much data as possible as this would improve the accurateness of predictions.

It this study, a limitation appeared to be the small amount of recurrences for which it was not possible to investigate the predictive performance using a cross-validation procedure for the time-to-recurrence outcome. However, we used the time-to-event model for non-random dropout correction, which enables more fair predictions. Another limitation of our study is the choice for specific (sub)models including specific variables. We have based our models on the results of our previous study, however, model selection remains arbitrary. Including other variables, or different structures for (non-)linear time can provide other results. Due to missing data, we were not able to include depth of cordectomy nor smoke cessation behavior. Both showed to be an important factor for functional outcomes in ESGC[49,50]. In our Cohort 60% underwent TLM, which could cause treatment bias.

Conclusion

In this study we developed and cross-validated multiple individualized prediction models for longitudinal patient-reported voice quality for patients treated for Early-stage glottic cancer. Best performing joint model was a construct of a mixed effect model (voice outcome as the function of the interaction of time with treatment)

and time-to-event model (including treatment and age). This dynamic model is able to provide updated predictions during follow-up. We were not able to combine these qualitative predictions with quantitative predictions for recurrent disease due to the small number of events. This model will be integrated within our electronic health record. It has the potential to empower patients and professionals in making well-informed and shared decisions and enable tailor-made counseling and customized solutions during follow-up.

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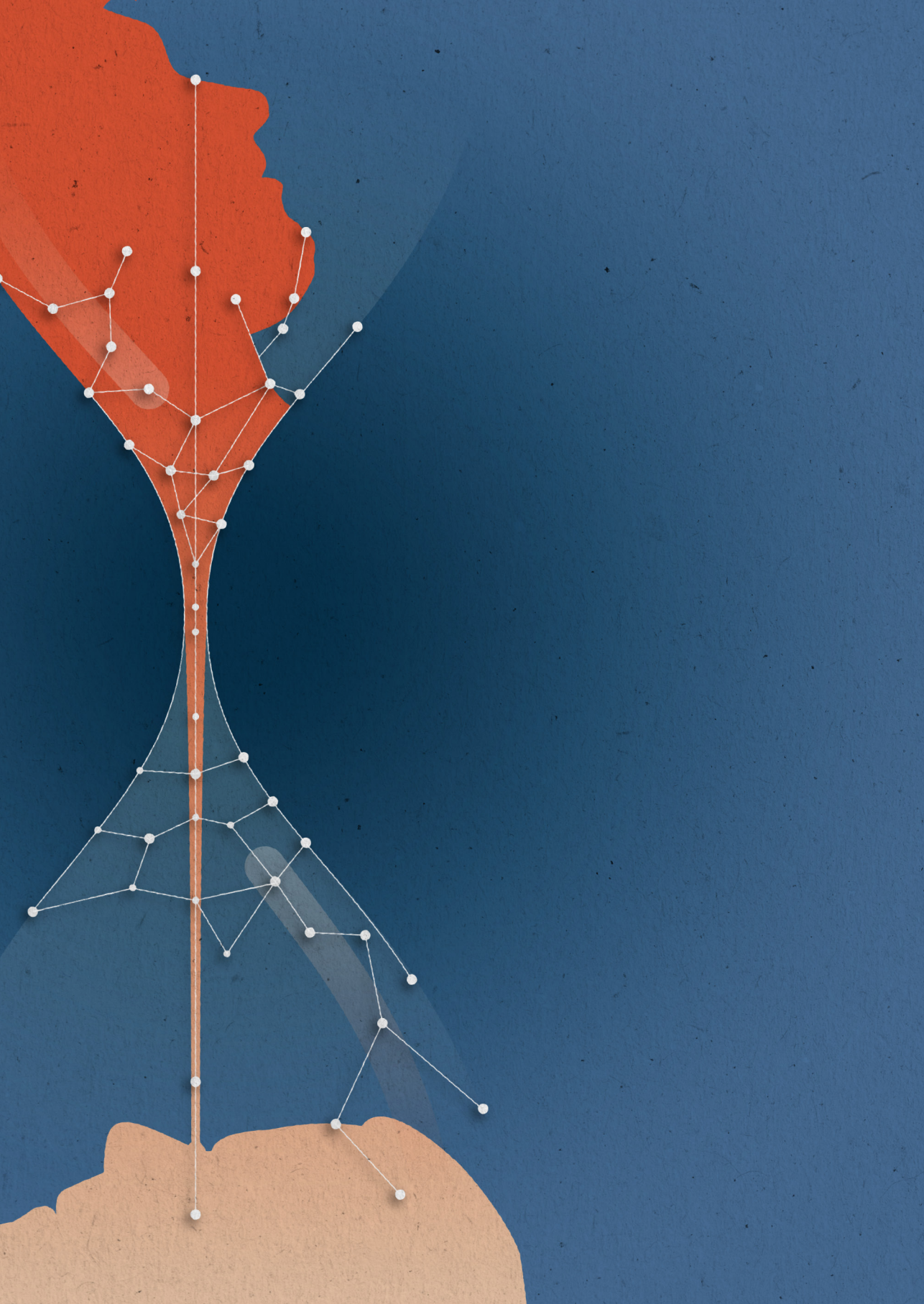
Appendix 1. Median absolute errors with 25th and 75th percentiles corresponding to figure 2

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8	Model 9
1	16.9 (9.0–24.1)	16.7 (8.8-24.5)	16.8 (9.7-24.7)	17.9 (9.1-24.7)	18.3 (8.7-24.5)	17.9 (9.6-24.7)	17.7 (9.3-23.9)	17.7 (9.3-23.9)	17.6 (9.7-24.0)
2	10.6 (5.9-16.7)	10.5 (5.7-16.9)	11.0 (5.9-17.2)	10.6 (6.1-16.0)	10.5 (5.6-16.2)	10.6 (5.4-16.2)	11.2 (6.7-16.9)	11.0 (6.0-17.0)	10.8 (5.9-16.6)
3	8.3 (4.1-15.8)	7.9 (4.1-15.5)	11.0 (4.3-15.5)	8.5 (3.7-15.0)	8.2 (3.8-15.2)	8.3 (3.9-15.0)	9.0 (4.2-15.2)	8.8 (4.2-15.1)	8.5 (4.0-15.3)
4	6.8 (3.3-13.9)	6.4 (3.1-13.3)	8.0 (3.4-15.5)	6.5 (3.3-13.7)	6.2 (3.1-13.8)	6.5 (3.3-13.5)	7.2 (3.6-13.6)	7.0 (3.4-13.2)	6.7 (3.4-13.1)
5	6.7 (2.8-14.0)	6.4 (2.4-13.3)	6.9 (2.8-13.9)	5.8 (2.3-13.6)	5.6 (2.1-13.6)	5.7 (2.3-13.6)	6.2 (3.6-13.3)	6.0 (3.4-13.5)	6.0 (3.4-13.7)
6	6.6 (2.2-13.1)	6.1 (2.2-12.9)	7.3 (2.3-12.8)	5.6 (2.2-12.4)	5.4 (2.1-12.5)	5.5 (2.2-12.4)	5.5 (3.2-14.2)	5.1 (3.0-14.1)	5.1 (2.9-14.1)
7	4.4 (1.9-11.2)	4.7 (2.0-10.6)	5.1 (2.3-10.7)	5.3 (2.4-10.0)	5.4 (2.2-10.0)	5.6 (2.5-10.3)	3.8 (2.3-12.1)	3.7 (2.3-12.1)	3.7 (2.2-12.0)
8	2.6 (1.1-4.8)	2.7 (1.1-5.6)	2.6 (1.5-5.5)	3.1 (2.0-7.8)	3.1 (2.0-7.9)	3.4 (2.2-7.4)	1.9 (1.1-3.3)	2.1 (1.2-3.1)	2.2 (1.4-3.0)
9	1.7 (2.5)	1.1 (0.6-1.9)	2.1 (1.6-2.8)	2.5 (2.1-2.8)	2.4 (2.1-2.8)	2.4 (2.7-3.7)	3.1 (3.0-3.7)	3.3 (2.9-3.6)	3.3 (3.0-3.6)



Chapter 7

Quality improvements of healthcare trajectories by learning from aggregated patient reported outcomes: a mixed methods systematic literature review

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Abstract

Background: In health care, analysing patient-reported outcome measures (PROMs) on an aggregated level can improve and regulate health care for specific patient populations (meso level). This mixed-method systematic review aimed to summarize and describe the effectiveness of quality improvement methods based on aggregated PROMs. Additionally, it aimed to describe barriers, facilitators and lessons learned when using these quality improvement methods.

Methods: A mixed-method systematic review was conducted. Embase, Medline, CINAHL and the Cochrane library were searched for studies that described, implemented or evaluated a quality improvement method based on aggregated PROMs in the curative hospital setting. Quality assessment was conducted via the Mixed Methods Appraisal Tool. Quantitative data were synthesized into a narrative summary of the characteristics and findings. For the qualitative analysis, a thematic synthesis was conducted.

Results: From 2360 unique search records, thirteen quantitative and three qualitative studies were included. Four quality improvement methods were identified: benchmarking, plan-do-study-act cycle, dashboards and internal statistical analysis. Five studies reported on the effectiveness of the use of aggregated PROMs, of which four identified no effect and one a positive effect. The qualitative analysis identified the following themes for facilitators and barriers: 1) conceptual (i.e. stakeholders, subjectivity of PROMs, aligning PROMs with clinical data, PROMs vs. Patient reported experience measures (PREMs); 2a) methodological – data collection (i.e. choice, timing, response rate and focus); 2b) methodological – data processing (i.e. representativeness, responsibility, case-mix control, interpretation); 3) practical (i.e. resources).

Conclusion: The results showed little to no effect of quality improvement methods based on aggregated PROMs, but more empirical research is needed to investigate different quality improvement methods. A shared stakeholder vision, selection of PROMs, timing of measurement and feedback, information on interpretation of data, reduction of missing data, and resources for data collection and feedback

infrastructure are important to consider when implementing and evaluating quality improvement methods in future research.

Introduction

Since the introduction of value-based health care by Porter[1] in 2006, an increase in patients' perspectives on health outcomes for quality and safety improvement in health care has been observed[2], in addition to process and clinical outcomes[3-5]. These so-called patient-reported outcome measures (PROMs) capture a person's perception of their own health through standardized, validated questionnaires[6]. The main purpose of PROMs is to improve quality of care and provide more patient-centred care by quantifying important subjective outcomes, such as perceived quality of life and physical and psychosocial functioning.

For the purpose of quality improvement in health care, PROMs are used on a micro, meso and macro level. On a micro level, PROMs are useful screening and monitoring tools to facilitate shared decision-making and patient-centred care[7-9]. On a meso level, aggregated PROMs (i.e., PROM outcomes on the group level) provide analytical and organizational angles for improving and regulating health in specific populations as a result of enhanced understanding, self-reflection, benchmarking and comparison between health care professionals and practices[10-12]. At a macro level, PROMs are used for overall population surveillance and policy[2,13,14]. The use of structurally collected PROMs is increasingly adopted in national quality registries[15,16] and it increased even further after the Organization for Economic Co-operation and Development (OECD) recommended the collection of aggregated PROMs to obtain insight into system performance and to enable comparative analysis between practices[17].

The field of using aggregated PROMs is relatively young. In 2018, Greenhalgh et al. showed that there was little empirical evidence that PROMs, at a meso level, led to sustained improvements in quality of care[18]. However, since then, there has been growing interest in this field, with a plethora of quantitative and qualitative research currently available. Therefore, the aim of this mixed method systematic review was threefold: 1. to summarize quality improvement methods based on aggregated

PROMs at the meso level in hospital care; 2. to describe the effectiveness of quality improvement methods; and 3. to describe barriers, facilitators and lessons learned when using aggregated PROMs for quality improvement in health care.

Method

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were used to design and report this review[19]. The review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) 07-12-2020 (PROSPERO 2020: CRD42020219408)

Search strategy

Embase, Medline, CINAHL and the Cochrane library were searched for studies published up to May 2021. The search strategy (Appendix I) included terms related to outcome measurements, quality management and quality improvement. Search terms consisted of medical subject headings (MeSH) and free text words, whereby for most terms, synonyms and closely related words were included. The search was performed without date or language restriction. Additional references were obtained by hand-searching reference lists of included studies and systematic reviews (backwards selection) and by identifying studies that cited the original included studies (forward selection). Duplicate studies were removed.

Eligibility criteria

Studies were considered eligible for inclusion if they described, implemented or evaluated a quality improvement method based on aggregated PROMs in the curative hospital setting. Both quantitative and qualitative studies were included in this review. Quantitative studies included experimental study designs, such as randomized controlled trials, controlled trials, cluster trials, controlled before-after studies and time-series studies. Qualitative studies included semi-structured interviews, focus groups or studies with a mixed-methods approach (e.g. process evaluation studies). Studies were excluded if (a) the quality improvement was based on the use of PROMs in the individual setting only (e.g., in the consultation room); (b) written in a language other than English; (c) not peer-reviewed; (d) conference and editorial papers and reviews; or (e) the full text could not be obtained.

Study selection

All records found were uploaded to Rayyan, an online web application that supports independent selection of abstracts[20]. Two researchers (KvH and MD) independently screened the titles and abstracts of the identified studies for eligibility. Discrepancies were resolved by discussion with the involvement of a third researcher (JJ) when necessary. Subsequently, full texts were screened against the eligibility criteria by two researchers independently (KvH and MD).

Data extraction and synthesis

Due to the mixed-method design of this review, two researchers (KvH and MD) extracted data from qualitative and quantitative studies separately[21] using a standardized form. Details on the study design, aims, setting, sample size, quality improvement method, PROMs and outcomes were extracted and synthesized into a narrative summary. The described quality improvement methods were summarized, and when available, the effect of these methods was reported.

For the qualitative synthesis, the approach outlined by Thomas and Harden[22] were followed, which involved a thematic synthesis in the form of three stages: 1) free line-by-line coding of the findings was performed by three researchers; 2) organization of these codes into related areas to construct descriptive themes; and 3) the development of analytical themes. A fourth researcher (MO) was consulted for verification and consensus. The qualitative synthesis was structured around facilitators, barriers and lessons learned for the implementation of quality improvement interventions based on PROM data. Finally, both quantitative and qualitative synthesis were combined in the discussion section.

Quality assessment

Study quality was assessed independently by two researchers (KvH and MD) with the validated Mixed Methods Appraisal Tool (MMAT)[23] informing the interpretation of findings rather than determining study eligibility. The MMAT is a critical appraisal tool that is designed for mixed-methods systematic reviews and permits us to appraise the methodological quality of five study designs: qualitative research, randomized studies, non-randomized studies, descriptive studies and mixed methods studies. Aspects covered included (dependent on study design) quality of study design, randomization, blinding, selection bias, confounding, adherence and completeness

of data. The MMAT does not provide a threshold for the acceptability of the quality of the studies[23].

Results

A flow diagram of the study selection process is presented in Figure 1. A total of 3700 records were identified. After removing duplicates, 2360 records were screened on title-abstract, and 83 records were screened on full-text. Three studies were found through hand searching[24-26]. Finally, thirteen quantitative studies[24,25,27-36] and three qualitative studies[10,11,37] met the inclusion criteria. Research questions 1 and 2 is addressed in the 'Quantitative studies' section, and research question 3 is addressed in the 'Qualitative studies' section.

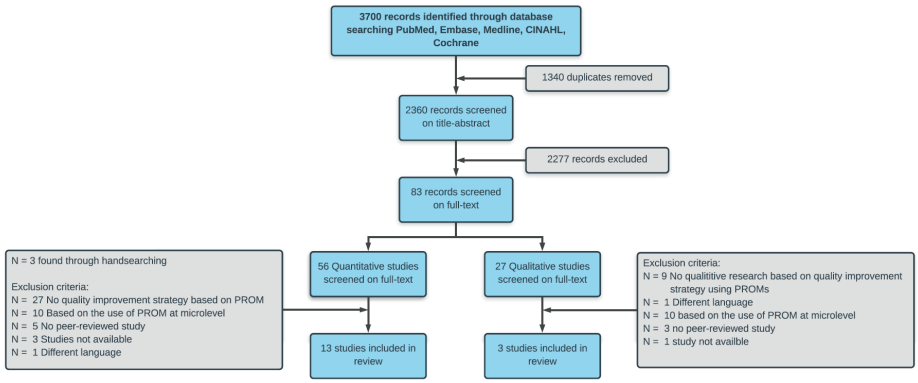

Figure 1. Flow diagram of the search process and study selection

Quality of the studies

The quality assessment was performed according to study design: quantitative randomized[24,28], quantitative non-randomized[25-27,29,30,33,34,36], quantitative descriptive[31,32,35] and qualitative studies[10,11,37]. Five studies were assessed as good quality studies, and the other eleven were assessed as moderate quality studies. Both randomized studies were not able to blind health care professionals to the intervention provided, although since receipt or non-receipt of feedback in these studies could not be disguised, this was not weighed as bad quality. Complete

outcome data were a shortcoming in 5 of the studies[24,26,29,30,33,34]. In addition, for two descriptive studies[31,35], it was not possible to assess response bias. The quality assessment can be found in appendix II.

Quantitative studies

Study characteristics

Table 1 summarizes the study characteristics of the thirteen included quantitative papers. The search resulted in two randomized controlled trials[24,28], 8 non-randomized controlled studies[25-27,29,30,33,34,36] and three single centre descriptive studies[31,32,35]. Studies were performed in the US[24,26,27,35], UK[30,32,34], Netherlands[25,33], Sweden[31], Denmark[29], Canada[36] and Ireland[28]. Twelve studies focused on patients from surgical specialties, including orthopaedic-[26,28,30,32,35], thoracic-[29,33], urologic-[27,36], ophthalmic-[31], rhinoplastic-[25] and general surgery[34]. One study focused on primary care[24]. In eight studies, data were obtained from a regional or national quality registry[27,29-35]. The included studies used generic PROMs[30,33], disease-specific PROMs[25,27,29,31] or a combination of generic and specific PROMs[24,26,28,32,34-36].

Table 1. Study characteristics, quality improvement methods and/or outcome

Reference	Aim	Design	Setting	PROM	Quality improvement method	Outcome
Boyce et al.[201528]	To assess if peer benchmarked feedback is effective in improving patient outcomes.	Randomized	Orthopaedics N = 21 surgeons Ireland	Oxford Hip Score (DS) Hip Osteoartritis Outcome Score (DS) EuroQol 5D (G)	Peer benchmarked feedback and educational intervention	(-) No effect from peer benchmarked feedback was found on patient reported outcomes.
Weingarten et al.2000[24]	To determine whether providing physicians with peer-comparison feedback can improve patient functional status.	Randomized	Primary care N = 48 surgeons USA	Dartmouth Primary Care Cooperative Information Project chart	Peer-comparison feedback and educational intervention	(-) No improvement in patient functional status
Varagunam et al.2014[34]	To determine the impact of introduction PROMs on the selection of patients and on outcome.	Non-Randomized	General surgery N = 409 surgeons UK	Oxford Hip Score (DS)Oxford Knee Score (DS) Aberdeen varicose vein questionnaire (DS) EuroQol 5D	Peer benchmarked feedback	(+/-) No to a minimal impact of routine use and feedback of PROMs was found.
Kumar et al.[202136]	To determine if providing surgical report cards to surgeons resulted in improved patient outcomes.	Non-Randomized	Urologic surgery N = 8 surgeons Canada	Expanded Prostate Cancer Index Composite (DS) EuroQol 5D (G)	Peer benchmarked feedback	(-) No improvement in functional or oncologic outcomes

Table 1. Study characteristics, quality improvement methods and/or outcome (*Continued*)

Reference	Aim	Design	Setting	PROM	Quality improvement method	Outcome
Van Veghel et al.[201633]	To assess patient-relevant outcomes of delivered cardiovascular care, to establish and share best practices by comparing outcomes and to embed value-based decision-making to improve quality and efficiency.	Non-Randomized	Cardiac surgery N = 12 centers Netherlands	Short Form Health Survey 36 (G) Short Form Health Survey 12 (G)	PDSA-cycle and benchmarking	Not applicable
Bronserüd et al.[201929]	To propose a model for the use of PROs as quality indicators, enabling comparison across surgical departments	Non-Randomized	Thoracic surgery N = 4 departments Denmark	EORTC-QLQ-C30 (DS)	Benchmarking surgical departments	Not applicable
Van Zijl et al.[202125]	To present a method to measure and evaluate data-based performance.	Non-Randomized	Rhinologic surgery N = 1 surgeon Netherlands	Nasal Obstruction Symptom Evaluation (DS) Utrecht Questionnaire (DS) Visual Analog Scale (DS)	IT application Dashboarding	Not applicable

Table 1. Study characteristics, quality improvement methods and/or outcome (*Continued*)

Reference	Aim	Design	Setting	PROM	Quality improvement method	Outcome
Reilly et al.[202026]	To develop a novel approach to consistently and pragmatically measure the value of total knee and hip arthroplasty.	Non-Randomized	Orthopaedics N = 6 surgeons	Physical function domain from the PROMIS-10 (G) Hip Osteoartritis Outcome Score (DS) Knee Osteoartritis Outcome Score (DS)	IT application Dashboarding	Not applicable
Lucas et al.[201727]	To report on the establishment of a web-based collection system and measure variability in outcome among practice groups.	Non-Randomized	Urologic surgery, > 40 centers USA	Symptom Tracking and Reporting (DS)	Benchmarked reports for individual surgeons	Not applicable
Gutacker et al.[201330]	To Measure the extent to which treatment impact varies across hospitals.	Non-Randomized	Orthopaedics 153 hospitals UK	EuroQol 5D (G)	Hospital benchmarking	Not applicable
Partridge et al.2016[32]	To improve PROMs after implementation of evidence-based change in practice.	Descriptive	Orthopaedics N = 14 surgeons UK	Oxford Knee Score (DS) EuroQol 5D (G)	PDSA-cycle	(+) Significant improvement on the OKS and EQ-5D

Table 1. Study characteristics, quality improvement methods and/or outcome (*Continued*)

Reference	Aim	Design	Setting	PROM	Quality improvement method	Outcome
Lundström et al.[201331]	To analyze three models enabling data connection between PROMs and clinical data in order to identify opportunities for improvement of quality of care.	Descriptive	Ophthalmology N = 41 surgeon Sweden	Catquest-9SF (DS)	Aggregated internal analyses	Not applicable
Zheng et al.[201435]	To present the design and implementation of a website which is enable to return comparative PRO reports for participating surgeons in order to monitor and improve quality and health outcomes.	Descriptive	Orthopaedics >130 surgeons USA	Short Form Health Survey 36 (G) Knee injury and Osteoarthritis Outcome Score (DS)	Site, practice and individual benchmarking	Not applicable

Abbreviations: G: general measurement instrument; DS: disease specific measurement instrument: NR: no results; PDSA: plan-do-study-act cycle

Effect and impact

Only five out of thirteen studies reported on the effect of quality improvement methods based on aggregated PROMs[24,28,32,34,36]. Four of these studies, including both randomized controlled trials, showed no effect[24,28,36] to a minimal effect[34] on patient-reported outcomes after the use of individual benchmarking as a quality improvement method (Table 1). One of the studies showed a significant improvement in the Oxford Knee Score after a Plan-Do-Study-Act (PDSA) cycle in a cross-sectional postintervention cohort[32]. The other eight studies described the method of implementation without effect measurement[25,27,33,35] or discussed (statistical) models for using aggregated outcomes as performance indicators[29-31].

Methods used to accomplish quality improvements

Four quality improvement methods were identified: benchmarking[24,27-30,34-36], Plan-Do-Study-Act cycle (PDSA-cycles)[32,33], Dashboards as feedback tool[25,26] and internal statistical analysis[31] (Table 2).

Table 2. Quality improvement methods

Quality improvement method	Aim
Benchmarking	Method in which PROMs are used by departments or individual health care professionals to compare their own performance with peers in order to improve their performance.
Plan-Do-Study-Act (PDSA) cycle	An iterative, four-stage problem-solving model used for improving a process.
Dashboard as feedback tool	A dashboard summarized and visualizes data. It enables monitoring and managing of performance outcomes.
Aggregated statistical analysis	Use of data analysis in order to identify opportunities for quality improvement.

Benchmarking

Benchmarking was applied in eight studies[24,27-30,34-36]. Aggregated data were used to provide peer-benchmarked feedback for individual health care professionals[24,27,28,34,36] or at a practice and individual level[35]. Two studies proposed different statistical models to use data as a performance indicator to benchmark surgical departments[29,30]. Benchmarking was performed once[24,27-30] or more frequently[34-36], and feedback was provided via web-based systems[27,28,34,35], individual report cards[24,36], or via a peer-reviewed study[29,30]. When individual health care professionals

were benchmarked, most studies used adjusted outcome information to provide fair comparisons between individual health care professionals[28-30,34-36]. In addition to benchmarked feedback, two studies also provided individual health care professionals with educational support[24,28]. Four of eight studies reported on the impact of benchmarking, all showing no clinical effect.

Plan-do-study-act cycle

Two studies used a PDSA cycle to improve the quality of care[32,33]. Van Veghel et al. (2014) reported on the establishment of an online transparent publication service for aggregated patient-relevant outcomes. Subsequently, these data enable benchmarking between Dutch heart centres to improve quality and efficiency. However, this study was not able to provide benchmarked patient-reported data due to a low response rate and a lack of data[33]. The study from Partridge et al. (2016) was a cross-sectional postintervention study and compared their outcomes with a previously published report from the Health & Social Care Information Centre (HSCIC) from August 2011. A significant improvement in the Oxford knee score was found after changing the practice of care[32].

Dashboard as a feedback tool

Two studies used a web-based dashboard as a feedback tool[25,26]. In the study of van Zijl et al. (2021), feedback was available through graphical analysis of patient characteristics and PROMs for individual rhinoplastic surgeons. The purpose of this dashboard was to identify learning and improvement needs or provide data-driven motivation to change concepts or surgical techniques[25]. In Reilly et al. (2020), a dashboard was established to consistently measure the value of total hip and total knee arthroplasty by combining surgeon-weighted PROMs, clinical outcomes, and direct costs[26]. Both studies did not report on the impact of these methods.

Aggregated statistical analysis:

One study investigated how clinical outcome measures can be linked to PROMs and concluded that the following methods were most appropriate: 1. analysing the factors related to a good or poor patient-reported outcome; and 2. analysing the factors related to agreement or disagreement between clinical and patient reported outcomes[31].

Qualitative studies

Study characteristics

Table 3 shows the study characteristics of the qualitative studies included in this research. All three studies comprised semistructured interviews[10,11,37]. Interviews were conducted amongst experts from the UK[10,11], US[11], Ireland[37], Sweden[10] and the Netherlands[11]. The study from Boyce et al. (2018) comprises the qualitative evaluation[37] of a randomized controlled trial, which is discussed in the quantitative section[28].

Barriers, facilitators and lessons learned

In the qualitative analysis, barriers were derived from (B), facilitators (F) and lessons learned/neutral statements (N) into the following three themes: 1) conceptual, 2) methodological and 3) practical (Table 4). The overview and description of the themes (i.e., codebook) with the occurrence of facilitators, barriers and lessons learned can be found in Table 4. The most important lessons learned for future implementation and research can be found in Table 5.

Ad 1) Conceptual

The following four themes were derived: 'stakeholders', 'subjectivity of PROMs', 'Aligning PROMS with clinical data', 'PROMs vs. PREMs'. A mentioned facilitator for success is the engagement and commitment from stakeholders at both the meso and macro levels from the beginning[10,11,37]. Champions can advocate the added value of collecting PROMs, and governance and political will can be decisive for its success and sustainability[10,37]. Health care providers differ in their attitudes regarding the usage of PROMs for quality improvements; some advocate for sceptics[37]. As a start, small-scale projects with willing clinicians is recommended instead of teams with limited interest or readiness[11].

These advocates often need to convince other health care professionals due to concerns about the scientific properties of PROM measures, in particular the subjective characteristics of these measures. Thus, health care professionals have an underlying doubt about the patient's ability to answer PROM questionnaires[10,37]. Furthermore, difficult to accept discrepancies between the PROM outcome and the clinical experience from health care professionals' point of view were found, since

expectations were that these two outcome measures would align[37]. Moreover, Boyce et al. (2018) found that health care professionals were not able to distinguish the difference between PROMs and measures of patient-reported experience measures (PREMs)[37].

Ad 2) Methodological

Within this main theme, a distinction between data collection (2a) and data processing (2b) was made.

2a) Data collection

The following four themes were derived: 'choice of measure', 'timing of data collection', 'response rate of measurement' and 'focus of measurement'. Patient-reported measures should be selected cautiously to be appropriate for the targeted population[37], to ensure comparability and to prevent burdening the patient[10,11]. The combination of generic and disease-specific measures was seen as feasible and complementary[10,11,37], especially since generic measures facilitate good comparison, but are less able to detect variation[10]. Moreover, standardization of time points for data collection is advocated, as timing may influence the results[10]. For example, outcomes were measured during short-term follow-up when patients were not fully recovered[37]. Furthermore, to obtain high response rates, it is important to discuss the results of PROMs with the patient during consultation, especially during long-term follow-up[11]. Another reported barrier concerned the clinical value of performance measurement for interventions in a field where small variability a priori could be expected[37].

2b) Data processing

Four themes were derived: 'representativeness of collected data', 'responsibility of health care professionals', 'inadequate case-mix control' and 'interpretation of feedback'.

It was mentioned that some health care professionals mistrusted quality improvement measures based on aggregated PROMs. First, the representativeness of the data used for benchmarking or quality improvement was seen as a barrier. Health care professionals expressed concern that the data would not reflect practice, the individual practitioner or the population of patients[10,11,37]. Furthermore, some

patient groups were identified as a possible source of information and recall bias, such as patients with low health literacy or those with comorbidities who might confuse problems from one condition with another[37]. Additionally, patients' answers might be influenced by their care expectations, with the belief that this information is used to rate care, or by the need to justify their decision to have an operation[10,37]. Additionally, health care professionals may be tempted to manipulate data to obtain good performance rates by recruiting patients who are more likely to have good outcomes (i.e. selection bias)[10,11,37]. Second, health care professionals were afraid to be held unfairly responsible for outcome data that could be biased by differences in resources across hospitals[37], differences in support services at the community level[37] or factors that occurred outside of their control[10,11]. Third, health care professionals worried that inadequate case-mix control of confounders would bias comparisons of health care providers. In addition, the lack of transparency of the statistical analysis made it difficult to engage with the data. Two solutions were provided to address these barriers: 1) only providing aggregated data collection for quality improvement at a very generic level, or 2) presenting results stratified into subgroups instead of risk- or case-mix adjustment[11]. Furthermore, health care professionals expressed difficulties understanding the data, a lack of norms for good or poor performance[11], and a need for training or guided sessions to correctly interpret the aggregated PROM data[10,37]. Quality improvement reports were able to identify how hospitals and health care professionals stand relative to one another, but they are often general and lack the ability to identify opportunities for real quality improvement or action[10], which is key for clinicians in engaging with data and processes[11].

Ad 3) Practical

Statements related to practical implementation were grouped under 'practical'.

One theme, 'resources', was derived. Funding to get the programs started was seen as a key facilitator for further development in structural embedding in routine care. Overall, commitment and support from the government and health care organizations were seen as facilitators[10,37]. The availability of resources for routine data collection and monitoring without disruption of workflow or additional workload was seen as important[10,11,37]. For example, the need for sufficient IT capacity and software to analyse the data enabled the data to be available quickly for health care professionals[10,11,37]. Additionally, the availability of tablets and assistance in the

waiting room for completing questionnaires, the establishment of infrastructure for developing and disseminating annual reports[10], and the opportunity for data linkage and integration in hospital records were mentioned.

Table 3. Study characteristics of qualitative studies

Reference	Aim	Design	Setting
Boyce et al.[201837]	To explore surgeon's experiences of receiving peer benchmarked PROMs feedback and to examine whether this information led to changes in their practice.	Semi-structured interviews	Orthopeadic surgeons N = 11 (feedback arm from Boyce et al.[28])
Prodinger et al.[201810]	To examine supporting and hindering factors relevant to integrating PROMs in selected health information systems tailored toward improving quality of care across the entire health system.	Semi-structured interviews	Experts related to NHS, England (N = 7) and to SHPR and SKAR, Sweden (N = 3)
Vd Wees[201411]	To inform policymakers of prudent next steps for implementing patient reported outcomes in clinical practice and performance measurement programs in order to maximize their impact on the quality of care.	Semi-structured interviews	Clinical practitioners, measure developers, and leaders of performance measurement programs. N = 58 from 37 organizations US, UK and the Netherlands

Table 4. Codebook: Facilitators (F), Barriers (B) and Neutral statements (N) per qualitative theme

Theme	**Conceptual**	**Boyce**[37] (2018)	**Prodinger**[10] (2018)	**Vd Wees**[11] (2014)
Stakeholders	Any statements about the engagement of stakeholders at meso and macro level in order to succeed	B/F	B/F/N	F/N
Subjectivity of PROMs	Any statements indicating that PROMs are subjective measures, and patients are not able to distinguish between consequences and complications of treatment.	B	B	-
Aligning PROMs with clinical data	Statements concerning the discrepancy between PROMs and clinical outcome.	B		-
PROM vs PREMs	Any statements indicating that clinicians (consultants) did not distinguish the difference between PROMS and measures of patient satisfaction or experience.	B	-	-
	Methodological	Boyce	Prodinger	V Wees
Data collection				
Choice of measure	Any statements indicating the choice of measure, such as type of measurement (generic vs disease specific), length of measurement, reliability and validity of measurement	B	B/F/N	B/N
Timing of data collection	Any statements indicating the timing of data collection and how this would influence performance ranking at different time points.	B	-	-
Response rate of measurement	Any statements indicating the response rate from patients, for example short-term follow-up (high response rate), while the collection of longitudinal data with repeated measures (low response rate). Clinician discusses results with patients (high response rate even though long-term follow up)	-	B	B

Table 4. Codebook: Facilitators (F), Barriers (B) and Neutral statements (N) per qualitative theme (*Continued*)

Theme	Conceptual	**Boyce**[37] (2018)	**Prodinger**[10] (2018)	**Vd Wees**[11] (2014)
Focus of measurement	Any statements indicating the importance to focus on this measurement within this field, such as clinical value of expected improvements on outcome and variability between professionals.	B	-	-
Data processing				
Representativeness of collected data	Any statements concerning representativeness of the data when using PROMs for quality improvement strategies. On the one hand related to patients, such as selection bias, inadequate answers, health literacy, non-response. On the other hand related to health care professionals, such as selection and treatment bias, comparison between health care professionals, confidentiality of reporting.	B	B	B/N
Responsibility of healthcare professionals	Any statements concerning being held responsible for outcome data and its consequences.	B	B	B/N
Inadequate case-mix control	Any statements concerning the use of case-mix and effect on making comparisons between professionals.	-	B	B/N
Interpretation of feedback	Any statements about the (mis)interpretation of feedback by experts, training for interpretation, or norm values for performance indicators	B/N	B	-
	Practical			
Resources	Any statements indicating the infrastructure of data collection, such as availability or complexity of electronic data collection methods, or incorporation and use of resources for data collection in normal work flow / routine care related to additional workload for PROM collection, interpretation and usage	B	B/F/N	B/F

Table 5. Lessons learned for future implementation and research

• Involve stakeholders from the very start and create a shared vision between stakeholders.
• Use generic and disease specific patient reported outcome measures.
• Ensure that PROMs are administered at the right time during the health process.
• Providing feedback of performance to individual healthcare professionals.
• Make sure that the data is representative and statistical analysis are comprehensible.
• Provide healthcare professionals with training for adequate interpretation of aggregated PROM data.
• Enable a good infrastructure for adequate data collection and analysis by trained and qualified staff.

Discussion

The aim of this mixed method systematic review was to describe and investigate the experience and effectiveness of quality improvement methods based on aggregated PROMs. Four quality improvement methods were identified, including benchmarking, Plan-Do-Study-Act cycles, web-based dashboards as feedback tools, and the provision of aggregated statistical analysis reports. In total, 13 quantitative and three qualitative studies revealed that there is limited empirical evidence concerning quality improvements based on aggregated use of available PROMs. Only five studies reported on the effectiveness of the applied quality improvement method, and only one descriptive study reported a significant improvement of PROMs after implementation of aggregated PROM feedback. The qualitative studies identified that the belief of stakeholders, the use of generic and disease-specific PROMs, and the availability of funding and resources were important facilitators for success. A barrier was that skeptic health care professionals mistrusted the use of aggregated PROMs due to the subjectivity of PROMs and the contradictory results of PROMs and clinical outcomes. Furthermore, they were afraid to be held unfairly accountable for biased results as a result of case mix, differences in resources across hospitals, differences in support services at the community level or factors that occurred outside of their control. Lessons learned from the qualitative studies included creating a shared stakeholder vision and that feedback of individual performance should be directed to individual health care professionals to learn from the outcomes of their own patients.

One quantitative study did find an effect of using aggregated PROMs in the PDSA cycle[32] and used specific facilitating factors to generate representative data, such as engagement of all stakeholders, the use of a combination of generic and disease-specific questionnaires, and obtainment of a high response rate. However, the results of this methodologically inferior cross-sectional postintervention study should be interpreted cautiously.

Methodological and practical barriers were considered a reason for not finding an effect of benchmarking. Weingarten et al. (2002) suggested that no effect of peer-benchmarked feedback was found due to the *choice of measure,* since only one generic outcome measure (functional status) was used[24]. The theme *timing of data collection* and *timing of feedback* were mentioned as important barriers in the included quantitative studies as well; a follow-up measurement was taken rather too early after providing peer-benchmarked feedback[28], provision of feedback started too late in the study[34], or the authors mentioned that the duration of the intervention was too short to be fully adapted by all participating health care professionals[36]. Multiple studies had shortcomings in reporting on bias due to an insufficient *response rate of the measurement*. As PROMs are prone to missing data, it is important that studies adequately report on the completeness of data and take possible bias into account when drawing conclusions.

Another issue mentioned was the *representativeness of the collected data*, as some outcomes could not be linked to one specific surgeon or low volume surgeons were excluded from the analysis, which caused less variation[34]. Kumar et al. (2021) mentioned that the difficulty of *feedback interpretation* for health care professionals caused a lack of effect[36]. To improve understanding and interpretation, the use of training (e.g., statistics and visualization) and educational interventions was mentioned explicitly within the two randomized controlled trials addressing the quality improvement method of peer-benchmarked feedback[24,28]. The importance of training was also addressed by the qualitative findings[10,11,37]. Previous research indicates that educational support is an important contextual factor for success in quality improvement strategies[38].

Additionally, the importance of good *resources* was mentioned in the discussion of the quantitative studies[24,28,34]. The importance of structural implementation was

underlined by Varagunam et al. (2014), who stated that the small effect of the National PROMs program was partly caused by the delay in the representation of the collected data.

Strengths and limitations

A major strength of this review is the mixed-method design with the inclusion of overall moderate- to good-quality studies, which enabled a comprehensive overview of all available quantitative and qualitative research within this field. Furthermore, due to the mixed-methods design of this review, the quantitative findings were discussed in light of the derived qualitative barriers, facilitators and lessons learned. As a result of the lack of empirical research concerning quality improvement methods based on the aggregated use of PROMS, a meta-analysis was not performed. Additionally, it was purposively chosen to only include peer-reviewed studies, and it is acknowledged that important studies from the grey literature may have been missed.

Future perspective

Future implementation of aggregated PROM feedback can be substantiated with the reported facilitators, barriers and lessons learned from the current review (Tables 4 and 5). It is important that every institution using aggregated PROMs make their results available, including possible biases and completeness of outcome data. Furthermore, the strength of combining PROMs, clinical data and PREMs should be recognized. The use of aggregated clinical data and PREMs has already been shown to be effective in quality improvement[5,39-41], while using aggregated PROMs for quality improvement is still in its infancy.

As qualitative outcomes mainly addressed the issue of obtaining accurate data and consequently gaining professionals' trust in the concept and relevance of quality improvement, this research did not find the best practices on how to learn and improve based on aggregated PROM data. Future research should focus on organizational and individual aspects that contribute to the optimal use of the obtained aggregated PROMs for quality improvement[42].

Conclusion

This review synthesized the evidence on the methods used and effectiveness for quality improvement in health care based on PROMs. The findings demonstrate that four quality improvement methods are used: benchmarking, plan-do-study-act cycles, dashboards, and aggregated analysis. These methods showed little to no effect, which may be due to methodological flaws, as indicated by the qualitative results. In conclusion, this field of research is in its infancy and more empirical research is needed. However, the descriptive and effectiveness findings provide useful information for the future implementation of value-based health care at the meso level and further quality improvement research. In future studies, it is important that a shared stakeholder vision is created; PROMs and timing of measurement and feedback are appropriately chosen; interpretation of the feedback is optimal; every effort is made to reduce missing data; and finally, practical resources for data collection and feedback infrastructure are available.

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Appendix I - Search strategy

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('patient-reported outcome'/mj/de OR (('questionnaire'/mj/exp OR 'self report'/mj/de OR 'patient satisfaction'/mj OR 'patient preference'/mj OR 'personal experience'/mj) AND ('quality of life'/mj/de)) OR (((patient* OR client* OR self) NEAR/3 (report* OR satisf* OR prefer* OR priorit* OR voice* OR centre* OR center* OR experience* OR assess*) NEAR/6 (outcome* OR measure* OR assess* OR quality-of-life)) OR ((questionnaire*) NEAR/6 (outcome* OR measure* OR assess*)) OR proms OR prom OR pros OR prem OR prems):ti) AND ('total quality management'/mj/de OR 'health care quality'/mj OR benchmarking/mj OR ('clinical effectiveness'/mj/exp AND ('program evaluation'/exp OR 'evaluation study'/exp)) OR 'performance measurement system'/mj OR 'safety'/de OR 'patient safety'/de OR (((benefit* OR advantage* OR disadvantage* OR effectiveness OR efficac* OR quality* OR impact* OR improv* OR evaluat* OR enhanc*) NEAR/3 (care OR healthcare OR communicat* OR decision-mak* OR practice*)) OR (((quality* OR performance*) NEAR/3 (impact* OR improv* OR Measure* OR indicator*)) NOT quality-of-life) OR (evaluat* NEAR/3 method*) OR benchmarking):ti) NOT ([conference abstract]/lim AND [1800-2018]/py)

Medline ALL Ovid

(*Patient Reported Outcome Measures/ OR ((*"Surveys and Questionnaires "/ OR *Self Report/ OR *Patient Satisfaction/ OR *Patient Preference/) AND (*Quality of Life/)) OR (((patient* OR client* OR self) ADJ3 (report* OR satisf* OR prefer* OR priorit* OR voice* OR centre* OR center* OR experience* OR assess*) ADJ6 (outcome* OR measure* OR assess* OR quality-of-life)) OR ((questionnaire*) ADJ6 (outcome* OR measure* OR assess*)) OR proms OR prom OR pros OR prem OR prems).ti.) AND (*Total Quality Management/ OR *Quality of Health Care/ OR *Benchmarking/ OR (*Treatment Outcome/ AND (*Program Evaluation/ OR *Evaluation Study/)) OR Safety/ OR Patient Safety/ OR (((benefit* OR advantage* OR disadvantage* OR effectiveness OR efficac* OR quality* OR impact* OR improv* OR evaluat* OR enhanc*) ADJ3 (care OR healthcare OR communicat* OR decision-mak* OR practice*)) OR (((quality* OR performance*) ADJ3 (impact* OR improv* OR Measure* OR indicator*)) NOT quality-of-life) OR (evaluat* ADJ3 method*) OR benchmarking).ti.)

Cochrance CENTRAL register of trials

((((patient* OR client* OR self) NEAR/3 (report* OR satisf* OR prefer* OR priorit* OR voice* OR centre* OR center* OR experience* OR assess*) NEAR/6 (outcome* OR measure* OR assess* OR quality-of-life)) OR ((questionnaire*) NEAR/6 (outcome* OR measure* OR assess*)) OR proms OR prom OR pros OR prem OR prems):ti) AND ((((benefit* OR advantage* OR disadvantage* OR effectiveness OR efficac* OR quality* OR impact* OR improv* OR evaluat* OR enhanc*) NEAR/3 (care OR healthcare OR communicat* OR decision-mak* OR practice*)) OR (((quality* OR performance*) NEAR/3 (impact* OR improv* OR Measure* OR indicator*)) NOT quality-of-life) OR (evaluat* NEAR/3 method*) OR benchmarking):ti)

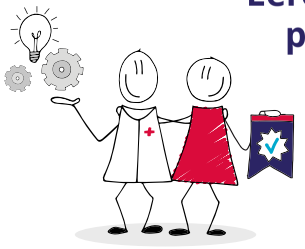
CINAHL EBSCOhost

(MM Patient-Reported Outcomes OR ((MM " Questionnaires" OR MM Self Report OR MM Patient Satisfaction OR MM Patient Preference) AND (MM Quality of Life)) OR TI(((patient* OR client* OR self) N2 (report* OR satisf* OR prefer* OR priorit* OR voice* OR centre* OR center* OR experience*) N5 (outcome* OR measure* OR assess*)) OR ((questionnaire*) N5 (outcome* OR measure* OR assess*)) OR proms OR prom OR pros OR prem OR prems)) AND (MM Quality Improvement OR MM Quality of Health Care OR MM Benchmarking OR (MM Clinical Effectiveness AND (MM Program Evaluation OR MM Evaluation Research)) OR TI(((benefit* OR advantage* OR disadvantage* OR effectiveness OR efficac* OR quality* OR impact* OR improv* OR evaluat* OR enhanc*) N2 (care OR healthcare OR communicat* OR decision-mak* OR practice*)) OR (((quality* OR performance*) N2 (impact* OR improv* OR Measure* OR indicator*)) NOT quality-of-life) OR (evaluat* N2 method*) OR benchmarking))

Appendix II - Quality appraisal of included studies

		Boyce, 2015[28]	Weingarten, 2000[24]	Kumar, 2021[36]	Varagunam, 2014[34]	Bronserud, 2019[29]	Van zijl, 2021[25]	Lucas, 2017[27]	Gutacker, 2013[30]	van Veghel, 2016[33]	Lundstrom, 2013[31]	Zheng, 2014[35]	Partridge, 2016[32]	Boyce, 2018[37]	van der Wees, 2014[11]	Prodinger, 2018[10]
Randomized studies	Is randomization appropriatly performed?	Yes	Yes													
	Are the groups comparable at baseline?	Yes	Yes													
	Are there complete outcome data?	Yes	No													
	Are outcome assessors blinded to the intervention provided?	No	No													
	Did the participants adhere to the assigned intervention?	Yes	Yes													
Non-randomized studies	Are the participants representative of the target population?			Yes	Yes	Yes	Yes	Yes	Yes	Yes						
	Are measurements appropriate regarding both the outcome and intervention (or exporsure)?			Yes	Yes	Yes	yes	Yes	Yes	Yes						
	Are there complete outcome data?			Yes	Can't tell	No	Yes	yes	Can't tell	No						
	Are the confounders accounted for in the design and analysis?			Yes	Yes	Yes	Can't tell	No	Yes	Can't tell						
	During the study periode, is the intervention administered (or exposure occurred) as intended?			Yes	Yes	Yes	Yes	Yes	Yes	Yes						
Descriptive studies	Is the sampling strategy relevant to address the research question?										Yes	Yes	Yes			
	Is the sample representative of the target population?										Yes	Yes	Yes			
	Are the measurements appropriate?										Yes	Yes	Yes			
	Is the risk of nonresponse bias low?										Can't tell	Can't tell	Yes			
	Is the statistical analysis appropriate to answer the research question?										Yes	Can't tell	Yes			
Qualitative	Is the qualitative approach appropriate to answer the research question?													Yes	Yes	Yes
	Are the qualitative data collection methods adequate to address the research question?													Yes	Yes	Yes
	Are the findings adequately derived from the data?													Yes	Yes	Yes
	Is the interpretation of results sufficiently substantiated by data?													Yes	Yes	Yes
	Is there coherence between qualitative data sources, colelction, analysis and interpretation?													Yes	Yes	Yes

Leren en verbeteren op basis van geaggregeerde patiënt gerapporteerde uitkomstinformatie

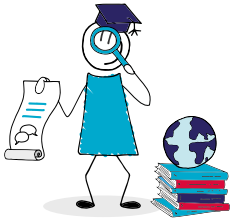


Auteurs: M.C. Dorr, K.S. van Hof, J.G.M. Jelsma, E. Dronkers, R.J. Baatenburg de Jong, M.P.J. Offerman, M.C. de Bruijne

Programma Uitkomstgerichte Zorg

▶ **Links** naar externe documenten

Onderzoek naar de toepassing, effectiviteit en ervaring van het gebruik van PROMs op geaggregeerd niveau



Onderzoeksvragen

1. Welke methodes van kwaliteitsverbetering op basis van geaggregeerde PROMs worden er in de literatuur beschreven?
2. Wat zijn de beschreven effecten van de gebruikte methodes van kwaliteitsverbetering?
3. Wat zijn belemmerende en bevorderende factoren en welke lessen zijn er te leren bij het gebruik van geaggregeerde PROMs?

Methode

Wereldwijde peer-reviewed artikelen.

13 kwantitatieve studies

3 kwalitatieve studies

Resultaten

Kwantitatief

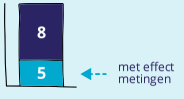
4 Methodes voor kwaliteitsverbetering

Benchmarking

Plan-Do-Study-Act cycles

Dashboarding

Geaggregeerde rapportages



Weinig studies met effect metingen

Geen tot beperkt effect van de gebruikte methodes

Conclusies

Het is een jong implementatie- en onderzoeksveld

Combinatie kwantitatief en kwalitatief onderzoek kan dienen als handvat voor verdere implementatie en onderzoek

Kwalitatief

Thema's: conceptueel, methodologisch en praktisch

Bevorderende factoren

Vertrouwen stakeholders

Generieke + ziektespecifieke PROMs

Onder-steunende IT

Representatieve data

Belemmerende factoren

Subjectiviteit PROM

Interpretatie data

Complexe statistiek

Individuele verantwoording

Aanbevelingen

▶ Lees meer over de specifieke artikelen in het volledige rapport.

Praktijk

Vertrouwen in de uitkomsten en representativiteit van conclusies is belangrijk voor kwaliteitsverbetering.

Draag zorg voor een **infrastructuur** waarmee data collectie en analyse adequaat ondersteund wordt.

Voor adequaat gebruik en interpretatie is **training** van alle betrokkenen belangrijk.

Hoog responspercentage cruciaal voor valide uitkomsten en adequate feedback: individueel terug-koppelen en eenvoudig systeem.

Vervolgonderzoek

Aandacht voor het **meten van het effect** bij implementatie van een kwaliteitsverbetering.

Denk bij onderzoek en effectmeting na over een **referentiegroep**. (controle arm of mogelijke nulmeting)

Motivatie verhogen en behouden: **regelmatige feedback** aan zorgverleners of afdelingen.

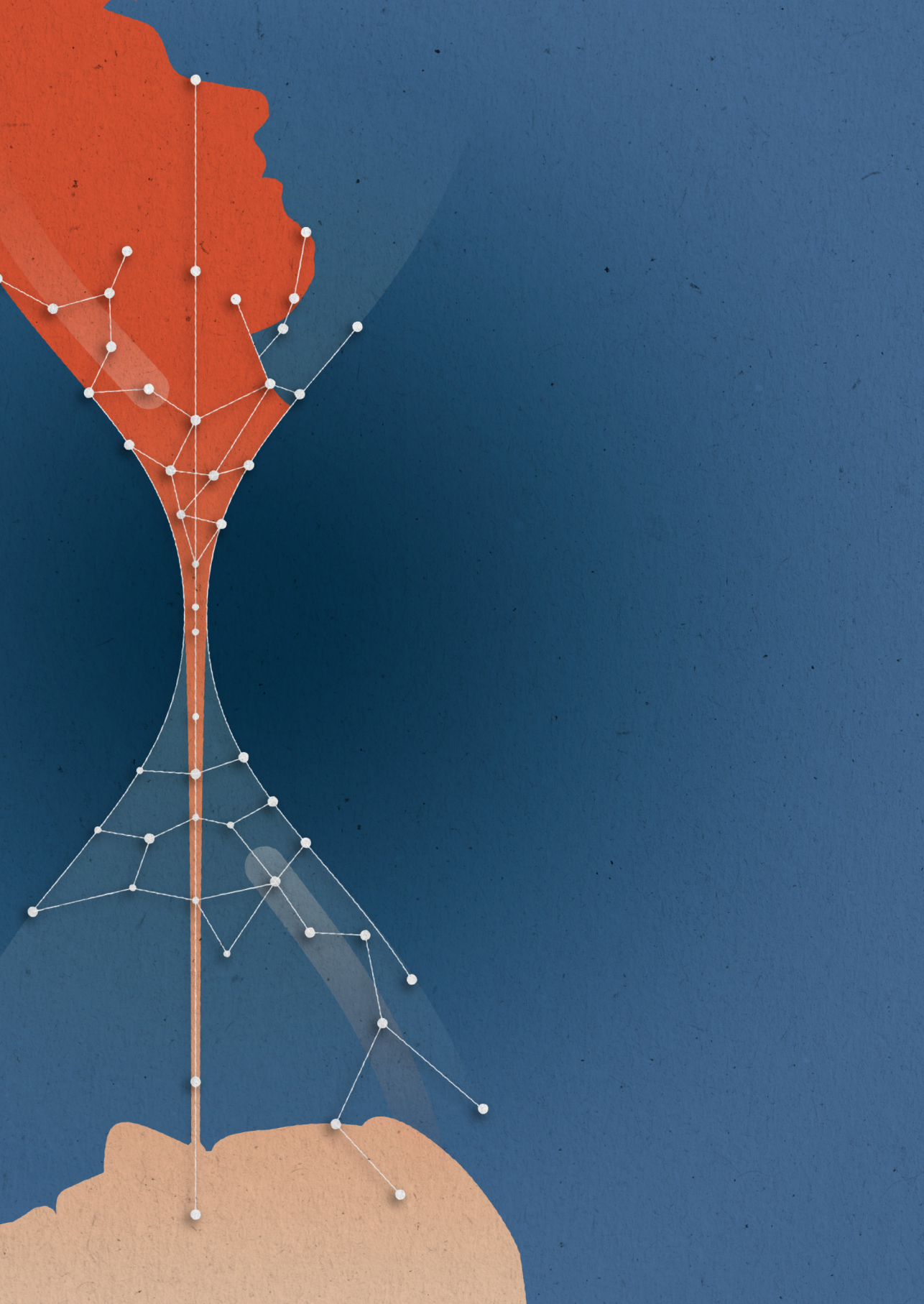
Effect van kwaliteitsverbeteringen op basis van de combinatie van PROMs, PREMs en klinische uitkomstinformatie op geaggregeerd niveau.

Linnean initiatief

Amsterdam UMC Universitair Medische Centra

Erasmus MC

▶ Bekijk de webcast



Chapter 8

Quality of Life of Oligometastatic and Polymetastatic Head and Neck Squamous Cell Carcinoma Patients

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Laryngoscope, 134:3170–3176, 2024

Abstract

Objective: Evidence suggests that distant metastasis in head and neck squamous cell carcinoma is a spectrum of disease. Previous studies show that oligometastasis has favorable survival compared to polymetastasis. The quality of life of patients with oligometastasis, remains unknown. To further solidify the position of oligometastasis as a separate entity, we hypothesized that oligometastatic patients experience better quality of life than polymetastatic patients.

Methods: Patients with distant metastasis were stratified into three groups: oligometastasis (≤3 metastatic foci in ≤2 anatomic sites), explosive metastasis (≥4 metastatic foci at one anatomic site) and explosive-disseminating metastasis (spread to ≥3 anatomic sites). Quality of life was assessed every two months post distant metastasis diagnosis.

Results: Between January 1, 2016 and December 31, 2021, 161 patients with distant metastasis were identified with in total 397 measurements. In this group, 57 (35.4%) patients had oligometastasis, 35 (21.7%) patients had explosive metastasis and 69 (42.9%) patients had explosive-disseminating metastasis. Their median post-distant metastasis survivals were 8.5 months, 3.2 months and 3.2 months respectively ($p<.001$). A significantly better overall quality of life was observed in the oligometastasis group compared to the polymetastatic groups (+0.75 out of 7, $p<.05$). Furthermore, oligometastatic patients performed better in the subdomains of “physical functioning”, “fatigue” and “pain”.

Conclusion: Results from this study underscore that subgroups exist regarding quality of life and survival within distant metastasis, with polymetastatic patients performing worse than oligometastatic patients. This highlights the significance of tailored interventions that consider the unique challenges faced by each metastatic group of patients.

Introduction

Every year, 850,000 cases of head and neck cancer (HNC) are diagnosed worldwide[1], with distant metastasis (DM) developing in 10% to 24% of the cases[2-4]. Hellman and Weichselbaum suggested in 1995 that DM should not be regarded as a binary phenomenon (DM do or do not exist), but rather as a spectrum of disease, in which gradations of DM can be defined[5]. There is growing evidence that this theory can also be applied to head and neck squamous cell carcinoma (HNSCC)[6-8]. Sinha et al. created a classification system of DM categories for p16-positive oropharyngeal squamous cell carcinoma[7]. In their study, three categories of DM were defined, ranging from limited disease (oligometastasis) to more extensive spread (explosive or disseminating metastasis), showing that oligometastasis yields better survival rates than explosive or disseminating metastasis[7].

In our previous study[8], we assessed whether the hypothesis of Hellman and Weichselbaum applied to all subsites in HNSCC. Using a modified form of the existing classification system of Sinha et al.[7], we determined that three distinct categories of DM can indeed be identified for survival in HNSCC, with oligometastasis (OM) resulting in the best survival rates, followed by explosive metastasis (EM) and explosive-disseminating metastasis (EDM).

In addition to survival, HNC can disproportionally impact quality of life (QoL). Impairments include difficulties in vital functions, such as swallowing, speaking and breathing[9]. In addition, systemic symptoms such as fatigue, pain and weakness are also present in more than three-quarters of the patients[10]. Despite the introduction of OM in HNSCC more than a decade ago[11], its effect on QoL in comparison to more extensive spread still remains ill-defined in literature.

To further solidify the position of OM as a separate entity within the distant metastatic spectrum of disease, we hypothesize that the QoL of patients with OM is more favorable than those with an EM or EDM pattern. The primary aim of this study is therefore to assess the QoL for the three distinct categories of DM in patients with HNSCC.

Furthermore, 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) has been established to be valuable in the work up of HNC[12]. In distant metastatic disease, the limited number of DM foci detected on conventional imaging may be an underrepresentation of the true extent of disease, as morphological changes on conventional imaging are preceded by metabolic changes on FDG-PET[13]. The secondary aim of this study is therefore to reevaluate the survival of the three DM categories in a cohort that underwent more frequent use of FDG-PET in the follow-up.

Materials and Methods

Patient and data selection

This retrospective study was approved by the Erasmus Medical Center ethics committee (MEC-2020-0314).

All patients diagnosed between January 01, 2016 until December 31, 2021 with HNSCC DM and available Healthcare Monitor (HM) data were included in this study. Since 2005, an Expert Center of Palliative Care for patients with HNC is operational in the Erasmus Medical Center with specialized oncology nurses as case managers[14]. The HM is an electronic patient-reported outcome based clinical support system[15,16], with results from this system used to guide individual patient interactions throughout their trajectory. DM was determined through radiological imaging, cytological and histological sampling or clinical examination when applicable. Loss of heterozygosity analyses were performed if uncertainty existed whether a focus constituted a second primary tumor or a distant metastatic lesion. Patients were excluded in case of synchronous non-HNSCC, except when the distant metastatic foci were pathologically proven to have derived from the HNSCC.

Endpoints and definitions

The primary endpoint was QoL using the EORTC QLQ-C15-PAL in relation to patterns of DM. The EORTC QLQ-C15-PAL is a shortened 15-item questionnaire based on the EORTC QLQ-C30, assessing physical and emotional functioning in the palliative phase of care[17]. The first fourteen items assess physical and emotional functioning on a scale of one (no impairment at all) to four (severe impairment),

whereas on the last item, the patient is asked to rate their overall QoL for the past week on a scale of one (very poor) to seven (excellent). A higher score indicates a better QoL for the domains of emotional functioning, physical functioning, and global health status. For the remaining domains, a lower score indicates better QoL. Patients completed QoL questionnaires every two months online or at every outpatient clinic visit.

As defined in our previous study[8] and based on a classification proposed by Sinha et al.[7], patterns of DM were divided into three categories. In this classification, OM constituted ≤3 metastatic foci in ≤2 anatomic sites and EM was defined as ≥4 metastatic foci at one anatomic site. The remainder of the patterns were defined as EDM, constituting spread to ≥3 anatomic sites or >3 metastatic foci in 2 anatomic sites. Using this subdivision, skeletal metastases were considered to be distinct anatomic sites in case of spread to separate bones.

The date of DM diagnosis was defined as the date on which the patient was informed of the palliative diagnosis. The pattern of DM was recorded as found at the time of DM diagnosis.

Workup and management

In the workup of primary HNC, guidelines at our center indicated a CT-scan of the thorax to exclude the possibility of DM to the lungs. In the recent years, FDG-PET CT-scans have gradually replaced other diagnostic modalities as the sole and primary diagnostic modality. Following treatment, FDG-PET CT-scans or CT-scans of the thorax and abdomen were performed when applicable in case of possible recurrent disease. Radiological imaging of other anatomical sites was only performed in case of clinical symptoms.

Treatment for distant metastatic HNSCC was solely offered with a palliative intent, in which the primary aim was alleviation of symptoms. Palliative treatment consisted of systemic therapy (chemotherapy or immunotherapy) or radiotherapy to focal metastatic lesions.

Statistical analysis

Statistical analyses were conducted using SPSS (IBM SPSS Statistics, version 28.0.1.0) and R version 4.1.2 with the JointAI package. The mixed-effects model framework with three natural cubic splines was used to investigate the longitudinal trajectories of QoL over time between the different patterns of DM and other clinical parameters. Using this framework, correlation in repeated measurements in patient-reported outcome measures (PROMs) over time from the same person is accounted for. Random patient factor was used to account for within-patient correlations, whereas a random intercept was added to account for different baseline levels of the patients. Covariates consisting of time, pattern of DM and treatment were added. QoL outcomes were analyzed for significance and clinical relevance was considered using minimal clinically important differences (MCID)[18]. Post-DM disease specific survival (DSS) was estimated using the Kaplan-Meier estimator. Heterogeneity between groups was assessed using the Chi-squared test and Fisher's exact test when appropriate. Two-tailed significance levels of ≤5% were used for all analyzes. For frequencies and proportions, descriptive statistics were used.

Results

A total of 161 patients developed DM in the period between January 01, 2016 and December 31, 2021. Seven patients (4.3%) had synchronous non-HNSCC, of which five were localized in the lung. In all seven cases, loss of heterogeneity analyses determined the metastatic lesions to have derived from the HNSCC. Two patients (1.2%) had a second primary in the head and neck region. The median and mean post-DM DSS for all 161 patients was 4.7 months (IQR 1.9–9.8) and 10.0 months (95% CI 7.9-12.2) respectively, with a two-year survival of 15.0%.

The majority of the patients developed an EDM pattern (42.9%), followed by an OM and EM pattern (35.4% and 21.7% respectively, Table 1). The OM group showed the most favorable survival as opposed to the polymetastatic groups, with a median post-DM DSS of 8.5 (IQR 5.1-26.6) months. The EM and EDM showed comparable survivals with a median post-DM DSS of 3.2 (IQR 1.3-7.8) months and 3.2 (IQR 1.5-6.1) months respectively (Figure 1). In the OM and EDM group, PET-CT was the

most frequently used diagnostic modality as opposed to the EM group, nevertheless no significance was reached (Table 2, p = 0.14).

Table 1. Baseline characteristics of the included patient population.

Characteristic		**No. (%)**
Gender	Male	127 (78.9)
	Female	34 (21.1)
Mean age at DM detection in years ± SD		66.4 ± 9.9
Index site	Oropharynx	49 (30.4)
	Hypopharynx	33 (20.5)
	Oral cavity	32 (19.9)
	Supraglottic	17 (10.6)
	Unknown primary	9 (5.6)
	Glottic	8 (5.0)
	Skin	5 (3.1)
	Nasopharynx	4 (2.5)
	Nasal cavity and paranasal sinuses	4 (2.5)
Chronology of DM	Synchronous with index tumor	36 (22.4)
	DM as 1st recurrence	81 (50.3)
	DM as 2nd recurrence	36 (22.4)
	DM as 3rd recurrence	8 (5.0)
Index tumor recurrence at time of DM	No recurrence	70 (56.0)
	Local	15 (12.0)
	Regional	22 (17.6)
	Locoregional	18 (14.4)
Treatment of metastatic foci	No treatment	104 (64.6)
	Local therapy (surgery or radiotherapy)	19 (11.8)
	Systemic therapy	27 (16.8)
	Local and systemic therapy	11 (6.8)
Pattern of DM	Oligometastasis	57 (35.4)
	Explosive	35 (21.7)
	Explosive-disseminating	69 (42.9)

Abbreviations: DM, distant metastasis; SD, standard deviation.

Table 2. Patient and palliative care characteristics per pattern of distant metastasis.

Variable	OM, N = 57. No. (%)	EM, N = 35. No. (%)	EDM, N = 69. No. (%)	P value
Dietitian consultation				.99
Yes	40 (70.2)	25 (71.4)	49 (71.0)	
No	17 (29.8)	10 (28.6)	20 (29.0)	
Pain management team consultation				.13
Yes	6 (10.5)	2 (5.7)	13 (18.8)	
No	51 (89.5)	33 (94.3)	56 (81.2) .)	
Gastric tube placement				.75
Yes	8 (14.0)	7 (20.0)	12 (17.4)	
No	49 (86.0)	28 (80.0)	57 (82.6)	
Direct cause of death				.45
No sedative intervention	14 (32.6)	8 (25.8)	21 (34.4)	
Palliative sedation	21 (48.8)	17 (54.8)	29 (47.5)	
Euthanasia	3 (7.0)	5 (16.1)	9 (14.8)	
Blow-out	5 (11.6)	1 (3.2)	2 (3.3)	
Location of death				.24
At home	33 (75.0)	26 (81.3)	44 (67.7)	
Hospice	6 (13.6)	2 (6.3)	15 (23.1)	
Hospital	3 (6.8)	4 (12.5)	3 (4.6)	
Nursing home	2 (4.5)	0 (0.0)	3 (4.6)	
Mean weight loss in kilograms ± SD				**.04**
in the past 6 months	2.2 ± 3.2	3.9 ± 4.8	4.2 ± 5.3	
WHO status				.15
WHO 0	14 (24.6)	6 (17.1)	5 (7.2)	
WHO 1	21 (36.8)	16 (45.7)	32 (46.4)	
WHO 2	17 (29.8)	7 (20.0)	22 (31.9)	
WHO 3 and 4	5 (8.8)	6 (17.1)	10 (14.5)	
Diagnostic modality				.14
PET-CT	25 (43.9)	7 (20.0)	35 (50.7)	
CT chest	9 (15.8)	9 (25.7)	13 (18.8)	
CT neck and chest	11 (19.3)	11 (31.4)	7 (10.1)	
CT chest and abdomen	6 (10.5)	3 (8.6)	5 (7.2)	
CT neck, chest and abdomen	2 (3.5)	2 (5.7)	6 (8.7)	
Other	4 (7.0)	3 (8.6)	3 (4.3)	

Table 2. Patient and palliative care characteristics per pattern of distant metastasis. (*Continued*)

Variable	OM, N = 57. No. (%)	EM, N = 35. No. (%)	EDM, N = 69. No. (%)	P value
Treatment of metastatic foci				**.01**
No treatment	29 (50.9)	32 (91.4)	43 (62.3)	
Local therapy	9 (15.8)	1 (2.9)	9 (13.0)	
Systemic therapy	15 (26.3)	0 (0.0)	12 (17.4)	
Local and systemic therapy	4 (7.0)	2 (5.7)	5 (7.2)	

Abbreviations: SD, standard deviation; OM, oligometastasis; EM, explosive metastasis; EDM, explosive-disseminating metastasis.

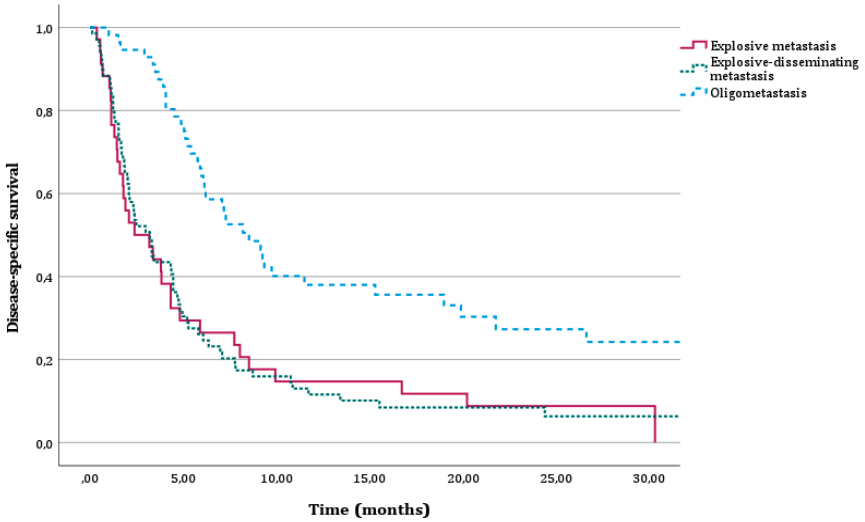

Fig. 1. Kaplan-Meier curve of post-distant metastasis disease-specific survival by distant metastasis pattern (log-rank test $p < .01$).

Quality of life analysis

Linear mixed model analysis on longitudinal patient-reported QoL up to 12 months was performed, with EM and EDM combined set as reference category. In total 397 measurements were collected and analyzed. A significant difference in intercept in favor of patients with OM on all EORTC QLQ-C15-PAL domains (Table 3, $p < 0.001$) was observed. In addition to intercept, patients with OM show significantly better QoL on the domains "global health status", "physical functioning", "fatigue"

and "pain" ($p < 0.05$). Despite the different rates of treatment between the two groups, patients with OM remained showing more favorable QoL. In the "global health status" domain with EM and EDM combined set as reference category, a QoL of 4.64 out of 7 is observed at diagnosis. Compared to OM, a QoL of +0.75 out of 7 is measured over the whole course of the follow-up in favor of OM. A physical functioning of +20.8% in the OM group over the polymetastatic group is observed ($p < 0.001$). In addition, less fatigue and pain is observed in the OM group (-11.7% and -14.4% respectively, $p < 0.05$).

Plotting of the domain "global health status" showed initial quick deterioration in both groups over the course of two months, followed by slight improvement and stabilization of the experienced QoL. Nevertheless, in the later course of the follow-up, further deterioration was observed in both groups (Figure 2).

Table 3. Linear mixed model analysis of the EORTC QLQ-C15-PAL domains with explosive metastasis combined with explosive-disseminating metastasis set as reference category. In the context of this linear mixed model analysis, "intercept" marks the starting point of the two groups, "Patterns of DM" denotes the difference in quality of life over the whole course of the two groups, "Time" portrays the effect of time on the quality of life (i.e. the quality of life worsens over time), and "Treatment" portrays the effect of treatment as a potential confounder on the quality of life of the patients.

EORTC QLQ-C15-PAL domains	Mean (SD)	P value
Global health status		
Intercept	4.64 (0.17)	**< .001**
Pattern of DM (OM)	0.75 (0.30)	**.01**
Time	1.20 (0.51)	**< .001**
Treatment	0.15 (0.23)	.52
Physical functioning		
Intercept	56.25 (3.25)	**< .001**
Pattern of DM (OM)	20.80 (5.39)	**< .001**
Time	16.83 (8.44)	**< .001**
Treatment	7.38 (4.36)	.09
Emotional functioning		
Intercept	69.27 (3.25)	**< .001**
Pattern of DM (OM)	4.82 (5.91)	.38
Time	24.87 (6.95)	**< .001**
Treatment	0.58 (4.55)	.93

Table 3. (*Continued*)

EORTC QLQ-C15-PAL domains	Mean (SD)	P value
Fatigue		
Intercept	41.20 (3.26)	**< .001**
Pattern of DM (OM)	-11.68 (5.54)	**.03**
Time	6.24 (4.99)	**< .001**
Treatment	-6.75 (4.33)	.11
Pain		
Intercept	38.15 (3.32)	**< .001**
Pattern of DM (OM)	-14.41 (5.69)	**.02**
Time	0.75 (1.55)	.79
Treatment	-3.12 (4.55)	.49
Dyspnea		
Intercept	26.85 (3.12)	**< .001**
Pattern of DM (OM)	-6.39 (5.19)	.25
Time	2.17 (0.73)	.25
Treatment	-6.76 (4.58)	.17
Nausea and vomiting		
Intercept	7.52 (1.71)	**< .001**
Pattern of DM (OM)	-4.46 (3.11)	.15
Time	1.90 (1.20)	**.04**
Treatment	-2.58 (1.86)	.16
Insomnia		
Intercept	33.82 (4.03)	**< .001**
Pattern of DM (OM)	-7.48 (5.60)	.18
Time	-0.48 (1.27)	.69
Treatment	-3.70 (4.47)	.42
Appetite loss		
Intercept	30.17 (3.83)	**< .001**
Pattern of DM (OM)	-7.09 (6.48)	.25
Time	-0.10 (3.13)	.67
Treatment	-10.32 (4.69)	**.01**
Constipation		
Intercept	18.92 (3.04)	**< .001**
Pattern of DM (OM)	-9.90 (5.22)	.05
Time	1.37 (1.39)	.60
Treatment	2.08 (3.99)	.63

Abbreviations: SD, standard deviation; OM, oligometastasis.

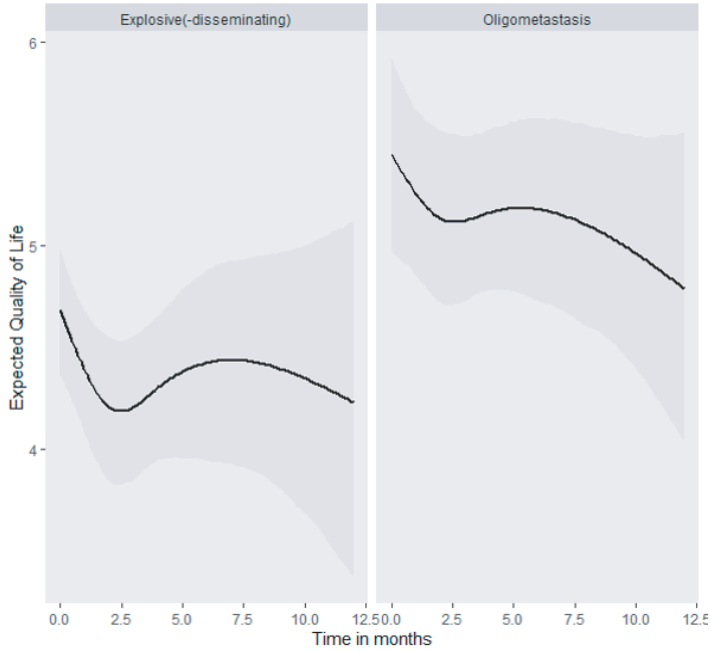

Fig. 2. Predicted global health status by distant metastasis pattern with "time", "pattern of distant metastasis" and "treatment" included as factors (linear mixed model $p < .01$).

No significant differences existed in dietitian consultation, pain management team consultation or gastric tube placement between the three DM categories. The most common intervention was palliative sedation in all three DM categories, with the most frequent place of death being at home.

Treatment of metastatic foci differed significantly between the three groups, with 91.4% of all EM patients abstaining from palliative treatment, compared to 50.9% and 62.3% in the OM and EDM groups respectively (Table 2, $p = 0.01$).

Discussion

In this study, we observed that oligometastatic patients experience better QoL over the whole course of their disease than patients with a polymetastatic pattern. In addition, in this cohort a more favorable survival was again seen in patients with OM compared to patients with EM or EDM. These results have clinical implications in daily practice, as more accurate prognostic information can be provided to patients with DM. While the palliative phase is short, with a median post-DM DSS of 4.7 months, patients with a polymetastatic pattern are distinguished by an even more limited survival and poor QoL. This leaves a shorter period of time in which palliative care can be optimized in comparison to oligometastatic patients. Results from the linear-mixed model analysis can aid in increasing non-anti-tumor interventions for the more vulnerable polymetastatic group. Patients with a polymetastatic pattern experience more pain during the entire course of the palliative phase, with early consultation of the pain management team being an example of an intervention which could improve the QoL of this group. In addition, increasing the frequency of consultations with specialized oncology care nurses and transferring more concise information regarding prognosis to the patient's primary care physician are steps that can be taken to strengthen the position of the polymetastatic group. By tailoring interventions to address the unique challenges faced by polymetastatic patients, we aim to contribute to an improved holistic care framework that goes beyond traditional anti-tumor treatments.

The position of patients with OM is also subject to change, as the prolonged survival and favorable physical functioning permit more aggressive palliative therapies. This study endorses recent studies showing patients with OM treated successfully with curative intent[19,20]. In the past, chemotherapy had been the standard systemic therapeutic option in distant metastatic HNSCC patients, with the aim of prolonging survival and symptom alleviation[21]. Nevertheless, chemotherapy-induced toxicities are well known adverse events in patients with DM[22], causing the decision for treatment to be a delicate balance between its efficacy and side effects. The novel immunotherapeutic agents are known to increase survival in palliative HNSCC[23], however, it remains unknown how this affects the QoL in patients with prolonged survival. Therefore, while the physical functioning of patients with OM allows for

treatment intensification, its effect on QoL and the risk of adverse events should always be taken into consideration.

In our previous study with patients in the period from 2006 until 2013, median post-DM DSS of 4.7 months, 4.1 months and 1.7 months were observed in the OM, EM and EDM groups respectively[8]. In this series, the median post-DM DSS of OM and EDM patients has substantially increased, whereas a less optimistic survival was found in the EM patients (3.2 months). A possible explanation for the increased survival rates is the use of novel immunotherapeutic agents[24,25], reflected in low systemic therapy rates in the EM group. The question that arises here concerns the cause for the low treatment rates in the EM category. The EM category was in previous studies identified as a middle category, with a distinct survival from the EDM category[7,8]. In patients with EM unwillingness may exist on one hand for systemic treatment due to the relatively limited metastatic spread confined to merely one anatomic location. On the other hand, stereotactic radiation therapy may be deemed unfeasible due to the extensive number of foci within that anatomic location.

Nevertheless, survival of HNSCC patients is often overestimated in the palliative phase[26], possibly leading to suboptimal use of palliative and end-of-life care. A vital part of implementing shared decision making consists of, among others, providing accurate and unbiased information about: (1) prognosis, (2) the treatment options and (3) the pros and cons of each relevant option[27,28]. The first step can be achieved through personalized prognostic modeling for palliative patients, which can assist physicians in estimating survival more accurately. For this, multiple facets that predict prognosis should be taken into account, including the patterns of DM[29]. The bottleneck exists in the second and third part, in which a research gap exists in the treatment options and its impact on survival and QoL for the different patterns of DM. Therefore, information is needed on how treatment decisions are made by physicians and patients and what weighs into these decisions.

FDG-PET imaging

The use of FDG-PET imaging has been established as an essential component of the work-up of HNC[30-32], but consensus is lacking regarding its role in the follow-up[33]. In our cohort, FDG-PET CT imaging was increasingly used in the follow-up, constituting the most common imaging modality. The clinical significance of this is

that OM diagnosed with FDG-PET imaging can be considered true oligometastatic disease, whereas those diagnosed with conventional methods may have DM foci outside imaged areas. Nevertheless, when comparing the rates of the different patterns of DM, similar rates are found to our previous cohort, where FDG-PET imaging did not constitute a routine part of the work-up and follow-up[8]. Due to the fact that morphological changes on conventional imaging are preceded by metabolic changes on FDG-PET[13], the question arises whether this leads to a higher rate of synchronous DM over metachronous DM. In our previous cohort, synchronous and metachronous DM as 1st recurrence accounted for 16.4% and 60.8% of the total DM cases respectively. When comparing this with the current cohort, a shift to more synchronous than metachronous DM is observed (22.4% and 50.3% respectively)[8].

Identification and prediction of metastatic patterns

Currently, the question remains whether OM constitutes an indolent biological state with a distinct tumor environment, or a small clinically apparent tumor burden in the presence of more aggressive occult metastatic disease[34]. The identification of OM in a patient as a separate clinical entity is essential for its subsequent management.

The determination of biomarkers could constitute a valuable part in the work-up of distant metastatic disease for the correct and early identification of oligometastatic disease.

Study strengths and limitations

This study paves the way for individualized counseling regarding prognosis and QoL in patients with DM. Prognostic information on QoL gained from this study will aid in the shared decision making process, as patients in the palliative phase prefer more extensive information on prognosis than those in the curative phase[36]. To our knowledge, it is the first study in oncology in which PROMs are used in relation to patterns of DM, further solidifying the position of OM as a separate entity within the distant metastatic spectrum of disease. At our center, a prognostic model for palliative HNSCC patients is under development to estimate overall survival. Insights from this study allow the addition of distant metastatic patterns as a prognosticator for survival, while also paving the way for the development of a prognostic model for QoL in the palliative phase. Another major strength is the frequent use of FDG-PET imaging in this cohort, ensuring diagnostic certainty for OM.

However, one limitation of this study derives from the general evolving definition of OM. In this cohort, OM was defined according to criteria modified from Sinha et al[7], whereas different definitions are reported in literature, ranging from 1 – 5 metastatic foci[37]. As of now, it remains unclear what number of metastatic foci and affected anatomic locations can still be regarded as oligometastatic disease. Another limitation stems from the choice of abstaining from treatment in the majority of the patients. The diagnosis of OM may allow potential eradication of metastatic foci, with novel therapies, such as immune checkpoint inhibitors, altering disease progression and affecting both survival and QoL. As of now, it is unknown how such a prolonged survival with therapies without serious adverse events impacts QoL in patients with metastatic HNSCC. Results from our patient population may therefore not represent patient populations in countries with higher treatment rates of DM.

Conclusion

Our study demonstrated that oligometastasis is associated with better QoL compared to polymetastatic disease. Patients with OM show favorable QoL on all EORTC QLQ-C15-PAL domains at diagnosis compared to polymetastatic patients. In addition to the differences at baseline, the QoL remains better over the course of the whole follow-up for the domains “global health status”, “physical functioning”, “fatigue” and “pain”. The results from this study can aid in providing more accurate information on survival and QoL in patients with DM.

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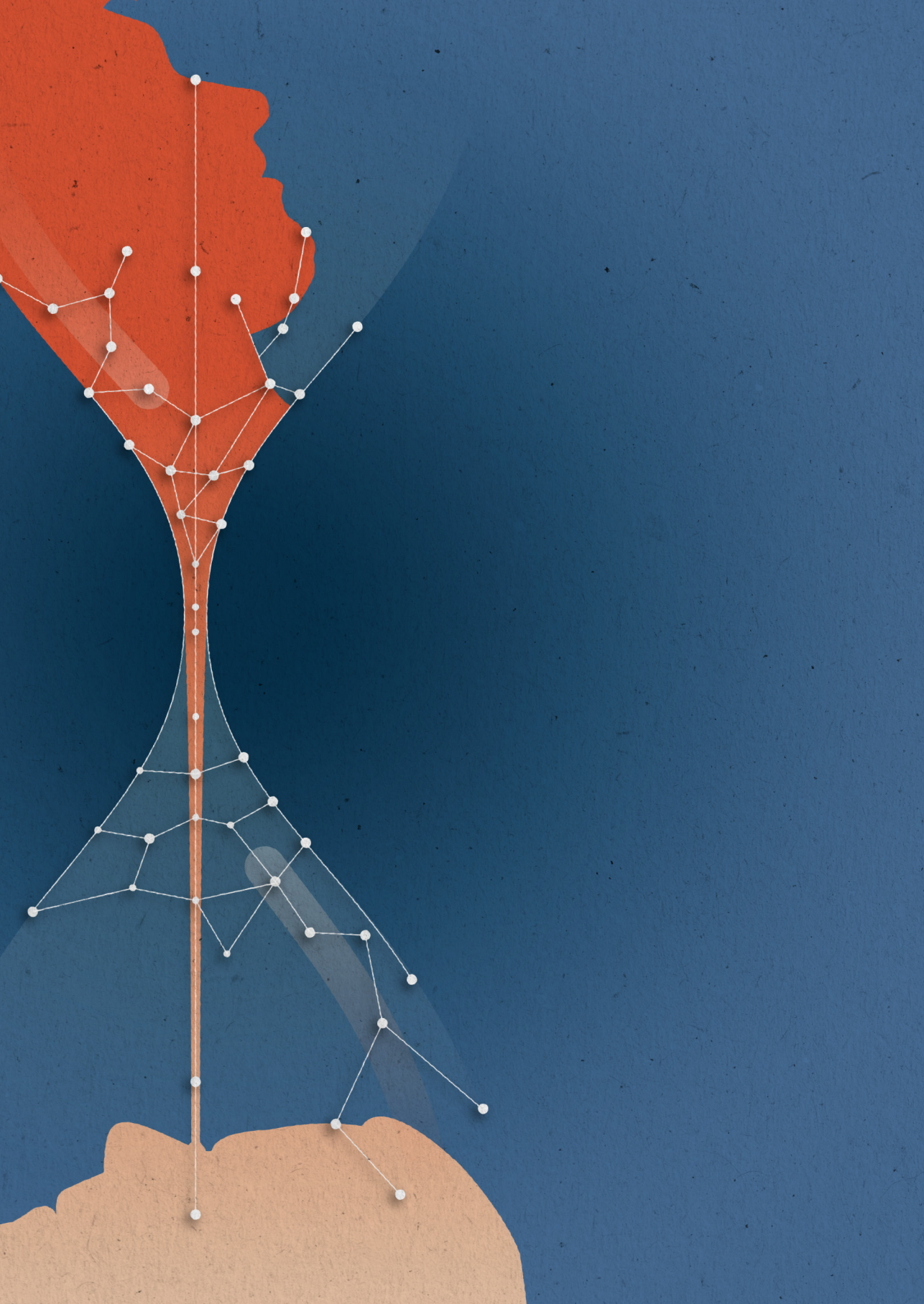

Chapter 9

Learnings From Longitudinal Patient-Reported and Clinical Outcomes in Palliative Head and Neck Cancer Care

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Abstract

Objective: Palliative head and neck cancer patients experience many symptoms in a short period of time. Longitudinal data on patient-reported outcomes in this phase is lacking. The aim of this study is to use structurally obtained patient-reported outcome data combined with clinical patient data and obtain insight in patient-reported outcomes, survival, circumstances of death, and interventions and treatment during the palliative phase in order to improve the quality of end-of-life care and patient-centered counseling.

Study Design: Longitudinal observational cohort study.

Setting: Tertiary cancer center.

Method: Quality of life was prospectively collected using the European Organization for Research and Treatment of Cancer QLQ-C15-PAL. Tumor- and patient-specific data were retrospectively collected. Descriptive statistics, linear mixed models and regression analyses were performed.

Results: A significant deterioration was found in global health status, physical functioning, fatigue, dyspnea, appetite loss and constipation over time. However, emotional functioning improved. Median survival was 5.1 months and only a low percentage of in-hospital death was observed (7.8%). Higher global health status at intake was associated with prolonged survival.

Conclusion: Structural measurement of patient-reported outcome together with clinical outcomes provide unique insight which enables improvement of patient-centered counselling and care.

Introduction

Palliative care in general aims to improve Quality of Life (QoL) for patients and their families by providing relief from symptoms and stress of the disease[1]. Approximately 25-30% of the patients with Head and Neck Cancer (HNC) will at a certain moment reach the palliative phase in which no curative treatment options are available. This phase is rather short with a median survival of five months[2-4]. During the palliative phase, patients often develop specific problems with swallowing, speech and airway, (fatal) bleeding, and dramatic appearance changes. The most frequently reported somatic symptoms during the palliative phase are pain, fatigue and weight loss[5,6]. These physical problems, combined with the knowledge of limited survival, can have significant psychosocial impact on patients and their loved ones[2,7-10]. Therefore, patients should be offered individualized palliative care focusing on early identification and treatment of symptoms[11-13]. A multidisciplinary patient-centered approach has the potential to alleviate the burden of disease, preserve QoL as long as possible for both patients and their families, assist with decision-making and reduce hospital admissions[14-22].

Since 2005, an Expert Center of Palliative Care for HNC patients is operational in the Erasmus Medical Center with dedicated head and neck surgeons and specialized oncology nurses as case managers. When patients become palliative due to exhaustion of curative treatment options or by refraining from curative treatment, we provide structural multidisciplinary patient care focused on symptom control and psychosocial support for patient and family. This set-up led to improved psychosocial support, better doctor-patient relation, and fewer hospital admissions[23,24]. Since 2016, this working method is complemented with the structural implementation of electronic Patient-Reported Outcome Measurement data (ePRO) which we called the 'Healthcare Monitor'[25]. This monitor is used during every patient encounter and works as a 'guide' during individual patient contacts and it helps to early detect issues in the palliative phase. This can lead to more individualized symptom management and end-of-life counselling and care[25].

Literature and learnings on palliative HNC care stay scarce due to a relatively short palliative phase and often vulnerable patients not being able to participate in research. Our working method guides optimal care and at the same time provides

us with useful insights on the development of patients functioning and burden during the entire palliative phase. The aim of this study is to evaluate structurally obtained outcome data from our palliative care program in order to obtain insight in: 1. longitudinal patient-reported outcomes; 2. survival and associated factors; 3. circumstances of death; 4. interventions and treatment during the palliative phase.

Methods

Institutional routine and ePROs.

Following the palliative diagnosis, the patient is referred to a specialized oncology nurse. They are the patients' case manager and keep contact with the patients' general practitioner (GP), which has a central role during the palliative phase. However, due to the rarity of HNC, our Expert Center of Palliative Care provides accessible information for all GP's[3]. The patient can contact the team of specialized oncology nurses whenever needed via remote care or during a physical appointment. On the other hand, the nurses proactively contact the patient every 6-8 weeks. The patient fills in the ePRO (EORTC QLQ-C15-PAL) prior to these encounters. When patients are vulnerable or lack digital skills, they will be supported by the specialized oncology nurse. Results act as a guideline for individual patient contacts.

Research ethics and patient consent

This study was approved by the institutional review board and ethics committee from the Erasmus University (MEC-2020-0314). All participating patients provided electronic written informed consent.

Case selection and data collection

All palliative patients diagnosed between 01-01-2016 and 01-05-2020 with a head and neck carcinoma were retrospectively included in this study. This included squamous cell carcinoma, melanoma, sarcoma and salivary gland tumors. Head and neck metastases from other tumors were not included. Patients could be declared palliative due to exhaustion of curative treatment options or by refraining from curative treatment. Patients were excluded when ePROs were incomplete, lost to follow up or if the palliative status was revoked when there was no evidence of disease after palliative (experimental) treatment.

Instruments used

Patient-reported QoL was assessed from intake up to 6 months with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL[26]. This questionnaire is a shortened version of the EORTC QLQ-C30 and recommended for use in patients with advanced, incurable, and symptomatic cancer with a median life expectancy of a few months. It consists of 15 questions, assessing ten domains. A score for physical functioning is a combination of three separate items. Emotional functioning, fatigue and pain are two-item scales. Dyspnea, insomnia, appetite loss, constipation, nausea/vomiting and global health status are single-item scales. All questions are scored on a four-point scale, ranging from 1 ('not at all') to 4 ('very much'). A higher score indicates a better QoL for the domains of emotional functioning, physical functioning, and global health status. In contrast, for the remaining domains, lower scores indicate better QoL.

At baseline, the following clinical variables were scored: patient physical capability of functioning in daily life by means of the WHO Performance Status[27], Adult Comorbidity Evaluation-27 (ACE-27)[28], age, sex, weight loss (yes/no), marital status, tumor location and TNM-stage, tumor chronology (primary or recurrent disease), social network Clinical outcome information assessed during follow-up period are: place and cause of death, gastric tube placement within the first two months, involvement of the dietician and pain team, starting and ending palliative treatment.

Statistical analysis

Statistical analyses were performed using R[29]. Descriptive statistics were used to calculate the frequencies and proportions for baseline characteristics. The evolution over time and effect of clinical variables was assessed for each domain of the EORTC-QLQ-C15-PAL with linear mixed model analysis. Mixed model analyses are most appropriate for this multilevel data as it accounts for the correlations between repeated measurements within each individual and takes missing data into account[31]. For every model, comprising one domain, a fitting procedure was performed, and an optimal covariance matrix was chosen based on the -2 restricted log likelihood. Within every model, the effect and estimated mean of the random intercepts of the following variables were investigated: age, sex, performance status, ACE-27, treatment, tumor chronology, metastatic disease, weight loss, marital status and tumor stage. Predicted means with 95% confidence intervals were derived from the

best-fitted models. Changes over time were analyzed for significance and clinical relevance was considered using minimally important differences (MCID) proposed by the EORTC[32,33]. Disease-specific survival (DSS) was defined as the time from palliative diagnosis until death or last day of follow-up. Cox proportional hazard regression model was used to calculate the multivariable hazard ratios for clinical variables and one patient-reported outcome measure (global health status). Two-tailed significance levels of ≤5% were used for all analyses. Correction for multiple testing was performed.

Results

Between 01-01-2016 and 01-05-2020, 337 patients with HNC in the palliative phase were retrospectively identified. Four patients were excluded due to revocation of the palliative status, one patient was excluded due to incomplete ePROs, and one patient was excluded due to loss to follow-up. In total, 331 patients were included in this study for further analysis. The number of patients lost to attrition were 86 (26.0%) at two months, 151 (54,4%) at four months and 194 (58,6%) at six months.

Baseline characteristics

The mean age at the time of palliative diagnosis was 70 years, with 65.9% of the patients being male. In total, 145 patients (43.8%) lived alone, and 60 patients (18.1%) had an inadequate social network. Comorbidity was present in almost all patients; only 7.3% of the patients had no comorbidities. The majority of patients (88.3%) had squamous cell carcinoma. Distant metastasis was present in 40.5% of all patients. At the time of inclusion, 74 patients (22.4%) were still alive. For all baseline characteristics, see Table 1.

Table 1. Patient characteristics

Variable	N = 331
Mean age (SD)	70.0 (11.2)
Sex	
Male	218 (65.9%)
Female	113 (34.1%)
Marital status	
Married / Living together	186 (56.2%)
Alone	145 (43.8%)
WHO Performance Status	
0	59 (17.8%)
1	117 (35.3)
2	88 (26.6%)
3	55 (16.6%)
4	12 (3.6%)
Comorbidity (ACE-27)	
0	24 (7.3%)
1	48 (14.5%)
2	95 (28.7%)
3	164 (49.5%)
Weight loss	
Yes	152 (45.9%)
No	161 (48.6%)
Unknown	18 (5.4%)
Smoking	
No	76 (23.0%)
Yes	120 (36.3%)
Former	123 (37.2%)
Unknown	12 (3.6%)
Social network	
Adequate	271 (81.9%)
Inadequate	60 (18.1%)
Tumor location	
Oral cavity	90 (27.2%)
Oropharynx	77 (23.3%)
Nasopharynx	12 (3.6%)

Table 1. Patient characteristics (*Continued*)

Variable	N = 331
Mean age (SD)	70.0 (11.2)
Larynx	38 (11.5%)
Hypopharynx	41 (12.4%)
Skin	24 (7.3%)
Unknown primary	12 (3.6%)
Salivary glands	16 (4.8%)
Nasal cavity and paranasal sinuses	21 (6.3%)
M-stage	
M0	197 (59.5%)
M1	134 (40.5%)
Stage	
I	4 (1.2%)
II	20 (6.0%)
III	32 (9.7%)
IVa	83 (25.1%)
IVb	68 (20.5%)
IVc	114 (34.4%)
IV (p16+)	10 (3.0%)
Tumor chronology	
Primary	118 (35.6%)
2nd to 6th primary	26 (7.9%)
Recurrent	183 (55.3%)
Residual	4 (1.2%)
Median time to recurrent (Q1 – Q3)	11 months (7.0 – 19.0)
Synchronic tumor	
No	298 (90.0%)
Yes, synchronic HNC	12 (3.6%)
Yes, not HNC	21 (6.3%)
Lung	*9 (42.9%)*
Esophageal	*4 (19.0%)*
Prostate	*4 (19.0%)*
Colorectal	*2 (9.5%)*
Leukemia	*1 (4.8%)*
Bladder	*1 (4.8%)*

Table 1. Patient characteristics (*Continued*)

Variable	N = 331
Mean age (SD)	70.0 (11.2)
Deceased	
Yes	257 (77.6%)
No	74 (22.4%)

Palliative characteristics

Palliative characteristics can be found in Table 2. In 269 patients (81.3%) the palliative phase started because no curative options were available. The other 62 patients (18.7%) refrained from curative treatment or even necessary diagnostic tests. In the group that refrained from curative treatment a significant higher proportion were females (47.6% vs. 31.2%, p = 0.014), had synchronous tumors (20.6% vs. 7.4%, p = 0.002), or eventually choose for euthanasia (26.5% vs. 9.6%, p = 0.001)

In-hospital death occurred in only 19 patients (7.8%). Reasons for hospital admissions in this final phase of life were mainly acute deterioration, e.g. imminent bleeding or acute dyspnea. Living together with a partner was significantly associated with dying at home. In contrast, patients living alone or without adequate social network died was associated with dying in a nursing home or palliative hospice.

Natural death occurred in 195 patients (75.9%), ten patients died of a carotic blowout (3.9%), and 33 chose for euthanasia (12.8%). Euthanasia was performed mainly at home (81.8%) and in patients who did not receive any palliative treatment (78.8%). Patients who chose for euthanasia were predominantly diagnosed with stage IV disease (81.6%). Carotic blowout occurred most in oropharyngeal (40.0%), laryngeal (20.0%) and oral cavity (20.0%) tumors. Of the patients dying from a carotic blowout, nine patients (90.0%) suffered from recurrent disease.

Table 2. Palliative characteristics

Variable	N = 331
Reason palliative phase	
No curative options	269 (81.3%)
Patient refrains from curative option	53 (16.0%)
Patient refrains from diagnostic phase	9 (2.7%)
Place of death	
At home	170 (66.4%)
Hospital	19 (7.4%)
Nursing home	18 (7.0%)
Palliative hospice	43 (16.7%)
Unknown	7 (2.7%)
Cause of death	
Natural death	195 (75.9%)
Euthanasia	33 (12.8%)
Blow-out	10 (3.9%)
Unknown	19 (7.4%)
Palliative treatment	
No	231 (69.8%)
Local radiotherapy	49 (14.8%)
Systemic therapy	34 (10.3%)
Systemic and radiotherapy	17 (5.1%)
Status palliative treatment	
Finished	45 (45.0%)
Stopped early	45 (45.0%)
Active	9 (9.0%)
Unknown	1 (1.0%)
Reasons stopping early	
Disease progression	18 (40.0%)
Patient request	13 (28.9%)
Toxicity / side effects	7 (15.6%)
Untimely death	7 (15.6%)

Patient-reported outcome measures

Longitudinal patient-reported QoL up to 6 months is presented in Table 3. In total 704 measurements were completed. Significant deterioration during the 6 months follow-up was seen in the domains of global health status (-6.6), physical functioning (-8.4), fatigue (+10.4), dyspnea (+5.6), appetite loss (+9.1) and constipation (+4.9). A significant improvement was seen for the domain of emotional functioning (+6.0). Longitudinal mean differences for patients with high performance status compared to low performance status were observed for global health status (-11.8), physical functioning (-29.9), fatigue (17.3), pain (15.4), dyspnea (11.4) and appetite loss (11.3). Patients with higher comorbidity scores were associated with worse scores for physical functioning (ACE 2: -16.4; ACE 3: -12.0), as were patients with recurrent disease (-9.6) and absence of treatment (-10.3). Mean estimates for other clinical and demographic factors can be found in Table 4.

Survival analysis

The median DSS of all patients was 5.1 months (range 0.1 – 40.5 months). Higher age at entry in the palliative phase, higher performance status, severe comorbidity, higher tumor stage and receiving no palliative treatment were significantly associated with a lower DSS. Moreover, a higher reported global health status at intake was associated with prolonged survival (HR 0. 988, p =.000). The multivariable Cox regression analysis can be found in Table 5.

Palliative interventions and treatment

Palliative treatment was given to 100 patients (31.2%). At the time of inclusion, nine patients (9.0%) were still in the palliative treatment process, 45 finished (45.0%), and 45 (45.0%) had stopped prematurely. Reasons for stopping treatment were mainly disease progression (40.0%) and patient request (28.9%). The pain team was consulted in 41 patients (12.4%). The dietitian was consulted in 196 patients (59.2%) and most often in the care for oropharyngeal and laryngeal patients. In 68 patients (20.5%), a gastric tube was in situ, consisting of 45 (66.2%) nasal tubes, 21 (30.9%) gastrostomies and two (2.9%) jejunostomies.

Table 3. Longitudinal mean estimates for patient-reported quality of life from intake to 6 months.

Quality of life domains	Reference threshold	Intake n = 331	95% CI	2 months n = 245	95% CI	4 months n = 180	95% CI	6 months n = 137	95% CI	Δ	p-value*	Predictors^
Global health status	**≥ 64.5**	**64.2**	59.7 – 68.7	**59.6**	55.1 – 61.1	**58.9**	54.0 - 63.8	**57.6**	52.3 – 63.0	**-6.6**	**0.01**	Performance status
Physical functioning	**≥ 81.2**	**59.8**	53.7 – 65.9	**51.7**	45.8 – 57.7	**52.8**	46.5 -58.9	**51.4**	44.7 – 58.0	**-8.4**	**<0.001**	Performance status, ACE, Treatment, Tumor Chronology
Emotional functioning	**≥ 72.5**	**75.6**	71.9 – 79.3	**77.7**	74.0 – 81.5	**77.5**	73.3 – 81.7	**81.6**	76.8 – 86.4	**+6.0**	**0.04**	-
Fatigue	**≤ 26.9**	**34.8**	29.3 – 40.3	**48.3**	43.0 – 53.6	**48.0**	42.3 – 53.6	**45.2**	39.1 – 51.3	**+10.4** **-3.3** **-0.4** **-5.6** **-0.7**	**0.001**	Performance status
Nausea /Vomiting	**≤ 5.3**	**7.4**	4.9 – 9.9	**11.8**	8.2 – 15.3	**7.4**	4.5 – 10.2	**10.7**	6.4 – 15.0	+3.3	0.08	Gastric tube
Pain	**≤ 23.2**	**33.5**	27.9 – 39.2	**35.9**	30.5 – 41.4	**35.0**	29.2 – 40.8	**33.9**	27.6 – 40.2	+0.4	0.7	Performance status
Dyspnea	**≤ 18.2**	**15.9**	11.0 – 21.0	**22.6**	17.4 – 27.7	**20.4**	14.9 – 25.9	**21.5**	15.5 – 27.5	**+5.6**	**0.004**	Sex, Performance status, Treatment
Insomnia	**≤ 27.3**	**22.8**	18.7 0 26.9	**26.3**	21.9 – 30.6	**24.4**	19.6 – 29.3	**23.5**	18.0 – 29.0	+0.7	0.05	-
Appetite loss	**≤ 17.7**	**23.4**	17.8 – 29.0	**32.7**	26.9 – 38.6	**29.4**	23.0 – 35.8	**32.5**	25.6 – 39.5	**+9.1**	**0.001**	Performance status, Weight loss
Constipation	**≤ 11.1**	**11.9**	8.5 – 15.2	**18.0**	14.1 – 21.9	**14.0**	9.8 – 18.2	**16.8**	12.0 – 21.6	**+4.9**	**0.025**	Sex

*Significance for a longitudinal trend.

^Significant variables affecting the longitudinal evolution over time.

Table 4. Estimates of significant random intercepts. Showing the mean longitudinal differences between different clinical and demographic factors.

Time-points	Estimated mean	SE	p-value	95% CI
Global health status				
Performance status 3,4 (ref: 0,1,2)	-11.8	4.1	0.004	-19.8 – -3.8
Physical functioning				
Performance status 3,4 (ref: 0,1,2)	-29.9	4.7	<0.001	-20.6 – -39.1
ACE 2 (ref: 1)	-16.4	5.0	0.001	-26.2 – -6.6
ACE 3 (ref: 1)	-12.0	4.7	0.011	-21.2 – -2.8
Recurrent disease (ref: Primary disease)	-9.6	3.6	0.008	-16.6 – -2.5
Treatment no (ref: Treatment yes)	-10.3	3.5	0.004	-17.2 – -3.4
Emotional functioning				
Fatigue				
Performance status 3,4 (ref: 0,1,2)	17.3	4.9	0.001	7.6 – 27.0
Nausea /Vomiting				
Gastric tube Yes (ref: No)	5.7	2.1	0.08	1.5 – 9.9
Pain				
Performance status 3,4 (ref: 0,1,2)	15.4	5.0	0.002	5.5 – 25.2
Dyspnea				
Performance status 3,4 (ref: 0,1,2)	11.4	4.5	0.012	2.3 – 20.1
Sex male (ref: Female)	8.6	3.4	0.012	1.9 – 15.4
Treatment no (ref: Yes)	8.4	3.3	0.012	1.8 – 15.0
Appetite loss				
Performance status 3,4 (ref: 0,1,2)	11.3	5.1	0.03	1.3 – 21.3
Weight loss yes (ref: No)	12.0	3.7	0.001	4.6 – 19.4
Constipation				
Sex male (ref: Female)	6.4	2.8	0.023	0.9 – 11.9

Table 5: Multivariate Cox regression analysis - impact on DSS

Variable	Regression Coefficient (exp β)	P value	95% confidence interval
Sex			
Male	Referent	.837	
Female	0.966		0.70-1.34
Age at entry in palliative phase			
Mean age (70.0)	Referent	**.028**	
Δ year	0.982		0.97-1.00
Marital status			
Married or living together	Referent	.905	
Alone	1.020		0.74-1.40
Performance Status			
0 and 1	Referent	**.013**	
2	1.524		1.08-2.15
3 and 4	1.599		1.09-2.35
Comorbidity (ACE-27)			
0 and 1	Referent	**.024**	
2 and 3	1.568		1.06-2.32
Percentage weight loss			
Mean original weight (73.0)	Referent	.114	
Δ percentage	1.022		1.00-1.05
Smoking			
No	Referent	.674	
Yes	.991		0.64-1.53
Former	1.148		0.77-1.71
Social network			
Adequate	Referent	.617	
Inadequate	0.899		0.59-1.36
Stage			
I-II	Referent	**.024**	
III	2.045		0.93-4.50
IVa	2.493		1.32-4.70
IVb	2.787		1.46-5.32
IVc + IV (p16+)	1.904		1.01-3.60
Tumor chronology			
Primary tumor	Referent	.437	

Table 5: Multivariate Cox regression analysis - impact on DSS (*Continued*)

Variable	Regression Coefficient (exp β)	P value	95% confidence interval
Recurrent disease	0.873		0.62-1.23
Palliative treatment			
No treatment	Referent	**.000**	
Local treatment	0.471		0.30-0.73
Systemic treatment	0.342		0.19-0.60
Local and systemic treatment	0.245		0.09-0.64
Intake EORTC QLQ-C15-PAL			
Mean Global Health Status (64.5)	Referent	**.000**	
Δ score	0.809		0.73-0.89

Discussion

The aim of this study is to evaluate structurally obtained outcome data from our palliative care program in order to obtain insight in: 1. longitudinal patient-reported outcomes; 2. survival and associated factors; 3. circumstances of death; 4. interventions and treatment during the palliative phase. With this study, we fill in the paucity of longitudinal studies in palliative Head and Neck Cancer (HNC) patients. Our study reports a median survival of 5.1 months in which palliative HNC patients experience significant deterioration in global health status, physical functioning, fatigue, dyspnea, appetite loss and constipation. It is important to see these longitudinal patient-reported outcomes within the light of clinical significance and relevance[32,33]. Changes are clinically small (5-10) for global health status, physical functioning, dyspnea and appetite loss, and clinically moderate (10-20) for fatigue[33]. According to the EORTC Head and Neck and Quality of Life Groups, all longitudinal changes in these domains, except for constipation, exceed the threshold for a minimally important difference[32]. The fact that the increase in scores for fatigue is the only clinical relevant change does not surprise as fatigue is seen as most common symptom experienced in overall palliative care[6].

There is little research available, longitudinal in particular, on patient-reported outcome measures in palliative HNC care. Compared to previous, however cross-sectional research using the EORTC-QLQ-C15-PAL in HNC, our results show

similar median scores at baseline for physical functioning, fatigue, pain, nausea and vomiting, dyspnea and constipation[5,34]. This is also in accordance to a recent review in which the domains physical functioning, fatigue and pain were mentioned as most prevalent[6].

Despite the overall deterioration over time for most domains, emotional functioning appeared to improve during follow-up. This is an interesting outcome considering previously reported major depressive disorders and high incidence of suicide in HNC populations[35-38]. To our knowledge, the longitudinal evolution of emotional functioning hasn't been investigated before in HNC. A study from van Roij et al. found that quality of care elements (eg. more satisfaction with care provided, continuity of care and information) was associated with higher emotional functioning[39]. We would argue that an excellent healthcare system, our expert clinic approach with psychosocial support during individual follow-up counselling and close contact with general practitioner can be an explanation for this improvement.

Place of death is a critical outcome in palliative care[40,41]. In our study, two-thirds died at home, and only a minority of 20 patients (7.8%) died in the hospital. These results reveal an improvement within our department since 2008 when 38% died in the hospital, and 18% in[201324]. This is noteworthy as previous international research in palliative HNC stated that 47-70% of the patients died in the hospital[9,42]. However, we are aware that this comparison should be made cautiously as the place of death can be culturally determined. In our study euthanasia was performed 33 times (12.8%). In contrast to other countries, this is a legal option for patients with unbearable suffering with no prospect of improvement. It is no absolute right and strict guidelines should be followed[43].

Strengthen patient-centered counseling and care

From our results, implications for clinical practice can be derived to strengthen patient centered care. Overall, patients and healthcare professionals should be aware of the limited survival, which leaves a short period for optimizing palliative care. It is important to inform patients on what to expect.

Patients with high performance status are prone to lower outcomes on the domains patient-reported physical functioning, fatigue, pain and appetite loss. Patients who

did not receive palliative treatment had lower overall survival and score significantly worse on the domains physical functioning and dyspnea. These insights can be used by healthcare professionals for screening and providing adequate counseling and support. Furthermore, monitoring patients without adequate social network more closely is also advised. Our results concerning place of death show that it is feasible to achieve a very low rate of in-hospital death. We would argue that advanced care planning and discussing the circumstances of death should be done early in the palliative phase. In addition, we would advise that a dietician and pain team are part of the multidisciplinary palliative team for all patients.

Strengths and limitations

A significant strength of our research is the availability of rich data concerning clinical and patient-reported outcomes. A strength is also the use of linear mixed models which enables the use of all available information without excluding patients due to missing data. Another strength of our study is the comparison we were able to make with previous research from our department[5,23,24].

A limitation of our study is the heterogeneity of the studied population. Outcomes can differ between tumor locations and morphologic types. Also, we are aware of the exploratory analysis and the need for caution in interpreting and drawing conclusions. Another limitation can be found in the absence of an item on patient-reported dysphagia, trismus, xerostomia and loss of speech in the EORTC QLQ-C15-PAL[26,44]. These domains should be incorporated into future measures of patient-reported outcomes. Other important factors that have not been included in our study are: loss of sensation, body image, sense of dignity, fears of mortality. In addition, we did not have the data available on race, ethnicity, socioeconomic status and education levels. It should also be noted that the generalizability is impacted by a different healthcare system compared to the Netherlands.

Future perspectives

As improvement in healthcare is a continuous process of implementation and evaluation, our team developed an easy-to-use professional improvement dashboard. This dashboard provides healthcare professionals real-time feedback on clinical and patient-reported outcomes on an aggregated level and is used periodically.

Following previous evaluation research with our Expert Center[24], we will evaluate our current value-based approach from the patients' point of view. This research will comprise patients' experiences and wishes concerning remote palliative care with our ePRO structure, the Healthcare Monitor. A next step would be to include familial or caregiver insights into the end of life experience and quality of death in our approach[45-47]. Currently, we are working on our ideas of an app for remote care which enables continuous symptom control and easy facilitation of contact with experts from our hospital. Our hypothesis is that this will lead to less hospital visits, enhance patients empowerment and improve end-of-life care.

Our team is currently developing a prognostic model for survival for patients in the palliative phase. The use of this model will provide patients and their caregivers with adequate information on expected survival, which consequently enables patient centered end-of-life decision making.

Corresponding to previous research[48-51], our results showed that global health status at baseline is a significant predictor for survival. Therefore, we believe that our data provides opportunities for further prognostic research, modelling longitudinal QoL and incorporating QoL in prediction models for survival.

Conclusion

This study provides a unique insight into the palliative phase of a large cohort of head and neck cancer patients. A short median survival was observed with a low rate of in-hospital death. Patient-reported global health status, physical functioning, fatigue, dyspnea, appetite loss and constipation deteriorated over time and higher global health status at intake was associated with improved survival. Emotional functioning improved over time. By analyzing structural obtained outcome information we are able to learn and improve our patient centered end of life counseling and care.

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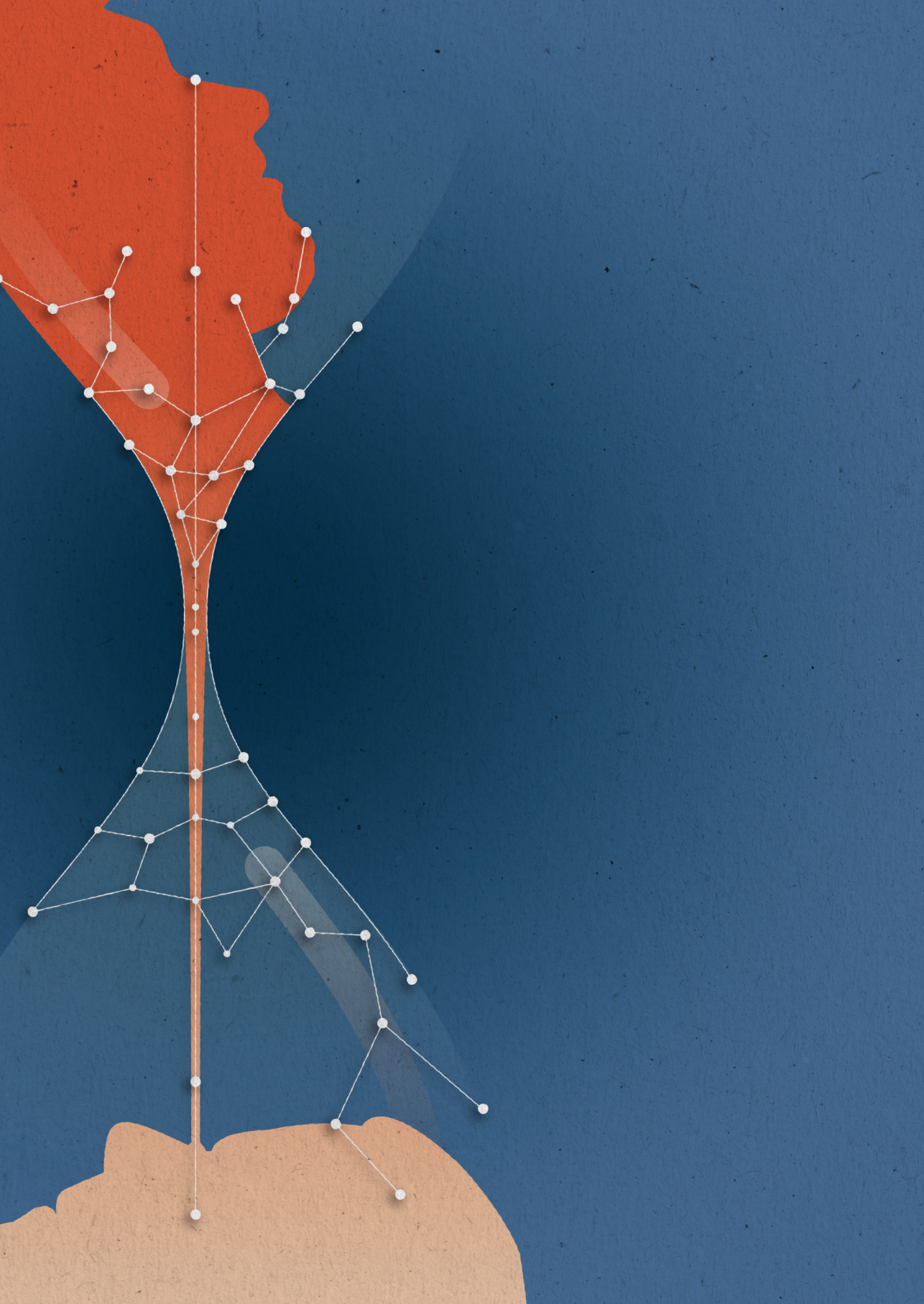

Chapter 10

General discussion

General discussion

Given global challenges such as an aging population, staff shortages, and affordability, the need for a value-based and outcome-driven approach to optimize care delivery has become increasingly important. To enable this, it is important to focus on active patient participating during the decision-making process and following healthcare trajectory combined with the ability of continuous healthcare improvement through the iterative process of using outcome information at the individual and aggregated population level.

The aim of this thesis was to investigate the use of quantitative and qualitative outcome information for individual decision-making and quality improvement in Head and Neck Squamous Cell Cancer (HNSSC) care. All clinical research conducted in this thesis adresses knowledge gaps in research and fits the agenda of 'outcome based healthcare' and 'appropriate care'. Both are Dutch national governmental programs with the goal of securing high quality, and cost-conscious care, now and in the future[1-3]. Our conclusions and recommendations can be used to deliver value-based care. An in-depth discussion is provided based on the questions 'What we have added to the literature?', 'What recommendations provide our results for future clinical practice?', and 'What are our future perspectives?'.

Part I: Outcome-based individual decision-making

In healthcare, everything starts with the individual patient. In order to empower individual decision making in HNSSC, studies in part I are conducted. This part is divided into three sub-parts:

Informed and shared decision making.

In this part we investigated the decision-making process in HNSCC care. Due to a lack of knowledge into the individual decision-making process for HNSCC patients, we were interested in how this process is experienced through the eyes of the patient. To what extent do patients experience decisional conflict, shared decision making (SDM), and what factors are associated with these outcomes?

The use of quantitative outcome information

Studies have been conducted in which the prognostic model OncologIQ is used for improving the individual and multidisciplinary decision-making process.

The use of qualitative outcome information

When patients are counselled, they want to know what to expect from their disease and treatment in terms of daily functioning and quality of life. Quality of life gained much attention in recent literature. We investigated how routinely obtained PROMs could be used to develop a dynamic prediction model in HNSCC care.

Part II: Outcome-based healthcare quality control and improvement.

In healthcare, the standard of care can be improved by using the clinical- and ePRO-data obtained from the individual healthcare process. In this part we investigated to what extent routinely obtained PROMs can be used to improve the quality of care, both at the individual and population level. Two studies were conducted into the use of structurally obtained clinical and patient-reported outcome measures in order to improve the quality of care for the individual patient.

Part I: Outcome-based individual decision-making

Informed and shared decision making.

With the research in ***chapter 2***, we were able to shed light on the individual decision-making process and the experience of decisional conflict and SDM in different subtypes of HNSCC. Clinically significant decisional conflict was experienced by 50% of the patients counselled for SLSCC, and 46% for patients counseled for other HNSCC. Identification of patients prone to high decisional conflict and offering them additional counseling is recommended. Regarding SDM, our research showed that 43.1% of the patients counseled for SLSCC, and 34.1% patients counseled for other HNSCC, felt they made a shared decision. These outcomes are consistent with recent literature, in which a recent Dutch report from the Ministry of Health, Welfare and Sport, showed that 37% of patients experience that they made the decision together with the healthcare professional[4]. Nevertheless, we believe these outcomes provide room for improvement in clinical practice as another report showed that 94% of patients have the need for a shared decision-making process[5]. The question, however, is how this can be improved. A critical note should be made with regard to SDM. It is proposed that SDM is particularly helpful when patients have an actual treatment choice, and can make a so-called preference sensitive decision. However, often only one option exists within treatment protocols in HNSCC care. Nevertheless, we believe that this should be also seen as decision-making as well because choosing no treatment is also an option. The latter is not uncommon in HNSCC care, as the disease and all types of treatment are associated with high morbidity, sometimes comprising vital functions like swallowing and speech. This is in line with the philosophy of patient-centered care, introduced in the introduction of this thesis, in which choice in all matters is one of the pillars[6].

Moreover, SDM comprises more than choosing between two treatments. It is an interactive play between the patient's view and values, and the healthcare professional's scientific expertise and medical experience[7,8]. Research showed that patients want to be involved, and healthcare professionals consequently underestimate this[7]. Involvement differs per patient, and is based on different factors such as personal values and coping styles[9-11]. During the decision-making process, patients need adequate information concerning their disease and treatment (eg. alternative treatments, risks, prognosis)[5]. This echoes in our finding from *chapter*

2, namely that patients scored high on the subscale values clarity. This subscale focused on the patients' experience in being provided with information on treatment choices, risks and benefits. Healthcare professionals should be aware of this fact, also because using adequate outcome information based on real data from previous treated patients could be the answer. There are many ways to use this outcome information correctly. In the next part, the focus has been to use quantitative outcome in the form of overall survival within an individualized prediction model in order to improve decision-making in HNSCC.

What we have added to the literature

- During the individual decision-making process, nearly half of all patients (48%) experienced significant Decisional Conflict.
- High median scores were found in the subscale values clarity, meaning that patients were not always clear on the risks, benefits and side effects and therefore what the best decision was.
- Patients who received counseling for the treatment of SLSCC feel more uncertain and find it difficult to make a decision.
- When patients experience lower quality of life, and increased anxiety and depression, they are more prone to experience clinically significant decisional conflict.
- A large proportion of patients (43.1%) counseled for SLSCC felt that they made a shared decision, in contrast to the patients counseled for other HNSCC, in which the physician decided significantly more often.

Recommendations for future clinical practice

- Identification of patients prone to high decisional conflict can aid in individual counseling and decision making.
- Make information about outcome, treatment, risks and benefits structurally available for patients. Doing this, enables patients to make an informed decision.

The use of quantitative outcome information for individual decision making.
With the studies performed in ***chapter 3 and 4,*** we have added unique research in to the field of prognostic research and counseling. Conclusions from these studies may form part of the answer to the question raised, how to improve the informed-

and shared decision-making process? As mentioned earlier in this thesis, many prognostic models on other types of cancer have been developed and described in literature. It is advocated that they could support and individualize the decision-making process[12-14]. However, clinical implementation and scientific testing of those models are lacking. In ***chapter 3*** we showed that healthcare professionals within a multidisciplinary team valued the model OncologIQ as a tool within the decision-making process in HNSCC. Qualitative results from our interviews showed that OncologIQ enabled patient-centered decision-making in a multidisciplinary consultation meeting, especially for more complex patients realated with a more poor prognosis. It should be noted that treatment plans did not change significantly more often. However, healthcare professionals expressed that they had a more holistic view of the patient. This study was used as a pilot prior to the implementation of OncologIQ during individual patient counseling. It was a first clinical introduction into OncologIQ for most healthcare professionals. This step follows a long line of research in our department[15-21]. Besides development and validation, there was a focus on understanding and communicating prognosis during individual patient encounters[18,22,23]. For example, by understanding patients' preferences when receiving prognostic information, we were able to train our healthcare professionals to communicate individualized prognostic outcome.

The study exposed in ***chapter 4*** showed the results of a clinical trial with two sequential cohorts. It concluded that the use of OncologIQ at an individual level improves the decision-making process by lowering decisional conflict and giving patients a more active role during the shared decision-making process. In addition, we saw a significant improvement on the subscales informed decision making and values clarity. These conclusions contribute to the conclusion of *chapter 3,* showing the benefit of an individualized prognostic model during the individual and multidisciplinary decision-making process. We recommend that healthcare professionals inform patients about the possibility to receive prognostic information. This can be provided qualitatively (terms like 'your cancer can be well treated') or quantitatively (numbers and percentages via OncologIQ). Previous research found that 62% found it very important to receive information about their life expectancy, in which a majority prefers qualitative terms[18]. Another study concluded that there is a higher need for prognostic information in patients with a lower prognosis[24]. Literature shows that prognostic counseling can benefit the patient-

physician relationship and strengthens the therapeutic alliance between patients and healthcare professional[25]. However, it is also known that healthcare professionals can be hesitant in disclosing prognostic information to patients. This could be due to inexperience and uncertainty with disclosing the prognosisby healthcare professionals , or to prevent the occurrence of fear of hopelessness or significant emotional impact, both of which would affect motivation. .

From the conclusion of the studies in ***chapter 3 and 4***, we would highly recommend to make OncologIQ one of the tools used during the multidisciplinary work-up, and for individual patient counseling. We believe that the results from both chapters warrant the use of data-driven individualized survival predictions for HNSCC patients. However, it should be emphasized that patients have a choice in receiving prognostic information, and that this information should be placed in context of other important outcomes, such as functional and psychosocial outcome, and QoL

What we have added to the literature

- The prognostic model OncologIQ enabled patient-centered decision-making in a multidisciplinary consultation meeting.
- Significant impact on the decision-making process from the multidisciplinary consultation meeting was seen when OncologIQ was used for more complex patients (older, WHO performance score ≥ 2, or high tumor stage).
- The use of OncologIQ within individual patient counseling decreased decisional conflict scores in patients.
- Patients experienced a more active role in the decision-making process when OncologIQ was used.

Recommendations for future clinical practice

- OncologIQ can be seen as a tool in the clinician's toolbox. When needed and desired, OncologIQ can help in obtaining reliable predictions and help multidisciplinary and individual decision making.
- Inform your patient about the possibility of receiving prognostic information, as it could improve the decision-making process.

The use of qualitative outcome information for individual decision making.
Disclosure of information on the expected daily functioning and quality of life after treatment is important. It provides realistic expectations from their disease and treatment and empowers patients to make informed decisions. In ***chapter 5***, longitudinal analysis of prospectively routinely obtained PROMs is performed. This is a representation of long-term dynamic trajectories and associated risk factors for voice quality after three preferred treatments for ESGC. Non-linear and heterogeneous trajectories for voice quality were found. No significant differences between treatments were found however. The results provide useful long-term longitudinal insight into one PROM. Consequently, these results can be used during individual counseling in addition to oncological and practical considerations. This study included a large sample size and adequate longitudinal statistical analysis. In contrast to previous literature, which were mainly based on cross-sectional data or short-term data comprising small sample sizes[26-33].

In healthcare, there is a growing need for longitudinal studies. Using longitudinal analysis, as opposed to static cross-sectional analysis, enables a better understanding of the dynamic trajectories of clinical and patient-reported outcomes during follow-up[34]. However, obtaining longitudinal data requires adequate and continuous measurement. Therefore, dedicated teams, infrastructure and funding is needed[35,36]. Within our institute, structural collection of patient-reported outcome measurements (PROMs) is embedded in our routine care since 2013 with the Healthcare Monitor[37]. The data is obtained and used at the individual level, during patient-doctor consultation, for improved decision-making. However, in ***chapter 5 and 6***, we show that this PROM-data from the individual level can be used on an aggregated population level for obtaining longitudinal insights and to develop individualized prediction models. The latter hasn't been done before in HNSCC research. Prediction modelling, however, is not new. Much is known about prediction models for binary outcome such as survival or recurrence. However, prediction modelling for patient-reported outcomes is new and more difficult as structural collected longitudinal data is scarce, and specific statistical techniques for repeated measurements data are required[38]. This could be done via methodological innovative statistical methods based upon mixed-effects models and joint models for longitudinal and time-to-event data. These methods have enjoyed a renaissance in recent years in the statistics and biostatistics literature[38-40]. Mixed-effect models

enable longitudinal analysis by using all available data and account for unbalanced data and correlation between measurements from the same patients[41]. Joint-models combines mixed-effect modelling with a time-to-event cox regression model. These statistical techniques enable the use of all available longitudinal and time-to-event data in order to make reliable individualized predictions from intake to end of follow-up. Within other fields, efforts have been made to develop dynamic prediction models[42-45]. We believe that dynamic prediction modelling for longitudinal PROMs is the future and we recommend to acqure statistical know-how, or collaborate with a biostatistician.

What have we added to the literature

- No clinically significant differences in longitudinal trajectories for voice quality were found between transoral CO2 laser microsurgery, single vocal cord irradiation, and local radiotherapy.
- Patients with a greater age, increased tumor stage, or severe comorbidity were associated with longitudinal voice quality.
- The framework of joint modeling can be used for the development of an individualized dynamic prediction model for patient-reported voice quality.

Recommendations for future clinical practice

- PROMs provide unique opportunities for obtaining longitudinal insight, and support patient-centered counseling by means of individualized dynamic prognostic models.
- Longitudinal analysis comes with statistical challenges, which are important to acknowledge in order to obtain trustworthy results.
- For the development of dynamic prediction models for longitudinal PROM-data, adequate statistical know-how or collaboration with a biostatistician is required.

Part II: Outcome-based healthcare quality control and improvement.

The addition of part III marks a transition from the individual level to a population level for healthcare quality control and improvement. The mixed methods systematic review in ***chapter 7*** showed that the field of research into the use of PROMs for healthcare quality improvement is still in it's infancy. However, important steps

have been taken that form the basis for further research. The most commonly used quality improvement method was benchmarking. This is according to our expectations, as benchmarking is a well-known and commonly used strategy for quality improvement in healthcare[46-48]. However, for PROMs, using aggregated data on a population level for quality improvement strategies appeared to be difficult and comes with conceptual, methodological and practical challenges. ***Chapter 7*** provides the reader also with a qualitative review of the literature in which we examined the facilitators, barriers and lessons learned from using PROMs for quality improvement. Based on our conclusions we would recommend for future quality improvement studies based on PROMS, that a shared stakeholder vision is created, PROMs and timing of measurement and feedback are appropriately chosen, interpretation of the feedback is optimal, every effort is made to reduce missing data, and practical resources for data collection and feedback infrastructure are available. In addition, we would recommend that PROM-data obtained is made available, including possible biases and completeness of outcome data. This is done preferably in combination with clinical and process outcome measures. By doing this, data analysis and benchmarking can be performed, and consequently, improvement strategies can be developed and implemented. Future research should focus on organizational and individual aspects that contribute to optimal use of the obtained aggregated PROMs at a population level for quality improvement[49].

In ***chapter 8 and 9***, we adopted the above-mentioned recommendations. We conducted research with the aim of obtaining longitudinal insight into clinical and patient-reported outcomes in order to improve the healthcare process and quality. In addition to results from these studies, we developed a quality improvement dashboard in ***chapter 9***. Together with a data scientist, we developed an easy-to-use dashboard which provides healthcare professionals with real-time feedback on clinical and patient-reported outcomes on an aggregated population level. Based on these insights, we were able to improve the healthcare process for palliative HNSCC patients at the individual level. This is an example of how continuous outcome measurement offers quality improvement opportunities within the entire process of care. **In *chapter 9*,** we were also able to continue research from the expert center of palliative care. Our results are promising, especially the fact that only 20 patients (7.8%) died in the hospital. Compared with international literature, and our own previous results, this is significantly low. We would argue that our expert

center approach, in which remote care from specialized oncology nurses and case-managers, and the close contact with the general practitioner are an explanation for these outcomes.

What have we added to the literature

- Four quality improvement methods based on PROMS were identified in literature, including benchmarking, PDSA cycles, dashboards and aggregated population analysis.
- There are no studies in literature that have demonstrated an effect of using aggregated PROMs for quality improvement strategies.
- Within our cohort of palliative HNSCC patients, during the median survival of 5.1 months there was a significant and clinical relevant deterioration in global health status and physical functioning, fatigue, dyspnea and appetite loss.
- A higher global health status at intake was associated with improved survival.
- A minority of patients (7.8%) died in the hospital, which is significant lower compared to international available data.
- Patients with oligometastasis experience a higher QoL compared to patients with polymetastasis.

Recommendations for future clinical practice

- Adequate and timely advanced care planning is advised in palliative HNSCC care. Ensure patients receive follow-up from an HNSCC palliative expert center, in addition to support from the general practitioner.
- It is highly recommended that obtained aggregated PROMs are made available and used for quality improvement strategies, preferably in combination with clinical and process outcome measurements.
- Future quality improvement studies based on PROMs should take into account that a shared stakeholder vision is created, PROMs and timing of measurement and feedback are appropriately chosen, interpretation of the feedback is optimal, every effort is made to reduce missing data, and finally, practical resources for data collection and feedback infrastructure are available.

- Patients with polymetastasis are more vulnerable, and early intervention is advised for this group.

Future perspectives

Since the adoption of value-based healthcare in the Netherlands, our department has played leading role in the transition to a value-based approach, especially within our own hospital. The focus of our department is measuring outcomes over the full care cycle, integration of value in patient communication, and setting up value-based quality improvement. In this we succeeded, however, it is far from finished. The results of this thesis form a building block within the total construct of value-based healthcare. Based on the presented conclusions, strengths and limitations of this research in this thesis, plans and recommendation for a future perspective can be made.

Individualized counseling

With the studies conducted in chapter 3 and 4, we have taken an important step step in prognostic research. However, the line of research and clinical implementation does not end here. It is important to ensure that OncologIQ is fully implemented and adopted in clinical practice. Clinical implementation after the research phase is a challenge as it is difficult to bridge the know-do gap in a real-world setting[50]. With the use of OncologIQ within the multidisciplinary consultation meeting, we are embedding the model in the work process. The goal is that the OncologIQ algorithm is incorporated within the digital registration form and provides automatically the 2- and 5-year overall survival estimates for that specific patient. It requires no additional action from the healthcare professional. During the MCM, this outcome information can be used during the decision-making. OncologIQ for individual use during the treatment decision consultation has been incorporated within a dashboard which is embedded in the electronic patient record. When prognosis is discussed, healthcare professionals can easily open a pre-filled OncologIQ. This is off course only for local implementation. Currently, we are working on making OncologIQ for other institutions by complying with the Medical Device Regulation, which are a set of European Union regulations that aim to ensure the safety and effectiveness of medical devices. It is new that prognostic models also fall under this regulation, and therefore it is challenging and not always clear on how this

regulation should be best applied to OncologIQ. OncologIQ can however already be found via www.oncologiq.com

The study in *chapter 4* was conducted within a curative HNC population. From experience and literature, we know that cancer patients in the palliative phase have a higher need for prognostic information than curative patients[18]. In addition, healthcare professionals find it difficult to provide trustworthy predictions for palliative HNC patients[51]. To date, no comprehensive prognostic model is available for palliative HNC patients. This model has recently been developed by our research team. Currently a study is being conducted into the use of this model in clinical practice. The aim of this model is to empower palliative HNC patients to make well considered end-of-life choices and shared decision making by providing them with individualized prognostic information on life expectancy.

Besides the development of a palliative OncologIQ, we plan to expand the current OncologIQ into a dynamic model which is able to provide new and updated predictions throughout the entire follow-up for overall survival estimates, recurrent disease and QoL. Previous research by Schroeff et. al. showed that dynamic prediction modelling for overall survival is feasible[20], and *chapter 5 and 6* showed feasibility for patient-reported outcomes. Such a model will be incorporated into the electronic patient dashboard via the Healthcare Monitor. By doing this, health care professionals can obtain real-time individualized graphical predictions for survival and patient-reported outcomes at any given moment during follow-up. The first step is to continue developing individualized prediction models for other PROMs. For example, we can use domains from other validated and internally used QoL questionnaires (EORTC-QLQ-C30, EORTC-QLQ-HN35, Hospital Anxiety Depression Scale, and Eating Assessment Tool-10). Especially, there is a need in the prediction of recurrent disease, as this often occurs. Keeping these models up-to-date is very important. Through our data-driven approach, we acquire new data every day. This is systematically obtained and form the basis of updating our current prognostic models. Based on our experience with the development and update of OncologIQ, we would not advise to add more variables to the model. Currently, we are not aware of any prognostic variables that would make predictions more accurate. However, if new variables, for example new biomarkers, would provide better predictions, we should investigate whether it improves the predictive performance of OncologIQ.

The experience from this thesis (chapter 5 and 6), is that more variables do not always improve predictions.

In addition to facilitate better counseling for the individual patient, the health literacy and the role of caregivers into providing patient-centered care should not be overlooked. Currently, healthcare professionals fail to recognize patients with limited health literacy. Research shows that 5-30% of patients is illiterate. The impact of limited health literacy extends beyond patients' comprehension; it hampers active participation in the communication and decision-making process[52]. It affects HNC patients QoL and is associated with post-treatment regret[53,54]. Future research will focus on this aspect of individual decision making. Considering the role of caregivers, within our research group, Kira van Hoff has extended previous research from Marinella Offerman to the role of caregivers in HNC[55-58]. The conclusions are currently being adopted in clinical practice.

Continuous improvement in Head and Neck cancer care

This thesis illustrates how the aggregation and analysis of individual-level data can uncover patterns, trends, and variations in care delivery. These insights are instrumental in shaping strategies for quality improvement. Part II of this thesis specifically focuses on quality control and improvement.

Our department's mission is to facilitate quality improvement in Head and Neck Cancer (HNC) care by providing healthcare providers and policymakers with real-time access to outcomes and meaningful analyses. Our primary objective is to gain insights into outcomes that will enhance our care processes and patient counseling. Notable examples include the palliative dashboard discussed in Chapter 9, the lead-time dashboard, which provides insights into the timeline from diagnosis to treatment, and our PROM dashboard, designed to improve patient counseling. A secondary goal is to utilize outcome data to compare institutions and, where feasible, healthcare professionals. Benchmarking will play a crucial role in this effort. To enable this, the use of valid data for analysis is paramount. Our experience indicates that connecting diverse data sources, validating preregistered data, and maintaining a continuous data collection process pose significant challenges. To address these issues, we collaborate closely with the Department of Data Analytics and IT.

It is crucial to recognize that quality improvement initiatives must extend beyond departmental and hospital settings. Currently, there is a shift from local to national quality registries in HNC care. Our department collaborates on a national level through a clinical audit board as part of the Dutch working group for head and neck tumors. The clinical audit board aims to standardize the outcomes used in HNC care, making them accessible for individual decision-making as well as for both local and national analysis. However, as shown in Chapter 7, improving the standard of care by aggregating outcomes, particularly patient-reported outcomes, presents significant challenges and obstacles. For future practices, the lessons learned from this study should be leveraged to maximize the impact of quality improvement initiatives in HNC care.

Data-driven and digital health technology

In healthcare's future, data and technology will have an increasing influence. Within this thesis we show how data obtained from the individual patient, can provide insight at the population level and improve the healthcare process. To enable data-driven quality improvement, partnerships are necessary in which open science and exchange of data are the norm. Currently, this is still very difficult in healthcare as most departments function as separate silos in research and improvement strategies. Similar to the impact Nightingales research had, it is expected that in the upcoming years, a revolutionary change is expected from the availability of big data and advanced statistical techniques[38,59]. Both will greatly expand the scope and scale of the use of outcome information in healthcare to improve healthcare for each individual patient[59]. In addition, the use of artificial intelligence techniques will also become standard. The literature suggest that it could enhance the efficiency of healthcare operations, reduce costs and administrative burdens, and helps healthcare providers make data-driven decisions[60]. For example, artificial intelligence can be used in assessing surgical margins during or after head and neck surgery. Another example is the development of a language model to provide patient information on head and neck cancer. These models could incorporate clinical and patient-reported outcomes and provide patients-like-me dashboards.

In healthcare, there is a lot potential of digital technologies. As the long-term sustainability of healthcare is increasingly under pressure, new solutions must be found and digital health technologies can be a solution. Within HNC we need to

explore how digital solutions impact the process of care. Can technology enhance patient empowerment, education and interaction between patients and healthcare professional? Examples from this thesis are prediction models, ePRO-structures, remote care, and dashboards. Especially for dashboards, our research demonstrated that developing an interactive dashboard for quality improvement is a strenuous task. The promise is that they capture, analyze and present data and enable insight in clinical-, patient-reported- and process outcome information. However, designing effective dashboards is challenging and despite the amazing look, the effect of using dashboards for quality improvement is far from evident[62]. Other solutions for digital technology could be the use of apps for patient education and monitoring, virtual reality and wearables. Currently, our research group is part of a joint coalition of researchers, industrial designers, clinicians and policy makers from the TU Delft, Erasmus MC and Erasmus University within a convergence project. They will investigate the conceptual, methodological, and practical groundwork for the sustainable embedding of digital health technologies[61].

Unlocking value in head and neck cancer care: start with the individual patient

As showed in this thesis, continuous improvement in healthcare relies on insightful analysis of data obtained from the healthcare process. At the heart of this approach is the recognition that every patient encounter represents an opportunity to learn and refine care processes. Empowering patients to make well-informed decisions during their healthcare trajectory is the primary goal of our research team. We are convinced that the use of outcome information during individual decision making shows patients the added value of our value-based approach. Tailoring healthcare trajectories to the specific needs, preferences, and circumstances of each patient enhance patient engagement, satisfaction, and ultimately health outcomes. This completes the circle of continuous healthcare improvement in Head and Neck Cancer care.

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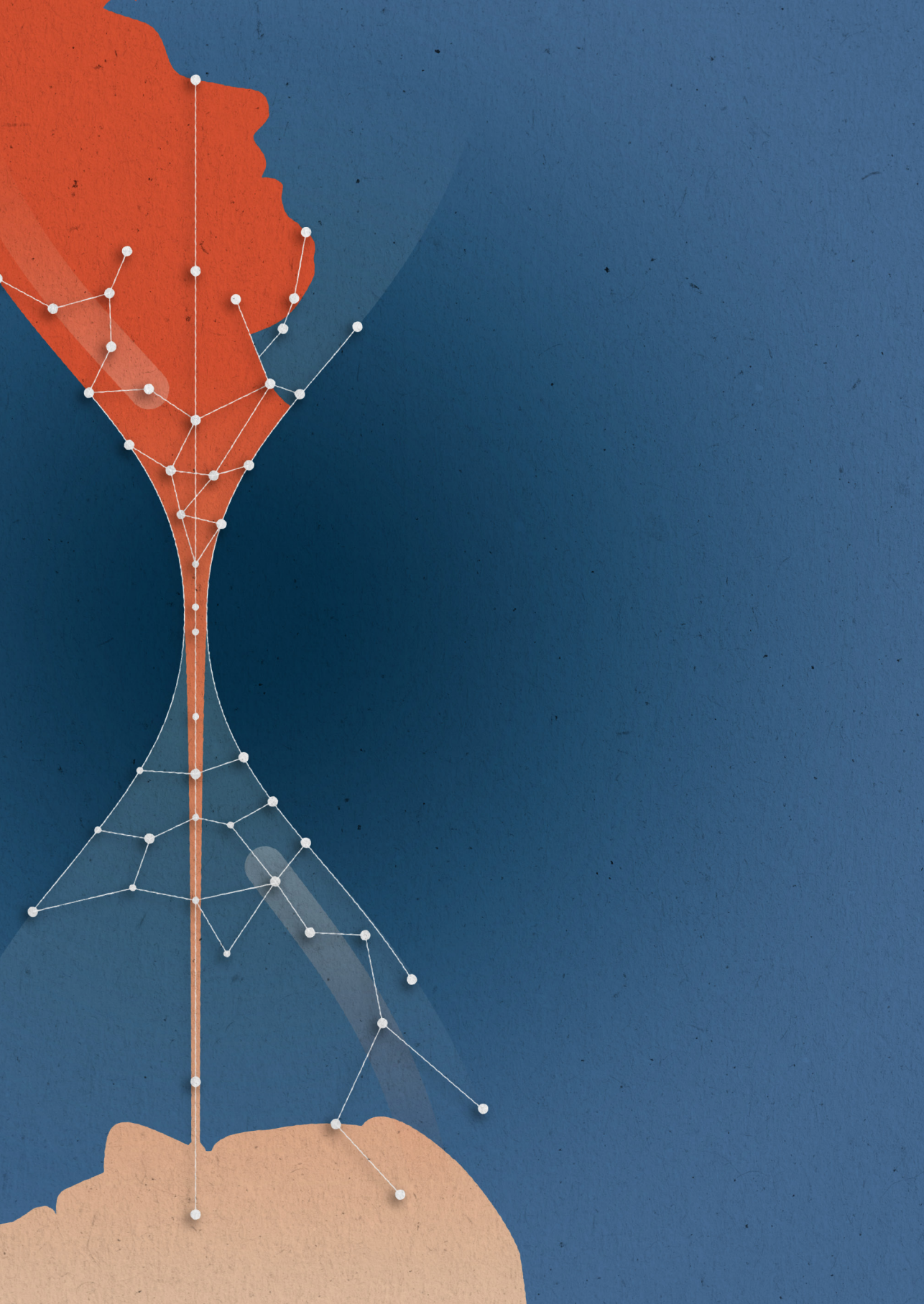


Chapter 11

English summary

English summary

Head and Neck squamous cell cancer (HNSCC) is a malignant disease that has a significant impact on the life and well-being of patients and their caregivers. When patients are diagnosed with cancer, they are confronted with difficult treatment decisions comprising a trade-off between survival and quality of life (QoL). During the decision-making process, healthcare professionals have a significant role in, and bear responsibility for adequate counseling and managing patients' expectations regarding long-term functioning and QoL. In recent years, there is a growing awareness for individualized counseling and shared decision-making. Routine measurement of quantitative and qualitative outcome information within the healthcare process is pivotal as basis for optimizing healthcare. This outcome information can be used for both individual counseling and quality improvement strategies. This thesis provides new scientific insights into the use of outcome information for individual decision-making and quality improvement in HNSCC care.

This thesis is written in two parts. It follows the use of outcome information within the healthcare process: from the individual patient level for empowering individual decision making (Part I) to the aggregated population level for healthcare quality control and improvement (part II).

Part I: Outcome-based individual decision-making

Informed and shared decision making

In order to understand how patients experience the decision-making process for the treatment of head and neck cancer, we conducted the research in ***chapter 2.*** Within this chapter, the personal perception of patients regarding their (un)certainty of the decision-making process and the decision made is assessed. In addition, the degree of shared decision making experienced during that decision-making process is measured. Notably, significant decisional conflict was observed in approximately half of the patients counseled for small laryngeal cancer and other HNSCC, indicating a need for additional counseling for those prone to high decisional conflict. Regarding shared decision-making (SDM), around 43.1% of small laryngeal cancer patients

and 34.1% of other HNSCC patients felt they made a shared decision, aligning with recent literature and leaving room for improvement.

The use of quantitative outcome information

In this part, studies into the use of quantitative outcome information from an individualized prognostic model were conducted. In ***chapter 3,*** we conducted a clinical trial in which the effect of implementation of the prognostic model OncologIQ within a head and neck cancer multidisciplinary consultation meeting was assessed. During the decision-making process for individual patients, estimates of the 1- to 10-year overall survival chances from OncologIQ were used as supplementary information. User value of OncologIQ and its impact on the decision-making process was assessed by quantitative and qualitative outcome measures. Results displayed in ***chapter 3*** showed that healthcare professionals within a multidisciplinary team valued the model OncologIQ as a tool within the decision-making process in HNSCC. Qualitative results from our interviews showed that OncologIQ enabled patient-centered decision-making in a multidisciplinary consultation meeting, especially for more complex patients in which prognostic outcome is lower. It should be noted that treatment plans did not significantly change. However, healthcare professionals expressed that they had a more holistic view of the patient.

We continued part I with a clinical trial in ***chapter 4***. In this trial we assessed the impact of the added individualized prognosis from the prognostic model OncologIQ during the treatment decision consultations. The study concluded that the use of OncologIQ at an individual level improves the decision-making process by lowering decisional conflict, and by giving patients a more active role during the decision-making process.

The use of qualitative outcome information

Disclosure of information on what patients can expect of their daily functioning and quality of life after treatment is important. It supports the provision of realistic expectations from their disease and treatment and empowers patients to make informed decisions. We conducted research into the use of qualitative outcome measures in order to empower individual decision-making. In ***chapter 5***, the impact of early-stage glottic cancer on voice quality is assessed by means of longitudinal analysis of routinely obtained patient-reported outcome information for three

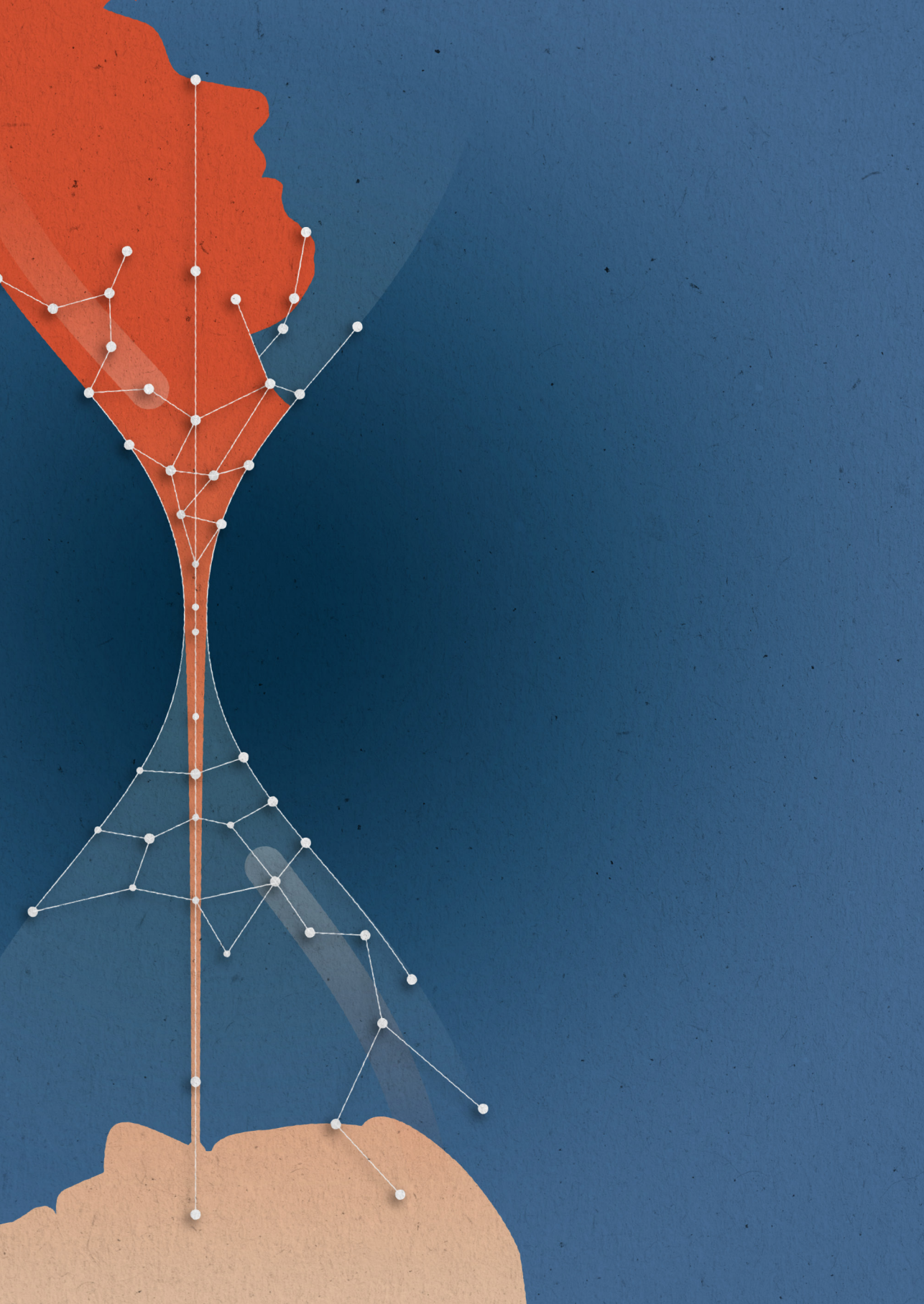
different treatment modalities used in early-stage glottic cancer. The results show long-term dynamic trajectories and associated risk factors for patient-reported voice quality after transoral CO2 laser microsurgery, single vocal cord irradiation and local radiotherapy. Trajectories appeared to be non-linear and heterogeneous. No significant differences between treatments were found. Results can be used during individual counseling in addition to oncological and practical considerations. Consequently, the results of this chapter are used in ***chapter 6,*** in which we describe the development and validation of an individualized prediction model for voice quality of HNSCC patients. This study showed that predictive performance of the investigated models is improved when more previous measurements of patient-reported voice quality are included. With other words, the longer the trajectory of the patient, the better the models predicts individual patient-reported voice quality. Overall, little differences in predictive performance between models were found and including more clinical and demographic variables did not provide better predictions. This model has the potential to empower patients and professionals in making well-informed decisions and enables tailor-made counseling.

Part II: Outcome-based healthcare quality control and improvement

In part II, we used routinely obtained outcome information from the individual patient level for healthcare quality control and improvement on a population level. A systematic review of the literature on the use and effect of quality improvement methods based on aggregated patient-reported outcomes on a population level is conducted in ***chapter 7***. This review showed that the field of research into the use of PROMs for healthcare quality improvement is still in its infancy. However, important steps have been taken and form the basis for further research. Four quality improvement methods were identified, including benchmarking, Plan-Do-Study-Act cycles, web-based dashboards as feedback tools, and the provision of aggregated statistical analysis reports. Benchmarking was the most commonly used method. Another finding that is revealed by this review is that it is difficult to use aggregated PROM-data for quality improvement strategies and that this comes with conceptual, methodological and practical challenges. Elaboration on these challenges, along with facilitators and lessons learned can be found within the qualitative part of

this chapter. Consequently, recommendations from ***chapter 7*** have been used for ***chapter 8 and 9*** in which research is conducted with the aim of obtaining longitudinal insight into clinical and patient-reported outcome information in order to improve the healthcare process and quality. ***Chapter 8*** gives insight into the impact of different patterns of distant metastasis on longitudinal quality of life for palliative head and neck cancer patients. The different patterns included oligometastasis, explosive metastasis and explosive-disseminating metastasis. Conclusions from this study highlights the significance of the counselling of tailored interventions that consider the unique challenges faced by each metastatic group of patients. Part two of this thesis ends with ***chapter 9***, in which we obtained learnings from longitudinal patient-reported and clinical outcome information in palliative head and neck cancer care. In this chapter we were able to continue the extensive research from the Expert Center of Palliative Care for HNSCC. Structurally obtained longitudinal outcome information in the palliative phase provides unique insight which enables improvement of patient-centered counselling and care.

Chapter 10 provides a general discussion in which the following questions were addressed: 'What have we added to the literature?', 'What recommendations provide our results for future clinical practice?', and 'What are our future perspectives?'.



Chapter 12

Nederlandse samenvatting

Nederlandse samenvatting

Plaveiselcelkanker van het hoofd-halsgebied is een kwaadaardige aandoening met een enorme impact op het leven en welzijn van patiënten en hun naasten. Wanneer patiënten de diagnose kanker krijgen, worden ze geconfronteerd met behandelbeslissingen waarbij een afweging gemaakt moet worden tussen overleving en kwaliteit van leven. Tijdens het besluitvormingsproces hebben zorgprofessionals de verantwoordelijkheid adequaat voor te lichten over de verwachtingen van de behandeling. Er is de laatste jaren veel aandacht voor geïndividualiseerde voorlichting en gedeelde besluitvorming. Het routinematig meten en gebruiken van kwantitatieve en kwalitatieve uitkomstinformatie binnen het gezondheidszorgproces is belangrijk. Deze uitkomstinformatie kan zowel worden gebruikt op individueel patiëntniveau als op populatieniveau. Dit proefschrift biedt nieuwe wetenschappelijke inzichten in het gebruik van uitkomstinformatie voor individuele besluitvorming en kwaliteitsverbetering binnen de zorg voor patiënten met hoofd-halskanker.

Dit proefschrift is geschreven in twee delen. Het volgt het gebruik van uitkomstinformatie binnen het gezondheidszorgproces: van het individuele patiëntniveau voor het versterken van individuele besluitvorming (deel I) tot het geaggregeerde populatieniveau voor controle en verbetering van de kwaliteit van de gezondheidszorg (deel II).

Deel I: uitkomstinformatie voor individuele besluitvorming

Geïnformeerde en gedeelde besluitvorming

Om te begrijpen hoe patiënten het besluitvormingsproces voor de behandeling van hoofd-halskanker ervaren, hebben we het onderzoek in ***hoofdstuk 2*** uitgevoerd. In dit hoofdstuk wordt de persoonlijke perceptie van patiënten met betrekking tot hun (on)zekerheid over het besluitvormingsproces en de genomen beslissing onderzocht. Daarnaast wordt de mate van gedeelde besluitvorming gemeten die door de patiënten wordt ervaren. In de resultaten is het opvallend dat er een significant beslissingsconflict werd waargenomen bij ongeveer de helft van de patiënten. De uitkomsten van deze studie wekken de indruk dat patiënten die vatbaar zijn voor een hoge mate van beslissingsconflict baat hebben bij aanvullende counseling. Met

betrekking tot gedeelde besluitvorming had ongeveer 43,1% van de patiënten met klein larynxcarcinoom en 34,1% van de patiënten binnen de groep overige hoofd-halskanker patiënten het gevoel dat ze een gedeelde beslissing hadden genomen. Dit is in lijn met de recente literatuur en biedt mogelijk ruimte voor verbetering.

Het gebruik van kwantitatieve uitkomstinformatie

In dit deel zijn onderzoeken gedaan naar het gebruik van de kwantitatieve uitkomst overleving binnen de individuele besluitvorming. Dit is gedaan met behulp van het in het Erasmus MC ontwikkelde geïndividualiseerd prognostisch model OncologIQ. OncologIQ geeft geïndividualiseerde voorspellingen van de overlevingskansen voor patiënten met hoofd-halskanker. In ***hoofdstuk 3*** is een klinische studie uitgevoerd waarin is gekeken naar het effect van de implementatie van het prognostische model OncologIQ binnen een multidisciplinair overleg over hoofd-halskanker. Tijdens het besluitvormingsproces voor individuele patiënten werden schattingen van de overlevingskansen uit OncologIQ gebruikt als aanvullende informatie. De ervaren gebruikerswaarde van OncologIQ en de impact ervan op het besluitvormingsproces werden onderzocht aan de hand van kwantitatieve en kwalitatieve uitkomstmaten. De resultaten weergegeven in ***hoofdstuk 3*** laten zien dat zorgprofessionals binnen een multidisciplinair team het model OncologIQ waardeerden als hulpmiddel binnen het besluitvormingsproces bij hoofd-halskanker. Kwalitatieve resultaten uit onze interviews laten zien dat OncologIQ de mogelijkheid geeft tot patiëntgerichte besluitvorming binnen een multidisciplinair overleg. Dit is vooral het geval voor complexere patiënten bij wie de prognostische uitkomst lager is. Opgemerkt moet worden dat de behandelplannen niet vaak aangepast werden. Echter gaven zorgprofessionals aan dat het gebruik van OncologIQ een meer holistische discussie op gang bracht.

Een andere klinische studie wordt beschreven in ***hoofdstuk 4***. In deze studie hebben we de impact onderzocht van het gebruik van geïndividualiseerde prognoses met OncologIQ tijdens het besluitvormingsproces tussen arts en patiënt. De studie concludeert dat het gebruik van OncologIQ op individueel niveau het besluitvormingsproces verbetert door beslissingsconflict te verminderen.

Het gebruik van kwalitatieve uitkomstinformatie

Het is belangrijk dat informatie over wat patiënten na de behandeling kunnen verwachten van hun dagelijks functioneren en kwaliteit van leven beschikbaar is tijdens de besluitvorming. Het ondersteunt in het creëren van realistische verwachtingen ten aanzien van ziekte en behandeling en stelt patiënten in staat weloverwogen beslissingen te nemen. In ***hoofdstuk 5 en 6*** hebben we onderzoek gedaan naar het gebruik van kwalitatieve uitkomstmaten om individuele besluitvorming mogelijk te maken. Specifiek gebruiken we de kwalitatieve uitkomstmaat van patiënt-gerapporteerde stemkwaliteit. In ***hoofdstuk 5*** wordt de impact van het hebben van klein larynxcarcinoom onderzocht door middel van longitudinale analyse van routinematig verkregen patiënt gerapporteerde uitkomstinformatie. Hierbij zijn de uitkomsten voor drie verschillende behandelingsmodaliteiten geanalyseerd. Resultaten uit dit hoofdstuk laten dynamische lange termijn trajecten met bijbehorende risicofactoren zien voor patiënt-gerapporteerde stemkwaliteit. Deze longitudinale trajecten bleken niet lineair en heterogeen te zijn. Bovendien werden er geen significante verschillen gezien tussen de drie behandelingen. Resultaten uit deze studie kunnen gebruikt worden tijdens het besluitvormingsproces met de individuele patiënt. Daarom zijn de resultaten ook gebruikt als basis voor ***hoofdstuk 6,*** waarin we de ontwikkeling en validatie beschrijven van een geïndividualiseerd voorspelmodel voor de stemkwaliteit voor patiënten met klein larynxcarcinoom. Deze studie toonde interessante modellen welke stemkwaliteit redelijk tot goed konden voorspellen. De voorspellende prestaties van de onderzochte modellen worden verbeterd als meer voorafgaande metingen worden meegenomen in het model. Met andere woorden: hoe langer het traject van de patiënt, hoe beter de modellen de te verwachten stemkwaliteit voorspellen. Er werden kleine verschillen in voorspellende prestaties tussen de onderzochte modellen gevonden. Daarbij leverde het opnemen van meer klinische en demografische variabelen geen betere voorspellingen op. Dit model heeft de potentie om patiënten en zorgprofessionals te ondersteunen in het nemen van goed geïnformeerde beslissingen en daarmee voorlichting op maat mogelijk te maken.

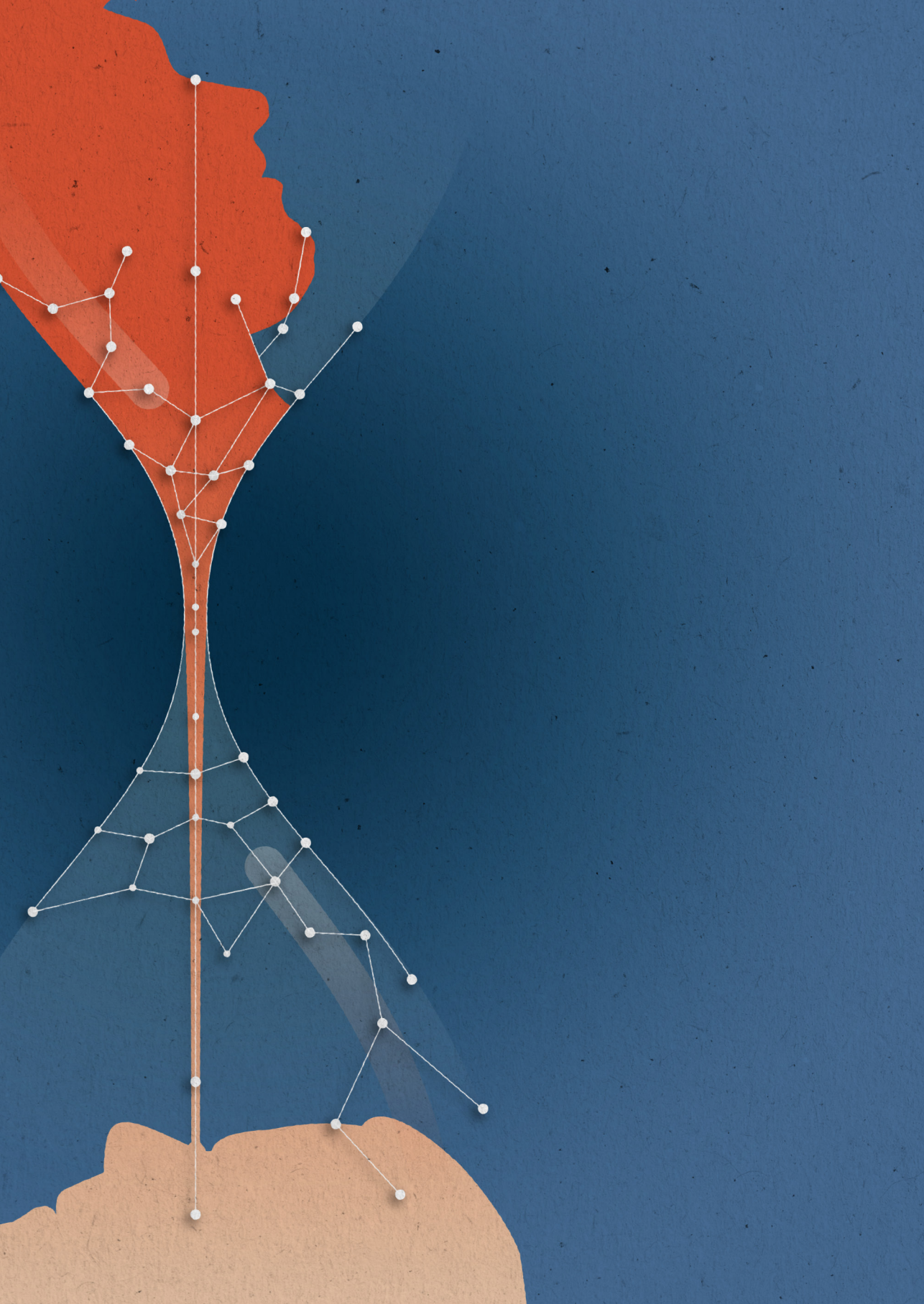
Deel II: uitkomstinformatie voor verbetering van de kwaliteit van zorg op populatieniveau

In deel II hebben we routinematig verkregen uitkomstinformatie van het individuele patiëntniveau gebruikt voor verbetering van de kwaliteit van zorg op populatieniveau. In ***hoofdstuk zeven*** is een systematische review uitgevoerd van de literatuur over het gebruik en effect van methoden voor kwaliteitsverbetering, gebaseerd op geaggregeerde patiënt-gerapporteerde uitkomsten. Uit deze review blijkt dat het onderzoeksveld naar de inzet van patiënt-gerapporteerde uitkomsten voor kwaliteitsverbetering van de zorg nog in de kinderschoenen staat. Er zijn vier methoden voor kwaliteitsverbetering geïdentificeerd, waaronder benchmarking, Plan-Do-Study-Act cycli, dashboarding als feedbackinstrumenten en het aanbieden van geaggregeerde statistische analyses. Benchmarking was de meest gebruikte methode. Een andere bevinding die uit dit onderzoek naar voren komt, is dat het moeilijk is om geaggregeerde patiënt-gerapporteerde uitkomst informatie te gebruiken voor kwaliteitsverbeteringsstrategieën. Dit gaat gepaard met conceptuele, methodologische en praktische uitdagingen. Een uitwerking van deze uitdagingen, samen met facilitators en geleerde lessen is te vinden in het kwalitatieve deel van dit hoofdstuk**.** Deze aanbevelingen en geleerde lessen zijn gebruikt in ***hoofdstukken 8 en 9.*** In deze hoofdstukken is onderzoek verricht met als doel het verbeteren van de kwaliteit van zorg op basis van longitudinaal inzicht in klinische en patiënt-gerapporteerde uitkomstinformatie. In **hoofdstuk 8** wordt inzicht verkregen in de impact van verschillende patronen van metastasering op de longitudinale kwaliteit van leven van patiënten met palliatieve hoofd-halskanker. De verschillende onderzochte patronen van metastasering zijn: oligometastase, explosieve metastase en explosief verspreidende metastase. De conclusies van deze studie benadrukken het belang van advies op maat, waarbij rekening wordt gehouden met de unieke uitdagingen waarmee elke gemetastaseerde groep patiënten wordt geconfronteerd.

Deel twee van dit proefschrift wordt afgesloten met ***hoofdstuk 9***, waarin we lessen hebben getrokken uit longitudinale klinische en patiënt-gerapporteerde uitkomsten in een cohort patiënten met palliatieve hoofd-halskanker. In dit hoofdstuk hebben we het uitgebreide onderzoek van ons Expertcentrum Palliatieve Zorg voor hoofd-halskanker kunnen voortzetten. De belangrijkste conclusie is dat structureel

verkregen longitudinale uitkomstinformatie in de palliatieve fase unieke inzichten biedt die verbetering van patiëntgerichte voorlichting en zorg mogelijk maken.

In ***hoofdstuk 10*** wordt een algemene discussie gegeven waarin de volgende vragen aan de orde komen: 'wat hebben we toegevoegd aan de literatuur?', 'welke aanbevelingen leveren onze resultaten op voor de toekomstige klinische praktijk?', en 'wat zijn onze toekomstperspectieven?'.



Addendum

List of abbreviations

ACE-27	Adult Comorbidity Evaluation-27
AI	Artificial Intelligence
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ANOVA	Analysis of variance
AUC	Area Under the Curve
BMI	Body Mass Index
CI	Confidence Interval
COREQ	Consolidated Criteria for Reporting Qualitative Research
CPS	Control Preference Scale
C-statistic	Harrell's concordance statistic
DCS	Decisional conflict scale
DM	Distant Metastasis
DRS	Decisional regret scale
DSS	Disease Specific Survival
EBM	Evidence Based Medicine
EBV	Epstein-Barr virus
EORTC-QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ePRO	Electronic Patient Reported Outcome
FDG-PET	18F-Fluorodeoxyglucose positron emission tomography
EDM	Explosive-disseminating metastasis
ESGC	Early-stage glottic cancer
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HM	Healthcare Monitor
H&N	Head and Neck
HNC	Head and Neck Cancer
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papilloma Virus
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
IKNL	Comprehensive Cancer Centre the Netherlands

IQR	Interquartile Range
LRT	Local Radiotherapy
MCM	Multidisciplinary Consultation Meeting
MDT	Multidisciplinary team (MDT)
MEC	Medical Ethical Committee
MeSH	Medical Subject Headings
ML	Machine learning
OECD	Organization for Economic Co-operation and Development
OM	Oligometastasis
OR	Odds Ratio
OS	Overall survival
PDSA	Plan-Do-Study-Act
PREM	Patient-reported Experience Measures
PRO	Patient-reported Outcome
PROM	Patient-reported Outcome Measures
QoL	Quality of Life
RCT	Randomized Clinical Trial
RMSE	Root Mean Square Error
RONCDOC	Rotterdam Oncological Documentation
SCC	Squamous Cell Carcinoma
SD	Standard Deviation
SDM	Shared Decision Making
SLSCC	Small Laryngeal Squamous Cell Carcinoma
SE	Standard Error
SES	Socio Economic Status
SVCI	Single Vocal Cord Irradiation
TLM	Transoral CO2 laser microsurgery
VBHC	Value Based Healthcare
VC	Vocal Cord
VHI	Voice Handicap Index

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PhD Portfolio

Summary of PhD training and teaching activities

Name of PhD student Maarten Christiaan Dorr

Erasmus MC dept. of Otorhinolaryngology and Head & Neck Surgery

Promotor Prof. dr. R.J. Baatenburg de Jong

Co-promotors Dr. M.P.J. Offerman, dr. A. Sewnaik

PHD TRAINING

PHD TRAINING	Year
Advanced courses	
Basic course Rules and organization for Clinical researchers (BROK)	2019
Basic introduction course in SPSS	2019
Repeated Measurements	2020
Using R for Statistics in Medical Research	2020
Advanced Analysis of Prognosis Studies	2020
Quality of Life Measurement	2020
General academic courses	
Patient Oriented Research	2019
Systematic literature retrieval in Pubmed	2020
Systematic literature retrieval in Embase	2020
Biomedical English writing course	2020
Scientific integrity	2021
Presentations on (inter)national conferences	
ZIN – waardegedreven zorg congres	2018
ECHNO ICHNO, online (poster and pitch)	2021
AHNS, online (oral)	2021
ICHNO-ECHNO, Brussel, Belgium (poster)	2022
NWHHT young researchers day, Utrecht, the Netherlands (oral)	2022
NWHHT congress Groningen (oral)	2022
ISOQOL, Prague, Czech Republic (oral)	2022
CEORL-HNS, Milan, Italy (oral)	2022
ECHNO, Lisbon, Portugal (oral)	2023
Scientific meeting of Dutch Society for ENT (oral), Kamerik	2023
	Year
Conferences	

ZIN – waardegedreven zorg congres ZIN – consortium congres Radboud UMC Conference 'Programma Uitkomstgerichte zorg', online	2018 2019 2021
ECHNO ICHNO, online	2021
AHNS, online	2021
NWHHT young researchers day, Groningen, the Netherlands	2021
ICHNO-ECHNO, Brussel, Belgium	2022
Scientific meeting of Dutch Society for ENT, Nieuwegein, the Netherlands	2022
NWHHT young researchers day, Utrecht, the Netherlands	2022
NWHHT: 'passende zorg is de norm', Groningen, the Netherlands	2022
ISOQOL, Prague, Czech Republic	2022
CEORL-HNS, Milan, Italy	2022
ECHNO, Lissabon, Portugal Congres ESPCI	2023 2023
Scientific meeting of Dutch Society for ENT, Kamerik, the Netherlands	2023
ESPCI, Rotterdam, the Netherlands	2023
Afscheidssymposium prof. Baatenburg, Rotterdam, the Netherlands	2023
Linnean Symposium: 'Geen woorden maar waarden', Rotterdam, the Netherlands	2023
Teaching activities	
Workgroup tutorship 1st year medical students	2021
Supervision Master student: Tamara Hendriks	2023
Workgroup 3rd year medical students physical examination ENT	2022
Education – operation assistants – surgical techniques	2023
Other activities	
Member of workgroup value-driven quality improvement (Linnean Innitiative)	2023-2024
Member of systematic review consortium (VBHC – NFU)	2020-2022
Doctor meets director	2023-2024
AIOS talentenklas – Federatie Medisch Specialisten	2024
NEXTGEN – advisory board for Board of Directors Erasmus MC	2023-2024

List of publications

Van den Besselaar BN, Sewnaik A, Hoesseini A, **Dorr MC**, Baatenburg de Jong RJ, Offerman MPJ. *Causes and Ways of Death in Patients With Head and Neck Cancer.* JAMA Otolaryngology Head Neck Surg. 2024 Apr 1;150(4):303-310. doi: 10.1001/jamaoto.2023.4694.

Berzenji D, **Dorr MC**, Sewnaik A, Mast H, Offerman MPJ, Baatenburg de Jong RJ, Hardillo JA. *Quality of Life of Oligometastatic and Polymetastatic Head and Neck Squamous Cell Carcinoma Patients. Laryngoscope.* 2024 Feb 7. doi: 10.1002/lary.31325.

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About the author

Maarten Christiaan Dorr was born on December 25th 1990 in Zoetermeer. In 2009, he successfully completed high school education at the Oranje Nassau College, location Parkdreef, in Zoetermeer.

Maarten studied Medicine at Maastricht University, the Netherlands. During his time at university, Maarten served a year as president of the board of the student association M.S.V. Tragos. During his study, he conducted his research internship at the trauma surgery department in the Academic Medical Center of Amsterdam under the auspices of Dr. T. Schepers and Dr. M. Backes. He was convinced he wanted to become a surgeon until he started his internship at the department of otorhinolaryngology head and neck surgery in Maastricht. Captivated by the field of ENT diseases, with its diverse patient population, precision surgery and interesting pathophysiology, he wanted to become an ENT specialist. He undertook an internship in otorhinolaryngology at the Steve Biko Academic Hospital in Pretoria, South Africa.

Maarten graduated in 2016 and started his medical career as a senior house officer at the department of Surgery in the Sint Franciscus Hospital in Rotterdam, followed by a position at the department of Head and Neck Surgery at the Dutch Cancer Institute in Amsterdam. In 2018, Maarten obtained a position as PhD candidate at the department of otorhinolaryngology head and neck surgery at the Erasmus MC. He started specialty training in otolaryngology and head and neck surgery in 2022 under auspices of prof. dr. R.J. Baatenburg de Jong, prof. dr. B. Kremer, dr. R.M. Metselaar, dr. P.G.J. ten Koppel and G.K.A. van Wermeskerken. Maarten will finish his specialty training in 2027. During his specialty training, Maarten also focused on medical leadership and entrepreneurship in healthcare. He developed a training program for nursing homes in order to improve the care for patients with tracheotomy or laryngectomy.

Maarten lives in Rotterdam with his wife Judith. Together they have a daughter, Félien Marie Dorr.

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